DEVELOPMENT OF EVIDENCE-BASED BEHAVIOURAL INTERVENTIONS TO REDUCE INAPPROPRIATE USE OF ANTIBIOTICS BEYOND CLINICAL SETTINGS

Leesa Kuanhua Lin

Thesis submitted in accordance with the requirements for the degree of

Doctor of Philosophy
of the
University of London

September 2019

Department of Public Health, Environments and Society

Faculty of Public Health and Policy

LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

'No funding received'

DECLARATION

I, Leesa Kuanhua Lin, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

NAME IN FULL: LEESA KUANHUA LIN

Signature: [redacted]
Date: 13 September 2019

ACKNOWLEDGEMENTS

I would first like to thank the partner institute and collaborators of this PhD study, Zhejiang University (ZJU), specifically Professor Xudong Zhou and the Research Team on Prudent Antibiotic Use. Special thanks go to Dr. Xiaomin Wang and Weiyi Wang without whom the research would not have been possible. I am deeply grateful for the guidance and support of my supervisors: Professors James Hargreaves, Elizabeth Fearon, John Cairns, and Mark Petticrew. I would like to thank my advisors - Professors David Heymann, Stephan Harbarth (University of Geneva), Mishal Khan, Chunling Lu (Harvard Medical School), and Leah Li (University College London) - and my upgrading examiners - Professors Mark Petticrew and Shunmay Yeung - for their time and constructive feedback in shaping, delivering, and reporting my projects. I thank James and Liz for supervising my design and launch of the projects, commenting on data analyses plans, and reviewing draft manuscripts. I would like to express my gratitude to James, John, Mark, David, Mishal, and Stephan for guiding me through the thesis and viva stage, and reviewing thesis and manuscript drafts. Contributions to individual chapters are also reported in the respective cover pages. I am deeply grateful for my examiners, Professors Andrew Hayward (University College London) and Laurence Moore (University of Glasgow), for their time, commitment, and constructive feedback for a successful viva.

My PhD project greatly benefited from preparation for the bid to the joint global health trial (call 9) with Professors Katherine Fielding, Laith Yakob, Chunling Lu, and Xudong Zhou and his colleagues at Zhejiang University. This experience helped me position the proposed intervention and offered me an appreciation of the depths and implications of this PhD project in implementation research, the global efforts to contain antimicrobial resistance, and the context of China. I conducted two systematic literature reviews with Dr. Elizabeth Fearon, Prima Alma, Tingting Yao (ZJU) and Ruyu Sun (ZJU) which supported the screening and coding of a selection of titles, abstracts, and papers. I gained valuable knowledge from my visits and meetings with local partners in Zhejiang Province, China including local government officials, NGOs, doctors and residents. These experiences shaped my intervention design and contextualised my PhD findings in current practice, which supported the interpretation and conclusion sections

of the thesis. I am especially grateful for the time, knowledge and hospitality of the local partners involved for their interest in the proposed interventions and for supporting the proposed participatory approach. I am thankful for the time and input of research participants, who remain anonymous in this thesis. I am thankful for the Medical Research Foundation (MRF) National PhD Training Programme in Antimicrobial Resistance Research for providing the platform and training that has inspired my work.

Finally, I want to express my utmost gratitude to my family, Debbie and Henry Lin, Mary and Ed Mazza, John Mazza, Dr. Xin Yan; to my friends - Kaat, Kaiyi, Kelly, Lua, Lee (Fuwa), Noah, and Prima; and to my officemates at 9 Tavistock Place for supporting me at every step and for putting my doctoral research into perspective.

ABSTRACT

Human use of antibiotics in China accounts for a quarter of worldwide antibiotic consumption and mainly occurs in outpatient and community settings. Non-clinical factors for antibiotic use are main drivers of its excessive consumption. To date, almost every intervention has focused exclusively on antibiotic prescribing behaviours, with little attention being paid to antibiotic consumer's usage behaviours in the community.

This PhD study aimed to develop an evidence-based, theory-informed behavioural change intervention to reduce inappropriate use of antibiotics in the Chinese communities. To conduct this programme of research, I employed a mixed-methods approach throughout the study phases, which included: 1) systematic literature reviews on determinants of antibiotic use in China and on behavioural change interventions to reduce unnecessary or inappropriate use of medical interventions, 2) secondary data analyses of large-scale population data on antibiotic use-related knowledge and practice, 3) formative interviews to ensure acceptability and feasibility of proposed interventions, and finally 4) a mixed-methods feasibility evaluation of the pilot intervention.

The systematic reviews identified non-clinical factors and potential pathways influencing public's antibiotic use, and the components of promising behavioural change interventions. Using the survey data, some of the pathways were quantitatively-assessed to inform the development of a context-appropriate intervention - reducing access to non-prescription antibiotics in rural China was identified to be a priority. Additionally, (mis-)perceived antibiotic efficacy for upper respiratory tract infections (URTIs) was found to be associated with increased odds of antibiotic use in the community. The new knowledge contributed to the design of the proposed intervention. Working with local partners, I developed and conducted a feasibility assessment of a pilot antibiotic take-back programme aiming to reduce household antibiotic storage and unsafe disposal in rural China. The proposed intervention was deemed feasible and appropriate.

FIGURES AND TABLES

CHAPTER ONE

CHAPTER TWO

CHAPTER THREE

CHAPTER FOUR

CHAPTER FIVE

CHAPTER SIX

CHAPTER SEVEN

ACRONYMS AND ABBREVIATIONS

6SQuID	Six Essential Steps for Quality Intervention Development
ABR	Antibiotic resistance
AMR	Antimicrobial resistance
AAC	Antibiotic awareness campaigns
BCT	Behaviour change technique
BCTT	Behaviour change technique taxonomy
BCW	Behavioural change wheel
CASP	Critical appraisal skills programme
CBPR	Community-based participatory research
CI	Confidence interval
CNKI	China Knowledge Resource Integrated Database
CPP	Controlled pre- and post-study
CRT	Cluster randomized control trial
CS	Elective caesarean section
DPT	Dual processing theory
EBP	Evidence-based practice
EPHPP	Effective Public Health Practice Project's Quality Assessment Tool for Quantitative Studies
EUU	Expired, unwanted, or unused
GDP	Gross domestic products
HIC	High Income Country
IM	Intervention mapping
ITS	Interrupted times series
JGHT	Joint Global Health Trial
KAP	Knowledge, attitudes and practice
LMIC	Low and Middle-Income Country
LSHTM	London School of Hygiene and Tropical Medicine
MMAT	Mixed methods appraisal tool
MoD	Mode of delivery
MRC	Medical Research Council

MRF	Medical Research Foundation
NA	Not applicable
NCT	Nonrandomized controlled trial
NGO	Non-governmental organisation
NIH	National Institute for Health
NIHR	National Institute for Health Research
NR	Not reported
OTC	Over-the-counter purchases
OR	Odds Ratio
PDM	Prescription drug misuse
PPP	Purchasing power parity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials
RE-AIM	Reach, effectiveness, adoption, implementation, and maintenance
ROI	Returns on investment
RRR	Relative risk ratio
SMA	Self-medication with antibiotics
ToC	Theory of change
USD	United States Dollar
URTIs	Upper respiratory tract infections
VD	Normal vaginal delivery
WHO	World Health Organization
ZJU	Zhejiang University

THESIS ASSOCIATED PUBLICATIONS

Presentations

1. Lin L. Development of an evidence-based behavioural intervention to reduce inappropriate use of antibiotics beyond clinical setting. The 2018 Medical Research Foundation (MRF) National PhD Training Programme in Antimicrobial Resistance Research. August, 2018. Bristol, UK. *(Best presentation award)*
2. Lin L. Decisions on antibiotic use for upper respiratory tract infections across China: a large-scale cross-sectional survey. The 2019 Medical Research Foundation (MRF) National PhD Training Programme in Antimicrobial Resistance Research. August 2019. Bristol, UK.

Manuscripts under peer-review

1. Non-clinical factors influencing the general public's and healthcare providers' antibiotic use in the China: a mixed-methods review. *Social Science Medicine (Under review).*
2. Public-targeted behavioural change interventions to reduce inappropriate use of medicines and medical procedures: a systematic review. *Implementation Science (In press)*.
3. Contextualizing prevalent antibiotic misuse in children across China: a large-scale cross-sectional survey on parents' antibiotic use on children for common childhood illnesses. *Journal of Emerging Infectious Diseases (Under review).*
4. Parental treatment decisions for paediatric upper respiratory tract infections with respect to antibiotic use across China: a large-scale survey. *International Journal of Antimicrobial Agents (Under review)*.
5. Decisions on antibiotic use for upper respiratory tract infections across China: a large-scale cross-sectional survey among university students. *BMJ Open (In press)*
6. Development of an antibiotic take-back programme to reduce unsafe use and disposal in rural China: a mixed-methods approach. *BMC Medical Research Methodology (Under review)*.

7. Cleaning up China's medicine cabinet – an antibiotic take-back programme to reduce household antibiotic storage for self-medication in rural China: a mixed-methods feasibility study. *Antibiotics (In press)*.

TABLE OF CONTENTS

CHAPTER ONE: INTRODUCTION

1.1 Background

Since the discovery of the first antibiotic, penicillin, by Alexander Fleming in 1928, antibiotics have revolutionised modern medicine by making previously incurable infections and conditions, including pneumonia and other life-threatening bacterial infections, treatable. Today, many routine medical procedures, including caesarean sections, appendix removal, and chemotherapy, rely on effective antibiotics to prevent common infections from becoming fatal. However, decades of antibiotic misuse and overuse by doctors and patients (to treat minor ailments) and farmers (to promote growth in agriculture and aquaculture) have given rise to antimicrobial/antibiotic resistance (AMR or ABR), seriously threatening the health of humans, animals and the environment. Antibiotic resistance is a natural occurrence: when exposed to drugs, bacteria respond and evolve in ways that reduce or eliminate the effectiveness of antibiotics. Evidence has shown that excessive and inappropriate antibiotic consumption has accelerated the emergence and spread of AMR.[1,2] In 2014, the World Health Organization (WHO) issued a warning, stating the world is headed for a "post-antibiotic era" where minor infections, once considered defeated, could kill again.[1]

This PhD study aimed to develop an evidence-based, theory-driven, context-appropriate behavioural intervention that seeks to influence norms and cultural habits and encourage prudent use and disposal of antibiotics in the community. Through a set of inter-linked aims and research activities, I led the development of a community-based intervention that was implemented by local partners and conducted a feasibility evaluation to assess it. Specifically, I employed a mixed-methods approach throughout

the study phases, which included four aims: 1) evidence synthesis: systematic literature reviews on determinants of antibiotic use in China and on behavioural change interventions to reduce inappropriate use of medical interventions driven by non-clinical factors; 2) social epidemiological methods: quantitative data analyses of large-scale population data on antibiotic use-related knowledge and practice; 3) intervention development and adaptation: formative interviews to ensure acceptability and feasibility of proposed interventions, and finally; 4) evaluation: a mixed-methods feasibility evaluation of the pilot intervention. Findings from my study were used in 2018 to inform the development of a full grant proposal of a multi-level complex intervention in Zhejiang province to the Joint Global Health Trial. This study has contributed to the field of implementation science research by laying out an explicit roadmap of the development of community-based behavioural change interventions and to overall global action against AMR by providing empirically-derived, evidence-based interventions, examples of appropriate feasible evaluation designs, and solutions to the identified methodological challenges associated with feasibility studies for such interventions.

This chapter provides an introduction to the thesis and its structure. It briefly outlines the basis for this research with respect to the fields of implementation research and AMR, the aims and objectives, and the research methods and activities chosen.

1.2 The background to the research

1.2.1 Global health challenge of antimicrobial resistance

Antibiotic resistance is a natural process that happens when bacteria (or other microorganisms like fungi) develop the ability to reduce or eliminate the effectiveness of the drugs designed to kill them. The bacteria survive and continue to multiply,

thereby causing more harm. Therefore, infections caused by antibiotic-resistant bacteria pose a serious threat to infection control as they become difficult, and sometimes impossible, to treat and require extended hospital stays, additional follow-up doctor visits, and costly and toxic alternatives. According to the surveillance report released by the World Health Organization (WHO) in 2014, resistance to a wide range of anti-infective agents has become a worldwide public health threat that continues to grow, and its prevalence is closely related to the overuse of antibiotics.[1]China has one of the highest drug resistance rates in the world due to its excessive use. Take *methicillin-resistant* Staphylococcus aureus *(MRSA*), broad-spectrum antimicrobial resistance, for example. According to the CHINET AMR surveillance network, in the tertiary hospitals, the average MRSA isolation rate ranged from 29.1% to 74.2% in 2014, with an average of 44.6%, and as high as 76.9% in eastern China where the prevalence in large cities such as Beijing, Shanghai and Guangzhou is higher than those of smaller cities.[2,3] Another study based on data collected at 12 teaching hospitals across China from 2005 to 2010 reported the prevalence of MRSA and methicillin-resistant coagulase-negative staphylococci (MRSCoN) to be 46.8% and 81.5%, respectively.[4] The challenge is worse among Chinese children – it has been reported that 32.7% of S. aureus isolated from paediatric patients is MRSA, about twice of what has been observed in adult patients.[5]

1.2.2 Common cold and antibiotics

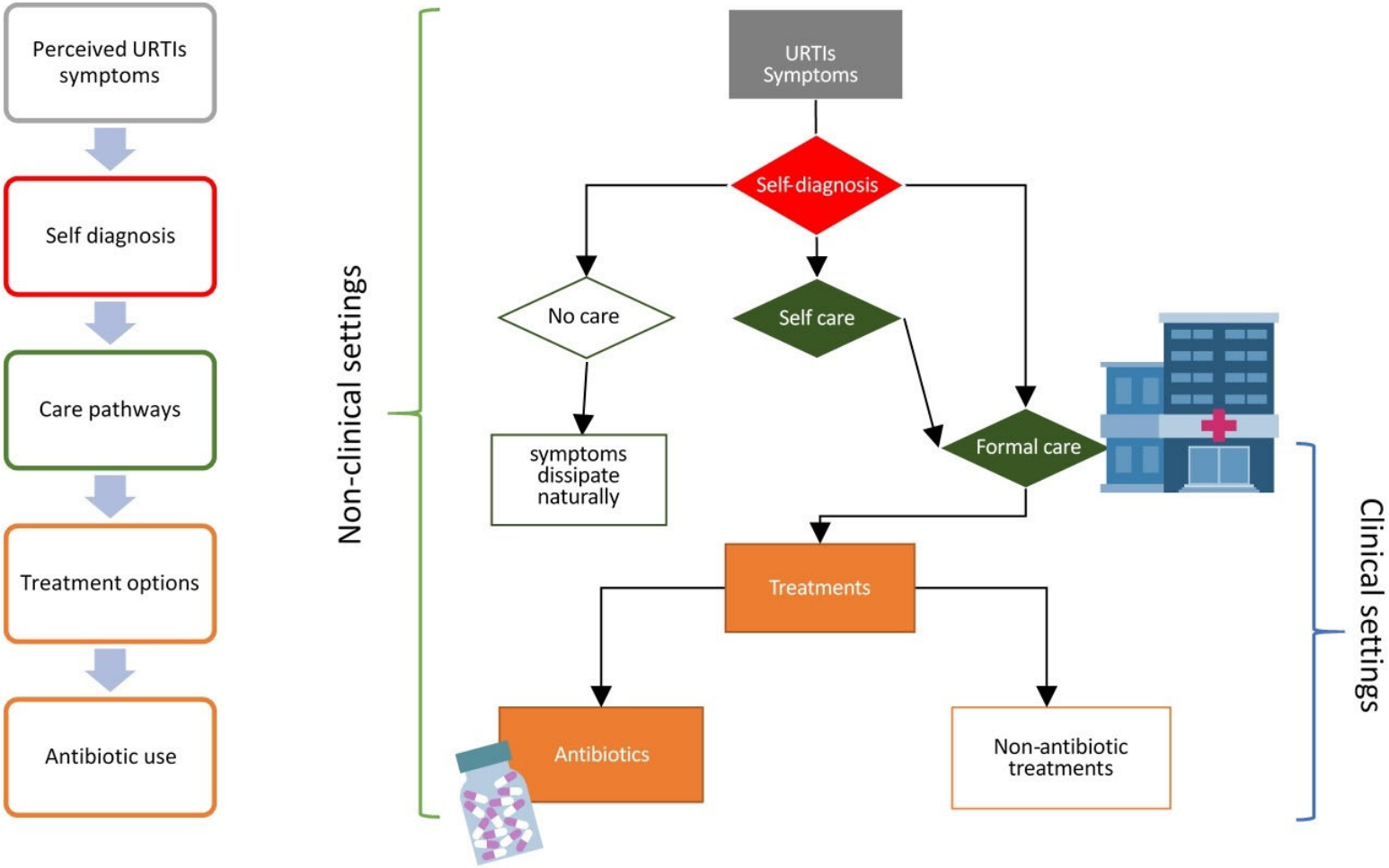
Considered the most common infectious disease among humans, the common cold - formally referred to as acute upper respiratory tract infections (URTIs) and usually informally described as a cough, runny nose, cold, or flu – refers to a group of diseases caused by members of several families of viruses.[6] These diseases are

diagnosed on symptomatology and treatments are mainly symptomatic, rather than focusing on changes in viral titres in the airway or viral shedding.[6] The symptoms of "Common cold" are triggered in response to the viral infection of the upper respiratory tract (i.e. nose and throat) and the immune response to infection may be the main factor in generating the symptoms, rather than damage to the airway.[6] Depending on the physiological and immunological experience of the person who contracts it, common cold could occur without symptoms, could cause death, or most commonly could be associated with an acute self-limiting illness.[6] Despite the common cold being a self-limiting viral infection for which antibiotics are both unnecessary and may result in adverse outcomes,[7] data show that the common cold is the most prevalent reason for primary care seeking and antibiotic prescribing in many countries.[8-11]

The common cold strikes frequently, affecting every age and race: adults experience colds two to five times per year while children may catch a cold seven to ten times per year.[12-14] The syndrome of the common cold is defined by experimental colds including a short mild illness with early symptoms of sneezing and sore throat and later symptoms of nasal discharge, nasal obstruction, and cough.[6] They are so well-recognised by patients and caregivers that, before consulting a physician, a layperson often engages in self-diagnosis and decides on a course of action, including whether or not to treat, to seek care, and/or to use medications.[15-18] Medical anthropologists have found that high familiarity with common cold symptoms has resulted in a high consistency in the diagnostic process and a response that is shared in the form of a "cultural concept and practice" within each community, across people, and between lay and physician groups.[19,20] Therefore, individual's decision-making process for treating the common cold can be viewed as a continuum of steps starting from identification of

symptoms and self-diagnosis to choice of care pathways (e.g. no care, self-care or formal care) and use of medications and/or antibiotics (Figure 1-1), where each step may be shaped more by individual and socio-contextual factors than by clinical diagnoses.

Figure 1-1. Decision-making for antibiotic use for upper respiratory tract infections (URTIs)



1.2.3 Health system in China

China has a three-tiered system for healthcare delivery, based on urban and rural residences; in rural areas, health care providers operate at county, township, and village levels and in urban areas at municipal, district, and community levels.[21] Hospitals in China can be public or private, non-profit or for-profit. Urban areas have both public and private secondary and tertiary hospitals whereas township hospitals and community hospitals are mostly public. In general, the capacity of and the quality of care given by primary care facilities are considered inadequate, especially in the rural areas.[22] Private facilities take up smaller market share, mainly offering ambulance services or specialised care, and are considered of lower quality and utilised by rural migrants in urban areas.[23,24] Additionally, every city and county have at least one independent traditional Chinese medicine (TCM) hospital, and most comprehensive medical institutions and grassroots health facilities have a TCM department that provide TCM services such as herbal medicines and acupuncture services.[25] Many Chinese people use traditional Chinese medicine (TCM) as a supplement to western medicine or self-care. TCM is considered a natural treatment with fewer side-effects and when a common cold is present, is often given by providers with a mixture of western medicine. The fee-for-service payment mechanism in the health care system, introduced in the late 1980s as a part of the economic reform, has reduced the role of the government in financing healthcare service and shifted a traditionally community-level, preventive care system to a commercialized, sub-specialty-oriented healthcare system over time.[26] To compensate for the reduced subsidy, health facilities are allowed to make profit from drug sales - a 15% or more mark-up on medicines.[26] Such a mechanism incentivises hospitals to attract and retain health care consumers who could have been cared for by primary care

facilities and to profit from excessive examinations, unnecessary treatment, and overuse of medicines by routine healthcare services.[22] The problem of over-prescribing (including antibiotics) was later improved after the introduction of the zero mark-up for essential medicines at primary level facilities.[27] Inequity in health and health care exists, with gaps between urban and rural areas, among regions of different economic development levels, and among different groups of people.[28]

Since 2003, China has undergone a comprehensive health care insurance reform and in 2011, achieved universal health insurance coverage (95.7%). The public are covered by three main basic health insurance schemes based on employment (urban only) and residence or *Hukou*, a household register system. The Urban Employee Basic Medical Insurance (UEBMI) covering urban employees and retired employees is a mandatory employee-based health insurance funded by employer and employee contributions.[22,25] People who are not covered by UEBMI can join the voluntary the Urban Residence Basic Medical Insurance (URBMI) or the New Rural Cooperative Medical Scheme (NRCMS), which are jointly financed by premiums and government (mainly by government subsidies, about 70% of the total funds).[22,25] These basic insurance systems cover inpatient and outpatient diseases in compliance with regulations and have specific deductibles, co-payment percentage, and a reimbursement cap.[22,25] An urban and rural medical assistance system, financed through various channels including government and public donations, provides subsidies that form a safety net in China to ensure that those in poverty who are unable to afford the basic medical insurance premium have access to basic health care.[25]

1.2.4 Antibiotic use and resistance in China

According to the Chinese Academy of Sciences, in 2013 total antibiotic usage in China was approximately 162,000 tons, accounting for roughly half of antibiotic usage worldwide.[29] With a per-capita use of antibiotics of 138 g – ten times higher than in the United States[30,31] – the AMR burden in China is reportedly much more serious than in other countries.[32] The majority of antibiotics for human use in China are consumed in the outpatient setting, often unnecessarily for viral URTIs.[33] Though usually benign and self-limiting, URTIs have been a critical driver of inappropriate and excessive use of antibiotics in China,[34-37] where antibiotics have been perceived for decades as a panacea by the general public and medical workers, and misused at all levels of Chinese medical care.[30,31,38-42] In his landmark 2016 global AMR Review,[43] Lord Jim O'Neill highlighted the importance of engaging China, and that the first step towards combating AMR is reducing demand through behavioural change interventions. However, despite WHO's efforts championing appropriate antibiotic use for the common cold, curbing antibiotic overuse and misuse has gained only limited traction in China.[44] The 2019 BMJ policy review[44] of China's 10-year effort in health reform concluded that, although its enhanced national antibiotic stewardship programmes may have had a positive effect on regulating antibiotic use in tertiary hospitals, there has been no improvement in primary care or rural settings, where most of the population resides and the majority of antibiotic use takes place.

Reasons for antibiotic misuse and antibiotic resistance in China include: improper prescribing and dispensing by clinicians, inadequate government oversight – especially poor policy enforcement at the local level - and inappropriate use among patients. [30,31,38,40-42] This misuse is due to cultural norms, as well as patients and

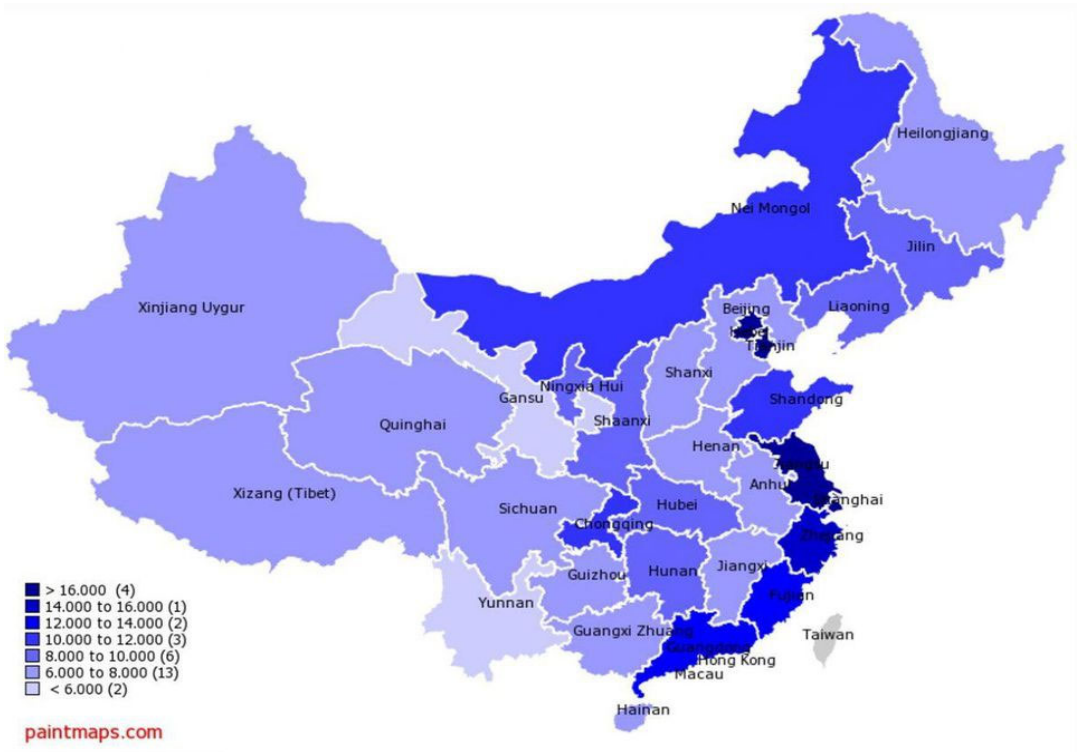
caregivers' misconceptions, demands, and unrealistic expectations.[30,31,38,40-42] Regional inequalities and disparities between urban-rural income per capita may also play a role.[45] (Figure 1-2)

Rising levels of AMR in China in recent years have become a serious healthcare problem, with high resistance rates of most common bacteria to clinically important antimicrobial agents including methicillin-resistant Staphylococcus aureus (MRSA), erythromycin-resistant Streptococcus pneumonia, ciprofloxacin-resistant E. coli, extended-spectrum β-lactamase-producing E. coli, imipenem-resistant Pseudomonas aeruginosa, and imipenem-resistant Acinetobacter baumannii—the so-called "superbugs" in nosocomial infections – and other bacteria that are resistant to fluoroquinolones, macrolides and third-generation cephalosporins.[46-48] In tackling AMR in recent years, the Chinese government has enacted a series of clinician-directed measures to control the consumption of antibiotics, including a comprehensive surveillance network involving tertiary hospitals in distinct regions nationwide that was first created in 2005.[2] A series of regulations and clinical guidelines were also introduced to tackle the irrational use of antibiotics by enhancing antimicrobial stewardship along with health system reform, [44] including the essential medicines scheme and zero-mark-up policy on antibiotic prescriptions,[49-51] systematic training and a stewardship program (e.g. guidelines, lectures, workshops),[52,53] and audit and feedback on antibiotic prescribing and dispensing practices.[54-56] Importantly, in 2011, the Ministry of Health set up a special task force on antibiotic stewardship, resulting in strict rulings that covered all aspects of antibiotic use in hospitals with clear indicators linked to hospital quality evaluation procedures. Chief among the rulings was that antibiotic prescriptions for hospitalized patients and outpatients was set at less than 60% and 20%

of all prescriptions, respectively, and antibiotic utilization in hospitalised patients should be less than 40 daily defined doses per 100 patient days.[48] These indicators have a direct impact on the allocation of future medical resources as well as the appointment or dismissal of hospital presidents, which has led to rapid reduction of the use of antibiotics in many tertiary hospitals.[44,48]

However, these measures have shown only minimal impact on curbing the misuse of antibiotics and the use of antibiotics in primary care and rural settings remains high. [44] A high percentage of URTI patients in China was prescribed antibiotics and overutilization of antibiotics is particularly problematic in rural areas and in lower-level hospitals and health clinics.[33-38,44,57] Further, though the sale of antibiotics in retail pharmacies without prescription was banned as early as 2004 it suffered from insufficient enforcement and absence of supervision, and was not addressed in the 2011 regulations. Both over-the-counter sales and self-medication of antibiotics have been prevalent.[58] In 2016, China announced a comprehensive national action plan to contain AMR, which included a prominent goal of prescription-only antibiotics at pharmacies in all provinces by 2020; however, specific details to achieve the goal were largely absent.[59] Most of these interventions to date have been designed to address structural issues that influence individual antibiotic use and focus on supply-side factors through the promotion of rational prescribing, dispensing, and enforcing prescription-only sales, leaving demand-side factors conspicuously unaddressed.

Figure 1-2. Map of Chinese provinces indicating GDP PPP per capita in USD[i]



Inappropriate demand and use of antibiotics for the common cold among various Chinese populations can be generally categorised into five types of ill-practice: asking/pressuring doctors for antibiotics,[45] self-medication with antibiotics,[34,41,45,60-64] taking antibiotics as prophylaxis,[45,61] storing antibiotics at home,[41,45,60,62] and deviation from medical instructions, including incomplete courses, using antibiotics intermittently rather than regularly, and increasing and decreasing doses.[38,45,61,65] Scientists have been attempting to dissect the complexity of the issue and investigating the reasons why interventions have been less effective than intended; they conclude that doctors are not solely to blame for misuse.[66] One study estimated that antibiotic misuse in China is more driven by the demand-side of the health system – patients and caregivers – than by

[i] Babones, Salvatore. China Quietly Releases 2017 Provincial GDP Figures. Forbes. Feb 12, 2018. https://www.forbes.com/sites/salvatorebabones/2018/02/12/china-quietly-releases-2017-provincial-gdp-figures/#64558dc820dc (Last accessed: July 1, 2018)

the supply side.[45] In other words, targeting clinicians without addressing demand side issues addresses less than half of the problem. Evidence showed that putting pressure on hospitals and doctors alone will not adequately tackle the challenge of antibiotic overuse[44]; rather, patients who sought care and displayed knowledge of appropriate antibiotics use could effectively reduce antibiotic prescription rates.[56] Furthermore, as discussed above, when encountering the symptoms of the common cold before seeking formal care at a clinic, a lay person or caregiver is likely to have already gone through a pre-existing self-diagnostic process (Figure 1-1.) and formulated a response that was heavily influenced by the culture and community in which they live. Not surprisingly, self-medication with antibiotics for the common cold by the Chinese general public has been consistently reported as prevalent and is heavily linked with inappropriate use of antibiotics[66], including using left-over antibiotics on a second occasion,[62,63] frequent change in dosage, or simultaneous use of the same antibiotic with different names.[34,45,62,65,67] In particular, non-prescription antibiotics have been very easy to access across China; without professional supervision, many Chinese households self-report to use antibiotics from their own household storage or over-the-counter purchases.[45,60,65,68-74] Depending on the region, 40-50% of those surveyed reported treating themselves with antibiotics without seeing a doctor, [31,61,75] and 20-30% had used antibiotics to prevent the common cold. [31,61] Even among the better-educated population - university students - many had misconceptions about antibiotic efficacy for self-limiting illnesses and inadequate knowledge, and similarly reported a high prevalence of antibiotic misuse.[61,67,75,76]

Medical decisions such as antibiotic use and treatments for the common cold are not made in a vacuum. They are influenced by factors at multiple levels, including

intrapersonal factors (e.g., knowledge and attitudes), interpersonal factors (e.g., social networks, communication with doctors), and societal environments (e.g. social norms, access to care, and laws and policy).[77,78] In spite of the magnitude of antibiotic misuse in China and its unique sociocultural context, there is a dearth of evidence examining how these different levels of influences affect people's medical decisions for the common cold, especially through their AMR awareness, attitudes, and knowledge about antibiotic use.

1.2.5 Implementation research

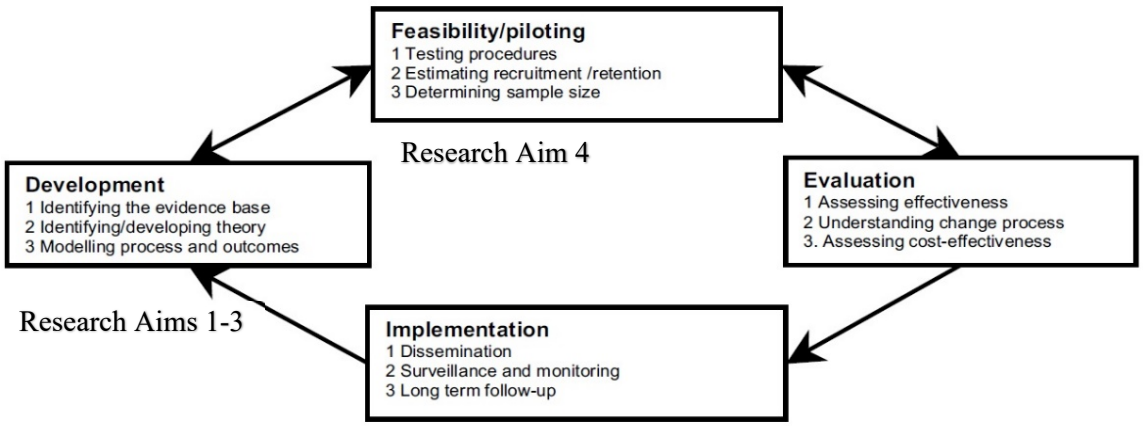
Implementation research, which focuses on the linkage between research and practice for effective implementation of proven interventions to improve health outcomes, emerged in recent years in response to the need to address the challenges of the know–do gap in real-world settings during the development and delivery of public health approaches.[79] Implementation research builds on several research traditions - each has its own research targets, research questions and sets of core disciplines - providing a set of methods, tools, and approaches for bridging research and practice to create and apply knowledge that improves the implementation of health policies, programmes and practices.[79] Implementation research is a growing but still not fully-understood field of health research; considerable confusion remains regarding its terminology, approach and scope.[80] In defining the scope of this PhD project and guiding the selection of methodology, I adopted the definition and principles first published by Peters et al[80] on BMJ in 2013 and later iterated on by Theobald et al[79] in the Lancet in 2018, which stated "Implementation research is the scientific inquiry into questions concerning implementation—the act of carrying an intention into effect, which in health research can be policies, programmes, or individual practices

(collectively called interventions)".[80] As implementation research seeks to understand and work within real world conditions, rather than trying to control them, Peter et al emphasised the central role that context plays in implementation research, which recognises the influence social, cultural, institutional and physical environments exert on people's health and health behaviours.[80] Theobald et al further identified a set of eight defining characteristics of implementation research, which were pinpointed during a series of structured and consultative international meetings with researchers, donors and policy makers, including *context specific, relevant and agenda-setting purpose, methods fits for purpose, demand driven, multi-stakeholder and multidisciplinary, real world, real time and focuses on processes and outcomes*.[79]

Implementation research is typically a multi-method inquiry that uses both quantitative and qualitative data to assess how the programmes and policies – i.e. "interventions", which are usually "complex" - produce their impacts. Interventions that have multiple interacting components with several "dimensions of complexity" can be described as "complex interventions," according to the Medical Research Council (MRC), with distinctive characteristics in their complexity, such as variations in number and difficulty of behaviours required by those delivering or receiving the intervention and degree of flexibility required for implementation.[81] The MRC guidance on developing and evaluating complex interventions provides a framework (Figure 1-3) that serves as a structured roadmap for the design and evaluation of such interventions.[81] The framework highlights the importance of the development, feasibility and piloting phases of intervention design before engaging in full scale evaluations for effectiveness and cost-effectiveness and the final phase of implementation and dissemination.[81] These initial phases ensure there is an evidence base and theory to support intervention

development, allow modelling the intervention implementation process and outcomes, and enable testing procedures, recruitment and retention. MRC also recommends the adoption of the RE-AIM (reach, effectiveness, adoption, implementation, maintenance)[82] and/or other formal frameworks for developing and testing complex interventions.

Figure 1-3. MRC framework of complex interventions[81]



[Research Decision: Study Aim] For this project, I aimed to apply implementation research frameworks in the development of and assessment of the feasibility of the proposed community-based intervention, where feasibility is defined as "the extent to which an intervention can be carried out in a particular setting,"[80] in this case, rural Zhejiang.

1.2.6 Feasibility and pilot studies

There has been an increasing emphasis by large public funding bodies, such as MRC, UK National Institute for Health Research (NIHR), and the US National Institute for Health (NIH), on the importance of engaging in sufficient preliminary work prior to

the main bids of large-scale trials of complex interventions, so as to determine whether comprehensive and multilevel evaluations are justified. Given resource constraints, feasibility and pilot studies are necessary to produce a set of evidence that can evaluate and prioritize interventions with the greatest likelihood of being efficacious.[83] Some researchers compare the spectrum of implementation research for complex interventions to that of pharmaceutical drug trials, which have a tradition of clearly defined stages from pre-clinical studies to phase 4-post-marketing studies,[80,84] and note that feasibility studies are conducted with both flexible methodology and a main goal of assessing the feasibility of a newly developed intervention, as opposed to a rigorous examination of outcomes.[85,86] This emphasis on preliminary work fuelled the rise of implementation research and the publishing of the results of feasibility and pilot studies; however, to date, the published literature has not proposed standards to guide the design and evaluation of feasibility studies.[83] In this project, I therefore followed the MRC guidance, which stated that feasibility and pilot studies should address the main uncertainties that could be anticipated in development work, including acceptability, compliance, delivery of the intervention (fidelity), recruitment and retention, and that a mixed-methods approach is likely needed.[81] In fact, a series of feasibility and pilot studies may be required to progressively refine the design before embarking on a full-scale evaluation; therefore, some have described feasibility studies as iterative, formative and adaptive, a so-called *kinaesthetic* developmental learning process.[81,83,87]

For the bid of the Joint Global Health Trial (Call 9), Zhejiang University funded and conducted a series of pilot studies to develop and test the feasibility of the proposed community-based behavioural change intervention. I contributed to the development of the intervention, designed and supervised a formal feasibility study nested within a

series of pilot projects, and interpreted and reported the evaluation data. Implementation research for behavioural change is largely influenced by a set of core disciplines in psychology, education, sociology, anthropology, education, and epidemiology,[79] which follows the traditions of programme evaluation, dissemination and implementation in evidence-based medicine and participatory action research, as presented in Table 1. Data reported in this study came from a pilot study conducted in June 2019, which had a controlled before and after design – a stricter study methodology than most non-trial feasibility and pilot studies – with the intention of laying the groundwork for further work.

Table 1-2. Implementation research traditions for behaviour change and their typical research targets, research questions, adapted from Peters et al[80] and Theobald et al[79]

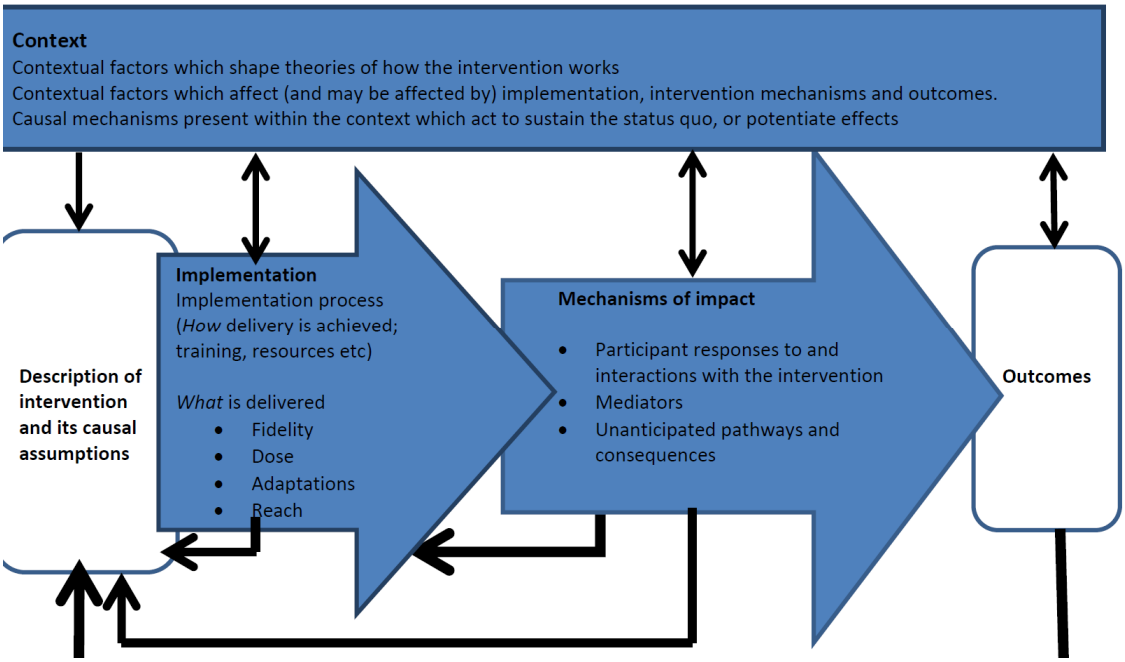
Traditions	Primary audience for research	Research Questions
Programme evaluation	Stakeholders of a programme (e.g., funders, implementers, or the intended beneficiary)	How is the programme designed, implemented, used, fit to context and problems, and with what results and programme changes?
Dissemination and implementation of evidence-based medicine	Practitioners, health organisation managers, and policy makers who do not use evidence-based interventions	What promotes the integration of research findings and evidence on interventions into health-care practice?
Participatory action research	Research participants and community members	How can we (community members and research participants) learn and be empowered to act?

The purpose of this pilot study was to assess important parameters that would be needed to design the main study, e.g., willingness of local partners to recruit participants, number of eligible participants, follow-up rates, response rates and adherence/compliance rates. Zhejiang University had a plan for further work after this

pilot study, and the aim was to identify any problems or areas of concern and amend the intervention before the implementation of a full-scale study.

Further, the MRC guidance on the feasibility/piloting phase has been extended to provide more detail on process evaluation through the publication of the MRC PHSRN process evaluation summary guidance,[88] which enhances the development phase of the original MRC guidance. Derived from the guidelines, Figures 1-4[88] present the key functions of process evaluation (in blue boxes) informed by the intervention descriptions, relationships amongst them, and how they inform interpretation of outcomes.

Figure 1-4. MRC PHSRN Process evaluation[88]



[Research Decision: Work Stream Plan, informed by implementation science frameworks] Table 1-1 presents a work stream plan that summarises how the MRC guidance was operationalised by this PhD project. To meet the objectives of a feasibility study and fulfil the kinaesthetic nature of the intervention developmental process, I created the work stream plan based on the core disciplines of implementation science-

related frameworks to guide the development and feasibility assessment of a behavioural change intervention, including RE-AIM, evidence-based medicine (e.g. intervention mapping[89,90]), intervention development model (e.g. MRC PHSRN Process evaluation Summary guidance,[88] Six Essential Steps for Quality Intervention Development (6SQuID)[91]), and participatory action research (e.g. community-based participatory research (CBPR) principles).

1.3 Research objective

The primary objective of this study was to employ implementation research methods in the development of a community-based behavioural change intervention that aims to reduce inappropriate use of antibiotics, especially non-prescription use and unsafe disposal of antibiotics, in rural China.

1.4 Research questions

On the basis of the research gaps and decisions mentioned above, the following research questions were investigated:

1. Question 1: What are the evidence-proven non-clinical determinants of various antibiotic use behaviours among Chinese clinicians, patients and caregivers? (Aim 1, chapter two)
2. Question 2: What are the "active ingredients" in behavioural change interventions that have been proven to be effective in reducing the inappropriate or non-essential demand/use of medications or medical services? (Aim 1, chapter three)
3. Question 3: What is the prevalence of antibiotic misuse for self-limiting illnesses among Chinese children in the community, within and beyond clinical settings? (Aim 2, chapter four)

4. Question 4: What are the factors influencing treatment decisions for the upper respiratory tract infections (URTIs, aka the common cold) with respect to antibiotic use in the Chinese community? (Aim 2, chapters five and six)
5. Question 5: What should be the components of a novel community-based behavioural change intervention aiming to reduce antibiotic misuse through a focus on reducing unnecessary demand and increasing safe disposal? (Aim 3, chapter seven)
6. Question 6: How feasible is it to implement the newly-developed behavioural change intervention that aims to reduce non-prescription use and unsafe disposal of antibiotics in rural Zhejiang, China? How well are the methodological issues around a feasibility study addressed in the pilot? (Aim 4, chapter eight)

1.5 Research aims and tasks

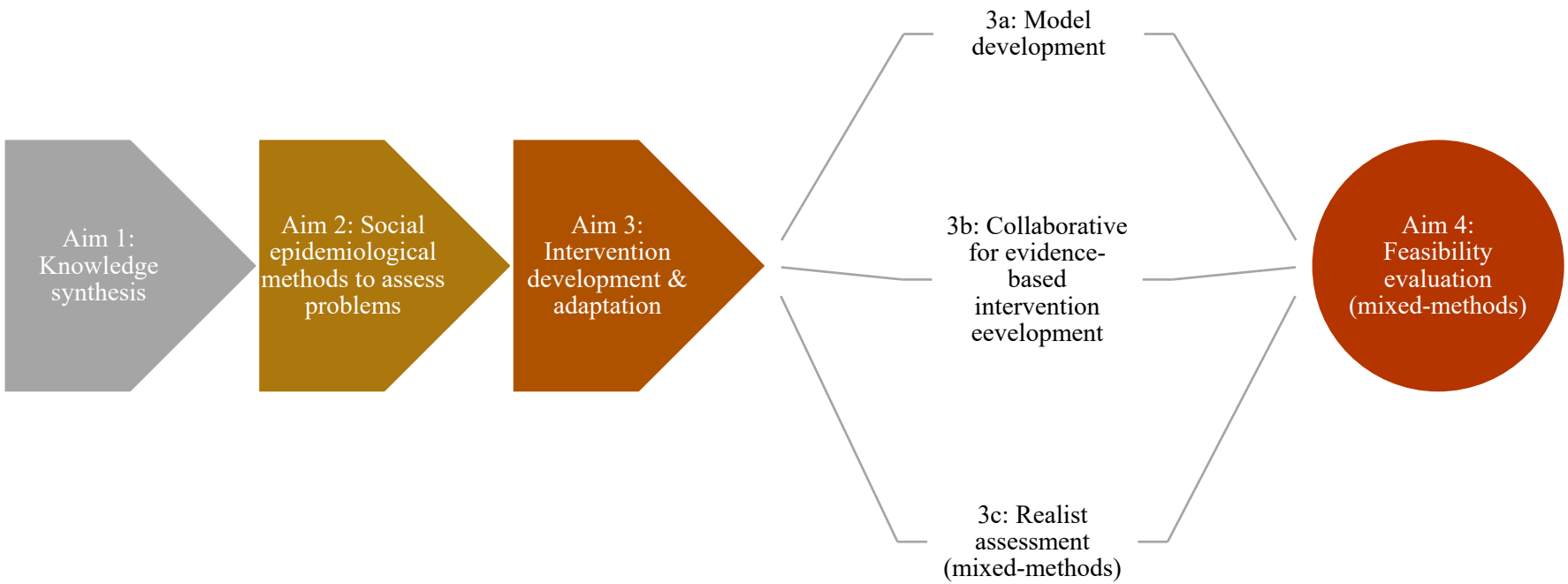
The research questions are addressed through 4 interlinked aims (Figure 1-5), each with associated methods, tasks, outputs:

1. Aim 1 - Knowledge synthesis: to conduct systematic literature reviews in identifying (1a) non-clinical factors influencing health care consumers' demand and use of antibiotics, and (1b) behavioural change interventions (BCIs) and techniques (BCTs) that have been proven to be effective in reducing health care consumers' demand and use of medications or medical services. (Chapters two and three)
2. Aim 2 - Social epidemiological methods to assess problems: to conduct quantitative data analyses and employ social epidemiological methods in exploring determinants of Chinese consumers' treatment decisions for the upper

respiratory tract infections (URTIs) with respect to of antibiotic use. (Chapters four, five, and six)

3. Aim 3 - Intervention Development & Adaptation: to employ a mixed-methods approach to develop a new behavioural change intervention to reduce non-prescription use and unsafe disposal in the context of China. (Chapter seven)
4. Aim 4 - Feasibility Evaluation: to employ a mixed-methods approach to assess the feasibility of the newly developed behavioural change interventions. (Chapter eight)

Figure 1-5. Research aims and tasks



1.6 Research methods and approaches

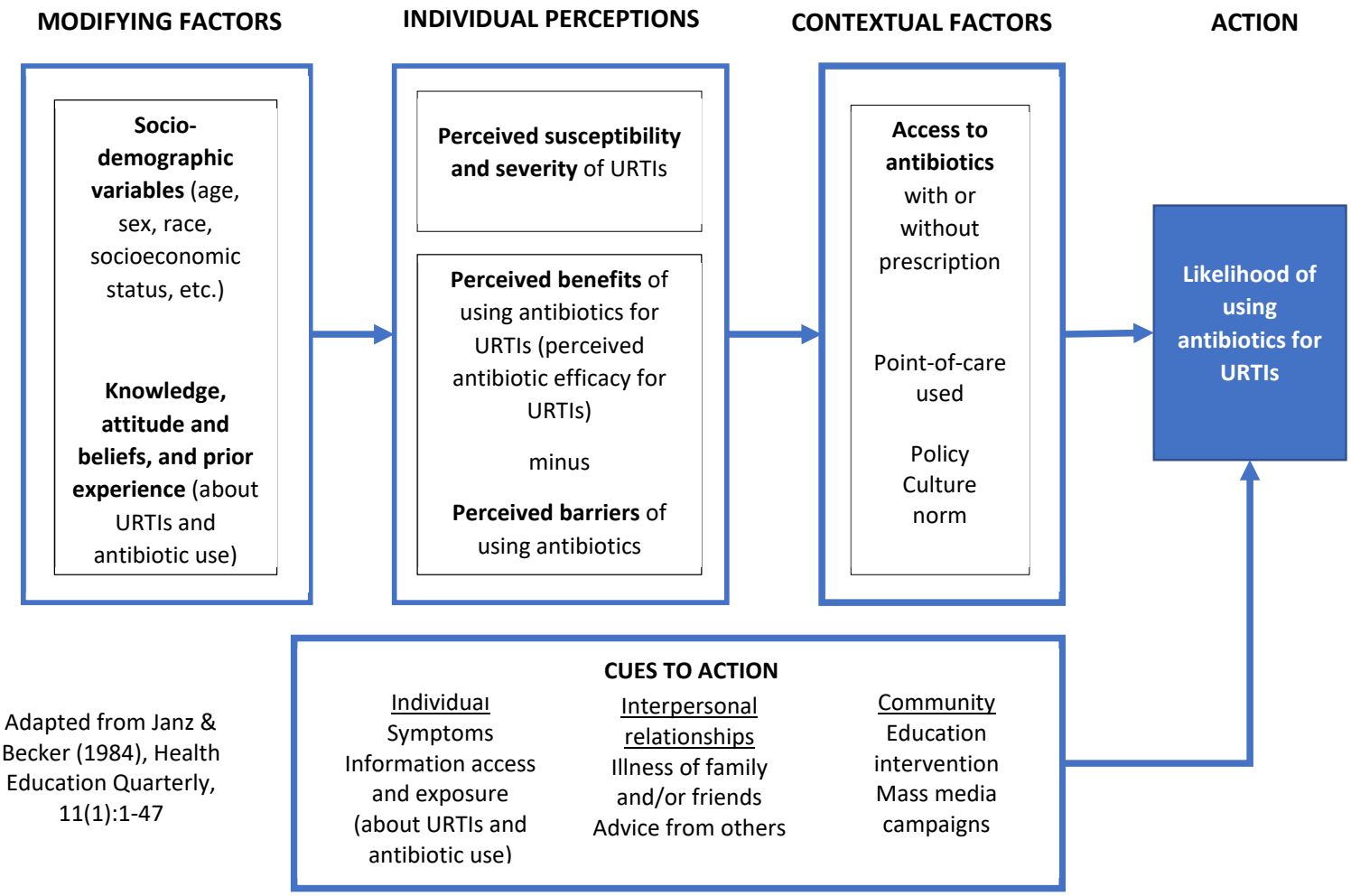
I briefly summarise below each of the methods used in this PhD project and present a short overview of the objectives and progress for each phase of research in their corresponding chapters.

Conceptual framework for behavioural change

Kok et al.[89,90] developed the Intervention Mapping (IM) taxonomy of behaviour change methods with an emphasis on an ecological approach, which was closely followed during the selection of methodology. In addition, Wight et al. mapped out six essential Steps for Quality Intervention Development (6SQuID).[91] For this thesis project, with an aim to reduce unnecessary and/or inappropriate use of antibiotics for URTIs in China, I set out to incorporate behavioural theories like the Health Belief Model (HBM),[92,93] which has been widely used since it was developed in 1966 in understanding a variety of long- and short-term health behaviours by focusing on the attitudes and beliefs of individuals, particularly in disease prevention behaviours.[92,94,95] However, individual's health decisions are not entirely driven by their cognitive and rational characteristics, and contextual factors – including access to antibiotics and interpersonal connections – are equally critical to healthcare decision-making processes.[96-99] HBM[92,93] does not account for the impact of habitual behaviours that are relatively independent of conscious, health-related decision making processes (e.g., storing leftover prescriptions) or socio-ecological environment (e.g. doctor-patient relationships, family dynamics, or overprescribing) on individuals' decisions.[92] To understand the impact of individuals' perception of illness and treatment on one's decisions for antibiotic use while accounting for the complex interplay between factors at different levels of socio-ecological environment (i.e. individual, interpersonal, and societal), in addition to HBM[92,93], the

conceptual framework of this thesis (presented in Figure 1-6) also consulted the constructs of the Social Ecological Model.[100] The two behavioural models helped explain and predict individual's uptake of antibiotics centred around one's risk appraisal of impending health threat (e.g. URTIs) while recognising multifaceted and interactive effects of personal and environmental factors that determine antibiotic use.

Figure 1-6. Conceptual Framework: Decisions about antibiotic use for upper respiratory tract infections (URTIs)



Adapted from Janz & Becker (1984), Health Education Quarterly, 11(1):1-47

Key modifying factors at individual, interpersonal, and societal levels that influence an individual's antibiotic use decision included their knowledge and attitudes around antibiotic use and the impending health threat (e.g. URTIs), perceived threat to sickness or disease (perceived susceptibility), belief of consequence of contracting the health threat (perceived severity), potential positive benefits of antibiotic use (perceived benefits), perceived barriers to antibiotic use, and exposure to factors that prompt antibiotic use (cues to action). The conceptual framework of this thesis underscores that behavioural change occurs in a social context with dynamic and reciprocal interactions between the person, community, and environment - both spatially and temporally – as an individual's behaviour is influenced by their past experiences through expectations and reinforcements. The modifying factors can potentially inform intervention design to change individual's antibiotic use behaviours whereas socio-contextual factors, also recognised in the multilevel model, are less amendable. The model was later employed to guide the literature review (reported in chapter two), quantitative data analyses (reported in chapters five and six) and to inform the theory of change for the development of a behavioural change intervention (presented in chapters seven and eight).

Because published feasibility study typologies for behavioural change interventions at the community level are rare, and practically non-existent in low and middle-income countries (LMIC), it was necessary to landscape what behavioural change techniques (BCTs) have been tested to be effective in improving consumers' use of medical interventions and the implementation strategies and associated conditions in order to develop a new behaviour change intervention for improving antibiotic use in rural China,. Therefore, I concurrently conducted a second systematic literature review on behavioural change interventions that have been proven effective in reducing inappropriate demand/use of medications and medical

procedures. [Chapter three] The BCTs identified from the review were used to inform the initial design and development of the proposed community-based behavioural change intervention. I concluded in the review that interventions consisting of both health education messages (e.g. *4.1 Instruction on how to perform the behaviour 4.2 Information about Antecedents, 5.1 Information about health consequences, or 5.2 Salience of consequences*) and a supporting environment that encourages and incentivises the adoption of a new behaviour (e.*g. 8.2 Behaviour substitution, 10.1 Material incentive, 10.2 Material reward, 12.1 Restructuring the physical environment, and 12.5.* Adding objects to the environment*)* are more likely to be successful.

Alongside the literature reviews, I conducted three quantitative data analyses on two large-scale survey datasets across various geographic regions and economic developmental stages in China collected by Zhejiang University on public antibiotic use. The main target populations of these surveys were young adults and young parents. [Chapter four] I conducted a descriptive analysis on the severity and prevalence of antibiotic misuse for self-limiting conditions among Chinese parents on their children aged 0-13 years. [Chapters five and six] Then, guided by HBM[92,93] and SEM[100] (presented in Figure 1-6. Conceptual Framework), I explored factors influencing treatment decisions for the common cold among young adults and young parents with respect to antibiotic use. Results from these analyses were used to inform socio-demographic priorities of target population and components for the proposed intervention. For example, I found that knowledge as a determinant of antibiotic use was in fact a complex domain; correcting misconceptions around antibiotic efficacy for the symptoms of the common cold and inflammation should be included as a core element of education interventions, as improvements in awareness of the risks of antibiotic resistance or ability to identify antibiotics without

clarifying such misconceptions might lead to unintended adverse impacts. Also, access to antibiotics is highly associated with self-medication for treatment of self-limiting conditions, especially the common cold. Sources of antibiotics included unnecessary prescriptions, inappropriate prescriptions resulting from patients' demands, and non-prescriptions antibiotics, such as over-the-counter purchases and household storage of antibiotics. As such, a complex intervention to simultaneously address all of the factors on both the supply-and-demand sides would be needed to effectively reduce antibiotic misuse in a Chinese community. Interventions on supply-side factors would be addressed by other components of the bid to joint global health trial, mentioned above. In this project, I focused on the development of a new community-based intervention that aimed to improve the awareness of the danger of antimicrobial resistance (AMR) and reduce unsafe antibiotic disposal in rural China.

[Chapter seven] Steps taken in the development of behavioural change interventions have been closely aligned with the 6SQuID model,[91] a pragmatic evidence-based guide to maximise likely effectiveness. I largely followed the first five steps of the six-step process of designing an intervention: 1) defining and understanding the problem and its causes (chapter two); 2) identifying which causal or contextual factors are modifiable: which have the greatest scope for change and who would benefit most (chapter four to six); 3) deciding on the mechanisms of change (chapter three); 4) clarifying how these will be delivered (chapter three and chapter seven); and 5) testing and adapting the intervention (chapter eight).[91] The final step of 6SQuID, *collecting sufficient evidence of effectiveness to proceed to a rigorous evaluation*[91], shall be conducted in the immediate future as a small pilot trial or a larger randomised controlled trial to establish its effectiveness. These five steps are presented in a theory-based work stream plan for the development and

feasibility-testing of behavioural change interventions at the community level with the intention for future full-scale implementation. The work stream plan (Table 1-1) for this project integrated the principles of RE-AIM, intervention mapping and 6SQuID model, and community-based participatory research (CBPR), which helped me to identify feasibility-related evidence addressing methodological questions set out by the MRC guidelines and for the future implementation of the full trial. Following these theoretical frameworks and principles carefully, I expected each step in the development process would be based on best available theory and evidence at the time and would allow me to better use scarce public resources.[91] I laid out four main research aims and associated tasks, which eventually led to the development of a community-based intervention to improve awareness of the danger of AMR and unsafe disposal and to reduce household storage of antibiotics for the target population, rural Chinese residents. The proposed interventions benefited from a broad variety of implementation research strategies, using multiple data sources to inform implementation changes. Evidence and intervention ideas generated by this PhD project Aims 1 and 2 were immediately used/field-tested by researchers at Zhejiang University in real time and real context for the development and testing of the proposed intervention in rural Zhejiang. The targeted interventions started with needs assessments to better understand the community of rural residents, revealing that a "proper" way of using and disposing of antibiotics should be established early on in the development of health education messages and the evaluation tool. I selected the health message content based on findings from secondary data analyses. Regarding the action design of the health education materials, of which the process and rationale are rarely reported, Zhejiang University adopted the design from products produced in an AMR crowdsourcing campaign they conducted with the UK Embassy in Shanghai in 2016. The behaviour component - an antibiotic take-back

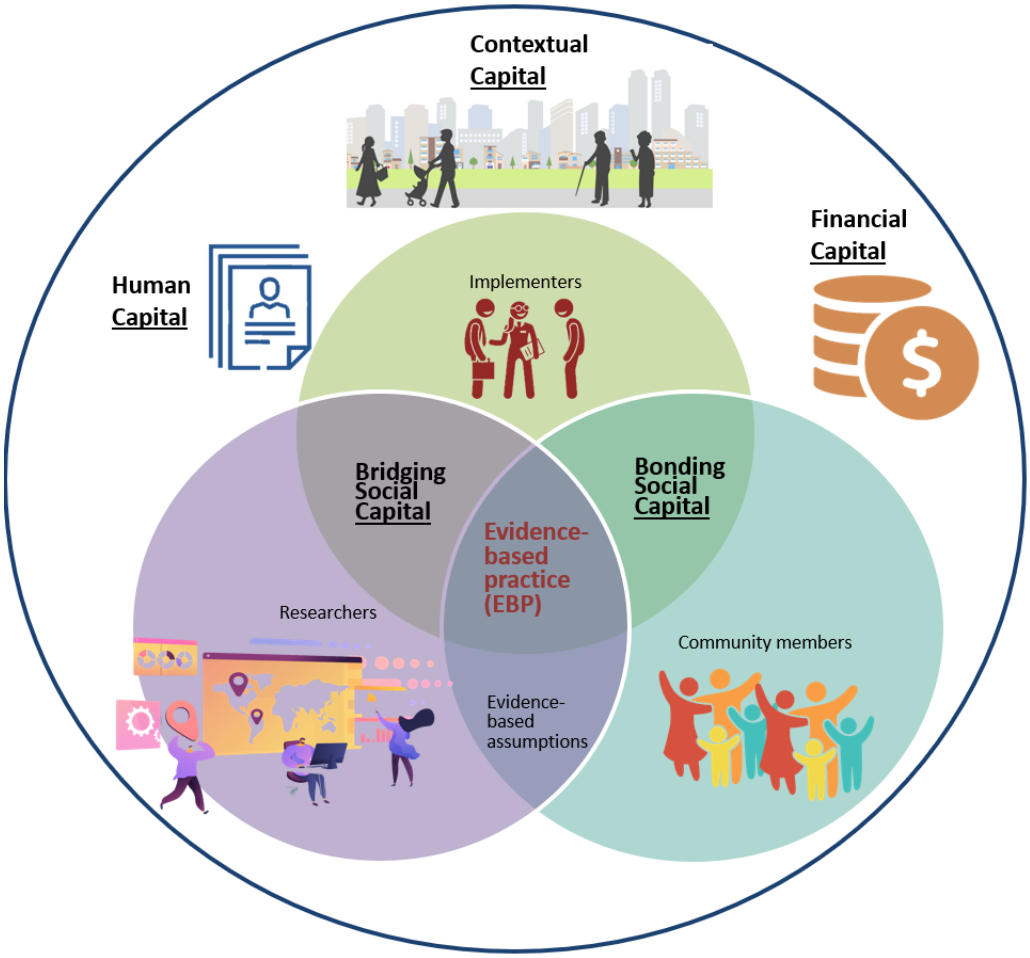
programme - was jointly decided upon by researchers at Zhejiang University and local stakeholders. See Appendices II and III for sample health education and training materials.

[Chapter eight] The design and delivery process of this chapter have relied heavily on the MRC's progress evaluation framework. Developing education materials and implementing a feasibility study for rural residents was challenging, because many were illiterate or possessed low ability to recognise antibiotics levels. In 2018 and 2019, Zhejiang University conducted a series of feasibility studies on the proposed intervention starting with flexible methodology, as the newly developed intervention materials required considerable testing and refinement to be appropriate for the target audience. In June 2019, I designed and led a formal feasibility study with a control group, nested within the feasibility and pilot work Zhejiang University was conducting. Feasibility data from this particular pilot are reported here. I found that the regular involvement by the Women's Federation in facilitated community-led interventions generated greater community participation and was cost-saving. Eventually my assessment of resources required for the full study, as suggested by Thabane et al,[101] prompted the conceptualization of the implementation capital for evidence-based practice (Figure 1-7) that enabled and determined the success of the knowledge translation process. I found that implementation capital for evidence-based practice consists of five key dimensions, which are bonding social capital, bridging social capital, human capital, financial capital and contextual capital. More detailed discussions on implementation capital were included in chapter seven.

All study participants were informed and consented. The study methods involving use of primary and secondary data were approved locally in China via

Zhejiang University Ethics Committee and the LSHTM Ethics Committee. The ethics approvals are attached in Appendix IV.

Figure 1-7. Implementation Capital for Evidence-Based Practice



1.7 Collaborations and partnership

Zhejiang University is a leading institution in Chinese AMR research and recently experienced a fatal outbreak of drug-resistant pneumonia in one of its affiliated hospitals.[102] I have served as an external expert for technical support and established a strong partnership with Zhejiang University since 2016 prior to the beginning of this PhD programme. I collaborated with the Institute of Social Medicine and Family Medicine on the investigations of many contemporary pressing public health issues in China, such as maternal and child health, public health emergency preparedness and response, and AMR. In recent years, the Zhejiang University Research Team on Prudent Use of Antibiotics, led by Professor Xudong Zhou (PI), have been pioneers in conducting large-scale surveys of public's antibiotic use and trials of AMR interventions to reduce antibiotic misuse in the Chinese context – most were facility-based. I identified an urgent need for an intervention to reduce antibiotic misuse in the community.

The nature of the proposed PhD project requires strong local support to ensure context-appropriateness and impact beyond lab settings. This PhD project – though a self-funded study – therefore was set up to collaborate closely with Zhejiang University. Since March 2018, I participated in weekly phone conferences with the PI and/or the team and whenever possible, conducted in-person meetings when I was on site. A signed letter of support laying out terms and conditions is attached in Appendix 1. In brief, for Aim 2, Zhejiang University agreed to share population data on antibiotic use for self-limiting illnesses by young adults (university students) and young parents with children under 13 years old. Prior to this PhD study, I contributed to the development and implementation of the surveys and during this PhD, I applied social epidemiological methods for secondary data analyses. I then created a theory-based work stream plan for the proposed

intervention, developed by this PhD project - a pilot antibiotic take-back programme embedded in local bartering markets for recyclables. This framework, presented in Table 1-1, was a working document used to guide the collaboration with local partners during the development and feasibility assessment.

Under Aim 3, I conceived the intervention idea and design, visited targeted communities to understand local needs and concerns, and participated in the introduction sessions with local government officials and shareholders organised by Zhejiang University. Zhejiang University provided the financial, social and human capital necessary to implement an evidence-based practice project. They obtained an Institutional Review Board approval in compliance with local ethics guidelines, facilitated stakeholder engagement, and supported the proposed pilot activities, including securing pilot sites, producing project materials, and facilitating the recruitment of project participants and collection of data according to the study design.

In preparation for a large community-based trial, building on their previous work, from January to June 2019, Zhejiang University conducted a series of pilot and feasibility work testing and refining various elements of the proposed intervention in targeted communities (e.g. the design of promotional materials, selection of household items for exchange at the bartering market, and the appropriate conversion rate between returned antibiotics and preferred household items). Evidence and intervention ideas generated by this project Aims 1 and 2 were immediately used/field-tested by the Zhejiang University research team in real time and real context in rural Zhejiang. To achieve Aim 4, I developed a feasibility study and associated assessment instruments, led the collection of formative and feasibility data, conducted data analyses, and drafted manuscripts for publication. The primary data collected to achieve Aims 3 and 4 came from a formal feasibility study in June

2019 that aimed to assess various elements altogether as a community-based intervention with a controlled pre- and post-design, nested within a series of pilot projects conducted by Zhejiang University. Having a strong local partner who provided critical contextual information and local network resources ensured the intervention achieved cultural sensitivity and local ownership. It will also catalyse and enable the process of translating findings into policy recommendations beyond this PhD.

Findings from this study have contributed to the development and submission of a grant application to the Joint Global Health Trials led by Zhejiang University for a multi-level, community-wide intervention which aimed to reduce inappropriate antibiotic use and antibiotic resistance in rural Zhejiang (See 1.2.4 for more details). The results of this study will be disseminated in the form of conference presentations, publications, and in a report or white paper to be released together with Zhejiang University. They will inform evidence-based policy recommendations that strengthen China's national effort to curb inappropriate antibiotic use.

Table 1-1. Work stream plan and associated chapters

Aims	Alignment with 6SQuID[91]	Methods/Tasks	Chapter	Activities	Products
Aim 1: Synthesise existing evidence about the problem and explore possible solutions	Step 1. defining and understanding the problem and its causes; Step 2. identifying which causal or contextual factors are modifiable: which have the greatest scope for change and who would benefit most;	Systematic Reviews	2 3	1) Systematic review (SR1) on determinants of antibiotic misuse in the community, including primary care and hospital outpatient clinics in the Chinese context. 2) Systematic review (SR2) on public-targeted behavioural change interventions to reduce inappropriate, unnecessary, and non-essential use of medicines or medical procedures. 3) SR1 and thematic synthesis of qualitative studies of views, attitudes and experiences of health care providers and users (i.e. health professionals, patients, and caregivers) about treatment choices and antibiotic use for self-limiting illnesses in the Chinese context. 4) Synthesis of SR1 and SR2 to identify knowledge gaps where determinants of antibiotic misuse in the community are insufficiently addressed.	Key assumptions about the problem
Aim 2:Assess problems in the context and form assumptions	Step 2. identifying which causal or contextual factors are modifiable: which have the greatest scope for change and who would benefit most; Step 3. deciding on the mechanisms of change;	Quantitative Research	4 5 6	1) Large-scale surveys on knowledge, attitudes and practice of treatment choice and antibiotic use among young adults (university students) regarding self-limiting illnesses in the Chinese context. 2) Large-scale surveys on knowledge, attitudes and practice of treatment choices and antibiotic use among young parents (with children under 13) with respect to self-limiting illnesses in the Chinese context.	Key assumptions about the problem
Aim 3: Develop and adapt intervention	Step 4. clarifying how these will be delivered;	Mixed-methods	**7**	**3a. Theoretical Model Development** 1) Development of a Theory of Change (ToC). 2) Formation of key assumptions for intervention development.	Theory of Change (Figure 1-5)
				3b: Preparation for Knowledge Translation 1) Scoping and stage-setting • Identify pilot sites • Introduce proposed project aims and explain rationale for an intervention • Confirm presence of problems identified and needs • Introduce intervention adaptation process • Establish partnership and collaboration 2) Preparation for adaptation of knowledge to local context • Define desired aim and the behavioural target of this intervention • Explore and identify intervention components • Discuss how the intervention may or may not address the problems and needs • Discuss how the intervention may or may not address key planning and evaluation issues: *reach, effectiveness, adoption, implementation, maintenance* **(RE-AIM).** • Identify areas for intervention adaption • Map resources needed to implement a pilot intervention and assess available ***Implementation Capital for evidence-based practice*** • Form logic model	Logic model
				Implementation (pilot)	
	Step 5. testing and adapting the intervention			**3c: Realist assessment** of problems and needs of local context and appropriateness of proposed intervention 1) Conduct pre-intervention (baseline) evaluation, which consists of face-to-face surveys with quantitative and qualitative components, to assess problems and needs in local context. 2) Interview stakeholders to assess appropriateness, acceptability and feasibility of the proposed intervention. 3) Evidence synthesis of findings from Aims 1-2 and realist assessments with target population and stakeholders: • Identify the objectives, content, and channels for delivery of key health messages for the proposed intervention. • Pilot-test health messages. 4) Critically synthesise mixed-methods findings revising the logic model and finalising the adapted intervention	Finalised logic model Finalised intervention design for feasibility study
Aim 4: Evaluation: Assess feasibility and acceptability of the intervention	Step 5. testing and adapting the intervention (Note: For this project, I only conducted feasibility evaluation)	Mixed-methods	8	1) Develop feasibility study design 2) Conduct endpoint and follow-up evaluations 3) Conduct process evaluation 4) Analyse evaluation outcomes 5) Address 14 methodological issues of feasibility research for full-scale intervention development 6) Identify strengths, limitations and next steps	Finalised intervention design for pilot study

1.8 Joint Global Health Trial (Call 9)

– Implementation Science to Combat Antimicrobial Resistance: a community-randomised trial to reduce inappropriate antibiotic use and disposal in China

In 2016, China released the National Action Plan to Contain Antimicrobial Resistance (2016-2020) with the following objectives: 1) All retail pharmacies will only sell antibiotics when provided with prescriptions; 2) Hospitals at the secondary level and above will establish clinical practice management mechanisms for antimicrobial drugs, and the growth rate of major antimicrobial resistance in medical institutions will be effectively controlled; 3) Medical staff across China will undergo training on the rational use of antimicrobial drugs; 4) Efforts towards public awareness and education on prudent antibiotic misuse will be strengthened strengthened; and 5) Antimicrobial pollution will be prevented and controlled. All relevant authorities are actively seeking solutions to contain AMR, but they lack experience and academic evidence of effective measures. Since 2016, Zhejiang University has conducted a series of pilot studies and trials testing various elements of a complex intervention, with the aim of taking a realist, evidence-based approach to implementing the national action plan with a rigorous design for evaluation and further adoption. Community-based trials in AMR are very rare, due to their high level of investment in terms of capacity to acquire stakeholders' buy-in, expertise in rigorous design, and evaluation expense. To date, most AMR trials are limited to clinical settings, leaving community use of antibiotics poorly addressed. To my knowledge, there have only been three trials[103-105] that aimed to reduce antibiotic misuse at the community-level and addressed both supply-and-demand-side factors of antibiotic misuse: all took place in the US over 15 years ago, with none being in China or another LMIC.

During my PhD studies, I collaborated with Zhejiang University in response to the call of the Joint Global Health Trial (JGHT call 9) aiming to create a novel complex intervention in addressing a major knowledge gap, which was directly relevant to this PhD study: there is currently no community-wide intervention targeting the demand-side of antibiotic misuse specifically in the Chinese context. Furthermore, there have been only a few behavioural intervention trials in the Chinese hospital setting that aim to improve prescribing practices.[52,54,106] We therefore proposed a first trial in China that integrates social science in its intervention design to contain AMR from both the supply-and-demand sides of the health systems. The proposed intervention had four components - 1) reduce pharmacy non-prescription sales, 2) improve hospital dispensing, 3) enforce doctor training and stewardship policies, and 4) institute community recycling and health education – which aim to remove the barriers at the structural, community and individual levels that lead to inappropriate antibiotic use in the community. Evidence generated from this trial (including behavioural and biomedical data) would provide a strong evidence base to advance the science of measuring AMR burdens of disease,[107] empower policy advocacy, and prompt changes in antibiotic use within the hospital and beyond.

In the last five years, Zhejiang University has conducted pilot studies and trials on the first three components and some elements of the fourth component (e.g. users testing the design of health education messages). In this PhD project, I report on the development process and formal feasibility assessment for component #4. Completed in June 2019, this feasibility assessment consisted of a pilot community-based antibiotic take-back programme that included health education strategies.

The JGHT bid successfully made it through the first two phases of outlines and full applications reviews but did not pass the final panel review; nevertheless, the process of preparing for these three phases and our responses to reviewers' comments were profoundly helpful to my professional development and the implementation of this project.

[Research Decision: Study Scope]

I aimed to develop a non-clinical behavioural change intervention at the community level beyond clinical settings, with objectives aligned with those of China's National Action Plan to Contain Antimicrobial Resistance (2016-2020) and the local context.

1.9 Thesis structure

Below I present the structure of this PhD thesis and the respective evidence generated to inform intervention design:

Thesis structure	Key findings to inform intervention design	Implications for intervention design
Chapter two identifies non-clinical factors influencing the general public's and healthcare providers' antibiotic use in the Chinese community	a) Identification of factors and their potential pathways influencing public's antibiotic use, guided by the conceptual framework.	• Intervention design to address some of these factors/pathways. • Theory of Change
Chapter three identifies behavioural change techniques (BCTs) that may effectively reduce inappropriate use of medicines and medical procedures	b) Interventions consisting of health education messages (BCTs 4.1, 4.2, 5.1, 5.2), incentives (BCTs 10.1, 10.2), and a supporting environment (BCT 12.1, 12.5) that encourages the adoption of a new behaviour (BCT 8.2) are more likely to be successful.	• Intervention design to include *health education messages, recommended alternative behaviour, incentives,* and *a supporting environment*.
Chapter four assesses the prevalence of antibiotic misuse in children in the Chinese context	c) Almost half of the surveyed parents kept antibiotics at home for children d) Many Chinese parents self-medicated children with antibiotics (prophylactic or treatment) and before seeking formal care. e) Household antibiotics primarily came from leftover prescriptions and over-the-counter purchases (OTC).	• Household storage of antibiotics is a critical gap in current efforts to contain AMR in China (and most LMIC). • Health education messages to include awareness of the danger of AMR and non-prescription use of antibiotics. *Note: Issues around OTC were going to be addressed by other intervention components of the JGHT bid.*
Chapter five assesses the factors influencing Chinese parents' treatment decisions for paediatric URTIs.	f) Perceived antibiotic efficacy for URTIs symptoms is associated with an increased odds of self-medication with antibiotics and demand of antibiotic prescriptions. g) Parents who kept antibiotics at home for children were associated with increased odds of self-medication with antibiotics for URTIs in children and over-the-counter purchases. h) Household antibiotics primarily came from leftover prescriptions and over-the-counter purchases (OTC).	• Health education message content selection (BCTs 4.1, 4.2, 5.1, 5.2) • Intervention design to reduce household storage of antibiotics. (BCTs 10.1, 10.2, 8.2, 12.1, 12.5) *Note: Issues around OTC were going to be addressed by other intervention components of the JGHT bid.*
Chapter six assesses the factors influencing Chinese young adults' treatment decisions for URTIs.	i) Not knowing URTIs are self-limiting and perceived antibiotic efficacy for URTIs symptoms are associated with increased odds of self-medication with antibiotics and demand of antibiotic prescriptions. j) Participants who kept antibiotics at home were associated with increased odds of self-medication with antibiotics. k) Household antibiotics primarily came from leftover prescriptions and over-the-counter purchases (OTC).	
Chapter seven reports the process of developing the proposed community-based intervention, the antibiotic take-back program with health education messages, in rural Zhejiang, China	l) There is a need for an operable, theory-based work stream plan, which integrated the principles of RE-AIM, intervention mapping and community-based participatory research (CBPR), for the synthesis of available evidence and the acquisition of feasibility-related evidence addressing methodological questions for future work. m) Next step is to conduct a pilot study to assess the feasibility (rather than effectiveness) of the proposed intervention	• Development of a work stream plan • Development of a logic model • Reflection on the Implementation capital for an evidence-based practice in a new context
Chapter eight reports the results of the feasibility study to examine the proposed behavioural change intervention in rural Zhejiang, China	n) The feasibility study established the acceptability and usability of the proposed intervention in which 14 implementation research methodological issues for future trials were carefully assessed.	• Pilot project to test feasibility to implement the intervention.

CHAPTER TWO

Non-clinical factors influencing the general public's and healthcare providers' antibiotic use in the Chinese community: a mixed-methods review

In this chapter, I report on a review of the literature to (1) identify non-clinical factors affecting the health care users' and providers' antibiotic use in China and (2) existing interventions to reduce inappropriate antibiotic use in China.

I conceived the project, developed the literature review design, methods, and conducted analysis independently. I conducted the review in close collaboration with two colleagues (native Chinese speakers) based in Zhejiang University. The findings and results have been prepared as a first draft of the manuscript, with comments on drafts from Tingting Yao, Ruyu Sun, Professors Stephan Harbarth, Mark Perricrew, and Xudong Zhou. This manuscript has been submitted to *Social Science Medicine* for the consideration of publication.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH1704488	**Title**	Ms.
First Name(s)	Leesa		
Surname/Family Name	Lin		
Thesis Title	Development of evidence-based behavioural interventions to reduce inappropriate use of antibiotics beyond clinical settings		
Primary Supervisor	Professor James Hargreaves		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Social Science Medicine
Please list the paper's authors in the intended authorship order:	Leesa Lin*, Ruyu Sun, Tingting Yao, Stephan Harbarth, Xudong Zhou
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Leesa Lin conceived of the study and developed the search string for analysis and contributed to piloting abstraction tools. Two reviewers (Leesa Lin and Ruyu Sun or Tingting Yao) independently screened titles and abstracts to select potentially relevant citations. Leesa Lin developed a standardised form based on Cochrane Review and behavioural theories specifically for this review prior to data extraction. Ruyu Sun and Tingting Yao reviewed and coded the studies. Leesa Lin served as the third reviewer. Leesa Lin, Ruyu Sun and Tingting Yao drafted and revised the manuscript, and all authors commented on it and the subsequent drafts. All authors read and approved the final manuscript.

SECTION E

Student Signature	[redacted]
Date	09/09/2019

Supervisor Signature	[redacted]
Date	09/12/2019

Non-biomedical factors influencing outpatient and community antibiotic use in China: a mixed-methods review

SYNOPSIS

BACKGROUND: This study aimed to identify and assess the factors of inappropriate use of antibiotics in the Chinese context to inform the development of future interventions to mitigate inappropriate consumption, namely antibiotics consumed in the absence of clinical indications.

METHODS: We conducted a mixed-methods systematic review and included empirical studies with original data conducted in mainland China, Hong Kong, and Taiwan that investigated factors of antibiotic use in the community including outpatient care among patients, caregivers, and prescribers. We searched MEDLINE, PubMed, EMBASE, the Cochrane Library, PsycINFO, Google Scholar, and one Chinese database CNKI (China Knowledge Resource Integrated Database), using a combination of the key terms 'antibiotic', 'antimicrobial', 'use', 'consumption', 'behaviour', 'prescribe', and related syntax for all peer-reviewed publications published before June 2019. Health Belief Model was employed for data synthesis.

FINDINGS: Forty-six studies were included in the full-text review: 39 quantitative, four qualitative, and three mixed-methods studies. Despite a high antimicrobial resistance (AMR) awareness, public perception/misconception of antibiotic efficacy and easy access to antibiotics for self-limiting conditions drive inappropriate demand and use in the community including primary care setting. Providers' prescribing behaviours are influenced by financial incentives, lack of diagnostic capacity, and concerns over complications.

CONCLUSIONS: Inappropriate outpatient and community antibiotic use is influenced by non-biomedical factors at the individual, community, health system, and societal levels in mainland China, contributing to a high antibiotic use rate. This study calls for multifaceted AMR interventions that simultaneously address drivers of inappropriate use from both the supply- and demand-sides within and beyond clinical settings.

SYSTEMATIC REVIEW REGISTRY: PROSPERO CRD42019139591

KEYWORDS: antibiotics, antimicrobial resistance, China, behaviour

Non-biomedical factors influencing outpatient and community antibiotic use in China: a mixed-methods review

ABSTRACT

BACKGROUND: This study aimed to identify and assess the factors of inappropriate use of antibiotics in the Chinese context to inform the development of future interventions to mitigate inappropriate consumption in the absence of clinical indications.

METHODS: We conducted a mixed-methods systematic review and included empirical studies with original data conducted in mainland China, Hong Kong, and Taiwan that investigated factors of antibiotic use in the community including outpatient care among patients, caregivers, and prescribers. We searched MEDLINE, PubMed, EMBASE, the Cochrane Library, PsycINFO, Google Scholar, and one Chinese database CNKI (China Knowledge Resource Integrated Database), using a combination of the key terms 'antibiotic', 'antimicrobial', 'use', 'consumption', 'behaviour', 'prescribe', and related syntax for all peer-reviewed publications published before June 2019. Health Belief Model was employed for data synthesis.

FINDINGS: Forty-six studies were included in the full-text review: 39 quantitative, four qualitative, and three mixed-methods studies. Despite a high antimicrobial resistance (AMR) awareness, public perception/misconception of antibiotic efficacy and easy access to antibiotics for self-limiting conditions drive inappropriate demand and use in the community including primary care setting. Providers' prescribing behaviours are influenced by financial incentives, lack of diagnostic capacity, and concerns over complications.

CONCLUSIONS: Inappropriate outpatient and community antibiotic use is influenced by non-biomedical factors at the individual, community, health system, and societal levels in mainland China, contributing to a high antibiotic use rate. This study calls for multifaceted AMR interventions that simultaneously address drivers of inappropriate use from both the supply- and demand-sides within and beyond clinical settings.

INTRODUCTION

For decades, antibiotics have been excessively consumed around the world, contributing to increased antimicrobial resistance (AMR) and negatively impacting health outcomes and expenditures.[9,108,109] Reducing inappropriate antibiotic use is a pressing global health priority. Human use of antibiotics in China accounts for a quarter of worldwide antibiotic consumption,[31,37] which mainly takes place in outpatient and community settings, often unnecessarily for self-limiting community-acquired infections - mostly viral and non-complicated, and untreatable by antibiotics.[37,57] A thorough examination of the prevalence of and factors influencing community antibiotic use in China is vital to inform the development of relevant policy and intervention strategies aiming to mitigate inappropriate or unnecessary antibiotic use, namely antibiotics consumed in the absence of clinical indications. This study aimed to conduct a mixed-methods systematic review that identifies and assesses factors influencing healthcare users' and providers' antibiotic use in the Chinese context.

METHODS

This mixed-methods review aimed to identify determinants for inappropriate antibiotic use in the community, including primary care and hospital outpatient settings, in Mainland China, Hong Kong, and Taiwan. We systematically searched the following databases: MEDLINE, PubMed, EMBASE, the Cochrane Library, and PsycINFO, Google Scholar, and one Chinese database CNKI (China Knowledge Resource Integrated Database), using a combination of the key terms 'antibiotic', 'antimicrobial', 'use', 'consumption', 'behaviour', 'prescribe', and related syntax for all peer-reviewed publications published before June 2019.

As a primary outcome of interest, 'inappropriate antibiotic use' included antibiotic use for viral infections (treatment or prophylaxis), self-medication with antibiotics by consumers, and antibiotic prescriptions for viral infections by providers. Relevant behavior outcomes, such as household storage of antibiotics, over-the-counter purchases, and demands for antibiotic prescriptions, were also identified. No restrictions were applied to language, populations or antibiotic use for specific medical conditions. The search strategy for each database is presented in Supplement 1. Studies that focused only on (1) knowledge, attitudes and beliefs with regard to antibiotic use or (2) antibiotic prescriptions analysis were excluded. For the quantitative component, data from cross-sectional and longitudinal studies, where relevant confounders were accounted for by the study design or analysis, were included. Qualitative studies where methods of data collection and analysis were explicitly reported were eligible for inclusion. Non-empirical studies or studies not reporting original data were excluded. A full list of inclusion/exclusion criteria is presented in Supplement 2. In addition, we conducted manual searches of the reference lists of included studies to identify additional relevant studies. All citations identified were imported to Endnote, and duplicates were deleted. Two reviewers (LL and TTY or RYS) independently screened titles and abstracts to select potentially relevant citations. Articles included in the full text review stage were retrieved and independently scrutinized. Any discrepancies in the process were resolved through discussion with a third reviewer until consensus was reached. (See Figure 1. Flowchart)

A standardised form based on Cochrane Review and behavioural theories including the Health Belief Model[93] and Social Ecological Framework[77] was developed specifically for this review prior to data extraction. Data were double

extracted by two reviewers (TTY and RYS). Disagreements were discussed with a third reviewer (LL) and resolved through consensus. The information extracted included characteristics of the study, methods, target population, sample size, antibiotic use behaviours, and associated factors influencing behaviours. Numerical data (numbers or percentages) that reported prevalence and non-medical factors of antibiotic use were extracted from the quantitative component; themes relevant to factors influencing antibiotic use behaviours were extracted for the qualitative component.

Quality assessment of included studies

Three reviewers (LL, TTY, RYS) independently assessed the risk of bias in all included studies using pre-determined tools and reached consensus through discussion when discrepancies arose. The quantitative studies and quantitative components from mixed-methods studies that met inclusion criteria were assessed by adapted BMJ survey appraisal tools;[110] qualitative studies and the qualitative components from mixed-methods studies were appraised by the Critical Appraisals Skills Programme (CASP) Appraisal Checklists.[111] We followed the PRISMA statement guidelines for reporting systematic reviews in structuring the review findings.

RESULTS

We identified 46 studies: 35 focused on the consumers of health care, nine on providers, and two on both, involving a total of 97,263 participants (Table 1, Appendix 1). All studies employed cross-sectional designs and included adult participants, with some (n=11; 23.9%) specifically involving the parents of children. Almost half (n=22; 47.8%) of the included studies were published after 2016. There were 39 quantitative (including three experiments), four qualitative, and three

mixed-methods studies. Nine studies were conducted in Hong Kong, one in Taiwan, and the rest (n=36) in mainland China, mostly in rural areas. Little evidence about community antibiotic use was available from Taiwan. Figure 2 summarised the characteristics of the included studies. Identified non-biomedical factors of antibiotic use in the community were analysed and synthesised, presented in Table 2.

Quantitative synthesis of factors influencing antibiotic use in the community

In Supplements 3.1-3.7 and 4.1-4.21, we summarized the identified factors of antibiotic use, measures (e.g. denominator, numerator, and recall period), and geographic distributions of antibiotic use practices that have been studied across China. We found inconsistency in defining and measuring various types of antibiotic use behaviors, which raises issues of cross-study comparability and evaluation. A total of 42 studies quantitatively investigated factors influencing inappropriate antibiotic use either by patients, caregivers or providers within and beyond clinical settings. The synthesis of quantitative data on public antibiotic misuse behaviours in the community by study region is presented in Figure 3**.**

Clinical settings

Antibiotic prescriptions for presumed self-limiting illnesses were widely reported. Three studies[45,65,112] reported that 31.7%[45] to about 50%[65] of participants prescribed with antibiotics were administered them through intravenous (IV) infusion. Five [45,63,113-115] studies investigated how patient-related factors influenced antibiotic prescribing and among them, three [45,63,113] identified knowledge as a determinant: those aware that unnecessary use of antibiotics makes them ineffective (i.e. antimicrobial resistance awareness) were more likely to accept physicians' non-antibiotic prescriptions.[63] People with a medical background[114] or a higher education level[63] were less likely to receive antibiotic prescriptions and more likely to approve

of that decision, yet having more than one type of health insurance had the opposite effect.[63] Regional differences were also noted: living in regions of lower economic development[114] was associated with an increased risk of antibiotic prescriptions for self-limiting illnesses.

Demand for antibiotic prescriptions was reported in 20 studies, ranging from 1.8%[60] to 74.5%[116] in mainland China, compared with around 8.7%[115,117-120] and 8.8%[121] in Hong Kong and Taiwan, respectively. Out of the 20 studies, eight[45,63,112,114,116,118,122,123] identified factors influencing demands for antibiotic prescriptions. Three found knowledge to be a factor associated with demands for antibiotics,[45,63,122] yet this relationship was inconsistent. Perceived antibiotic efficacy for upper respiratory tract infections (URTI) was associated with an increased risk of antibiotic prescriptions by request[63], whereas having some level of medical education was found to have mixed effects.[114,124] Older age,[112,114] lower education levels,[116] having more than one type of health insurance,[63] and living in rural areas[116] or regions with lower economic development[114] were associated with an increased risk of inappropriate prescriptions by demand among adult patients. Three experiments[56,125,126] were conducted in the past decade to investigate drivers of antibiotic misuse by providers and concluded that antibiotic dispensing practices in mainland China have been mainly influenced by financial incentives for prescribers and/or dispensing facilities,[56,125] lack of diagnostic capacity,[126] and concerns over complications.[35,126,127] Two Hong Kong-based studies[127,128] examined the reasons family doctors prescribed antibiotics for URTI, and found reasons for this included 'no energy to resist demand'[127], 'lack of time'[127,128] and 'as a way to terminate the consultation.'[128] They also found male doctors in Hong Kong to be more likely to over-prescribe antibiotics than their female peers.[127,128]

Community settings

Self-medication with antibiotics was reported in 31 studies, all in mainland China. The overall prevalence of antibiotic self-medication (for therapeutic purposes) ranged from 7.6%[113] to 82.6%[116] in mainland China, with high prevalence found in Gansu (82.6%),[116] Guangdong (63.5% in Guangzhou City),[75,129,130] Shaanxi (60.6% in Xi'an City),[60,61,131] and Jiangxi (62%).[65] Out of 31 studies, six [45,60,63,122,132,133] assessed the impact of knowledge on antibiotic self-medication with mixed results. Ability to identify or name different antibiotics,[63] having an accepting attitude towards antibiotic self-medication,[60] perceived susceptibility and perceived severity of the infection,[60,63,134] and perceived antibiotic efficacy against the infection[63] were associated with increased odds of antibiotic self-medication. Older age,[63,65,67,75,132] being female,[60,63,67,135] and having more than one child in the house[65] were associated with higher rates of antibiotic self-medication. The associations between antibiotic self-medication and education and urbanicity were inconsistent: some studies identified having higher education[63,65,116] or living in the urban areas[61,131,135] to be risk factors, while others came to the opposite conclusion.[60,65,68,116,130,132,135] Having some level of medical education was associated with a higher likelihood of antibiotic self-medication,[60,61,67,75,114,123,129,131,135] compared with peers. Patterns were similar for associations with **self-medication with antibiotics as prophylaxis** - often for URTI to prevent deterioration - measured in eight studies,[45,61,65,68,112,114,122,136] all in mainland China, with a prevalence ranging from 10.3%[112] to 30.6%.[61] Notably, regional differences were observed for antibiotic self-medication, both for therapeutic purposes and prophylaxis: consistently, those living in highly economically developed regions were less likely to self-medicate with antibiotics,

compared with their counterparts.[60,68,114] Having health insurance was also associated with higher rates of antibiotic self-medication.[60,63]

Access to non-prescription antibiotics, either via over-the-counter purchases or household storage, was strongly associated with antibiotic self-medication for therapeutic purposes[45,60,65,68,129,130,133] or prophylaxis.[68,72] The prevalence of **over-the-counter (OTC) purchases of antibiotics** ranged from 8.8%[113] to 84.9%[136] in mainland China, 7.3%[119,137] to 7.8%[115,117,118,120] in Hong Kong and was around 10.0%[121] in Taiwan. Depending on the region[138] and whether or not a licensed pharmacist was on duty,[138] antibiotics were easily obtainable with very limited barriers from almost 80.0% of local pharmacies across mainland China when a paediatric diarrhoea or adult acute URTI was present.[138] The prevalence of **household storage of antibiotics** ranged from 25.3%[60] to 80.2%[130] in mainland China and was around 6% in Hong Kong,[115,117,119,120] principally originating from over-the-counter purchases[45,68,129] and leftover prescriptions.[45,68,117,119,129] Being female,[63,68,112,114] of older age,[63,68] attaining higher education,[63,68,112,114] having higher income,[68,114] living in urban areas,[68,112,114] and having more than one type of health insurance[63] were associated with a higher likelihood of household storage of antibiotics. Unsurprisingly, over-the-counter purchases[119] were a risk factor for storing antibiotics at home.

Qualitative studies

Factors of antibiotic use identified from seven qualitative and mixed methods studies[35,67,117,119,120,139,140] generally supported the quantitative findings. Participants' trust in their doctors[119] made them not demand antibiotics; on the other hand, previous "successful" experiences with similar symptoms prompted them to ask for antibiotics.[139] Rural residents viewed self-medication, over-the-counter purchases

for self-limiting conditions such as diarrhoea and colds, and storing antibiotics at home for future use, as norms.[140] Inappropriate antibiotic dispensing was reported as a severe issue in less economically developed regions like Guizhou, where antibiotics became a routine prescription for patients suffering from any complaint other than fatigue, due to strong financial incentives for over-prescribing.[140] From the prescribers' perspective, lack of diagnostic capacity, such as inability to perform a routine blood test and a C-reactive test, and fears of complications, such as pneumonia, bronchitis and otitis media, were the most frequently reported reasons for antibiotic prescriptions.[35] Pressure to maintain a good doctor-patient relationship to maintain business was also reported as a reason to fulfil patients' requests for antibiotic prescriptions.[35]

Antibiotic use practices specific to the Chinese context

Among the 46 included studies, nine studies[45,60,61,65,117,119,122,139,141] found a misconception existed confusing anti-inflammatory medications and antibiotics, ranging in prevalence from 17.9%[45] to 71.6%.[60] Eleven studies[35,45,60,61,65,75,113,119,133,139,141] reported a preference for IV injection of antibiotics, where 21.3%[45] to 84.7%[133] of participants believed infusion is much more efficacious than oral administration. In a less economically-developed region like Guizhou, IV antibiotic treatment was common for mild diarrhoea, often in the absence of a proper diagnostic test.[140] Mixing antibiotics with traditional Chinese medicine or preferences for traditional Chinese medicine over antibiotics for relieving cold symptoms were observed.[115,140] One found users of traditional Chinese medicine were less likely to accept antibiotics when offered (OR = 0.38, 95% CI: (0.25, 0.60)) and were less likely to be treated with antibiotics for their last URTI (OR = 0.49, 95% CI: (0.27, 0.81)).[115] Others found doctors prescribed

antibiotics for URTI and combined antibiotic prescriptions with traditional Chinese medicine to relieve symptoms.[115,140] Self-medication is common in the Chinese community; doctors reported their patients had self-medicated with antibiotics before reaching health facilities.[35,142]

The results of quality appraisal of the 46 studies were reported in the Supplements 5-7. Adapted from Health Belief Model, Figure 4 presented a conceptual framework of non-biomedical factors that influence outpatient and community antibiotic use for common community-acquired infections.

DISCUSSION

Summary of findings

In this systematic review, quantitative synthesis showed that inappropriate antibiotic use is pervasive throughout mainland China, given the relatively easy access to antibiotics, with or without a prescription. Access to non-prescription antibiotics, either via over-the-counter purchases or household storage, was strongly associated with antibiotic self-medication.[45,60,65,68,129,130,133] Public AMR awareness levels were frequently measured to be high in mainland China;[45,60,61,63,65,67,75,112,115,117-119,123,133,134,137,141,143,144] however, there is little evidence that high awareness in China could lead to better antibiotic use. Striking regional differences were observed for antibiotic self-medication; those living in less economically developed regions were more likely to use antibiotics inappropriately.[60,68,114] Both quantitative and qualitative studies in this review revealed that doctor-patient relationships are critical in influencing unnecessary or inappropriate antibiotic prescriptions.[119] Patients who trust their doctors, as well as people with some medical education or a higher education level would likely accept non-antibiotic prescriptions.[63,114,116,119] Financial incentives for doctors led to

inappropriate over-prescription of antibiotics.[56,125] Antibiotic use is influenced by the local context in mainland China, where a misconception confusing anti-inflammatory medications and antibiotics,[45,60,61,65,117,119,122,139,141] and a preference for IV injection of antibiotics[35,45,60,61,65,75,113,119,133,139,141] are prevalent.

Strengths and limitations of the review

To the best of our knowledge, this is the first mixed-methods systematic review to assess quantitative and qualitative data on factors influencing antibiotic use in China and the interventions to address them. This review included studies across different regions of mainland China, Hong Kong, and Taiwan, published in English and Chinese. This study reported the prevalence, measures and factors of antibiotic misuse across China. It captured statistically assessed factors of actual antibiotic use behaviours by both healthcare providers and consumers, rather than only considering their knowledge, attitudes or intentions in isolation of these influencing factors. We further synthesised the findings using the Health Belief Model (see Table 2) to inform the development of future behavioural change interventions to reduce antibiotic use in the community. The data and study design presented in the Chinese language publications were lean in general and therefore, for our review, we limited the inclusion to studies that had demonstrated sufficient rigor and detail in their reporting for us to appraise their evidence.

Interpretation

Inappropriate use of antibiotics is influenced by non-biomedical factors within and beyond clinical settings that are unique to mainland China, yet common among low-and-middle income countries (LMIC), including public misconceptions, habitual use without professional guidance, incentivising the healthcare system towards prescribing,[56,125] lack of diagnostic capacity,[35,126] and the delicate

relationships between patients and prescribers.[35] To date, there have been only a few interventions implemented in primary care settings to reduce inappropriate prescribing,[52,54,55,106,145-147] largely targeting clinicians and ignoring demand-side factors.

This study found an urgent need to take an evidence-based approach to identify determinants of antibiotic use practices within the target context, programme parameters for improvement, and intervention components to optimise the use of antibiotics by the prescribers and the general public. These insights will be critical to tailor contextualized, multifaceted interventions for reducing inappropriate antibiotic use. For example, despite the AMR awareness campaigns invested in by the Chinese government, the inappropriate use of antibiotics was found to be prevalent across the country. Moreover, a study reported that well-intentioned government publicity about antibiotic abuse may have had the unintended consequence of increasing antibiotic prescriptions and exacerbating resistance.[140] Such a phenomenon might be explained by the non-rational strategies people lean on while managing the type of risk and uncertainty associated with an acute infection: so-called tacit or experiential knowledge such as trust, intuition, emotion, and prior "successful" experiences with similar symptoms for healthcare decision making.[139,148] Also, we found the national ban on over-the-counter purchases of antibiotics has been very limited in its impact - non-prescription purchases and use of antibiotics were reported across mainland China. Furthermore, few studies investigated the common practice – very much influenced by local context – in which physicians and pharmacists prepare cocktails of various medications, including traditional Chinese medicine and antibiotic agents for patients with URTI.[115,140] Inappropriate antibiotic consumption is unlikely to decrease without

multifaceted, context-tailored strategies targeting patients, prescribers, and healthcare systems.

CONCLUSION

This review revealed the impact of non-biomedical factors at individual, community, health system, and societal levels on outpatient and community antibiotic use by healthcare users and providers in the Chinese context and demonstrated that they impact each other in an interactive manner. Given the large population size and consumption volume, the threat to human health from the adverse side effects of inappropriate use and drug resistance calls for immediate action. Future AMR strategies should incorporate a multifaceted, evidence-based, context-tailored design that simultaneously addresses drivers of antibiotic misuse from both the supply- and demand-sides.

SYSTEMATIC REVIEW REGISTRY: PROSPERO CRD42019139591

FUNDING: We received no funding for this study.

TRANSPARENCY DECLARATIONS: The authors have declared no conflict of interests related to this study.

Table 1. Summary of characteristics of included studies that investigated non-biomedical factors influencing outpatient and community antibiotic use in China.

Characteristic	Number of studies	Studies
Total	***46***	***35,45,56,60,61,63,65,67,68,75,112-123,125-144,149-152***
Language		
Chinese	*11*	116,121,129-131,133,135,141,143,144,152
English	*35*	35,45,56,60,61,63,65,67,68,75,112-115,117-120,122,123,125-128,132,134,136-140,142,149-151
Year of study		
2001–2005	*2*	127,128
2006-2010	*3*	121,137,140
2011-2015	*19*	56,61,65,75,115-120,122,123,125,129-131,134,135,139,149
2016-later	*22*	35,45,60,63,67,68,112-114,122,126,132,133,136,138,141-144,150-152
Study design		
Quantitative study	*39*	*45,60,61,63,65,67,68,75,112-116,118,121-123,127-138,141,143,144,149-152*
Longitudinal	*0*	
Cross-sectional	*36*	*45,60,61,63,65,67,68,75,112-116,118,121-123,127-138,141,143,144,149-152*
Experiment	*3*	*56,125,126*
Qualitative study	*4*	*35,139,140,142*
Mixed methods	*3*	*117,119,120*
Study region		
Mainland China		
East	*15*	*35,56,67,123,125,129,130,133,135,136,139,141,143,144,151*
Central	*6*	*63,65,113,134,142,152*
West	*4*	*61,116,131,140*
Across regions	*11*	*45,60,68,75,112,114,122,126,132,138,150*
Hong Kong	*9*	*115,117-120,127,128,137,149*
Taiwan	*1*	*121*
Location		
Urban	*10*	60,121,123,129,130,138,142,143,149,152
Rural	*6*	35,63,113,126,136,139
Mixed	*26*	45,56,61,65,68,112,114-120,122,125,127,128,131-135,137,140,141,144
Unknown	*4*	67,75,150,151
Participants		
General public (adults >18 yrs.)	*29*	45,61,63,67,68,75,112-123,131,133-137,139,141,143,144,149
Parents or caregivers	*6*	60,65,129,130,132,152
Healthcare professionals	*9*	56,125-128,138,142,150,151
Mixed: Patients and Healthcare professionals	*2*	35,140
Antibiotic misuse in the community		
Self-medication with antibiotics	*33*	35,45,60,61,63,65,67,68,75,112-123,129-133,135-137,140,141,143,144
Taking antibiotics as prophylaxis	*9*	45,61,65,68,112,114,122,136,139
Over-the-counter purchases	*18*	60,63,65,67,68,115,117-121,129,131,136,137,139,140,152
Household storage of antibiotics	*22*	45,60,61,63,65,68,112-117,119,120,129,130,133,136,140,141,143,144
Demand for antibiotic prescriptions	*22*	35,45,60,63,65,112,114-123,134,139,141,143,144,152

Table 2. Non-biomedical factors influencing outpatient and community antibiotic use for common community-acquired infections

NON-BIOMEDICAL FACTORS	APPLICATION/ EXAMPLES	INAPPROPRIATE ANTIBIOTIC USE (INCLUDING PREVENTION USE)	
		ANTIBIOTIC USE BEHAVIOUR OUTCOMES	REFERENCES
Knowledge			
General knowledge about antibiotics/ Antimicrobial resistance (AMR)	Combined knowledge score	Asking/pressuring doctors for antibiotics Self-medication with antibiotics Over-the-counter purchases Storing antibiotics at home Taking antibiotics as prophylaxis Health care seeking behaviour The likelihood to be prescribed with antibiotics by doctors Combined behaviour score	45,63,113,133,144
Literacy	Being able to recognise antibiotics Knowing when/how to use antibiotics	Asking/pressuring doctors for antibiotics Self-medication with antibiotics Over-the-counter purchases Storing antibiotics at home Taking antibiotics as prophylaxis The likelihood to be prescribed with antibiotics by doctors	63
Knowledge about the infection	The participant's knowledge about the specific infection (e.g. URTI symptoms will dissipate naturally)	- No evidence available to date	-
AMR Awareness	The participant's awareness of AMR as a health threat on individual or on the society as a whole	Complying with the physician's decision not to prescribe antibiotics	63
Attitudes			
Attitudes towards antibiotic misuse behaviours	The participant's accepting attitudes towards self-medication with antibiotics	Self-medication with antibiotics	60
Self-efficacy	The participant's perception of his/her or others' competence in engaging in caring for the infection or in antibiotic use	No evidence available to date	-
Medical background	The participants or their family members Having some level of medical education	Asking/pressuring doctors for antibiotics Self-medication with antibiotics Over-the-counter purchases Storing antibiotics at home Taking antibiotics as prophylaxis The likelihood to be prescribed with antibiotics by doctors Combined behaviour score	60,61,67,68,75,112,114,123,129,131, 134,135
Prior experience	Participants use of antibiotics on previous occasions	Over-the-counter purchase	152
Perceptions			
Perceived susceptibility	Self-rated health status	Self-medication with antibiotics Combined behaviour score	60,133,144
Perceived severity	The participant's assessment/perception of the severity of the situation regarding the infection (e.g. self-diagnosed symptoms experienced) The participant's perception of potential harm of over-the-counter purchase	Over-the-counter purchase	120
Perceived benefits and disbenefits	The participant's assessment/perception of the benefits of engaging in antibiotic use (antibiotic efficacy) The participant's knowledge of the disbenefits/side effects of engaging in antibiotic use (antibiotic efficacy) The participant's mistaken understanding of antibiotics (e.g. considering antibiotics as Xiaoyanyao, anti-inflammatory drugs) (misconceptions)	Asking/pressuring doctors for antibiotics Self-medication with antibiotics Over-the-counter purchase Storing antibiotics at home Taking antibiotics as prophylaxis	63,122
Perceived barriers	The participant's assessment/perception of barriers to engaging in antibiotic use (health insurance and knowledge of current policy)	Self-medication with antibiotics Asking/pressuring doctors for antibiotics Storing antibiotics at home Health care seeking behaviour Complying with the physician's decision not to prescribe antibiotics	60,63,113
Family dynamics	Family members who might influence the healthcare decisions of caregiver or the patients	Self-medication with antibiotics	60,132
Doctor-patient relationships	Having a regular doctor Following all the advice from physicians	Asking/pressuring doctors for antibiotics Self-medication with antibiotics	65,118
Cues to action	External trigger mechanisms to prompt engagement in antibiotic use behaviour		
Symptoms	Presence of fever	No evidence available to date	-
Information Sources and seeking for therapeutic purposes decisions	Expectation for antibiotic use knowledge	Combined behaviour score	144
Socio-demographic factors			
Age	The age of the participant or caregiver	Asking/pressuring doctors for antibiotics Self-medication with antibiotics Over-the-counter purchase Storing antibiotics at home Health care seeking behaviour The likelihood to be prescribed with antibiotics by doctors (oral, IV or both) Combined behaviour score	63,65,67,68,75,112-114,120,129,132,134,152
Gender	The gender of the participant or caregiver	Self-medication with antibiotics Over-the-counter purchase Storing antibiotics at home Health care seeking behaviour Combined behaviour score	60,63,67,68,112-114,132,135,137,141
Education	The education level of the participant, his/her parent or the caregiver	Asking/pressuring doctors for antibiotics Self-medication with antibiotics Storing antibiotics at home Over-the-counter purchases Health care seeking behaviour Complying with the physician's decision not to prescribe antibiotics	60,63,65,68,112-114,116,130,132,135,144,152

		Combined behaviour score	
Income	The household income or monthly allowance of the participant or caregiver	Self-medication with antibiotics Storing antibiotics at home Taking antibiotics as prophylaxis	68,75,114,116,120,132
Location	The rural/urban of residence of the participant or caregiver	Asking/pressuring doctors for antibiotics Self-medication with antibiotics Over-the-counter purchases Storing antibiotics at home Taking antibiotics as prophylaxis The likelihood to be prescribed with antibiotics by doctors Combined behaviour score	56,61,65,68,112,114,116,131,132,134,135
Region	Region of residence of the participant or caregiver – geographic area or economic development stage	Asking/pressuring doctors for antibiotics Self-medication with antibiotics Over-the-counter purchases Storing antibiotics at home Taking antibiotics as prophylaxis The likelihood to be prescribed with antibiotics by doctors	60,68,114
Socio-contextual factors			
Access to antibiotics	Access to antibiotics, with or without prescription		
Access to non-prescription antibiotics	Over-the-counter purchase Antibiotics stored at home Leftover prescriptions	Self-medication with antibiotics Taking antibiotics as prophylaxis	45,60,65,68,119,129,130,133
Access to antibiotic prescriptions	Asking/pressuring doctors for antibiotics The education level, training, specialty or seniority of the doctors	The likelihood to be prescribed with antibiotics by doctors	56,125
Policy	Health policy or AMR programme that might affect prescribing or access to antibiotics (e.g. measures to de-incentivise over-prescription in public health facilities, including decoupling the link between facility income and the sale of medicines and policy that bans over-the-counter purchases) Financial incentives for antibiotic prescribing of doctors	Self-medication with antibiotics Over-the-counter purchases* The likelihood to be prescribed with antibiotics by doctors	56,60,125
Norm	Participants' view of how others treat illnesses and/or use antibiotics (non-China and non-predictor) * Health care providers reviewing others' prescriptions (non-predictor) *	The likelihood to be prescribed with antibiotics by doctors*	151,153-155
Point-of-care	Prescribing habits/capacity might vary at different levels of health facilities: tertiary hospital, secondary/county hospital, community health centres/township hospital or private clinics/village clinics	No evidence available to date	-

Figure 1: Flowchart of study identification and selection

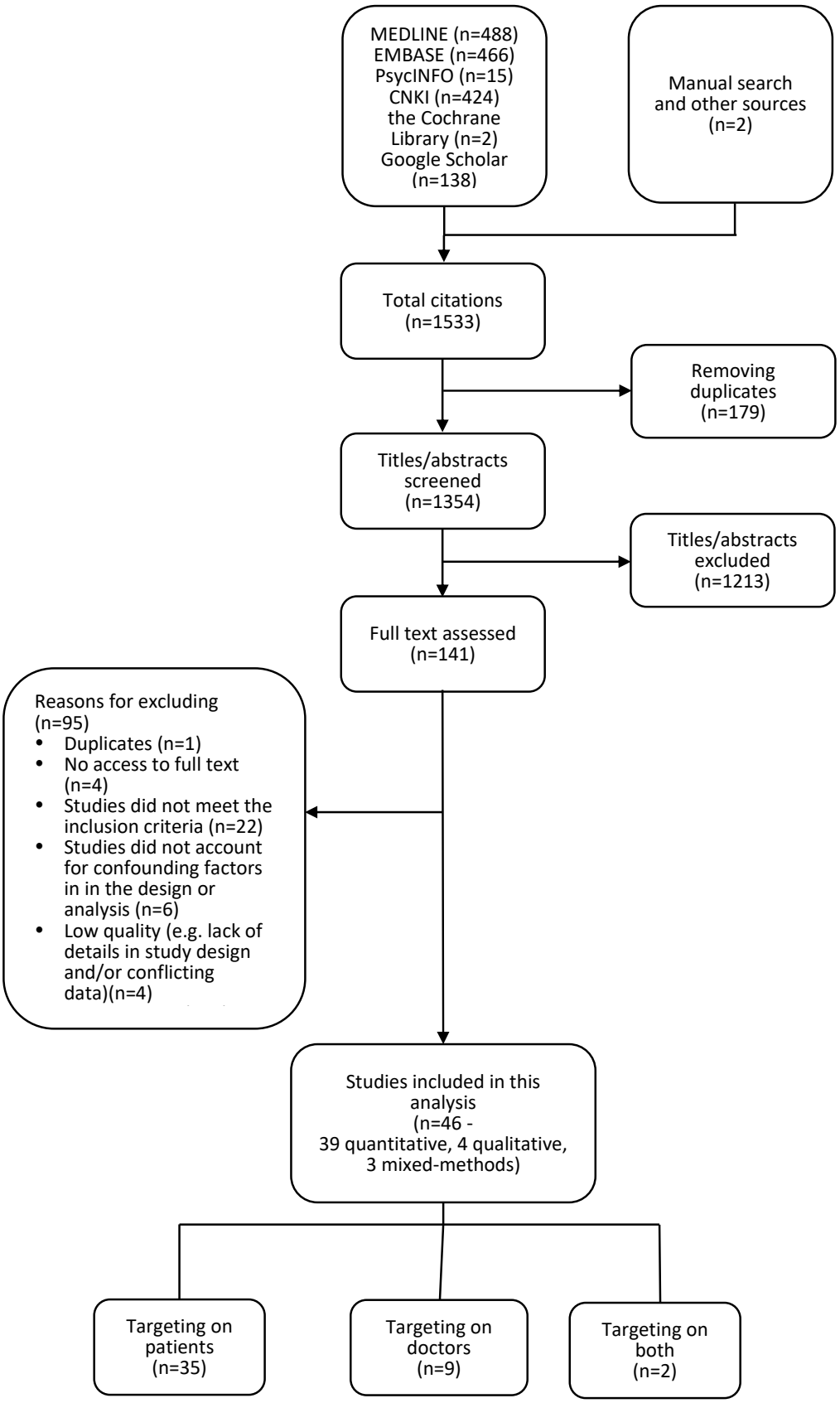


Figure 2. Summary of characteristics of included studies

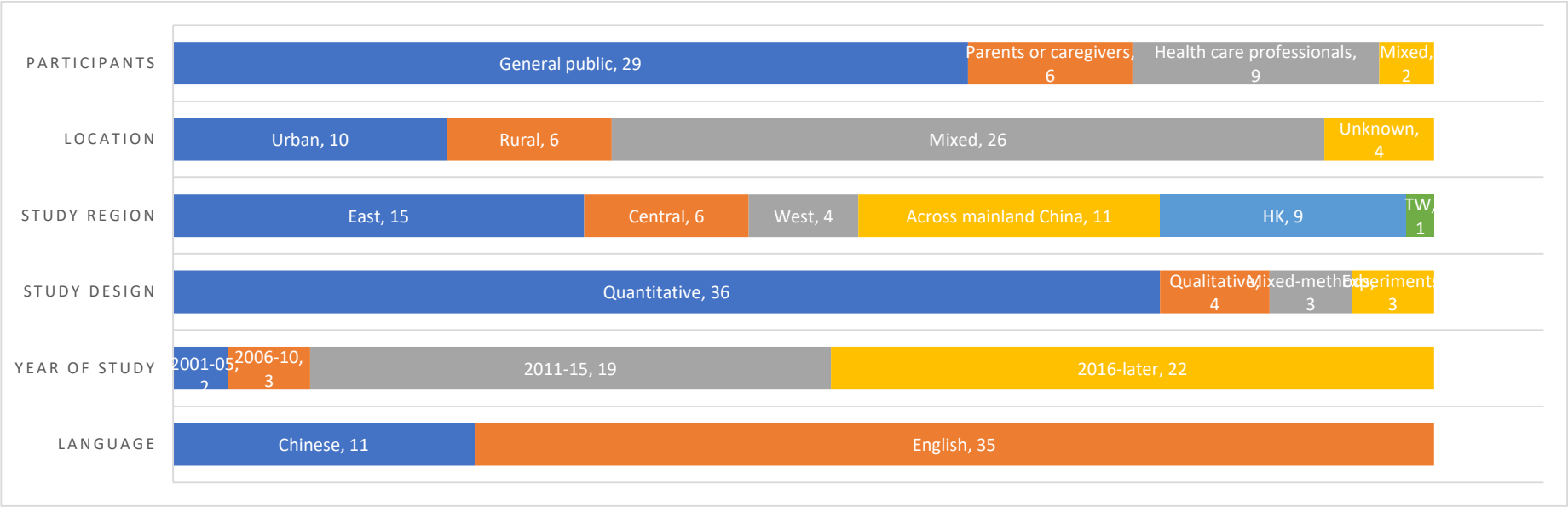
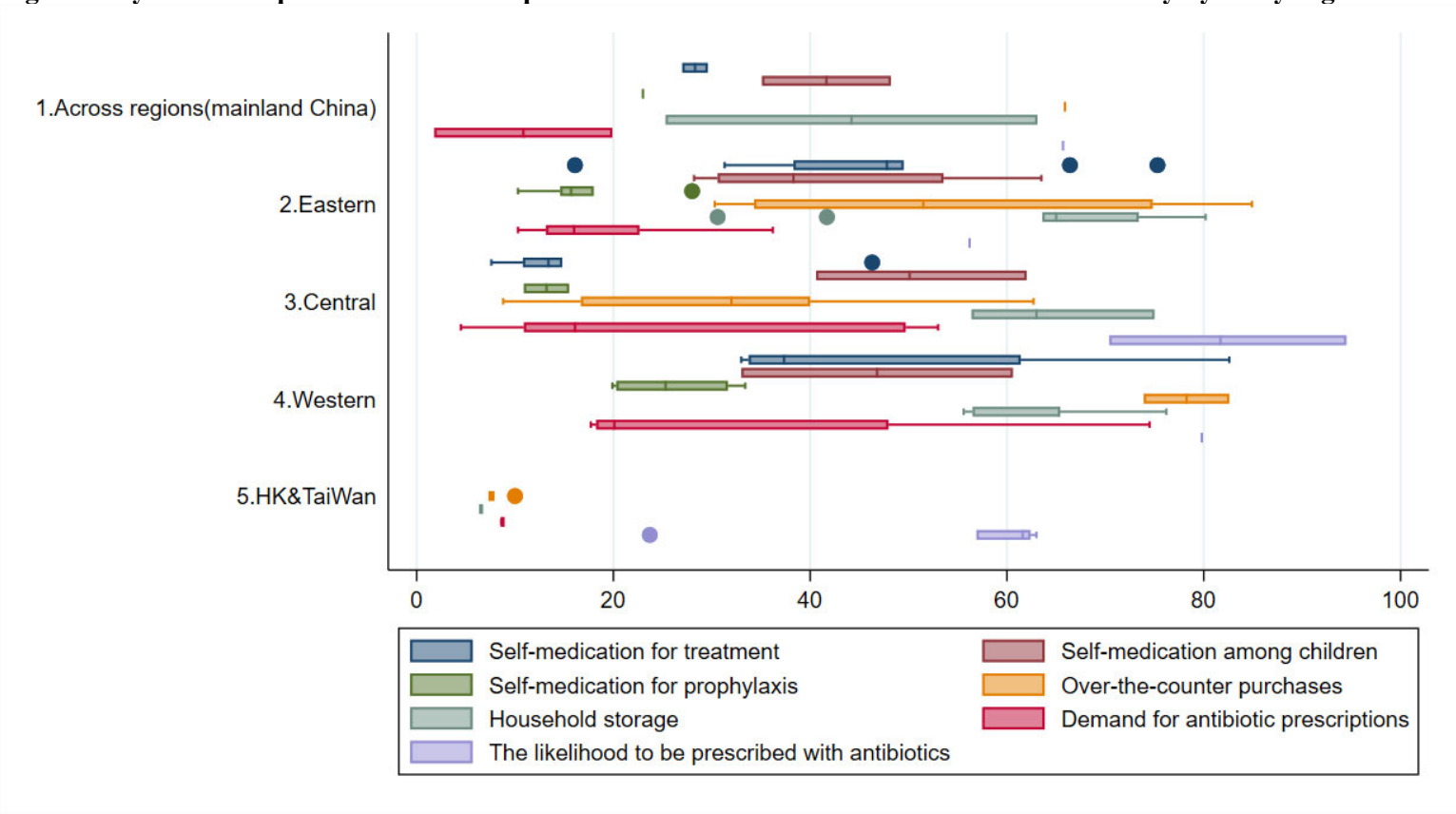
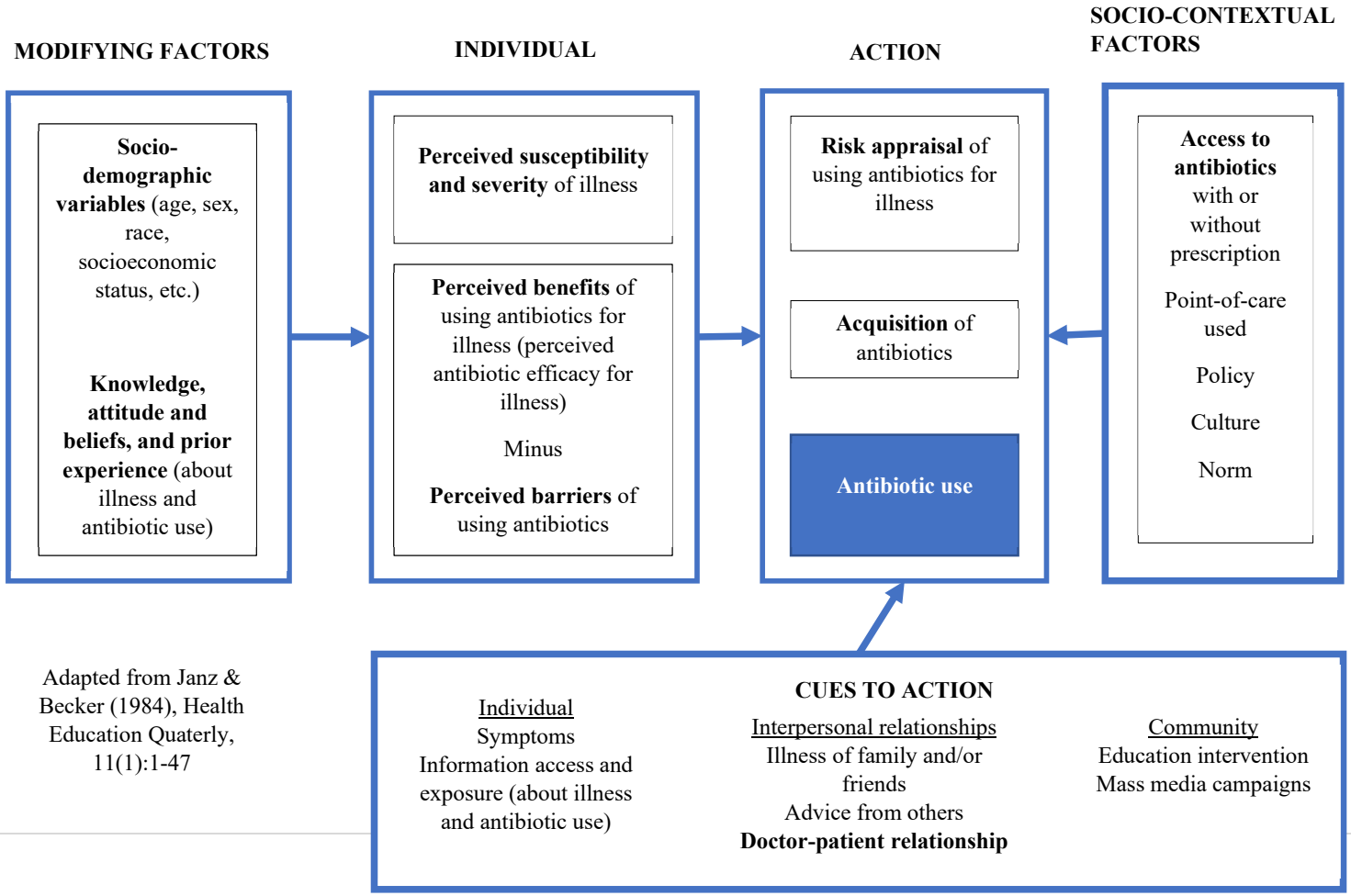


Figure 3. Synthesis of quantitative data on public antibiotic misuse behaviours in the community by study region



Median, IQR and range percentage of participants who self-reported to have performed the misuse behaviours

Figure 4. Non-biomedical factors influencing outpatient and community antibiotic use for common community-acquired infections



Adapted from Janz & Becker (1984), Health Education Quaterly, 11(1):1-47

Supplement 1. Search Criteria

Database	Search Strategy
MEDLINE	(("antimicrobial resistance"[tiab] OR "antibiotic*"[tiab] OR "Anti-Bacterial Agents/therapeutic use*"[Mesh] OR "Drug Resistance, Bacterial*"[Mesh]) AND ("behaviour*"[tiab] OR "use*"[tiab] OR "misuse"[tiab] OR "abuse"[tiab] OR "practice"[tiab] OR "consumption"[tiab] OR "supply"[tiab] OR "prescribing*"[tiab] OR "prescription*"[tiab] OR "prescribe*"[tiab] OR "utilization*"[tiab] OR "Practice Patterns, Physicians*"[Mesh] OR "Health Knowledge, Attitudes, Practice*"[mesh]) AND ("China"[tiab] OR "Hong Kong"[tiab] OR "Macau"[tiab] OR "Taiwan"[tiab]) AND ("1920/09/01"[EDAT] : "2019/05/31"[EDAT]) AND ("1920/09/01"[PDAT] : "2019/05/31"[PDAT]))
EMBASE	('awareness'/exp OR 'attitude to health'/exp OR 'clinical practice'/exp OR 'prescribe*':ab,ti OR 'prescription*':ab,ti OR 'prescribing*':ab,ti OR 'misuse':ab,ti OR 'abuse':ab,ti OR 'utilization*':ab,ti OR 'consumption*':ab,ti OR 'practice*':ab,ti) AND ('antibiotic agent'/exp OR 'antibiotic*':ab,ti) AND ('China':ab,ti OR 'Hong Kong':ab,ti OR 'Macau':ab,ti OR 'Taiwan':ab,ti) AND [1-1-1920]/sd NOT [31-05-2019]/sd NOT [animals]/lim NOT [medline]/lim
PsycINFO	(MA behaviour and behaviour mechanisms OR MA choice behaviour OR MA health knowledge, attitudes, practice* OR MA Practice Patterns, Physicians' OR AB usage OR AB use OR AB consum* OR AB behaviour* OR AB behaviour* OR AB "practice*") (AB AMR OR AB antimicrobial resistance OR AB antibiotic*) NOT ((animal* OR AB surgery OR AB Surgical OR AB dental OR AB cancer* OR AB Chronic obstructive pulmonary disease OR AB COPD OR AB alcohol OR AB tobacco OR AB addiction OR AB depression OR AB disorder* OR AB adherence OR AB diabet* OR MA Inpatients* OR AB inpatient* OR MA Hospitals OR AB tertiary OR AB HIV OR AB tuberculosis OR emergency[ti] OR ED[tiab] OR MA Intensive Care Units OR MA Economics OR AB analgesic* OR MA Hospitalization OR MA Health Care Facilities OR MA Health Care Facilities OR MA Patient Care Management)) NOT PO animal)) AND (AB China OR AB Taiwan OR AB hong kong OR AB macau)
CNKI (China National Knowledge Infrastructure)	((((题名=(抗生素+抗菌素+消炎药)) OR (Title=(抗生素+抗菌素+消炎药))) AND ((题名=(行为+使用)) OR (Title=(行为+使用)))) AND ((((摘要=(抗生素+抗生素滥用+抗生素使用+抗菌素+消炎药)) OR (ABSTRACT=(抗生素+抗生素滥用+抗生素使用+抗菌素+消炎药))) OR ((主题=(抗生素+抗生素滥用+抗生素使用+抗菌素+消炎药)) OR (题名=(抗生素+抗生素滥用+抗生素使用+抗菌素+消炎药)) OR (v_subject=(抗生素+抗生素滥用+抗生素使用+抗菌素+消炎药)))) AND (((摘要=(行为+自我治疗+自我药疗+无处方购买+处方)) OR (ABSTRACT=(行为+自我治疗+自我药疗+无处方购买+处方))) OR ((主题=(行为+自我治疗+自我药疗+无处方购买+处方)) OR (题名=(行为+自我治疗+自我药疗+无处方购买+处方)) OR (v_subject=(行为+自我治疗+自我药疗+无处方购买+处方)))))) 并且 发表时间 between (1900-1-1,2019-05-31) (精确匹配),专辑导航：医药卫生科技,社会科学II辑; 数据库：文献 跨库检索
Google Scholar	"antibiotics" and "China"

Supplement 2. Inclusion/Exclusion Criteria

	Inclusion Criteria	Exclusion
Language	English and Chinese	Other language
Time period	Inception of databases to June 2019	Everything else
Population	General public, caregivers of children (age < 18 years old), outpatients, adults; family doctors, physicians, clinicians, pharmacists, health care workers	Inpatients, animal only
Study setting	Community (primary care or outpatient setting)	Inpatient setting, Emergency Department
Illness	No restrictions	None
Outcome	Determinants of human antibiotic use behaviours (including self-medication with antibiotics or antibiotic prescribing, etc.)	Results of prescription analysis; antibiotic knowledge or attitudes; determinants of general self-medication, antibiotics not specifically mentioned; for quantitative studies, those not presenting significant association between determinants and antibiotic use behaviours by multiple logistic regression analysis.
Study design	Empirical studies with original data (quantitative, qualitative and mix-methods)	Editorials, commentaries, reviews or literature reviews, descriptive studies, poster abstracts
Others		Low-quality studies with obvious data mistakes (e.g. data in figures or tables were different with it in context); full-text article cannot be downloaded; other non-relevant studies.

Supplement 3.1 Prevalence of self-medication for therapeutic purposes among adults

First Author, Year	Region	Denominator	Numerator	Recall period	Reported Prevalence (%)
Cheng, J., 2018	Central (Anhui)	All respondents (rural residents) (n=2221)	Rural residents who used pills leftover from a previous illness or from relatives or friends (n=329)	Lifetime (past experience)	14.8 (329/2221)
Cheng, J., 2018	Central (Anhui)	All respondents (rural residents) (n=2274)	Rural residents with symptoms of common cold in the past year or gastrointestinal infection or UTIs over the past 3 months who reported use of over - the - counter or leftover medicines (n=1052)	Over the past 3 months or in the past year prior to the survey	46.3 (1052/2274)
Hu, Y., 2018	Across regions	Medical students who reported having self-limiting illness and self-treated (n=285)	Medical students who self-treated with antibiotics (n=77)	In the past month prior to the survey	27.0 (77/285)
Lv, B., 2014	Western (Shaanxi)	All respondents (undergraduate students) (n=731)	Students who had self-medicated with antibiotics (n=294)	In the past 6 months prior to the survey	40.2 (294/731)
Pan, H., 2012	Eastern (Guangdong)	All respondents (university students) (n=1300)	Students who had self-treated with antibiotics (n=621)	Lifetime (past experience)	47.8 (621/1300)
Peng, D., 2018	Eastern (Zhejiang University)	Students who reported self-limiting illness and self-treated (n=254)	Students who self-treated with antibiotics (n=41)	In the past month prior to the survey	16.1 (41/254)
Peng, D., 2018	Western (Guizhou University)	Students who reported self-limiting illness and self-treated (n=279)	Students who self-treated with antibiotics (n=92)	In the past month prior to the survey	33.0 (92/279)
Wang, X., 2018	Across regions	Students who reported self-limiting illness and self-treated (n=1711)	Students who self-medicated with antibiotics (n=507)	In the past month prior to the survey	29.6 (507/1711)
Wang, X., 2017	Across regions	Students who reported self-limiting illness and self-treated (n=1711)	Students who self-treated with antibiotics (n=507)	In the past month prior to the survey	29.6 (507/1711)
Zhu, X., 2016	Eastern (Jiangsu)	All respondents (university students) (n=660)	Students who had a history of self-medication with antibiotics (n=316)	Lifetime (past experience)	47.9 (316/660)
Jiang, H., 2017	Eastern (Hangzhou City)	All respondents (residents/general public) (n=449)	Residents who self-medicated with antibiotics when ill (n=449-252=197)	Lifetime (past experience)	43.9* (197/449)
Jiang, H., 2017	Eastern (Hangzhou City)	All respondents (residents/general public) (n=449)	Residents who self-medicated with leftover antibiotics when the same symptoms appeared (n=449-151=298)	Lifetime (past experience)	66.4 (298/449)
Jin, Y., 2014	Western (Gansu)	All respondents (residents of 45 to 74 years old) (n=2556)	Residents who purchased and used antibiotics over the counter when getting ill (often/sometimes) (n=1092+1019=2111)	Lifetime (habits)	82.6 (2111/2556) (42.72+39.87)
Jin, Y., 2014	Western (Gansu)	All respondents (residents of 45 to 74 years old) (n=2556)	Residents who self-medicated according to commercial advertisement with antibiotics purchased over the counter (often/sometimes) (n=412+471=883)	Lifetime (habits)	34.5 (883/2556) (16.12+18.43)
Li, Y., 2016	Eastern (Jiangsu)	All respondents (residents/general public) (n=1589)	Residents who self-medicated with antibiotics (n=498)	In the past 12 months prior to the survey	31.3 (498/1589)
Lu, T., 2016	Eastern (Nanjing City)	All respondents (university students) (n=600)	Students who reported had purchased and used antibiotics without prescriptions (n=non-reported)	In the past 3 months prior to the survey	38.3 (100-61.7) (unknown/600)
Lv, B., 2013	Western (Shaanxi)	All respondents (university students) (n=731)	Students who had self-medicated with antibiotics (n=294)	In the past 6 months prior to the survey	40.2 (294/731)
Chai, J., 2019	Central (Anhui)	Respondents (rural residents) who had ARTIs (n=290+1872=2162)	Residents who reported use of antimicrobials leftover from previous illness or given by relatives for ARTI symptoms (n=290)	In the past year prior to the survey	13.4 (290/2162)
Chai, J., 2019	Central (Anhui)	Respondents (rural residents) who had GTIs (n=43+356=399)	Residents who reported use of antimicrobials leftover from previous illness or given by relatives for GTI symptoms (n=43)	In the past year prior to the survey	10.8 (43/399)
Chai, J., 2019	Central (Anhui)	Respondents (rural residents) who had UTIs (n=122+10=132)	Residents who reported use of antimicrobials leftover from previous illness or given by relatives for UTI symptoms (n=10)	In the past year prior to the survey	7.6 (10/132)
Huang, Y., 2013	Eastern (Northeastern China)	All medical student respondents (n=1236)	Medical students who had frequently used antibiotics without the doctor's prescription previous occasions (n=non-reported)	Lifetime (past experience)	75.3 (unknown/1236)
Huang, Y., 2013	Eastern (Northeastern China)	All non-medical student respondents (n=852)	Non-medical students who had frequently used antibiotics without the doctor's prescription previous occasions (n=non-reported)	Lifetime (past experience)	49.5 (unknown/852)

*** Correction of minor published errors due to miscalculation**

Supplement 3.2 Prevalence of self-medication for therapeutic purposes among children

First Author, Year	Region	Denominator	Numerator	Recall period	Reported Prevalence (%)
Chang, J., 2018	Across regions	All respondents (caregivers) (n=3358)	Caregivers reported non-prescription use of antibiotics for children (n=1617)	In the past 6 months prior to the survey	48.2 (1617/3358)
Chang, J., 2018	Western (Xi'an)	All respondents (caregivers) (n=1388)	Caregivers reported non-prescription use of antibiotics for children (n=841)	In the past 6 months prior to the survey	60.6 (841/1388)
Chang, J., 2018	Central (Changsha)	All respondents (caregivers) (n=1008)	Caregivers reported non-prescription use of antibiotics for children (n=505)	In the past 6 months prior to the survey	50.1 (505/1008)
Chang, J., 2018	Eastern (Shanghai)	All respondents (caregivers) (n=962)	Caregivers reported non-prescription use of antibiotics for children (n=271)	In the past 6 months prior to the survey	28.2 (271/962)
Li, R., 2016	Across regions	All respondents (caregivers) (n=39224)	Children who have taken antibiotics to treat diarrhoea without any prescription (n=13775)	Lifetime (past experience)	35.1 (13775/39224)
Li, R., 2016	Middle China	All respondents (caregivers) (n=6479+4430=10909)	Children who have taken antibiotics to treat diarrhoea without any prescription (n=4430)	Lifetime (past experience)	40.6 (4430/10909)
Li, R., 2016	Eastern China	All respondents (caregivers) (n=9191+4523=13714)	Children who have taken antibiotics to treat diarrhoea without any prescription (n=4523)	Lifetime (past experience)	33.0 (4523/13714)
Li, R., 2016	Western China	All respondents (caregivers) (n=9779+4822=14601)	Children who have taken antibiotics to treat diarrhoea without any prescription (n=4822)	Lifetime (past experience)	33.0 (4822/14601)
Yu, M., 2014	Central (Jiangxi)	All respondents (caregivers) (n=non-reported)	Caregivers who had medicated their children with antibiotics without the advice of a physician (n=non-reported)	In the past 12 months prior to the survey	62 (unknown)
Liao, R., 2012	Eastern (Shenzhen City)	All respondents (primary school student caregivers) (n=509)	Caregivers who self-medicated their children with antibiotics (n=222)	Lifetime (past experience)	43.6 (222/509)
Yao, Z., 2013	Eastern (Guangzhou City)	All respondents (caregivers) (n=1295)	Caregivers had self-medicated their children with antibiotics (n=822)	In the past 12 months prior to the survey	63.5 (822/1295)

Supplement 3.3 Prevalence of self-medication for prophylaxis

First Author, Year	Region	Denominator	Numerator	Recall period	Reported Prevalence (%)
Hu, Y., 2018	Western (Lanzhou University)	All respondents (university medical students) (n=292)	Medical students who took antibiotics to prevent diseases (such as common cold) (n=58)	In the past year prior to the survey	19.9 (58/292)
Hu, Y., 2018	Eastern (Nankai University)	All respondents (university medical students) (n=281)	Medical students who took antibiotics to prevent diseases (such as common cold) (n=29)	In the past year prior to the survey	10.3 (29/281)
Hu, Y., 2018	Central (Jilin University)	All respondents (university medical students) (n=341)	Medical students who took antibiotics to prevent diseases (such as common cold) (n=53)	In the past year prior to the survey	15.5 (53/341)
Hu, Y., 2018	Central (Wuhan University)	All respondents (university medical students) (n=303)	Medical students who took antibiotics to prevent diseases (such as common cold) (n=33)	In the past year prior to the survey	10.9 (33/303)
Hu, Y., 2018	Eastern (Zhejiang University)	All respondents (university medical students) (n=302)	Medical students who took antibiotics to prevent diseases (such as common cold) (n=44)	In the past year prior to the survey	14.6 (44/302)
Hu, Y., 2018	Western (Guizhou University)	All respondents (university medical students) (n=300)	Medical students who took antibiotics to prevent diseases (such as common cold) (n=62)	In the past year prior to the survey	20.7 (62/300)
Lv, B., 2014	Western (Shaanxi)	All respondents (undergraduate students) (n=731)	Students who used antibiotics to prevent the common cold (n=244)	Lifetime (habits)	33.4* (244/731)
Peng, D., 2018	Western (Guizhou University)	All respondents (university students) (n=2073)	Students who took antibiotics prophylactically (n=620)	In the past year prior to the survey	29.9 (620/2073)
Peng, D., 2018	Eastern (Zhejiang University)	All respondents (university students) (n=1922)	Students who took antibiotics prophylactically (n=302)	In the past year prior to the survey	15.7 (302/1922)
Wang, X., 2018	Across regions	All respondents (university students) (n=11192)	Students who took antibiotics for prophylaxis (n=2572)	In the past year prior to the survey	23.0 (2572/11192)
Wang, X., 2017	Across regions	All respondents (university students) (n=11192)	Students who had taken antibiotics for prophylaxis (n=2572)	In the past year prior to the survey	23.0 (2572/11192)
Dyar, O. J., 2018	Eastern (Shandong)	All backyard pig farmer respondents (n=271)	Backyard pig farmers who always or often used antibiotics in feed to keep pigs healthy and prevent diseases (n=non-reported)	Lifetime (habits)	18 (unknown/271)
Dyar, O. J., 2018	Eastern (Shandong)	All backyard pig farmer respondents (n=271)	Backyard pig farmers who used antibiotic for all pigs in a pen when some were sick (n=non-reported)	Lifetime (habits)	28 (unknown/271)

*** Correction of minor published errors due to miscalculation**

Supplement 3.4 Prevalence of over-the-counter purchases

First Author, Year	Region	Denominator	Numerator	Recall period	Reported Prevalence (%)
Cheng, J., 2018	Central (Anhui)	Rural residents who were able to clearly recall the names of the medicines (n=624)	Rural residents who had bought at least one kind of antibiotic over the counter in a pharmacy (n=391)	Lifetime (past experience)	62.7 (391/624)
Cheng, J., 2018	Central (Anhui)	All respondents (rural residents) (n=2262)	Rural residents who reported they had bought medicines over the counter without prescription for symptoms of "common cold" in the past year, "GTIs" (over the past 3 months), or "UTIs" (over the past 3 months) (n=723)	Over the past 3 months or in the past year prior to the survey	32.0 (723/2262)
Peng, D., 2018	Eastern (Zhejiang University)	Students who went to pharmacies to purchase antibiotics (n=893)	Students who bought antibiotics without prescriptions (n=578)	In the past year prior to the survey	64.7 (578/893)
Peng, D., 2018	Western (Guizhou University)	Students who went to pharmacies to purchase antibiotics (n=1248)	Students who bought antibiotics without prescriptions (n=922)	In the past year prior to the survey	73.9 (922/1248)
Wang, X., 2017	Across regions	Students who bought antibiotics from a pharmacy (n=6269)	Students who bought antibiotics without prescriptions (n=4133)	In the past year prior to the survey	65.9 (4133/6269)
You, J. H., 2008	Hong Kong	All respondents (general public) (n=1002)	Residents who had acquired antibiotic without a prescription from a pharmacy (n=73)	Lifetime (past experience)	7.3 (73/1002)
Yu, M., 2014	Central (Jiangxi)	All respondents (caregivers) (n=non-reported)	Caregivers who had purchased antibiotics without a physician's prescription on at least one occasion (n=non-reported)	Lifetime (past experience)	40 (unknown)
Jin, Y., 2014	Western (Gansu)	All respondents (middle-aged residents) (n=2556)	Residents who purchased and used antibiotics over the counter when getting ill (often/sometimes) (n=1092+1019=2111)	Lifetime (habits)	82.6 (42.72+39.87) (2111/2556)
Lu, T., 2016	Eastern (Nanjing City)	All respondents (university students) (n=600)	Students who reported had purchased and used antibiotics without prescriptions (n=non-reported)	In the previous 3 months prior to the survey	38.3 (100-61.7) (unknown/600)
Wang, J., 2017	Central (Changsha City)	All respondents (child parents) (n=310)	Parents who would or sometimes would purchase antibiotics over the counter for their children (n=116)	Lifetime (habits)	37.4 (116/310)
Dyar, O. J., 2018	Eastern (Shandong)	Rural residents who reported that they had bought antibiotics for human use from a pharmacy (n=238)	Residents who reported they did not have a prescription for at least one antibiotic (n=202)	During the previous year prior to the survey	84.9 (202/238)
Dyar, O. J., 2018	Eastern (Shandong)	All backyard pig farmer respondents (n=271)	Backyard pig farmers who reported that they had bought antibiotics for their pigs without first speaking with a vet (n=82)	In the previous year prior to the survey	30.3 (82/271)
Lam, T. P., 2015 (BMC Pharmacol Toxicol)	Hong Kong	All respondents (patients) (n=108+77+1336+861=2382)	Patients who ever bought antibiotics over the counter (n=108+77=185)	Lifetime (past experience)	7.8 (185/2382)
Liao, C. C., 2006	Taiwan	Respondents who himself or children in the family had taken antibiotics before (n=548)	People who himself or family member ever purchased antibiotics over the counter (n=55)	Lifetime (past experience)	10.0 (55/548)
Wun, Y. T., 2014	Hong Kong	All respondents (general public) (n=162+21+249+1920=2352)	People who ever bought antibiotics over the counter (n=162+21=183)	Lifetime (past experience)	7.8 (183/2352)
Chai, J., 2019	Central (Anhui)	Respondents (rural residents) who had suspected ARTIs (n=354+1763=2117)	Residents who bought antimicrobials for suspected infection without prescriptions (n=354)	In the past year prior to the survey	16.7 (354/2117)
Chai, J., 2019	Central (Anhui)	Respondents (rural residents) who had suspected GTIs (n=36+371=407)	Residents who bought antimicrobials for suspected infection without prescriptions (n=36)	In the past year prior to the survey	8.8 (36/407)
Chai, J., 2019	Central (Anhui)	Respondents (rural residents) who had suspected UTIs (n=22+106=128)	Residents who bought antimicrobials for suspected infection without prescriptions (n=22)	In the past year prior to the survey	17.2 (22/128)
Lam, T. P., 2015 (Hong Kong Med J)	Hong Kong	All respondents (general public) (n=190+2250=2440)	People who ever bought antibiotics over the counter (n=190)	Lifetime (past experience)	7.8 (190/2440)
Wun, Y. T., 2013	Hong Kong	All respondents (general public) (n=2460)	People who had ever acquired antibiotics without prescription (n=191)	Lifetime (past experience)	7.8 (191/2460)
Wun, Y. T., 2015	Hong Kong	Local-born and recent immigrants (n=112+16+1518+116=1762)	People who ever bought antibiotics over the counter (n=112+16=128)	Lifetime (past experience)	7.3 (128/1762)

Supplement 3.5 Prevalence of antibiotic household storage

First Author, Year	Region	Denominator	Numerator	Recall period	Reported Prevalence (%)
Chang, J., 2018	Across regions	All respondents (caregivers) (n=3358)	Caregivers who always or often keep antibiotics at home (n=849)	Lifetime (habits)	25.3 (849/3358)
Hu, Y., 2018	Western (Lanzhou University)	All respondents (university medical students) (n=292)	Medical students who keep left-over antibiotics at home/dormitory (not for current use) (n=191)	Lifetime (habits)	65.4 (191/292)
Hu, Y., 2018	Eastern (Nankai University)	All respondents (university medical students) (n=281)	Medical students who keep left-over antibiotics at home/dormitory (not for current use) (n=201)	Lifetime (habits)	71.5 (201/281)
Hu, Y., 2018	Central (Jilin University)	All respondents (university medical students) (n=341)	Medical students who keep left-over antibiotics at home/dormitory (not for current use) (n=215)	Lifetime (habits)	63.0* (215/341)
Hu, Y., 2018	Central (Wuhan University)	All respondents (university medical students) (n=303)	Medical students who keep left-over antibiotics at home/dormitory (not for current use) (n=171)	Lifetime (habits)	56.4 (171/303)
Hu, Y., 2018	Eastern (Zhejiang University)	All respondents (university medical students) (n=302)	Medical students who keep left-over antibiotics at home/dormitory (not for current use) (n=192)	Lifetime (habits)	63.6 (192/302)
Hu, Y., 2018	Western (Guizhou University)	All respondents (university medical students) (n=300)	Medical students who keep left-over antibiotics at home/dormitory (not for current use) (n=196)	Lifetime (habits)	65.3 (196/300)
Lv, B., 2014	Western (Shaanxi)	All respondents (undergraduate students) (n=731)	Students who kept antibiotics frequently (n=413)	Lifetime (habits)	56.5 (413/731)
Peng, D., 2018	Western (Guizhou University)	All respondents (university students) (n=2073)	Students who kept antibiotics at dorm/home (n=1152)	In the past year prior to the survey	55.6 (1152/2073)
Peng, D., 2018	Eastern (Zhejiang University)	All respondents (university students) (n=1922)	Students who kept antibiotics at dorm/home (n=1233)	In the past year prior to the survey	64.2 (1233/1922)
Wang, X., 2018	Across regions	All respondents (university students) (n=11192)	Students who keep antibiotics at home (n=7057)	Lifetime (habits)	63.1 (7057/11192)
Wang, X., 2017	Across regions	All respondents (university students) (n=11192)	Students who kept a stock of antibiotics at home or in the dormitory (n=7057)	Lifetime (habits)	63.1 (7057/11192)
Yu, M., 2014	Central (Jiangxi)	All respondents (caregivers) (n=non-reported)	Caregivers who had kept antibiotics at home in case of future need (n=non-reported)	Lifetime (past experience)	75 (unknown, "three quarters" in text)
Jiang, H., 2017	Eastern (Hangzhou City)	All respondents (residents/general public) (n=449)	Residents who kept penicillin, amoxicillin, cephalosporin and other antibiotics at home (n=449-157=292)	Lifetime (habits)	65.0 (292/449)
Jin, Y., 2014	Western (Gansu)	All respondents (middle-aged residents) (n=2556)	Residents who kept antibiotics at home (often/sometimes) (n=1628+320=1948)	Lifetime (habits)	76.2 (63.69+12.52) (1948/2556)
Li, Y., 2016	Eastern (Jiangsu)	All respondents (residents/general public) (n=1589)	Residents who kept antibiotics at home (n=1167)	Lifetime (habits)	73.4 (1167/1589)
Liao, R., 2012	Eastern (Shenzhen City)	All respondents (primary school student caregivers) (n=112+263+134=509)	Caregivers who kept antibiotics at home (n=112+263=375)	Lifetime (habits)	73.7 (375/509)
Lu, T., 2016	Eastern (Nanjing City)	All respondents (university students) (n=600)	Students who reported keeping antibiotics at home in case presence of illness (n=non-reported)	Lifetime (habits)	>70 (unknown/600)
Yao, Z., 2013	Eastern (Guangzhou City)	All respondents (caregivers) (n=1295)	Caregivers had household antibiotic storage (n=1038)	Lifetime (habits)	80.2 (1038/1295)
Dyar, O. J., 2018	Eastern (Shandong)	All respondents (rural residents) (n=769)	Residents who were observed to be keeping antibiotics for human use (n=321)	At the time of the survey	41.7 (321/769)
Dyar, O. J., 2018	Eastern (Shandong)	All respondents (rural residents) (n=769)	Residents who reported keeping antibiotics for human use (n=343)	In the past year prior to the survey	44.6 (343/769)
Dyar, O. J., 2018	Eastern (Shandong)	All backyard pig farmer respondents (n=271)	Back yard pig farmers who were observed to be keeping at least one antibiotic for pig use (n=83)	At the time of the interview	30.6 (83/271)
Wun, Y. T., 2014	Hong Kong	All respondents (general public) (n=13+128+218+1815=2174)	People who generally kept left-over antibiotics (n=13+128=141)	Lifetime (habits)	6.5 (141/2174)
Lam, T. P., 2015 (Hong Kong Med J)	Hong Kong	All respondents (general public) (n=147+2100=2247)	People who kept left-over antibiotics for future use (n=147)	Lifetime (habits)	6.5 (147/2247)
Wun, Y. T., 2015	Hong Kong	Local-born and recent immigrants (n=93+17+1443+104=1657)	People who had kept left-over antibiotics for future use (n=93+17=110)	Lifetime (past experience)	6.6 (110/1657)
Wun, Y. T., 2013	Hong Kong	All respondents (general public) (n=2266)	People who ever kept leftover antibiotics (n=150)	Lifetime (past experience)	6.6 (150/2266)

*** Correction of minor published errors due to miscalculation**

Supplement 3.6 Prevalence of demand for antibiotic prescriptions

First Author, Year	Region	Denominator	Numerator	Recall period	Reported Prevalence (%)
Chang, J., 2018	Across regions	All respondents (caregivers) (n=3358)	Caregivers who always or often ask antibiotics for their sick child when visiting a physician (n=62)	Lifetime (habits)	1.8 (62/3358)
Cheng, J., 2018	Central (Anhui)	All respondents (rural residents) (n=2575)	Residents who reported that they asked their doctor to prescribe a specific drug (n=368)	Lifetime (past experience)	14.3 (368/2575)
Cheng, J., 2018	Central (Anhui)	All respondents (rural residents) (n=2583)	Residents who reported that they had asked multiple prescriptions (n=117)	Lifetime (past experience)	4.5 (117/2583)
Gu, J., 2015	Central (Heilongjiang)	All respondents (general public) (n=3600)	Participants who require a prescription for antibiotics for a common cold (n=1789)	Lifetime (habits)	49.7 (1789/3600)
Hu, Y., 2018	Western (Lanzhou University)	All respondents (university medical students) (n=292)	Medical students who asked for an antibiotic if did not receive one from a clinician during the consultation (n=55)	Lifetime (past experience)	18.8 (55/292)
Hu, Y., 2018	Eastern (Nankai University)	All respondents (university medical students) (n=281)	Medical students who asked for an antibiotic if did not receive one from a clinician during the consultation (n=29)	Lifetime (past experience)	10.3 (29/281)
Hu, Y., 2018	Central (Jilin University)	All respondents (university medical students) (n=341)	Medical students who asked for an antibiotic if did not receive one from a clinician during the consultation (n=61)	Lifetime (past experience)	17.9 (61/341)
Hu, Y., 2018	Central (Wuhan University)	All respondents (university medical students) (n=303)	Medical students who asked for an antibiotic if did not receive one from a clinician during the consultation (n=33)	Lifetime (past experience)	10.9 (33/303)
Hu, Y., 2018	Eastern (Zhejiang University)	All respondents (university medical students) (n=302)	Medical students who asked for an antibiotic if did not receive one from a clinician during the consultation (n=42)	Lifetime (past experience)	13.9 (42/302)
Hu, Y., 2018	Western (Guizhou University)	All respondents (university medical students) (n=300)	Medical students who asked for an antibiotic if did not receive one from a clinician during the consultation (n=53)	Lifetime (past experience)	17.7 (53/300)
Peng, D., 2018	Eastern (Zhejiang University)	All respondents (university students) (n=1922)	Students who asked for antibiotics when doctors did not initially prescribe them (n=300)	Lifetime (past experience)	15.6 (300/1922)
Peng, D., 2018	Western (Guizhou University)	All respondents (university students) (n=2073)	Students who asked for antibiotics when doctors did not initially prescribe them (n=444)	Lifetime (past experience)	21.4 (444/2073)
Wang, X., 2017	Across regions	All respondents (university students) (n=11192)	Students who had asked a doctor for antibiotics, including by infusion, even when the doctor had not initially been willing to prescribe (n=2230)	In the past year prior to the survey	19.9 (2230/11192)
Yu, M., 2014	Central (Jiangxi)	All respondents (caregivers) (n=non-reported)	Caregivers who had asked antibiotic treatment directly from physicians on at least one occasion (n=non-reported)	Lifetime (past experience)	53 (unknown)
Jiang, H., 2017	Eastern (Hangzhou City)	All respondents (residents/general public) (n=449)	Residents who ever asked doctors for antibiotics (n=449-332=117)	Lifetime (past experience)	26.1 (117/449)
Jin, Y., 2014	Western (Gansu)	All respondents (middle-aged residents) (n=2556)	Residents who asked for antibiotics when visiting a doctor (often/sometimes) (n=609+1296=1905)	Lifetime (habits)	74.5 (23.83+50.70) (1905/2556)
Lu, T., 2016	Eastern (Nanjing City)	All respondents (university students) (n=600)	Students who reported had asked for antibiotics when visiting a doctor (n=non-reported)	Lifetime (past experience)	36.2 (100-63.8) (unknown/600)
Wang, J., 2017	Central (Changsha City)	All respondents (parents) (n=310)	Parents who would not ask for antibiotic prescriptions for their children (n=268)	Lifetime (habits)	86.5 (268/310)
Huang, Y., 2013	Eastern (Northeastern China)	All respondents (university students) (n=2042)	Students who asked doctors to prescribe antibiotics when catching a common cold (n=335)	Lifetime (past experience)	16.4 (335/2042)
Huang, Y., 2013	Eastern (Northeastern China)	All non-medical student respondents (n=836)	Non-medical students who would actively ask doctors to prescribe antibiotics (n=104)	Lifetime (past experience)	12.4 (104/836)
Huang, Y., 2013	Eastern (Northeastern China)	All medical student respondents (n=1206)	Medical students who would actively ask doctors to prescribe antibiotics (n=231)	Lifetime (past experience)	19.2 (231/1206)
Lam, T. P., 2015 (BMC Pharmacol Toxicol)	Hong Kong	All respondents (patients) (n=129+78+1317+862=2386)	Patients who ever asked for antibiotics (n=129+78=207)	Lifetime (past experience)	8.7 (207/2386)
Liao, C. C., 2006	Taiwan	Respondents who himself or children in the family had taken antibiotics before (n=548)	People who had asking doctors for antibiotics or anti-inflammatory medications (n=48)	Lifetime (past experience)	8.8 (48/548)
Wun, Y. T., 2014	Hong Kong	All respondents (general public) (n=17+188+250+1896=2351)	People who ever asked for antibiotics (n=17+188=205)	Lifetime (past experience)	8.7 (205/2351)
Lam, T. P., 2015 (Hong Kong Med J)	Hong Kong	All respondents (general public) (n=212+2228=2440)	People who ever asked for antibiotics (n=212)	Lifetime (past experience)	8.7 (212/2440)
Wun, Y. T., 2015	Hong Kong	Local-born and recent immigrants (n=136+15+1493+118=1762)	People who ever asked doctors for antibiotics (n=136+15=151)	Lifetime (past experience)	8.6 (151/1762)
Wun, Y. T., 2013	Hong Kong	All respondents (general public) (n=2460)	People who ever asked doctors for antibiotics (n=216)	Lifetime (past experience)	8.8 (216/2460)

Supplement 3.7 The likelihood to be prescribed with antibiotics

First Author, Year	Region	Denominator	Numerator	Recall period	Target illnesses/conditions	Reported Prevalence (%)
Chan, Y. H., 2012	Hong Kong	All respondents (general public) (n=369)	People having been prescribed antibiotics (n=210)	In the past 2 years prior to the survey	General diseases	56.9* (210/369)
Peng, D., 2018	Eastern (Zhejiang University)	Medical students who reported self-limiting illness and went to see a doctor (n=162)	Students who were prescribed with antibiotics (n=91)	In the past month prior to the survey	Self-limiting illness	56.2 (91/162)
Peng, D., 2018	Western (Guizhou University)	Medical students who reported self-limiting illness and went to see a doctor (n=213)	Students who were prescribed with antibiotics (n=170)	In the past month prior to the survey	Self-limiting illness	79.8 (170/213)
Wang, X., 2017	Across regions	Medical students who reported self-limiting illness and went to see a doctor (n=913)	Students who were prescribed with antibiotics (n=600)	In the past month prior to the survey	Self-limiting illness	65.7 (600/913)
You, J. H., 2008	Hong Kong	All respondents (residents/general public) (n=1002)	Residents who received antibiotic treatment for the most recent episode of URTI (n=237)	The most recent episode of URTI	URTI symptoms	23.7 (237/1002)
Wun, Y. T., 2014	Hong Kong	All respondents (general public) (n=47+603+67+324=1041)	People accepting antibiotics when offered (n=47+603=650)	Lifetime (past experience)	URTI symptoms	62.4 (650/1041)
Lam, T. P., 2015 (Hong Kong Med J)	Hong Kong	All respondents (general public) (n=658+411=1069)	People accepting antibiotics when offered (n=658)	Lifetime (past experience)	URTI symptoms	61.6 (658/1069)
Wun, Y. T., 2015	Hong Kong	Local-born and recent-immigrants (n=464+46+278+22=810)	People accepting antibiotics when offered (n=464+46=510)	Lifetime (past experience)	URTI symptoms	63.0 (510/810)
Chai, J., 2019	Central (Anhui)	Residents who sought medical help for ARTIs and had clear memory of whether receiving antimicrobials (n=1051+61=1112)	Residents who said that they had been prescribed oral, intravenous antimicrobials or both (n=1051)	In the past year prior to the survey	ARTI symptoms	94.5 (1051/1112)
Chai, J., 2019	Central (Anhui)	Residents who sought medical help for GTIs and had clear memory of whether receiving antimicrobials (n=67+15=82)	Residents who said that they had been prescribed oral, intravenous antimicrobials or both (n=67)	In the past year prior to the survey	GTI symptoms	81.7 (67/82)
Chai, J., 2019	Central (Anhui)	Residents who sought medical help for UTIs and had clear	Residents who said that they had been prescribed oral,	In the past year prior to the survey	UTI symptoms	70.4 (38/54)

	memory of whether receiving antimicrobials (n=38+16=54)	intravenous antimicrobials or both (n=38)

*** Correction of minor published errors due to miscalculation**

Supplement 4.1. Factors associated with self-medication with antibiotics without a prescription (East)

(Chronological order, the list starts with the most recently published studies)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Zhu X, et al. 2016	Outpatient	East	N/A	Quantitative	Having some level of medical education	Prior knowledge of antibiotics	2.26 (1.59-3.22)	To investigate SMA behaviors and risk factors among Chinese university students, and further explore the association between SMA practices and adverse drug events (ADEs).
					Socio-Contextual (demographic characteristics)	Female gender	1.44 (1.01-2.05)	
						Older age	1.25 (1.12-1.38)	
Li Y, et al. 2016	Outpatient	East	N/A	Quantitative	Knowledge (combined knowledge score)	Combined knowledge score Squared combined knowledge score	1.257 (1.081-1.461) 0.978 (0.963-0.992)	To investigate the prevalence and determinants of self-medication with antibiotics (SMA) in Nantong, which made references for the rational use of antibiotics.
					Perceived barrier (or access) to antibiotics	Keeping antibiotics at home Never Often	Reference 3.759 (2.759-5.122)	
					Perceived Susceptibility	Self-rated health status Poor Good	Reference 0.779 (0.620-0.978)	
					Socio-Contextual (demographic characteristics)	Married Not married	Reference 0.600 (0.476-0.757)	
Tian L, et al. 2015	Outpatient	East	N/A	Quantitative	Having some level of medical education	Not majoring in medicine	2.746 (1.377-5.474)	To assess university students' antibiotic knowledge level (and its association with use behaviors).
					Socio-Contextual (demographic characteristics)	Female	2.542 (1.426-4.532)	
					Socio-Contextual (socio-economic status)	Education: Lower grade	3.550 (1.571-8.023)	
						Hometown: Urban	2.186 (1.129-4.231)	
Liao R et al, 2013	Outpatient	East	N/A	Quantitative	Having some level of medical education	Having caregivers working in the medical field	1.744 (1.107-2.746)	To investigate the influence of parents' cognitive level of antibiotics on independent use of antibiotics among pupils.
					Perceived barrier (or access) to antibiotics	Keeping antibiotics at home	1.529 (1.169-2.001)	
					Socio-Contextual (demographic characteristics)	Parents' age	0.807 (0.680-0.957)	
Yao Z et al, 2013	Outpatient	East	N/A	Quantitative	Perceived barrier (or access) to antibiotics	Keeping antibiotics at home	4.792 (3.541-6.485)	To assess the prevalence and determinants of self-medication with antibiotics among children in Guangzhou city, Guangdong province.
					Socio-Contextual (socio-economic status)	Education: Postgraduate and above Elementary school and below Junior high school High school or secondary school	Reference 5.042 (1.495-17.002) 2.358 (1.150-4.838) 2.104 (1.106-4.003)	
Huang Y, et al. 2013	Outpatient	East	N/A	Quantitative	Having some level of medical education	Medical students vs Non-medical students	OR not applicable	To analyze the present status of Chinese medical (MS)- and non-medical (NS) students' KAP on the use of antibiotics and examine the influence of Chinese medical curriculum on the appropriate usage of antibiotics among medical students.
Pan H, et al. 2012	Outpatient	East	N/A	Quantitative	Having some level of medical education	Prior knowledge of antibiotics	2.23 (1.74-2.87)	To evaluate knowledge and behaviors of university students and risk factors concerning SMA.
					Socio-Contextual (demographic characteristics)	Age	1.23 (1.16-1.30)	
					Socio-Contextual (socio-economic status)	Higher allowance: ≤500 RMB 500 to 1,000 RMB >1000 RMB	Reference 1.49 (1.17-1.91) 2.18 (1.29-3.68)	

Supplement 4.2. Factors associated with self-medication with antibiotics without a prescription (Central)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Cheng J et al. 2018	Outpatient	Central	N/A	Quantitative	Knowledge (ability to recognize antibiotics)	Could name at least one kind of antibiotic	1.88 (1.40-2.53)	To examine antibiotic-related knowledge and behaviors in rural Anhui, identify factors associated with knowledge, and explore the relationship between knowledge and antibiotic use.
					Knowledge (combined knowledge score)	Greater total KS (KS ≥ 5)	2.80 (1.55-5.06)	
					Knowledge (when and how to use antibiotics)	Able to name at least one disbenefit of antibiotic use	1.56 (1.17-2.07) for using pills leftover from relatives/friends	
					Cues to action (antibiotic efficacy)	Able to point out one symptom no need of antibiotics	1.49 (1.15-1.93)	
					Socio-Contextual (demographic characteristics)	Older age Females	2.85 (1.47-5.52) 1.41 (1.07-1.87)	
					Socio-Contextual (socio-economic status)	0 year's education ⩾10 years' education	Reference 1.86 (1.11 - 3.11)	
					Perceived barrier (or access) to antibiotics/care	With more than one type of health insurance	1.35 (1.01-1.80)	
Yu M, et al. 2014	Outpatient	Central	N/A	Quantitative	Perceived barrier (or access) to antibiotics	Once purchased antibiotics without physicians' prescription	6.264 (4.144-9.469)	To investigate parents' perceptions of antibiotic use for their children, interactions between parents and physicians regarding treatment with antibiotics, and factors associated with parents self-medicating children with antibiotics.
						Sometimes, often or always stores antibiotics at home	2.792 (1.961-3.975)	
					Antibiotic use behaviors	Would follow all the advice from physicians	0.639 (0.451-0.906)	
					Socio-Contextual (demographic characteristics)	Raising more than one child	2.174 (1.485-3.183)	
						Age of children	1.146 (1.037-1.266)	
					Socio-Contextual (socio-economic status)	Education: College or above Primary school	 Reference 0.191 (0.049-0.754)	
						Living in villages	1.643 (1.108-2.436)	

Supplement 4.3. Factors associated with self-medication with antibiotics without a prescription (West)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Lv B, et al. 2014.	Outpatient	West	N/A	Quantitative	Having some level of medical education	Medical students	1.612 (1.193–2.178)	To evaluate the knowledge, attitude and behaviors of university students on the use of antibiotics.
					Socio-Contextual (region/location)	From urban areas	1.495 (1.103–2.026)	
Lv B, 2013	Outpatient	West	N/A	Quantitative	Having some level of medical education	Majoring in medicine	1.697 (1.229-2.341)	To investigate university students' antibiotic use behaviors and related determinants in order to help improve their antibiotic use behaviors.
					Socio-Contextual (socio-economic status)	Hometown: Urban	1.527 (1.109-2.203)	
Jin Y, et al. 2014	Outpatient	West	N/A	Quantitative	Socio-Contextual (socio-economic status) Behaviour: over-the-counter purchase and use of antibiotics according to commercial advertisement	Hometown: Rural Urban	Reference 0.71 (0.60-0.84)	To examine the influence of social demographic characteristics on antibiotics use among middle aged and elderly people and to provide evidences for making health intervention strategies.
						Education: Senior high school and above Junior high school and below	Reference 1.72 (1.45-2.03)	
					Socio-Contextual (socio-economic status) Behaviour: over-the-counter purchase and use of antibiotics	Hometown: Rural Urban	Reference 0.56 (0.49-0.66)	
						Education: Senior high school and above Junior high school and below	Reference 0.70 (0.60-0.81)	

Supplement 4.4. Factors associated with self-medication with antibiotics without a prescription (across regions)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Wang W, et al. 2019	Outpatient	Across regions	N/A	Quantitative	Knowledge (misconceptions)	Having the misconception that antibiotic is a Xiaoyanyao	1.51 (1.21-1.89)	To examine whether university students hold the misconception that Antibiotic is a Xiaoyanyao (literally means anti-inflammatory drug in Chinese), and association between this misconception and antibiotic misuse behaviors.
Chang J, et al. 2018	Outpatient	Across regions	N/A	Quantitative	Perceived barrier (or access) to antibiotics	Knowing prescription-only regulation for sales of antibiotics at community pharmacies	0.77 (0.66-0.91)	To investigate primary caregivers' knowledge, attitudes, and practices of antibiotics use among children in urban China
					Attitudes (accepting attitudes towards SMA)	Caregivers' supportive attitude	2.66 (2.21-3.19)	
					Having some level of medical education	Having family member or relatives working in health sector	1.38 (1.14-1.66)	
					Perceived barrier (or access) to antibiotics	Keeping antibiotics at home	6.25 (4.73-8.26)	
					Perceived Susceptibility	Child's rated health status rated as fair, poor, or very poor	0.48 (0.40-0.57)	
					Socio-Contextual (demographic characteristics)	Caregiver's relationship with children was grandparents	0.68 (0.49-0.94)	
						Caregiver's gender: Female	1.25 (1.06–1.47)	

					Socio-Contextual (socio-economic status)	Caregivers with senior high school or equivalent	0.75 (0.57-0.98)	
					Socio-Contextual (region/location)	Xi'an Shanghai Changsha	Reference 0.34 (0.28-0.42) 0.78 (0.65-0.94)	
					Perceived barrier (or access) to antibiotics/healthcare	Having children's health insurance	1.30 (1.05-1.61)	
Peng D, et al. 2018	Outpatient	Across regions	N/A	Quantitative	Having some level of medical education	Parent's having medical background	3.01 (1.66-5.47)	To explore the antibiotic misuse behaviors among university students in western and eastern China and find out the regional differences.
					Socio-Contextual (region/location)	Zhejiang Guizhou	Reference 3.00 (1.84-4.90)	
Wang X, et al. 2019	Outpatient	Across regions	N/A	Quantitative	Perceived barrier (or access) to antibiotics (over-the-counter purchase, keeping antibiotics at home, leftover prescriptions)	Keep Antibiotics at Home: No Yes (Previously bought from pharmacies) Yes (Previously prescribed by doctors) Yes (Other)	Reference 5.29 (3.72-7.53) 4.03 (2.68-6.07) 6.06 (3.06-12.02)	To determine the sources of antibiotics leftover at home, the risk factors of keeping antibiotics at home, and the associations between keeping antibiotics at home and SMA among Chinese university students.
					Socio-Contextual (socio-economic status)	Urban	0.65 (0.49-0.88)	
					Socio-Contextual (region/location)	Zhejiang University Lanzhou University Jilin University Nankai University Guizhou University	Reference 2.38 (1.55-3.65) 3.07 (1.99-4.71) 2.37 (1.52-3.69) 2.27 (1.44-3.58)	
Wang X, et al. 2017	Outpatient	Across regions	N/A	Quantitative	Knowledge (combined knowledge score)	0-4 5-9 10-13	Reference 0.53 (0.39-0.72) 0.36 (0.24-0.54)	To explore behaviors related to antibiotic use in university students across China.
					Perceived barrier (or access) to antibiotics	Keeping antibiotics at home	5.05 (3.58-7.14)	
Li R, et al 2016	Outpatient	Across regions	N/A	Quantitative	Knowledge Socio-Contextual (demographic	Guardians having basic health knowledge	0.82 (0.79-0.86)	To investigate the antibiotics usage pattern among Chinese children and provide further
						Female children	0.92 (0.88-0.96)	
						Being raised by parents	0.90 (0.85-0.94)	

					characteristics)	Children's age: 1–3 years 4–6 years	 1.62 (1.54-1.71) 1.90 (1.77-2.03)	insight in developing strategies for promoting public health education.
						Higher education of guardians	0.60 (0.55-0.66)	
						Western China: Low income Middle income Higher income Eastern China: Low income Higher income Middle China: Low income Middle income	 Reference 1.63 (1.51-1.78) 1.71 (1.50-1.94) Reference 0.75 (0.65-0.86) Reference 0.86 (0.77-0.96)	
						Urban area	0.79 (0.76-0.83)	

Supplement 4.5. Factors associated with taking antibiotics as prophylaxis (across regions)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Wang W, et al. 2019	Outpatient	Across regions	N/A	Quantitative	Knowledge (misconceptions)	Having the misconception that antibiotic is a Xiaoyanyao	1.36 (1.24-1.50)	To examine whether university students hold the misconception that Antibiotic is a Xiaoyanyao (literally means anti-inflammatory drug in Chinese), and association between this misconception and antibiotic misuse behaviors.
Hu Y, et al. 2018	Outpatient	Across regions	N/A	Quantitative	Socio-Contextual (socio-economic status)	Hometowns were urban	0.69 (0.50-0.94)	To understand knowledge, attitude, and practice (KAP) with respect to antibiotic use for self-limiting illnesses among medical students in China.
Peng D, et al. 2018	Outpatient	Across regions	N/A	Quantitative	Having some level of medical education	Majoring in medicine	0.69 (0.55-0.87)	To explore the antibiotic misuse behaviors among university students in western and eastern China and find out the regional differences.
						Parent's having medical background	1.45 (1.08-1.95)	
					Socio-Contextual (region/location)	Zhejiang	Reference	
						Guizhou	2.28 (1.89-2.76)	
Wang X, et al. 2018	Outpatient	Across regions	N/A	Quantitative	Having some level of medical education	Majoring in medicine	0.52 (0.44-0.60)	To determine the sources of antibiotics leftover at home, the risk factors of keeping
						Parent with Medical Background	1.47 (1.26-1.72)	

					Perceived barrier (or access) to antibiotics (over-the-counter purchase, keeping antibiotics at home, leftover prescriptions)	Keep Antibiotics at Home: No Yes (Previously bought from pharmacies) Yes (Previously prescribed by doctors) Yes (Other)	Reference 2.55 (2.22-2.92) 2.62 (2.34-2.93) 2.72 (1.97-3.76)	antibiotics at home, and the associations between keeping antibiotics at home and SMA among Chinese university students.
					Socio-Contextual (socio-economic status)	Household Income: <3000 ($461 USD) 3000-10,000 ($462-$1538 USD)	Reference 0.88 (0.79-0.99)	
						Hometowns were urban	0.80 (0.71-0.90)	
					Socio-Contextual (region/location)	Zhejiang University Lanzhou University Jilin University Guizhou University	Reference 1.87 (1.58-2.22) 1.99 (1.69-2.35) 2.18 (1.83-2.58)	
Wang X, et al. 2017	Outpatient	Across regions	N/A	Quantitative	Knowledge (combined knowledge score)	0-4 5-9 10-13	Reference 0.64 (0.57-0.72) 0.35 (0.30-0.41)	To explore behaviors related to antibiotic use in university students across China.

Supplement 4.6. Factors associated with over-the-counter purchase of antibiotics (Central)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Cheng J, et al. 2018	Outpatient	Central	N/A	Quantitative	Knowledge (ability to recognize antibiotics)	Could name at least one kind of antibiotic	2.11 (1.38-3.22)	To examine antibiotic-related knowledge and behaviors in rural Anhui, identify factors associated with knowledge, and explore the relationship between knowledge and antibiotic use.
					Knowledge (combined knowledge score)	Greater total KS (KS=4)	2.23 (1.01-4.96)	
					Perception (Perceived antibiotic efficacy)	Are antibiotic combinations more effective?	1.53 (1.03-2.25)	
					Socio-Contextual (demographic characteristics)	Females	1.45 (1.01-2.10)	
Wang J, et al. 2017	Outpatient	Central	N/A	Quantitative	Prior experience	Whether been prescribed antibiotics by doctors or not	β =0.239	To investigate the knowledge and behavior of antibiotic usage for URTI among parents of young children in Changsha City, Hunan Province.
					Socio-Contextual (demographic characteristics)	Age of child	β =-0.074	
					Socio-Contextual (socio-economic status)	Parents' education level	β =0.090	

Supplement 4.7. Factors associated with over-the-counter purchase of antibiotics (West)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Jin Y, et al. 2014	Outpatient	West	N/A	Quantitative	Socio-Contextual (socio-economic status) Behaviour: over-the-counter purchase and use of antibiotics	Hometown: Rural Urban	Reference 0.56 (0.49-0.66)	To examine the influence of social demographic characteristics on antibiotics use among middle aged and elderly people and to provide evidences for making health intervention strategies.
						Education: Senior high school and above Junior high school and below	Reference 0.70 (0.60-0.81)	
					Socio-Contextual (socio-economic status) Behaviour: over-the-counter purchase and use of antibiotics according to commercial advertisements	Hometown: Rural Urban	Reference 0.71 (0.60-0.84)	
						Education: Senior high school and above Junior high school and below	Reference 1.72 (1.45-2.03)	

Supplement 4.8. Factors associated with over-the-counter purchase of antibiotics (across regions)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Peng D, et al. 2018	Outpatient	Across regions	N/A	Quantitative	Having some level of medical education	Parent's having medical background	0.62 (0.43-0.89)	To explore the antibiotic misuse behaviors among university students in western and eastern China and find out the regional differences.
					Socio-Contextual (socio-economic status)	Education: Undergraduate Graduate	Reference 1.94 (1.35,2.80)	
					Socio-Contextual (region/location)	Zhejiang Guizhou	Reference 1.71(1.36,2.15)	

Supplement 4.9. Factors associated with over-the-counter purchase of antibiotics (Hong Kong and Taiwan)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Lam TP, et al. 2015	Outpatient	Hong Kong	N/A	Mixed-methods (qualitative + quantitative)	Socio-Contextual (socio-economic status)	Local-born New immigrants All immigrants	Reference 2.205 (1.230- 3.953) 0.601 (0.436-0.829)	To investigate the differences in antibiotic use between patients with and without a regular doctor in a pluralistic health care system.
Wun YT, et al. 2015	Outpatient	Hong Kong	N/A	Mixed-methods (qualitative + quantitative)	Socio-Contextual (socio-economic status)	Local-born Recent-immigrants	Reference 2.37 (1.28-4.15)	To study the difference in KAP with antibiotics between the recent-immigrants from mainland China and the local-born of Hong Kong—places with significantly different healthcare and socio-economic systems.
Wun YT, et al. 2013	Outpatient	Hong Kong	N/A	Mixed-methods (qualitative + quantitative)	Socio-Contextual (demographic characteristics)	Age	Not reported	To examine the public's perspectives on antibiotic resistance in our study of the public's knowledge, attitude and practice with antibiotics.
					Risk perception/Perceived severity	Those who agreed with the potential harm of such practice 0.47, 0.341–0.654	0.47 (0.341-0.654)	

Supplement 4.10. Factors associated with storing antibiotics at home (Central)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Cheng et. Al, 2018.	Outpatient	Central	N/A	Quantitative	Knowledge (ability to recognize antibiotics)	Could name at least one kind of antibiotic	1.88 (1.40-2.53)	To examine antibiotic-related knowledge and behaviors in rural Anhui, identify factors associated with knowledge, and explore the relationship between knowledge and antibiotic use.
					Knowledge (combined knowledge score)	Greater total KS (KS⩾5)	2.80 (1.55-5.06)	
					Perception (antibiotic efficacy)	Being able to point out one symptom no need of antibiotics	1.49 (1.15-1.93)	
					Socio-Contextual (demographic characteristics)	Females	1.41 (1.07-1.87)	
						Older age	2.85 (1.47-5.52)	
					Socio-Contextual (socio-economic status)	0 year's education ⩾10 years' education	Reference 1.86 (1.11-3.11)	
					Perceived barrier (or access) to antibiotics/healthcare	With more than one type of health insurance	1.35 (1.01 - 1.80)	

Supplement 4.11. Factors associated with storing antibiotics at home (West)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Jin Y, et al. 2014	Outpatient	West	N/A	Quantitative	Socio-Contextual (socio-economic status)	Hometown: Rural Urban	Reference 1.30 (1.06-1.58)	To examine the influence of social demographic characteristics on antibiotics use among middle aged and elderly people and to provide evidences for making health intervention strategies.
						Education: Senior high school and above Junior high school and below	Reference 1.31 (1.11-1.55)	
						Household income (per month): ⩾2000 RMB <1000 RMB 1000-1999 RMB	Reference 0.46 (0.36-0.60) 0.69 (0.55-0.88)	

Supplement 4.12. Factors associated with storing antibiotics at home (across regions)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Hu Y et al, 2018	Outpatient	Across regions	N/A	Quantitative	Having some level of medical education	Mothers with medical backgrounds	0.53 (0.32-0.88)	To understand knowledge, attitude, and practice (KAP) with respect to antibiotic use for self-limiting illnesses among medical students in China.
					Socio-Contextual (demographic characteristics)	Female students	1.20 (1.04–1.56)	
					Socio-Contextual (socio-economic status)	Fathers had a higher educational level	1.60 (1.10-2.30)	
						Hometowns were urban	1.60 (1.20-1.90)	
Peng D, et al. 2018	Outpatient	Across regions	N/A	Quantitative	Having some level of medical education	Parent's having medical background	1.68 (1.24-2.27)	To explore the antibiotic misuse behaviors among university students in western and eastern China and find out the regional differences.
					Socio-Contextual (demographic characteristics)	Males	0.70 (0.61-0.80)	
					Socio-Contextual (socio-economic status)	Education level of parents: Illiteracy/primary school Junior high school Senior high school University/above	Reference 1.33 (1.07-1.66) 1.70 (1.32-2.17) 2.03 (1.53-2.69)	
						Household income per month: < 3000 RMB 3000-10,000 RMB	Reference 1.30 (1.10-1.53)	
						Hometowns were rural	0.64 (0.54-0.76)	

Wang X, et al. 2018	Outpatient	Across regions	N/A	Quantitative	Having some level of medical education	Parent with Medical Background	1.56 (1.33-1.84)	To determine the sources of antibiotics leftover at home, the risk factors of keeping antibiotics at home, and the associations between keeping antibiotics at home and SMA among Chinese university students.
					Socio-Contextual (demographic characteristics)	Females	1.47 (1.35-1.59)	
						Age	1.02 (1.00-1.04)	
					Socio-Contextual (socio-economic status)	Household Income: <3000 ($461 USD) 3000-10,000 ($462-$1538 USD)	Reference 1.15 (1.04-1.27)	
						Education level of parents: Illiteracy/primary school Junior high school Senior high school University/above	Reference 1.27 (1.09-1.47) 1.54 (1.32-1.81) 1.79 (1.51-2.13)	
						Hometowns were urban	1.50 (1.35-1.66)	
					Socio-Contextual (region/location)	Zhejiang University Wuhan University	Reference 0.83 (0.72-0.96)	
Wang X, et al. 2017	Outpatient	Across regions	N/A	Quantitative	Knowledge (combined knowledge score)	0-4 5-9	Reference 1.29 (1.15-1.45)	To explore behaviors related to antibiotic use in university students across China.

Supplement 4.13. Factors associated with storing antibiotics at home (Hong Kong and Taiwan)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Lam TP, et al. 2015	Outpatient	Hong Kong	N/A	Mixed-methods (qualitative + quantitative)	Socio-Contextual (socio-economic status)	Local-born New immigrants	Reference 2.490 (1.385-4.477)	To investigate the differences in antibiotic use between patients with and without a regular doctor in a pluralistic health care system.
Wun YT, et al. 2015	Outpatient	Hong Kong	N/A	Mixed-methods (qualitative + quantitative)	Socio-Contextual (socio-economic status)	Local-born Recent-immigrants	Reference 2.37 (1.29-4.15)	To study the difference in KAP with antibiotics between the recent-immigrants from mainland China and the local-born of Hong Kong—places with significantly different healthcare and socio-economic systems.
Wun YT et al. 2013	Outpatient	Hong Kong	N/A	Mixed-methods (qualitative + quantitative)	Socio-Contextual (demographic characteristics)	Age	Not reported	To examine the public's perspectives on antibiotic resistance in our study of the public's knowledge, attitude and practice with antibiotics.

					Socio-Contextual (socio-economic status)	Income	Not reported	

Supplement 4.14. Factors associated with asking/pressuring doctors for antibiotics (East)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Huang Y, et al, 2013	Outpatient	East	N/A	Quantitative	Having some level of medical education	Medical students vs Non-medical students	OR not applicable	To analyze the present status of Chinese medical (MS)- and non-medical (NS) students' KAP on the use of antibiotics and examine the influence of Chinese medical curriculum on the appropriate usage of antibiotics among medical students.

Supplement 4.15. Factors associated with asking/pressuring doctors for antibiotics (Central)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Cheng, et al, 2018	Outpatient	Central	N/A	Quantitative	Knowledge (ability to recognize antibiotics)	Could name at least one kind of antibiotic	1.41 (1.08-1.84) for asking for specific drug	To examine antibiotic-related knowledge and behaviors in rural Anhui, identify factors associated with knowledge, and explore the relationship between knowledge and antibiotic use.
					Knowledge (combined knowledge score)	A greater total KS (KS⩾5)	2.63 (1.49-4.65) for asking for specific drug	
						A higher KS (KS = 4)	2.83 (1.27-6.32) for requesting multiple prescriptions	
					Knowledge (when and how to use antibiotics)	Being able to name at least one disbenefit of antibiotic use	1.38 (1.05-1.18) for asking for specific drug	
					Cues to action	Being able to point out one symptom no need of antibiotics	1.61 (1.26-2.04) for asking for specific drug	
						Being able to point out one symptom no need of antibiotics	1.80 (1.19-2.71) for requesting multiple prescriptions	
					Perceived barrier (or access) to antibiotics/healthcare	With more than one type of health insurance	1.36 (1.03 - 1.79) for asking for specific drug	

Supplement 4.16. Factors associated with asking/pressuring doctors for antibiotics (West)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Jin Y, et al. 2014	Outpatient	West	N/A	Quantitative	Socio-Contextual (socio-economic status) Behaviour: asking doctors for antibiotics	Hometown: Rural Urban	Reference 0.73 (0.63-0.85)	To examine the influence of social demographic characteristics on antibiotics use among middle aged and elderly people and to provide evidences for making health intervention strategies.
						Education: Senior high school and above Junior high school and below	Reference 1.18 (1.01-1.37)	
					Socio-Contextual (socio-economic status) Behaviour: asking doctors for antibiotics via intravenous injection	Hometown: Rural Urban	Reference 0.78 (0.67-0.91)	

Supplement 4.17. Factors associated with asking/pressuring doctors for antibiotics (across regions)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Wang W, et al. 2019	Outpatient	Across regions	N/A	Quantitative	Knowledge (misconceptions)	Having the misconception that antibiotic is a Xiaoyanyao	1.34 (1.21-1.48)	To examine whether university students hold the misconception that Antibiotic is a Xiaoyanyao (literally means anti-inflammatory drug in Chinese), and association between this misconception and antibiotic misuse behaviors.
Hu Y et al, 2018	Outpatient	Across regions	N/A	Quantitative	Socio-Contextual (demographic characteristics)	Aged between 16 and 20 years old Aged between 21 and 30 years old	Reference 1.50 (1.00-2.20)	To understand knowledge, attitude, and practice (KAP) with respect to antibiotic use for self-limiting illnesses among medical students in China.
Peng D, et al. 2018	Outpatient	Across regions	N/A	Quantitative	Having some level of medical education	Majoring in medicine	0.71 (0.56-0.90)	To explore the antibiotic misuse behaviors among university students in western and eastern China and find out the regional differences.
					Socio-Contextual (demographic characteristics)	Age	1.05 (1.00-1.11)	
					Socio-Contextual (socio-economic status)	Education level of parents: Illiteracy/primary school Senior high school	Reference 1.39 (1.01-1.91)	
					Socio-Contextual (region/location)	Zhejiang Guizhou	Reference 1.48 (1.22-1.80)	
Wang X et al. 2017	Outpatient	Across regions	N/A	Quantitative	Knowledge (combined	0-4 5-9	Reference 0.71 (0.62-0.80)	To explore behaviors related to antibiotic use

					knowledge score)	10-13	0.50 (0.42-0.59)	in university students across China.

Supplement 4.18. Factors associated with antibiotic prescriptions (Central)

Outcome: accepting physician's decision not to prescribe antibiotics

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Cheng J, et al. 2018	Outpatient	Central	N/A	Quantitative	Knowledge (AMR awareness)	Knowing unnecessary use of antibiotics make them ineffective.	1.19 (1.00-1.42)	To examine antibiotic-related knowledge and behaviors in rural Anhui, identify factors associated with knowledge, and explore the relationship between knowledge and antibiotic use.
					Socio-Contextual (socio-economic status)	Education: 7-9 years ⩾10 years	Reference 1.39 (1.08-1.79) 1.46 (1.01-2.10)	
					Perceived barrier (or access) to antibiotics/healthcare	With more than one type of health insurance	0.75 (0.61 - 0.92)	

Supplement 4.19. Factors associated with antibiotic prescriptions (Central)

Outcome: likelihood of being prescribed with antibiotics

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Chai J et al. 2019	Outpatient	Central	N/A	Quantitative	Knowledge (combined knowledge score)	Zero ≥3 scores Outcome: being prescribed oral/intravenous antimicrobials	reference 0.32 (0.13-0.78)	To describe help seeking behavior from a medical doctor and antimicrobial use for common infections among rural residents of Anhui province, China.
					Socio-Contextual (demographic characteristics)	Age Outcome: being prescribed oral antimicrobial use	0.81 (0.71-0.93)	
						Age Outcome: being prescribed intravenous antimicrobial use	1.21 (1.10-1.33)	

Supplement 4.20. Factors associated with antibiotic prescriptions (across regions)

Outcome: likelihood of being prescribed with antibiotics

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Peng D et al, 2018	Outpatient	Across regions	N/A	Quantitative	Having some level of medical education	Majoring in medicine	0.49 (0.26-0.93)	To explore the antibiotic misuse behaviors among university students in western and eastern China and find out the regional differences.
					Socio-Contextual (socio-economic status)	Hometown were rural	2.01 (1.05-3.84)	
					Socio-Contextual (region/location)	Zhejiang Guizhou	Reference 2.95 (1.68-5.18)	
Wang X, et al. 2017	Outpatient	Across regions	N/A	Quantitative	Knowledge (combined knowledge score)	0-4 5-9 10-13	Reference 0.58 (0.39-0.87) 0.46 (0.27-0.76)	To explore behaviors related to antibiotic use in university students across China.

Supplement 4.21. Factors associated with antibiotic prescriptions (Hong Kong and Taiwan)

Reference	Setting	Region	Last year of data collection	Study design	Non-biomedical factors	Description of the factor influencing outpatient and/or community antibiotic use	ORs	Study objective
Wun YT et al. 2014	Outpatient	Hong Kong	N/A	Quantitative	Health care seeking behaviors Outcome:	TCM (Traditional Chinese medicine)-attenders	0.38 (0.25-0.60) for accepting antibiotics when offered	This study compares TCM attenders with the WM-attenders in Hong Kong about their KAP with antibiotics. The comparison could help future campaigns/education on appropriate antibiotic use.
					Health care seeking behaviors Outcome:		0.49 (0.27-0.81) for being treated with antibiotics in last URTI	

Supplement 5. Appraisal – quantitative

Author	Region of China	Study design	Data collection method	Target population	Eligibility criteria (yes/no)	Sample size	Response rate (%)	Clarity of the questions /statements (yes/no)	Ethical considerations (yes/no)	Clarity of data (including numerators, denominators, and missing values) (yes/no)	Consistency between the research question and data reported (yes/no)
Chan, Y. H., 2012	Hong Kong	Cross-sectional	Survey	General public	Yes	369	Not reported	Yes	Yes	Yes	Yes
Chang, J., 2018	Across regions	Cross-sectional	Survey	Caregivers of children under 7 years	Yes	3358	87.4	Yes	Yes	Yes	Yes
Cheng, J., 2018	Central	Cross-sectional	Survey	Residents in rural villages	Yes	2760	94.6	Yes	Yes	Yes	Yes
Gu, J., 2015	Central	Cross-sectional	Survey	Rural and urban residents	Yes	3631	Not reported	Yes	No	Yes	Yes
Hu, Y., 2018	Across regions	Cross-sectional	Survey	Medical students	Yes	1819	Not reported	Yes	Yes	Yes	Yes
Li, R., 2016	Across regions	Cross-sectional	Survey	Guardians of children aged 0–6 years	Yes	53665	87.6	Yes	Yes	Yes	Yes
Lv, B., 2014	Western	Cross-sectional	Survey	Undergraduate students	Yes	731	73.1	Yes	Yes	Yes	Yes
Pan, H., 2012	Eastern	Cross-sectional	Survey	Shantou University (STU) students	Yes	1300	47.7 (1300/2724)	Yes	Yes	Yes	Yes
Peng, D., 2018	Across regions	Cross-sectional	Survey	University students in western and eastern China (Guizhou University and Zhejiang University)	Yes	3995	Not reported	Yes	Yes	No	Yes
Wang, X., 2018	Across regions	Cross-sectional	Survey	University students	Yes	11192	Not reported	Yes	No	Yes	Yes
Wang, X., 2017	Across regions	Cross-sectional	Survey	University students	Yes	11192	Not reported	Yes	Yes	Yes	Yes
You, J. H., 2008	Hong Kong	Cross-sectional	Survey, interview	People aged 18 or older who were uninstitutionalized Hong Kong residents	Yes	1002	14	Yes	Yes	Yes	Yes
Yu, M., 2014	Central	Cross-sectional	Survey	Primary caregivers	Yes	854	92	Yes	Yes	Yes	Yes
Zhu, X., 2016	Eastern	Cross-sectional	Survey	Jiangsu university students	Yes	660	41.6	Yes	Yes	Yes	Yes

Jiang, H., 2017	Eastern	Cross-sectional	Survey	Community residents in Hangzhou City	No	449	92.84	Yes	No	Yes	Yes
Jin, Y., 2014	Western	Cross-sectional	Survey	Middle-aged community residents	Yes	2556	98.69	Yes	No	Yes	Yes
Li, Y., 2016	Eastern	Cross-sectional	Survey	Community residents	Yes	1589	93.47	No	No	No	Yes
Liao, R., 2012	Eastern	Cross-sectional	Survey	Primary school student's parents	Yes	509	94.43	Yes	No	Yes	Yes
Lu, T., 2016	Eastern	Cross-sectional	Survey	University students	Yes	600	97.1 (600/618)	Yes	No	Yes	Yes
Lv, B., 2013	Western	Cross-sectional	Survey	University students	Yes	731	73.1	Yes	No	Yes	Yes
Tian, L., 2015	Eastern	Cross-sectional	Survey	University students	Yes	377	94.25	No	No	No	Yes
Wang, J., 2017	Central	Cross-sectional	Survey		Yes	310	88.57	No	No	No	Yes
Yao, Z., 2013	Eastern	Cross-sectional	Survey	Child parents	Yes	1295	86.3	No	No	No	Yes
Zhong, M., 2018	Eastern	Cross-sectional	Survey		Yes	1096	90.01	No	No	No	Yes
Dyar, O. J., 2018	Eastern	Cross-sectional	Survey	Residents of villages	Yes	769	Not reported	Yes	Yes	Yes	Yes
Huang, Y., 2013	Eastern	Cross-sectional	Survey	University students	Yes	2088	83.5	Yes	No	Yes	Yes
Lam, T. P., 2015 (BMC Pharmacol Toxicol)	Hong Kong	Cross-sectional	Survey	Adult residents	Yes	2471	68.3	Yes	Yes	Yes	Yes
Liao, C. C., 2006	Taiwan	Cross-sectional	Survey	Adults over 20 years old all over Taiwan	Yes	1507	86.7 [1507/(1771-32)]	Yes	No	Yes	Yes
Wun, Y. T., 2014	Hong Kong	Cross-sectional	Survey	Adult residents	Yes	2471	68.3	Yes	Yes	Yes	Yes
Chai, J., 2019	Central	Cross-sectional	Survey, interview	Rural residents of Anhui province	Yes	2611	95	Yes	Yes	Yes	Yes
Wang, W., 2019	Across regions	Cross-sectional	Survey	University students	Yes	11192	Not reported	Yes	Yes	Yes	Yes

Chang, J., 2017	Across regions	Cross-sectional	Survey	community pharmacies pharmacists	Yes	256 (pharmacies)	Not reported	Yes	Yes	Yes	Yes
Lam, T. P., 2003 (J Clin Pharm Ther)	Hong Kong	Cross-sectional	Survey	Family doctors (fellows, members and associate members normally residing in Hong Kong)	Yes	801	65.0	Yes	No	Yes	Yes
Lam, T. P., 2003 (Int J Clin Pract)	Hong Kong	Cross-sectional	Survey	Family doctors (fellows, members and associate members normally residing in Hong Kong)	Yes	801	65.0	Yes	No	Yes	Yes
Guan, X., 2019	Across regions	Cross-sectional	Survey	Physicians	Yes	344 questionnaires 58512 valid medical records	95.6	Yes	Yes	Yes	Yes
Liu, C., 2019	Central	Cross-sectional	Survey	Primary care physicians	Yes	503	71	Yes	Yes	Yes	Yes
Lam, T. P., 2015 (Hong Kong Med J)	Hong Kong	Cross-sectional	Survey, interview, focus group	General public	Yes	2471	68.3	Yes	No	Yes	Yes
Wun, Y. T., 2015	Hong Kong	Cross-sectional	Survey, interview, focus group	General public	Yes	2471	68.3	Yes	Yes	Yes	Yes
Wun, Y. T., 2013	Hong Kong	Cross-sectional	Survey, interview	Adult residents	Yes	2471	68.3	Yes	Yes	No	Yes
Currie, J., 2014	Unknown	Cross-sectional	Experiment	Physicians	No	80	Not reported	Yes	No	Yes	Yes
Currie, J., 2011	Unknown	Cross-sectional	Experiment	Physicians	No	231 visits	Not reported	Yes	No	Yes	Yes
Xue, H., 2019	Unknown	Cross-sectional	Experiment	Providers	No	526 completed SP interactions	97.8 (545/557)	Yes	Yes	Yes	Yes

Supplement 6. Appraisal – qualitative (CASP)

	Section A: Are the results of the trial valid? (Yes/Can't Tell/No)						Section B: What are the results? (Yes/Can't Tell/No)			Section C: Will the results help locally? (Yes/Can't Tell/No)
Article	**1. Was there a clear statement of the aims of the research?**	**2. Is a qualitative methodology appropriate?**	**3. Was the research design appropriate to address the aims of the research?**	**4. Was the recruitment strategy appropriate to the aims of the research?**	**5. Was the data collected in a way that addressed the research issue?**	**6. Has the relationship between researcher and participants been adequately considered?**	**7. Have ethical issues been taken into consideration?**	**8. Was the data analysis sufficiently rigorous?**	**9. Is there a clear statement of findings?**	**10. How valuable is the research?**
Jin, C., 2011	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Reynolds, L., 2009	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Zhang, Z., 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zhu, X., 2018	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Lam, T. P., 2015 (Hong Kong Med J)	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Wun, Y. T., 2015	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Wun, Y. T., 2013	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes

Supplement 7. Appraisal – mixed-methods (MMAT)

	Questions	Lam, T. P., 2015 (Hong Kong Med J)	Wun, Y. T., 2015	Wun, Y. T., 2013
Screening Questions	S1. Are there clear research questions?	Yes	Yes	Yes
	S2. Do the collected data allow to address the research questions?	Yes	Yes	Yes
1. Qualitative	1.1. Is the qualitative approach appropriate to answer the research question?	Yes	Yes	Yes
	1.2. Are the qualitative data collection methods adequate to address the research question?	Yes	Yes	Yes
	1.3. Are the findings adequately derived from the data?	Yes	Yes	Yes
	1.4. Is the interpretation of results sufficiently substantiated by data?	Yes	Yes	Yes
	1.5. Is there coherence between qualitative data sources, collection, analysis and interpretation?	Yes	Yes	Yes
2. Quantitative randomized controlled trials	2.1. Is randomization appropriately performed?	N/A	N/A	N/A
	2.2. Are the groups comparable at baseline?			
	2.3. Are there complete outcome data?			
	2.4. Are outcome assessors blinded to the intervention provided?			
	2.5 Did the participants adhere to the assigned intervention?			
3. Quantitative non-randomized	3.1. Are the participants representative of the target population?	N/A	N/A	N/A
	3.2. Are measurements appropriate regarding both the outcome and intervention (or exposure)?			
	3.3. Are there complete outcome data?			
	3.4. Are the confounders accounted for in the design and analysis?			
	3.5. During the study period, is the intervention administered (or exposure occurred) as intended?			
4. Quantitative descriptive	4.1. Is the sampling strategy relevant to address the research question?	Yes	Yes	Yes
	4.2. Is the sample representative of the target population?	Yes	Yes	Yes
	4.3. Are the measurements appropriate?	Yes	Yes	Yes
	4.4. Is the risk of nonresponse bias low?	No	No	No
	4.5. Is the statistical analysis appropriate to answer the research question?	Yes	Yes	Yes
5. Mixed methods	5.1. Is there an adequate rationale for using a mixed-methods design to address the research question?	No	No	Yes
	5.2. Are the different components of the study effectively integrated to answer the research question?	Yes	Yes	Yes
	5.3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted?	Yes	Yes	Yes
	5.4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?	Yes	Yes	Yes
	5.5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?	Yes	Yes	Yes

Included Studies

Health care users (Patients and caregivers)

1. Chai J, Coope C, Cheng J, et al. Cross-sectional study of the use of antimicrobials following common infections by rural residents in Anhui, China. BMJ Open 2019;9:e024856.
2. Chan YH, Fan MM, Fok CM, et al. Antibiotics nonadherence and knowledge in a community with the world's leading prevalence of antibiotics resistance: implications for public health intervention. Am J Infect Control 2012;40:113-7.
3. Chang J, Lv B, Zhu S, et al. Non-prescription use of antibiotics among children in urban China: a cross-sectional survey of knowledge, attitudes, and practices. Expert Rev Anti Infect Ther 2018;16:163-72.
4. Cheng J, Coope C, Chai J, et al. Knowledge and behaviours in relation to antibiotic use among rural residents in Anhui, China. Pharmacoepidemiol Drug Saf 2018;27:652-9.
5. Dyar OJ, Yin J, Ding L, et al. Antibiotic use in people and pigs: a One Health survey of rural residents' knowledge, attitudes and practices in Shandong province, China. J Antimicrob Chemother 2018;73:2893-9.
6. Gu J, Zhao J, Huang Y, et al. Use of antibiotics by urban and rural residents in Heilongjiang Province, China: cross-sectional study. Trop Med Int Health 2015;20:1815-22.
7. Hu Y, Wang X, Tucker JD, et al. Knowledge, Attitude, and Practice with Respect to Antibiotic Use among Chinese Medical Students: A Multicentre Cross-Sectional Study. Int J Environ Res Public Health 2018;15.
8. Huang Y, Gu J, Zhang M, et al. Knowledge, attitude and practice of antibiotics: a questionnaire study among 2500 Chinese students. BMC medical education 2013;13:163.

9. Jin C, Ely A, Fang L, et al. Framing a global health risk from the bottom-up: User perceptions and practices around antibiotics in four villages in China. Health, Risk & Society 2011;13:433-49.
10. Lam TP, Lam KF, Ho PL, et al. Knowledge, attitude, and behaviour toward antibiotics among Hong Kong people: local-born versus immigrants. Hong Kong medical journal = Xianggang yi xue za zhi 2015;21 Suppl 7:S41-7.
11. Lam TP, Wun YT, Lam KF, et al. Differences in antibiotic use between patients with and without a regular doctor in Hong Kong. BMC Pharmacol Toxicol 2015;16:40.
12. Li R, Xiao F, Zheng X, et al. Antibiotic misuse among children with diarrhea in China: results from a national survey. PeerJ 2016;4:e2668.
13. Liao CC, Chang YK, Chen HH, et al. Knowledge and use of antibiotics among people in Taiwan. Taiwan Journal of Public Health 2006;25:135-42.
14. Lv B, Zhou Z, Xu G, et al. Knowledge, attitudes and practices concerning self-medication with antibiotics among university students in western China. Trop Med Int Health 2014;19:769-79.
15. Pan H, Cui B, Zhang D, et al. Prior knowledge, older age, and higher allowance are risk factors for self-medication with antibiotics among university students in southern China. PloS One 2012;7:e41314.
16. Peng D, Wang X, Xu Y, et al. Antibiotic misuse among university students in developed and less developed regions of China: a cross-sectional survey. Glob Health Action 2018;11:1496973.
17. Wang W, Wang X, Hu YJ, et al. The Misconception of Antibiotic Equal to an Anti-Inflammatory Drug Promoting Antibiotic Misuse among Chinese University Students. Int J Environ Res Public Health 2019;16.

18. Wang X, Lin L, Xuan Z, et al. Keeping Antibiotics at Home Promotes Self-Medication with Antibiotics among Chinese University Students. Int J Environ Res Public Health 2018;15.
19. Wang X, Peng D, Wang W, et al. Massive misuse of antibiotics by university students in all regions of China: implications for national policy. Int J Antimicrob Agents 2017;50:441-6.
20. Wun YT, Lam TP, Lam KF, et al. The public's perspectives on antibiotic resistance and abuse among Chinese in Hong Kong. Pharmacoepidemiol Drug Saf 2013;22:241-9.
21. Wun YT, Lam TP, Lam KF, et al. Are There Differences in Antibiotic Use Between the Recent-Immigrants from Mainland China and the Local-Born in Hong Kong? J Immigr Minor Health 2015;17:1177-84.
22. Wun YT, Lam TP, Lam KF, et al. Comparison of the knowledge, attitudes and practice with antibiotic use between traditional Chinese medicine and western medicine usual attenders in Hong Kong. Complement Ther Med 2014;22:99-106.
23. You JH, Yau B, Choi KC, et al. Public knowledge, attitudes and behaviour on antibiotic use: a telephone survey in Hong Kong. Infection 2008;36:153-7.
24. Yu M, Zhao G, Stålsby Lundborg C, et al. Knowledge, attitudes, and practices of parents in rural China on the use of antibiotics in children: a cross-sectional study. BMC Infect Dis 2014;14:112.
25. Zhu X, Pan H, Yang Z, et al. Self-medication practices with antibiotics among Chinese university students. Public Health 2016;130:78-83.
26. Jiang H, Jin Y, Ye J, et al. An Analysis on Knowledge, Attitude and Practice Regarding Antibiotics Use among Community Residents in Hangzhou [in Chinese]. Preventive medicine 2017;29(10):978-82.

27. Jin Y, Lu Y, Lu P, et al. Influence of Demographic Characteristics on Antibiotics Use among Middle-Aged and Elderly People [in Chinese]. Chin J Public Health 2014;30(09):1140-43.
28. Li Y, Song Y, Shao R, et al. Determinants of Self-medication with Antibiotics among Residents in Nantong [in Chinese]. The Chinese Health Service Management 2016;33(01):39-41.
29. Liao R. Investigation on the Impact of Parents' Cognitive Level of Antibiotics on Self-directed Use of Antibiotics in Pupils [in Chinese]. Practical Preventive Medicine 2013;20(01):42-45.
30. Lu T, Li X. A Study on the Knowledge, Attitude and Behavior of Antibiotic Use among Students in Five Universities in Nanjing [in Chinese]. ACTA UNIVERSITATIS MEDICINALIS NANJING (Social Sciences) 2016;16(04):274-80.
31. Studying on the Behaviours and Influencing Factors of Self-Medication with Antibiotics among University Students in China [in Chinese]. 2013 Annual Meeting of Pharmacy Management Professional Committee of Chinese Pharmaceutical Association and Academic Forum on "Medicine Safety and Scientific Development"; 2013 2013/08/01; Beijing, China.
32. Tian L, Dong J, Zeng Y, et al. Logistic Regression Analysis of Factors Affecting University Students' Antibiotics Self-Medication [in Chinese]. Science Popularity (Science Education) 2015(06):143.
33. Wang J, Huang C, Li Z, et al. Knowledge and Behaviours of Antibiotic Use for Upper Respiratory Tract Infections among Parents of Young Children in Changsha City [in Chinese]. Chin J Public Health 2017;33(03):415-18.

34. Yao Z, Zhou J, Li Y, et al. Prevalence of Self-Medication with Antibiotics in Kindergarten Children of Guangzhou City [in Chinese]. Chin J Public Health 2013;29(10):1485-87.
35. Zhong M, Yang W, Gao G, et al. Analysis on Antibiotic Knowledge and Uses among the Residents of Guangdong [in Chinese]. Chin J of PHM 2018;34(05):589-91.

Healthcare providers

1. Chang J, Ye D, Lv B, et al. Sale of antibiotics without a prescription at community pharmacies in urban China: a multicentre cross-sectional survey. J Antimicrob Chemother 2017;72:1235-42.
2. Currie J, Lin W, Meng J. Addressing Antibiotic Abuse in China: An Experimental Audit Study. Journal of development economics 2014;110:39-51.
3. Currie J, Lin W, Zhang W. Patient knowledge and antibiotic abuse: Evidence from an audit study in China. Journal of health economics 2011;30:933-49.
4. Guan X, Tian Y, Song J, et al. Effect of physicians' knowledge on antibiotics rational use in China's county hospitals. Soc Sci Med 2019;224:149-55.
5. Lam TP, Lam KF. What are the non-biomedical reasons which make family doctors over-prescribe antibiotics for upper respiratory tract infection in a mixed private/public Asian setting? Journal of clinical pharmacy and therapeutics 2003;28:197-201.
6. Lam TP, Lam KF. Why do family doctors prescribe antibiotics for upper respiratory tract infection? International journal of clinical practice 2003;57:167-9.
7. Liu C, Liu C, Wang D, et al. Determinants of antibiotic prescribing behaviours of primary care physicians in Hubei of China: a structural equation model based on the theory of planned behaviour. Antimicrob Resist Infect Control 2019;8:23.
8. Xue H, Shi Y, Huang L, et al. Diagnostic ability and inappropriate antibiotic prescriptions: a quasi-experimental study of primary care providers in rural China. J Antimicrob Chemother 2019;74:256-63.
9. Zhu E, Fors U, Smedberg A. Understanding how to improve physicians' paradigms for prescribing antibiotics by using a conceptual design framework: a qualitative study. BMC Health Serv Res 2018;18:860.

Healthcare users and providers

1. Reynolds L, McKee M. Factors influencing antibiotic prescribing in China: an exploratory analysis. Health Policy 2009;90:32-6.
2. Zhang Z, Zhan X, Zhou H, et al. Antibiotic prescribing of village doctors for children under 15 years with upper respiratory tract infections in rural China: A qualitative study. Medicine (Baltimore) 2016;95:e3803.

CHAPTER THREE

Public-targeted behavioural change interventions to reduce inappropriate use of medicines and medical procedures: a systematic review

In this chapter, I report on a systematic review of the literature to (1) landscape existing interventions aiming to reduce inappropriate or unnecessary use of medicines or medical services and (2) identify potential barriers, intervention designs, and critical methodological challenges in evaluating such interventions. I conducted the literature review design, methods, and analysis independently. I conducted the review in close collaboration with two LSHTM colleagues. The findings and results have been prepared as a first draft of the manuscript, with comments and feedback on drafts from Prima Alma, Professors James Hargreaves, Elizabeth Fearon, Mishal Khan, John Cairns, and Mark Petticrew. This manuscript has been accepted by *Implementation Science*.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH1704488	**Title**	Ms.
First Name(s)	Leesa		
Surname/Family Name	Lin		
Thesis Title	Development of evidence-based behavioural interventions to reduce inappropriate use of antibiotics beyond clinical settings		
Primary Supervisor	Professor James Hargreaves		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Implementation Science
Please list the paper's authors in the intended authorship order:	Leesa Lin*, Prima Alam, Elizabeth Fearon, James Hargreaves
Stage of publication	**In press**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Leesa Lin conceived of the study, developed the search string for analysis, and developed and piloted a data extraction tool. Leesa Lin and Prima Alam selected, reviewed and coded the studies. Elizabeth Fearon or James Hargreaves served as the third reviewer. Leesa Lin wrote the first draft and revisions of the manuscript, and all authors commented on it and the subsequent drafts. All authors read and approved the final manuscript.

SECTION E

Student Signature	[redacted]
Date	09/09/2019

Supervisor Signature	[redacted]
Date	09/12/2019

Public-targeted behavioural change interventions to reduce inappropriate use of medicines and medical procedures: a systematic review

SYNOPSIS

BACKGROUND An epidemic of health disorders can be triggered by a collective manifestation of inappropriate behaviours, usually systematically fuelled by non-medical factors at the individual and/or societal levels. This study aimed to (1) landscape and assess the evidence on interventions that reduce inappropriate demand of medical resources (medicines or procedures) by triggering behavioural change among healthcare consumers; (2) map out intervention components that have been tried and tested; and (3) identify the "active ingredients" of behaviour change interventions that were proven to be effective in containing epidemics of inappropriate use of medical resources.

METHODS For this systematic review, we searched MEDLINE, EMBASE, the Cochrane Library, and PsychINFO from the databases' inceptions to May 2019, without language restrictions, for behavioural intervention studies. Interventions had to be empirically-evaluated with a control group that demonstrated whether the effects of the campaign extended beyond trends occurring in the absence of the intervention. Outcomes of interest were reductions in inappropriate or non-essential use of medicines and/or medical procedures for clinical conditions that do not require them. Two reviewers independently screened titles, abstracts, and full-text for inclusion and extracted data on study characteristics (e.g. study design), intervention development, implementation strategies, and effect size. Data extraction sheets were based on the checklist from the Cochrane Handbook for Systematic Reviews.

RESULTS Forty-three studies were included. The behaviour change technique taxonomy v1 (BCTTv1), which contains 93 behavioural change techniques (BCTs),

was used to characterize components of the interventions reported in the included studies. Of the 93 BCTs, 15 (16%) were identified within the descriptions of the selected studies targeting healthcare consumers. Interventions consisting of education messages, recommended behaviour alternatives, and a supporting environment that incentivizes or encourages the adoption of a new behaviour were more likely to be successful.

CONCLUSIONS There is continued tendency in research reporting that mainly stresses the effectiveness of interventions rather than the process of identifying and developing key components and the parameters within which they operate. Reporting "negative results" is likely as critical as reporting "active ingredients" and positive findings for implementation science. This review calls for a standardised approach to report intervention studies.

PROSPERO registration number : CRD42019139537

Contributions to the literature

- This review identifies the types, components, and combinations of interventions more likely to successfully initiate and sustain public behaviour change in the context of complexity.
- It can inform practitioners' decisions about designing, implementing, and reporting interventions to reduce inappropriate use/demand of medical interventions while researchers and funders can use this review to determine where research is needed.
- No community-based interventions were found in LMICs; interventions were limited to primary care settings or policy restrictions on the supply side (e.g. ban on over-the-counter purchases).
- There is a need for standardised reporting of intervention development, adaptation, and implementation to maximize generalisability and replicability.

BACKGROUND

Epidemics, which traditionally refer to a widespread occurrence of an infectious disease in a community at a particular time, have in recent years been used to describe large-scale public health issues caused by a shared pattern of human behaviours that impact public health and well-being. An epidemic of health disorders can not only be triggered by organisms that cause communicable diseases, such as bacteria, viruses, fungi or parasites, but also by a collective manifestation of inappropriate behaviours, usually systematically fuelled by non-clinical factors at the individual and/or societal levels. When medicines or medical procedures are used for conditions for which they should not be used, they are deemed as inappropriate use of medical interventions. For example, the World Health Organisation and governments have warned about the recent spike in use of prescription drugs[156] and caesarean sections[157] globally, which has formed an epidemic that has caused avoidable damage to individual health and introduced excessive burdens on health systems.[158,159]

There have been experiments with programmes specifically designed to address factors driving the epidemics of inappropriate use of medical interventions. These countermeasures are often non-clinical behavioural change interventions targeting physicians and pharmacists as a point-of-entry for interventions, and are designed to improve clinical practices and policies that restrict unnecessary dispensing.[160,161] These programmes usually employed educational materials (e.g. guidelines, lectures, workshops),[162,163] auditing and feedback on prescribing practices,[164-167] or computer-aided clinical decision support systems.[168] A 2005 Cochrane review concluded that, for interventions occurring on multiple levels to be effective, local barriers to change – including the role patients play in driving inappropriate demand – must be addressed.[160,169] Current interventions to address the

pressure of inappropriate demands outside the clinical setting range from national mass media campaigns to local interventions targeted at smaller communities,[170] aiming to influence the knowledge, attitudes and practices towards medical use of the general public who have yet to become healthcare consumers: namely patients and caretakers of patients.[170-172] However, recent reviews highlighted that critical knowledge gaps exist in the evidence for engaging healthcare consumers as active decision-makers for appropriate medical use (as opposed to passive receivers of education materials).[173,174] Furthermore, the lack of evidence in the development of and evaluation of the impact of these interventions, especially in low- and middle-income countries (LMICs), complicates replication efforts.[171,172,175]

The Behavioural Change Wheel (BCW)[176] and the Behaviour Change Techniques Taxonomy Volume 1 (BCTTv1),[177] developed by Michie and colleagues, facilitates researchers in organizing the content and components of behavioural interventions into nine intervention functions: *education, persuasion, incentivization, coercion, training, enablement, modelling, environmental restructuring, and restrictions* and assists them in translating specific techniques that were employed in a given intervention into change behaviours. Scientists have supported the use of BCW and BCTTv1 as a reliable and validated methodology that offers a common language for describing intervention components that can be used for the standardization of intervention content analysis and the development of interventions.[178-180]

In this study, we aimed to (1) landscape and critically assess the evidence on non-clinical programmes that reduce inappropriate or unnecessary use of medical interventions (i.e. medicines or medical procedures) by triggering behavioural change among healthcare consumers; (2) map out intervention components that have been tried and tested; and (3) identify the "active ingredients" of behaviour change

intervention programmes that were proven to be effective in containing "epidemics of inappropriate use of medical interventions."

METHODS

Searches: For this systematic review, we searched MEDLINE, EMBASE, the Cochrane Library, and PsychINFO from the databases' inceptions to May 2019, without language restrictions, for behavioural intervention studies. A search strategy was first developed for MEDLINE and adapted to other databases. The full search strategy is detailed in Appendix 1. We searched for behavioural change interventions that aimed to reduce inappropriate or non-essential use of medical services or medicines that were driven by non-clinical factors and targeted health care consumers in the community, including primary care settings. For the purpose of this study, health care consumers included the public, patients, and caregivers (e.g. parents or guardians).

Study inclusion and exclusion criteria: Inclusion and exclusion criteria used for all stages of the screening process are stated in Appendix 2. Studies had to be empirically-tested by either randomized controlled trial (RCT), cluster-RCT (CRT), nonrandomized controlled trial (NCT), or interrupted times series (ITS) where the intervention time was clearly defined and there were at least three data points both before and after the intervention, or quasi-experiments with a control group. To enable assessment of effectiveness in included interventions, this review excludes before/after evaluations of public campaigns or interventions that failed to employ a control group and therefore cannot show whether the effects of the campaign extended beyond trends occurring in the absence of the intervention. Outcomes of interest were <u>reductions in inappropriate or non-essential use of medicines and/or medical procedures for clinical conditions that do not require them.</u> Four major types of behaviours were identified, namely inappropriate antibiotic

consumption (e.g. for viral infections or self-limiting conditions), elective caesarean section, demand for brand-name drugs that are available as generics, and non-medical use of prescription drugs, defined as "use without a prescription or use for reasons other than what the medication is intended for".[171,181,182] Studies that focused only on change of knowledge or attitudes, and did not report actual behavioural data were excluded. Studies mainly targeting clinicians, other healthcare staff, hospitals, inpatients, emergency care, or patients with mental health conditions were excluded. To create a distinction between interventions directed at health care consumers rather than providers, studies that aimed to modify clinical practices (e.g. prescribing) were excluded. Also, to differentiate behaviour change interventions from therapies/treatments addressing mental health conditions such as addiction or depression, we excluded interventions for substance abuse, where inappropriate use was an outcome of a clinical condition, not a cause.

Data extraction strategy: All titles retrieved from the searches were imported into Endnote referencing software. Duplicates were removed. Titles and abstracts were independently screened for inclusion by two reviewers (L.L and P.A.) and removed if deemed irrelevant. Both authors independently screened the full-text (n=347) of the remaining studies to assess eligibility. Substantial agreement was found at all three stages (>90%). Disagreements were resolved through discussion among reviewers to achieve consensus; any further discrepancies about study inclusion were resolved through discussion with a third reviewer (E.F. or J.H). We also manually searched the bibliographies of all the included studies and reference lists of relevant systematic reviews to identify additional citations.

We extracted the data on study characteristics: the country where the study was conducted, type of inappropriate use, target population, study design (e.g. RCT, controlled pre- and post-study [CPP]), data collection methods (e.g. survey,

interview, medical records) and, when focused on a population study, sampling methodology (e.g. cluster, convenience), primary or main outcome measure, and conclusions reported. We further examined reporting on intervention development/adaption, design, and implementation strategies. Additionally, we extracted underlying theoretical domains, effect size, and risk of bias by two independent review authors, who determined the domains within the Behavioural Change Wheel (BCW) and identified the "active ingredients" of the interventions according to BCTTv1. Data extraction sheets were based on the checklist from the Cochrane Handbook for Systematic Reviews.[183] The forms were modified after piloting on a sample of studies. When coding, we adopted the coding assumptions reported by Presseau et al[180] that BCTs worked through targeting the behaviour of health care consumers, or both the behaviour of health care consumers and providers. We also assumed policy interventions and national campaigns were driven by governments and therefore coded governments as implementers for respective interventions. After the data extraction phase, we identified critical evidence gaps in evaluation data and processes of intervention development and implementation. We therefore conducted another round of targeted, investigative searches, involving citation and publication searches on first, last and corresponding authors of selected interventions, seeking formative, process, and impact evaluation data.

Study quality assessment: We conducted and reported the review in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA). Risk of bias was assessed by two reviewers using the Effective Public Health Practice Project's (EPHPP) Quality Assessment Tool for Quantitative Studies,[184] which includes eight components (21 items): selection bias, study design, confounders, blinding, data collection methods, withdrawals or dropouts, intervention , and integrity. A rating of weak, moderate or strong was given to each

of the first six components and these scores contributed to a global rating for the study. Qualitative data was assessed by the Critical Appraisal Skills Programme (CASP) checklist.

Data synthesis on active ingredients: Using BCW domains and BCT taxonomies, we analysed descriptions of all interventions and identified the commonly targeted aspects by looking at the frequency with which BCW domain and BCT of the interventions were incorporated in the studies. We also explored the nature and pattern of the use of these active ingredients across the different studies, , and the associated magnitude of effect size. We descriptively reported the active ingredients and primary outcomes' effect sizes at the study-level, counting the number of times a BCW domain and a BCT had been identified across studies and in different types of use behaviours and presented a description of features of included interventions.

RESULTS

Review statistics: Our systematic search of the literature yielded 4045 results through database searching and an additional 238 were identified through bibliography searches. After de-duplication and title and abstract screening, 347 references were assessed in full text. A flow diagram of the study selection process is shown in Figure 1. Forty-three studies (representing 43 interventions, see Appendix 3) – conducted between 1994 and May 2019 and meeting inclusion criteria - were included in the systematic review. Twenty-five studied interventions focused on the reduction of antibiotic use – eight on elective caesarean section, four on the conversion from brand name drugs to generic equivalents, and six on nonmedical use of prescription drugs. Table 1 provides an overview of the included intervention studies for full-text extraction including intervention aims and components.

Study characteristics: All included studies were published in English. 24 in North America (excluding Mexico; USA: n=21, Canada: n=3), four in Latin America (Chile, Colombia, Venezuela, Brazil, and Mexico), four in the Middle East (Iran), eight in Europe (France, UK, Italy, Spain, and Moldova), three in East Asia and Pacific (Australia and Singapore), and none from Sub-Saharan Africa, South Asia, or the Caribbean.

The imbalance between high-income countries (HICs) and low-and-middle-income countries (LMICs) is apparent when characterising types of inappropriate use. Multifaceted interventions are scarce and limited to HICs while interventions in LMICs were limited to primary care settings or policy restrictions (on over-the-counter purchases) with zero community-based programs identified. No studies from LMICs focused on demands for brand-name drugs or non-medical use of prescription drugs.

Study design: The included studies consisted of 18 RCTs and five NCTs, eight ITS, and 12 quasi-experimental studies. These studies varied in their quality, methodological design, and implementation. Twenty-four studies reported longitudinal data; the rest employed cross-sectional study designs. All were outcome evaluation studies. In terms of data collection methods for evaluation, 23 studies employed surveys and 30 utilised medical record data – these were not mutually exclusive. Four studies reported cost data. One study employed interviews as part of the intervention procedure, but not for evaluation purposes.[185] No qualitative data were reported in the initial included studies; we therefore conducted a targeted, investigative search on the selected interventions, but only located minimal formative data on some of the studies.[186-190] One UK-based project that aimed to improve the decision-making around mode of delivery among pregnant women published comprehensive implementation research data from pilot results[191] and

study protocol[188] to outcome and economic evaluation.[186,187,192-194] Table 2 presents a summary of the key characteristics of each study measuring behavioural outcomes and reported formative and relevant evaluation data of the included interventions.

Study quality assessment: Study quality varied by domain assessed based on the primary behavioural outcomes (Appendix 4). There were 11 studies of overall strong quality, 12 of overall moderate quality, and 20 of overall low quality. In order to provide an overview of the entire literature, no studies were excluded based on their methodological quality. The majority of behaviour outcomes were derived from medical records, leaving minimal room for reporting errors with the exception that some only relied on self-reported data for evaluation.

Active ingredients of the behaviour change interventions: All of the interventions utilised multiple behaviour change techniques (BCTs) with a primary aim to improve health care consumers' behaviour. Table 3 presents the features of all the included interventions; the frequency distributions of BCTs employed are presented in Figure 2. Of all 93 BCTs in the taxonomy, 19 (19/93, 22.9%) were used as active ingredients in the included interventions: four BCTs were used exclusively for interventions targeting health care consumers *(BCTs 3.3, 6.1, 9.2, 12.2)*; another four were used exclusively for multifaceted interventions that also targeted providers *(BCTs 1.3, 2.2, 3.2, 14.2)*, with 11 BCTs used for both (*BCTs 3.1, 4.1, 4.2, 5.1, 5.2, 8.2, 9.1, 10.1, 10.2, 12.1, 12.5;* see Tables 4 and 5 for details). When compared with the principles in the Behavioural Change Wheel, 39 interventions employed education as an active ingredient followed by enablement (n=12), environmental restructuring (n=8), and restriction (n=4). Of the 43 included studies, 22 were interventions delivered only at the community-level, 12 in primary care settings, six in both community and primary care settings, and three in schools. 19 interventions were delivered on an individual basis, which tended to be shorter in duration,

ranging from one to multiple short sessions. The majority of studies focused on evaluation design and outcomes and only provided high-level descriptions of the intervention, with or without details on the development or implementation processes. 20 studies provided clear descriptions on the intervention adaption/development process, all on implementation strategies (e.g. channels and timing of dissemination), and, to a certain level, 15 on intervention dose (intensity)[195-197] and nine on designs (e.g. colour and format).[196-199] Some studies provided links to intervention designs, but most of these links had expired. Only eight interventions explicitly reported having adopted a theory or model of behavioural change, which included: Social Marketing,[104,197,200] Social Cognitive Theory,[196] Precede/Proceed Model,[201] Social Development Model,[202,203] and the Health Belief Model.[204] However, little was reported on how these underlying theories were used in the development and evaluation of the interventions.

Interventions targeting health care consumers: Table 4 reports the individual BCTs identified within the descriptions as active ingredients of the selected interventions targeting health care consumers. Of the 93 BCTs, the most frequently used active ingredients in the selected interventions targeting health care consumers were: *BCTs: 4.1-Instruction on how to perform the behaviour (n=34), 4.2 Information about Antecedents (n=22)*, *5.1 Information about health consequences (n=22),* followed by *12.5 Adding objects to the environment (n=12), 8.2 Behaviour substitution (n=11), and 12.1 Restructuring the physical environment (n=8).* Most studies employed education interventions aiming to improve public knowledge (including awareness or correcting misconceptions). Mass media campaigns were widely used to reduce antibiotic misuse,[105,195-197,200,205-209] and demand for brand-name drugs,[210] all in HIC. The effectiveness of such behavioural change interventions was mixed. Decision aids to assist pregnant women making decisions

about mode of delivery were tested in three different trials in Australia, UK and US; all reported to be ineffective.[193,211,212] Taylor et al,[213] Lee et al,[214] and Vallès et al[185] trialed patient-based education interventions in primary care settings to reduce antibiotic use or to substitute generic for brand-name drugs; only Vallès et al's[185] intervention found a positive impact on behaviour change. Mainous et al. and McNulty et al. assessed community-wide education interventions in U.S. and U.K. on their effectiveness in improving public antibiotic use and found the provision of educational messages itself was insufficient to overcome the influence of past attitudes and behaviours.[198,207] Formal and informal social support networks can be leveraged to influence individuals' behaviours through improving doctor-patient communication[103-105,199,200,213] or by actively engaging family members in the process.[202,203,215] Four interventions aimed to encourage disposal of leftover opioids among postoperative patients by employing a combination BCWs of education, enablement, and environment restructuring (BCTs: 4.1, 4.2, 5.1, 5.2, 8.2, 12.1, 12.5), which reported positive impact.[216-219] Two longitudinal RCTs on school-based universal preventive interventions in the U.S. that aimed to strengthen families and build life skills were introduced to middle schoolers[202,203] and reported a lasting impact on preventing non-medical use of prescription drugs into adulthood. Structural environmental conditions regarding access to healthcare services and medicines, and promotive and restrictive policies – or the lack thereof – can be pathways to shaping individual behaviours. Two trend analyses assessing the effectiveness of French public education campaigns[205,209] reported a significant reduction in antibiotic consumption rates; however, trials on community-wide public campaigns with academic detailing for practitioners did not demonstrate comparable levels of improvement in public antibiotic use. Belongia et al. and Fiskelstein et al. found little or no evidence – attributable to multi-year interventions in Wisconsin

and Massachusetts – on reductions in antibiotic prescribing in the intervention areas, despite improved public knowledge.[103,104,195] Gonzales et al. found that the state-wide "Get Smart Colorado" campaign did not improve prescription rates, but might be associated with a reduction in antibiotic use in the community through decreases in office visit rates among children.[105,197] Four studies evaluated the effectiveness of the restrictions on OCT purchases on antibiotic consumption in five Latin American countries with mixed results.[220-223]

Interventions also targeting health care providers: Table 5 reports the individual BCTs identified within the descriptions as active ingredients of the selected interventions targeting health care providers. The most frequently used BCTs targeting health care providers were similar with those targeting consumers, with small differences in the ranking: *BCTs: 4.1 Instruction on how to perform the behaviour (n=15), 4.2 Information about Antecedents (n=13)*, *12.5 Adding objects to the environment (n=10),* followed by *5.1 Information about health consequences (n=9), 8.2 Behaviour substitution (n=9), and 12.1 Restructuring the physical environment (n=4).* We noticed that, except for programs aiming to contain inappropriate use of antibiotics, other interventions had limited engagement between consumers and providers.

DISCUSSION

Summary of findings

Using the Behavioural Change Wheel (BCW) domains to identify the theoretical concepts underlying interventions and the behaviour change technique taxonomy v1 (BCTTv1) to identify the active ingredients of interventions, we found that the domain of education was the most commonly targeted by a majority of interventions with primary focus on the provision of information on *BCTs 4.1 how to perform the*

behaviour and *4.2 about antecedents and 5.1 the associated health consequences.* A plethora of evidence supports the view that human behaviours should be understood in their social ecological context, as products of intertwined influences at the personal, communal, societal, and structural levels.[224-226] Studies show that improving knowledge and awareness does not equate with appropriate behaviour change, as lack of information is often not the only barrier to changing behaviour.[105,207,227-229] The effects of education interventions have been mixed – most likely due to heterogeneity in context, population served, and intervention design and measures. Cabral et al. examined how communication affects prescription decisions for acute illnesses and demonstrated a clear miscommunication with cross-purposes between health care consumers and providers, as patients and/or caregivers focused on their concerns and information needs, which clinicians interpreted as an expectation for antibiotics.[230] This review supports the use of multifaceted (complex) interventions that incorporate BCTs related to provision of information (BCTs 4.1, 4.2, or 5.1) and, as an alternative to antibiotics, prescription pads with clear explanations on symptoms and appropriate treatment options (BCT 8.2), as education alone is not sufficient to be effective. Interventions consisting of health education messages (e.g. BCTs 4.1, 4.2, 5.1), recommended behaviour alternatives (BCT 8.2), and a supporting environment that incentivizes or encourages the adoption of a new behaviour (e.g. BCTs 10.1, 10.2, 12.1, 12.5) are more likely to be successful. Other types of utilised behaviour change techniques often aimed to encourage alternative behaviours and improve the physical environments via regulations or mass media.

The continuing tendency in research reporting has been to stress the effectiveness of interventions rather than the process of identifying and developing key components and the parameters within which they operate. There is a lack of

detail on how the intervention components were selected, designed and the process of implementing them, with limited descriptions provided on the "contexts" and "mechanisms" that determine the effectiveness of interventions. Few studies provided sufficient details on intervention development, dose/intensity, and design; some provided links to project materials that had expired.[195-197,200] The majority of the selected interventions did not describe the pilot or process data for implementation, nor did they discuss the dissemination of findings and pathways to impact. Even after identifying active ingredients of interventions using BCTTv1, without a complete "recipe" one cannot recreate successes in other contexts. Just like there are agreed-upon elements that constitute a rigorous and comprehensive reporting of evaluation studies, publications on behavioural change interventions should systematically cover a standardised list of intervention elements from the development, adaption and refinement, feasibility and pilot-testing, implementation, evaluation, and reporting of BCTs. The CONSORT-SPI team[231] have developed guidance and checklists for the reporting of BCT trials; however, the required details on the reporting are still primarily focused on evaluation study designs (e.g. process of randomization) rather than BCTs development and implementation. From implementation research perspective and following the Medical Research Council (MRC) guidance on developing and evaluating complex interventions, reporting of BCTs development and implementation should include: descriptions on the context, target behaviour determinants, theories and rationale (theory of change), intervention design features, adaption/development process, implementation strategy (e.g. implementor, dose/intensity), modifications made between the feasibility and effective assessment phases, and evaluation outcomes. The lack of detailed reporting among included intervention studies on evidence-based development and implementation processes undermines the generalisability of study findings, makes

cross-intervention comparisons difficult, and complicates future adaption and replication efforts.

This systematic literature review is the first on the effectiveness of public-targeted behavioural change interventions to reduce inappropriate use of medical interventions. It identified a serious lack of formative data, which means that interventions to change public use of medical interventions are often designed on the basis of "best guesses" of what needs to change, without an evidence base or explicit rationale for the selection of a specific intervention strategy. There is an urgent need to adopt a multidisciplinary, systematic approach to developing evidence-based behavioural change interventions to reduce inappropriate medical use and to develop an operational mechanism for knowledge translation and scale-up within and across different countries. We found limited evidence[202,205] on evaluating the impact of previous or ongoing education interventions on inappropriate use in terms of long-term impact, scalability, and replicability. The root causes of why certain interventions were unsuccessful are not systematically explored or reported, yet reporting "negative results" is likely as critical as reporting "active ingredients" and positive findings for the development and sustainability of implementation science.

Relation to other studies

Like most stewardship programmes, quaternary prevention - a relatively new category of medical prevention first raised in 1986 by Dr. Marc Jamoulle, a family physician, to addressing concerns around the protection of people and patients from being harmed by over-diagnosis or overtreatment - tends to focus mostly on health care providers while placing less attention on consumers.[160,232-234] The definition of quaternary prevention was later expanded by Brodersen et al. in 2014 to include patients and medical interventions as an 'action taken to protect individuals (persons/patients) from medical interventions that are likely to cause more harm than

good.[235,236] The expanded definition recognises the contemporary reality in medicine in which people may suffer harm from medical interventions throughout their entire lifetime - from conception to adulthood, in times of good health, as well as when experiencing self-limited disease, chronic conditions, or terminal disease. Therefore, quaternary prevention should include preventing all types of harm associated with medical interventions.[235,236] From this perspective, quaternary prevention is aligned with the aims of the behavioural change interventions and techniques identified in our review and should be considered alongside the other four classical levels of preventive activities, i.e. primordial (e.g. laws that restrict over-the-counter purchases of antibiotics), primary (e.g. prescription drugs disposal programs), and secondary and tertiary preventions (e.g. interventions that reduce fear of childbirth or convert demand of brand-name drugs to generic drugs).

Use of medicine or medical procedures is a highly complex set of behaviours involving multiple actions, including the self-diagnostic process, assessing benefit/risk, decision-making around healthcare seeking and treatment choice, and review of treatment – each performed at different time points across the care continuum.[19,20] It involves interactions with various stakeholders (i.e. family members and providers) and is often shaped more by individual and contextual factors than by a clinical diagnosis.[19,20] Therefore, developers and implementers of behavioural change interventions should be clear as to whose and which behaviours are being targeted for change and how – namely, who needs to do what differently, how, to whom, where, when, and for how long. A set of precisely specified behaviours would allow for easier measurement and therefore would offer a baseline and metric for evaluating the success of an intervention.

In order to develop effective behavioural change interventions, we first need to explain why people behave in certain ways, yet a more in-depth look at people's

lifeworld is lacking from every reviewed article. As the dual processing theory (DPT) posits, human behaviour is guided by two types of processing mechanisms: the implicit, intuitive System 1 and the explicit, rational System 2.[237] Behavioural economists elaborate that, due to limited self-control, rationality and social preferences, actual decisions are less rational and stable than traditional normative theory suggests.[237] They are usually made with a range of biases resulting from the way people think and feel, rather than with rationality or full information. However, most of the included interventions - appealing to System 2 processing - attempted to influence behaviours via improved knowledge and attitudes; disappointingly, many trials indicated that this did not automatically lead to preferred behaviours.[103,104,195,213] To complicate things further, Zinn argues that between rationality and irrationality, there is a third, "in-between" dimension that includes trust, intuition and emotion, which is an important aspect of decision-making when people deal with risk and uncertainty, especially in anticipation of the possible undesired outcomes of decisions.[238] This may explain why three RCTs on decision aids (System 1) to address individual emotions (System 2) had no real impact on choice of vaginal birth.[193,211] On the other hand, in addition to education programs, financial incentives (changes in co-payment), free medicine, advertisements (print media) and health policies have been experimented with as behavioural change interventions to influence healthcare consumers' choice of medicine – in particular, to promote uptake of generic medicines - though they have demonstrated inconsistent results.[239,240]

The most promising measure was an intervention delivered face-to-face, where consumers were told that they had the option of switching back to brand-name drugs anytime;[185,241,242] hence, an intervention that leverages human behavioural mechanisms may be more effective and cost-effective in optimizing decision-making

than repeated, expensive education campaigns. In response to the recent opioid epidemic across the globe, promising prevention programmes aimed not only to improve the knowledge and awareness of the risk of nonmedical use of prescription drugs among at risk individuals, but also to empower healthcare consumers by providing skills or tools that enable them to take action prior to the occurrence of misuse and/or before the development of poor habits.[202,203,216-219] These interventions further improved the socio-ecological surroundings of the target audience by involving family members and restructuring their social or physical environments.[202,203,216-219]

Our review showed only 19% of BCTs have been utilized by included interventions (i.e. 81% of BCTs unexplored), with great variation between different types of misuse - most were limited to education. Future studies should explore other BCTs. A wide range of disciplines engaging in social and behavioural sciences, such as psychology, sociology, anthropology, communication and marketing, can provide theories, models and methods for a more comprehensive and coherent approach to understanding or even modifying contextual, organizational and interpersonal determinants of behaviour. In terms of sustainability of the interventions themselves, other than a few longitudinal studies,[202,203] we do not know how long the reported effect of behavioural change will sustain. Few studies incorporated economic evaluations and therefore, it was not possible to determine the returns on investment (ROI) for these included interventions. Future intervention studies should consider the aspects of RE-AIM *(Reach Effectiveness Adoption Implementation Maintenance)* framework or follow the MRC Guidelines on Developing and Evaluating Complex Interventions during the planning stage to enhance the impact of interventions and the reporting of them.

Development of a behavioural change intervention has to start with a realist, comprehensive understanding of the complex environment that shapes individual and collective behaviours. The aetiology of inappropriate use of medical interventions should be studied and addressed within the context of its biological, psychosocial, behavioural and environmental factors and the interactions between them. In early 2000, Sallies et al developed a behavioural epidemiology framework, which specified a systematic sequence of studies on health-related behaviours leading to evidence-based interventions directed at populations in the following five phases: 1) establish links between behaviours and health; 2) develop measures of the behaviour; 3) identify influences on the behaviour; 4) evaluate interventions to change the behaviour; and 5) translate research into practice.[226,243,244] In 2011, Michie and colleagues mapped out various pathways to influencing behavioural change and recommended that interventions seeking to change behaviour should be designed on the basis of a thorough 'behavioural diagnosis' of why behaviours are the way they are and what needs to change in order to bring about the desired behaviour.[243] Conducting such diagnosis should be facilitated by the use of behavioural theory. Not until recent years did researchers systematically report efforts in the identification of the root causes of operational barriers and facilitators in designing, implementing, and evaluating interventions. For instance, in 2018 and 2019, Langdridge et al have attempted to decipher the intervention elements and visual imagery used in public antimicrobial stewardship.[178,245]

Consistent with the findings from recent reviews by Cochrane and the Department of Health and Social Care and Public Health in England,[160,246,247] our review found that few interventions employed behaviour change theories or techniques. Behavioural determinants and social influences are often not given sufficient consideration in the design and evaluations of interventions. To inform the

design of effective, context-specific behaviour change interventions, one must first define the problem in both behavioural terms and in its current context and adopt a theory-driven, systematic approach to intervention design. This points to another critical knowledge gap identified by this review in implementation science, namely early studies that take place prior to the implementation of behavioural change interventions. Following the Medical Research Council (MRC) guidelines on developing and evaluating complex interventions,[81] as presented in Table 1, we find there is little reporting on the feasibility, pilot or process data that generates the needed contextual information and evidence base for acceptance, adaption and uptake. Limited detail has been made available on the development of the included interventions regarding how key decisions were made, including feasibility and compliance. Future research on pilot and/or feasibility studies that aim to strengthen large-scale behavioural change intervention design can span the continuum of implementation science research from idea generation to intervention development, implementation, evaluation, and scale-up.

LIMITATIONS

The diversity in the design and outcome measures of the included interventions prevent us from performing a meta-analysis. We cannot make a conclusion that certain types of behavioural change intervention might be more effective than any other type of design due to the limitations of the literature relating to the lack of evidence-based development process and evaluation design. Behavioural data that were gathered via survey instruments were by nature self-reported from health care consumers who may have been reluctant to report practices that could be considered inappropriate or may have been subject to recall bias. Often there were more than one BCT identified for each included intervention, yet retrospective coding and the study design did not allow us to pinpoint which component was more effective.

Future work should focus on addressing the limitations and uncertainties surrounding existing behavioural change interventions.

CONCLUSION

Systematically assessing the evidence across behavioural change interventions allows for the identification of the "active ingredients" of effective interventions that improve healthcare consumers' use of medical interventions, as well as the identification of those with ineffective or uncertain outcomes. Although opportunities for behavioural change interventions are becoming more commonly recognised, multifaceted (complex) interventions are still new, scarce, limited to high-income countries, and, as is evident from our findings, highly heterogeneous. Public-targeted behavioural change interventions in low-and-middle-income countries (LMICs) were exclusively limited to primary care settings. Interventions that consist of health education messages, recommended behaviour alternatives, and a supporting environment that incentivizes or encourages the adoption of a new behaviour are more likely to be successful. Future research should also seek to unpack the distinctions between various audience segments, the influence of the social ecological context, and the utility of the unexplored 81% of behavioural change techniques (BCTs). It is critical to adhere to a rigorous framework that guides the development, implementation, evaluation, and reporting of evidence-based interventions, so that generated evidence can be documented, disseminated, compared and utilized for further research. The lack of reporting on evidence-based development and implementation processes makes cross-intervention comparisons and replication difficult. Our review further identified a need for standardised reporting of intervention development, adaptation, and implementation to maximize generalisability and replicability.

List of abbreviations

ABR	Antibiotic Resistance
AMR	Antimicrobial Resistance
BCT	Behaviour Change Technique
BCTT	Behaviour Change Technique Taxonomy
BCW	Behavioural Change Wheel
CPP	Controlled pre- and post-study
CRT	Cluster Randomized Control Trial
CS	Elective Caesarean section
DPT	Dual Processing Theory
EPHPP	Effective Public Health Practice Project's Quality Assessment Tool for Quantitative Studies
HIC	High Income Country
ITS	Interrupted Time Series
LMIC	Low-and-Middle-Income Country
MoD	Mode of delivery;
MRC	Medical Research Council
NA	Not applicable
NR	Not reported
NCT	Nonrandomized controlled trial
OTC	Over-the-counter purchases
PDM	Prescription drug misuse
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Control Trial
ROI	Returns on investment
VD	Normal vaginal delivery
WHO	World Health Organization

DECLARATIONS

Authors' contributions

LL conceived of the study. LL developed the search string for analysis and contributed to piloting abstraction tools. LL and PA selected, reviewed and coded the studies. EF or JH served as the third reviewer. LL wrote the first draft and revisions of the manuscript, and all authors commented on it and the subsequent drafts. All authors read and approved the final manuscript.

Competing interests

There are no conflicts of interest.

Funding

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Ethics approval and consent to participate

Not applicable.

Figure 1. Flow diagram of systematic review search

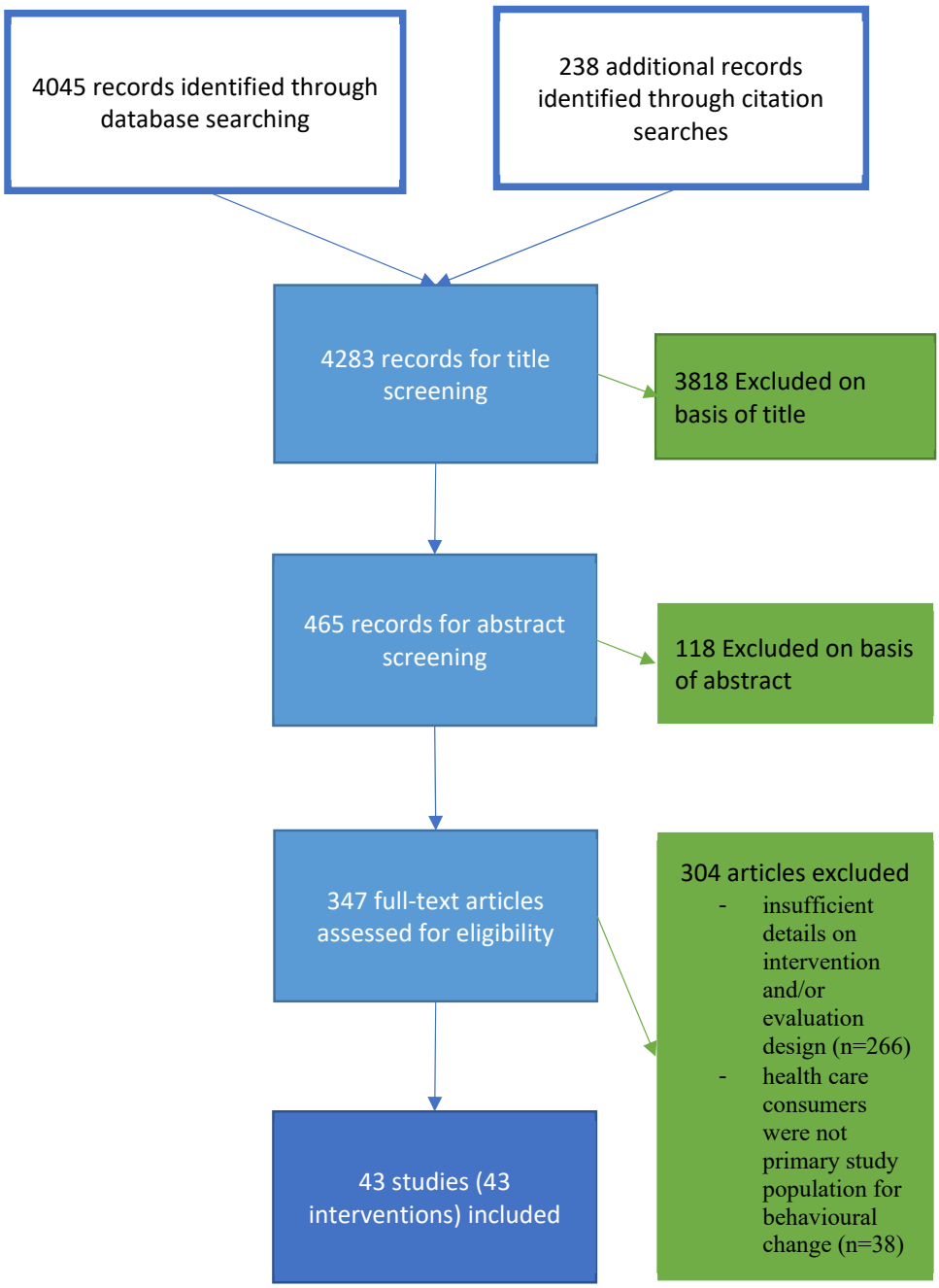
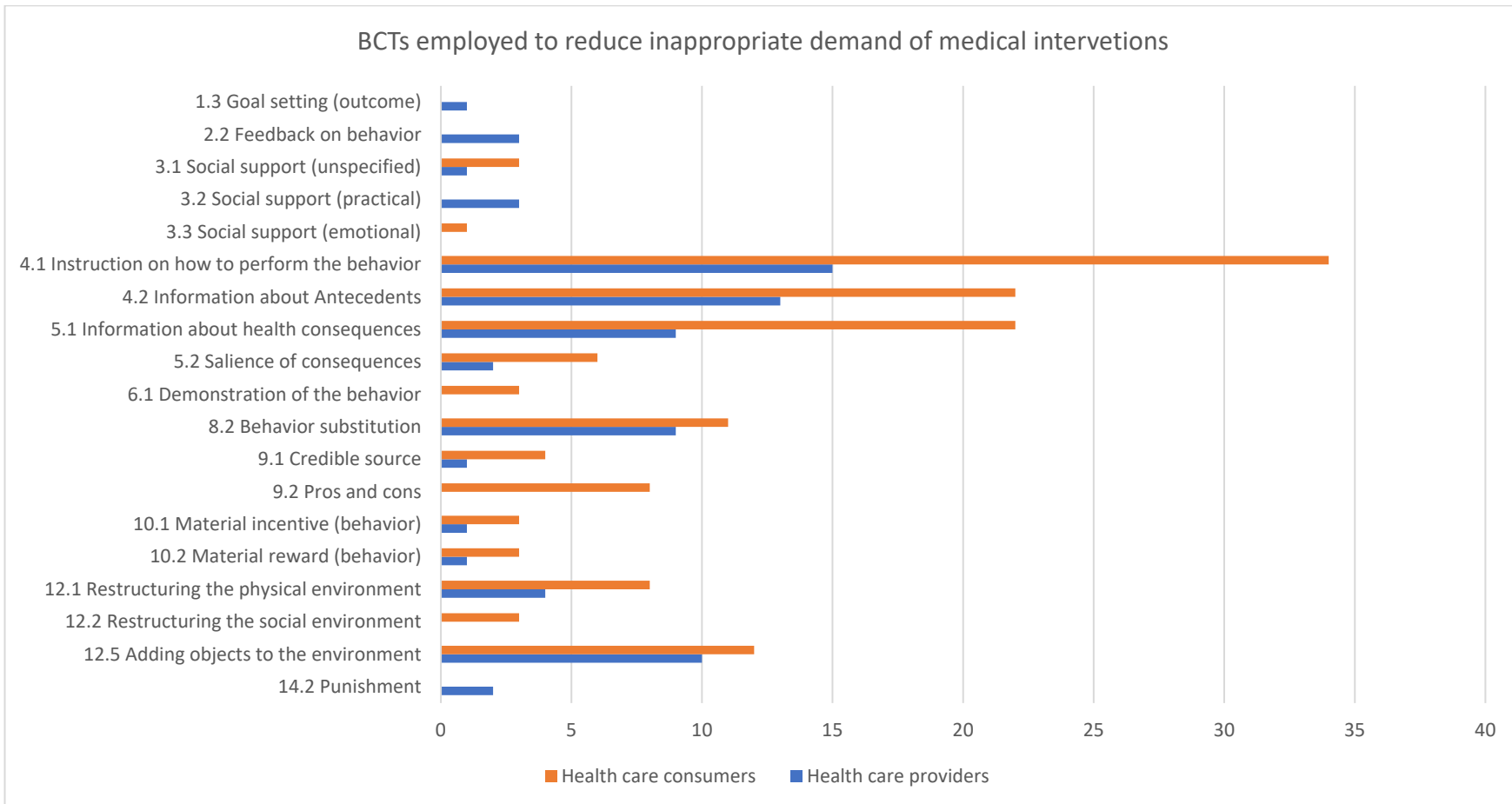
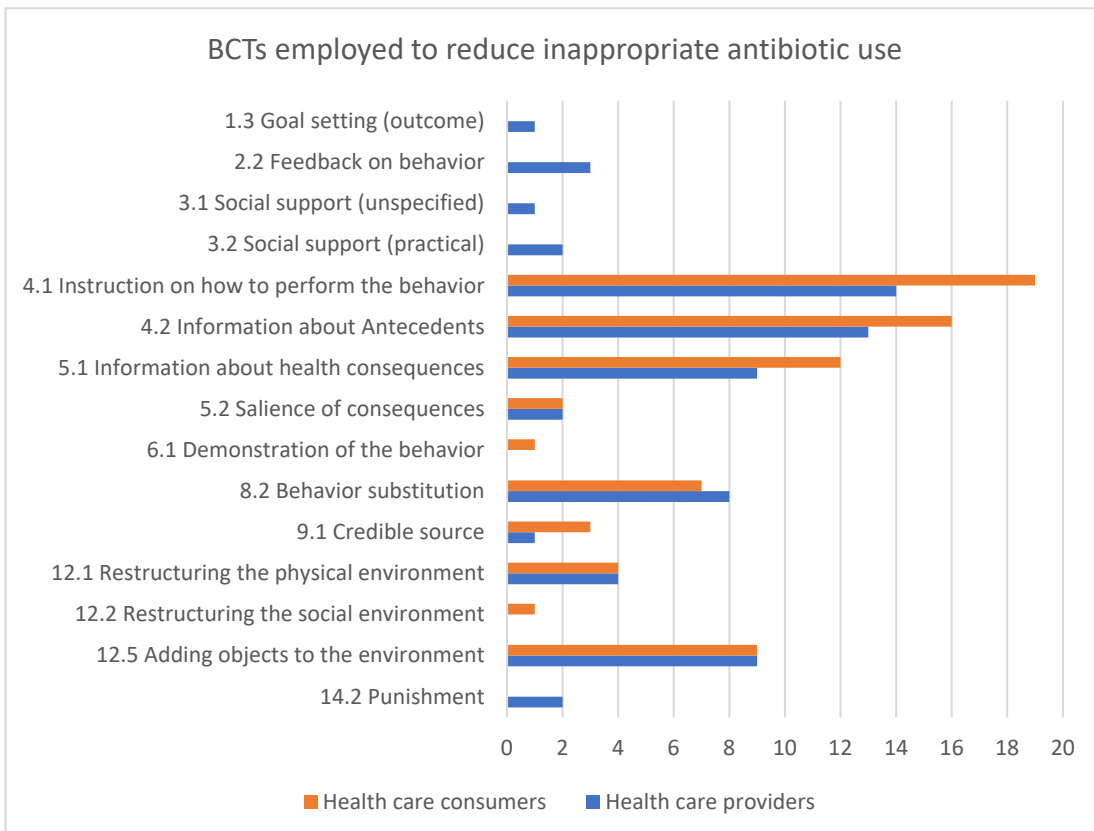
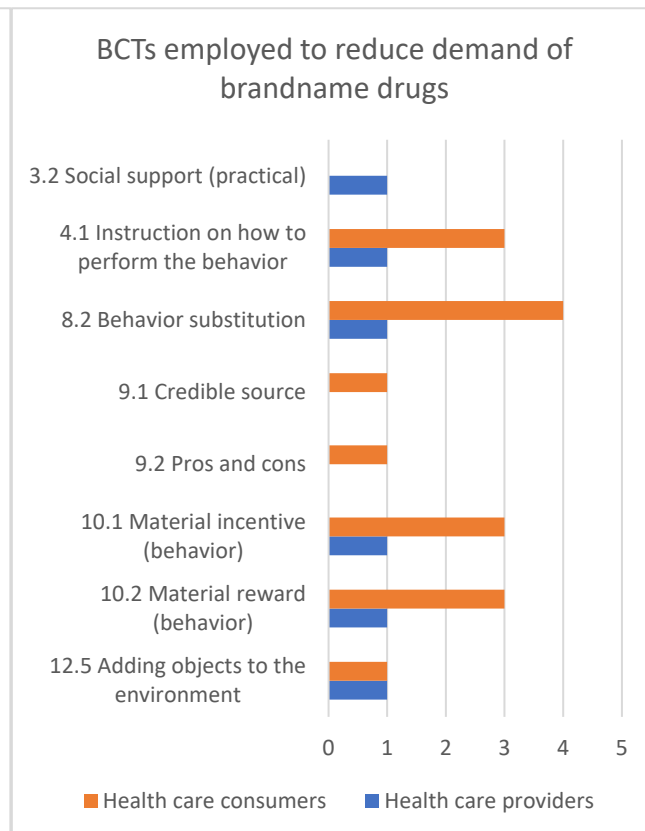
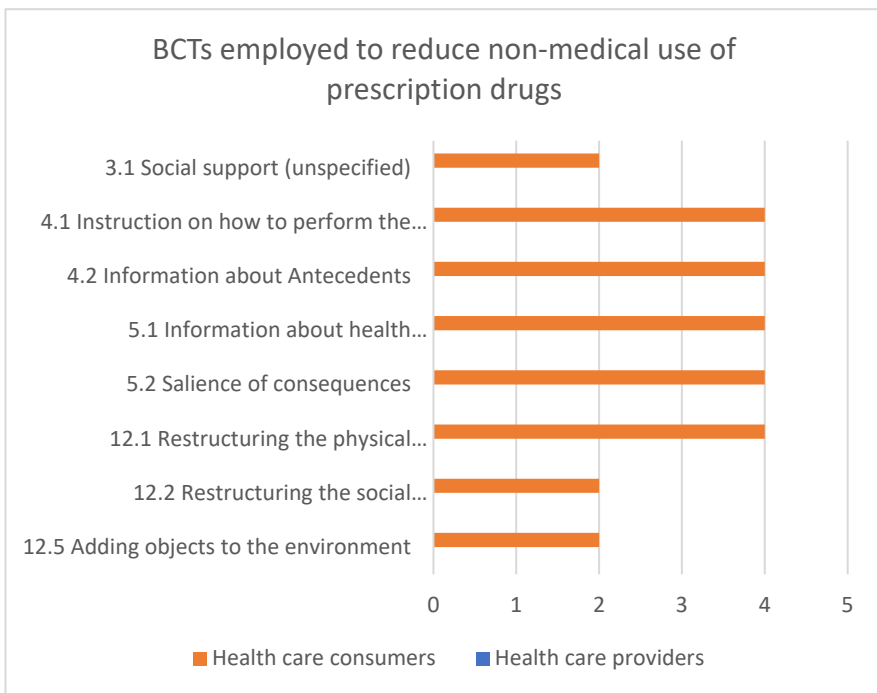


Figure 2. Frequency distribution of Behaviour Change Techniques (BCTs) coded for 43 interventions









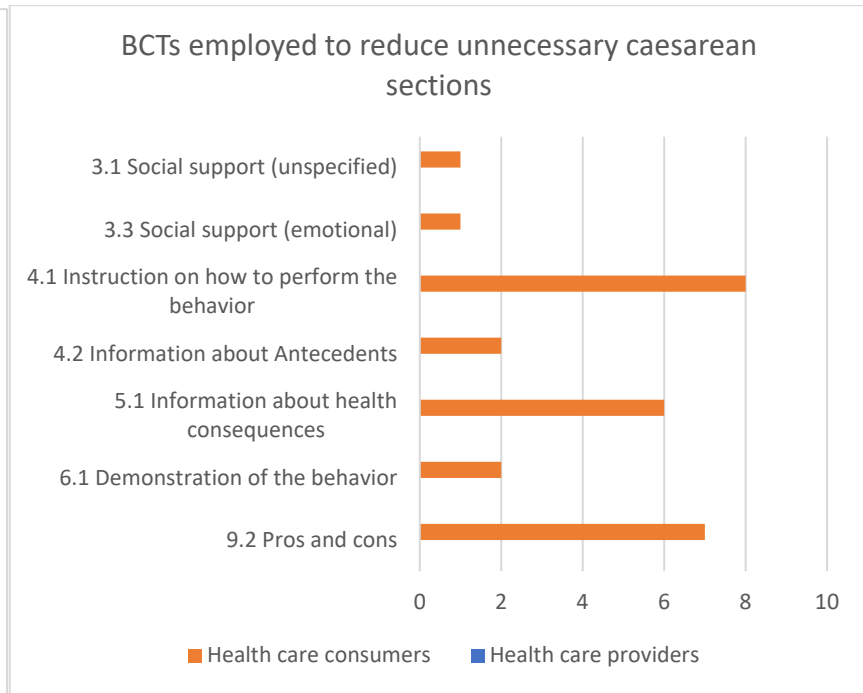


Table 1. An overview of the included studies: intervention aims, components and reporting

Context					Intervention Elements										Implementation									
First Author, Year	Target Illness/condition	**Country**	**Last month of data collected**	**Setting**	**Target Drivers/ Factors**	**Name**	**Slogan**	**Target audience**	**Healthcare providers**	**Healthcare consumers**	**BCT-provider**	**BCT-consumer**	**Behavioral Change Wheel**	**Theory-based**	**Intervention Adaption/ Development**	**Implementation strategy**	**Implementer(s)**	**Unit of intervention**	**Dose/intensity**	**Design**	**Costs**	**Duration**	**Data sources**	**Formative or process evaluation studies**
Inappropriate use of antibiotics																								
Belongia, 2001	RTIs	USA	June 1998	Community & Primary care setting	Knowledge (including awareness), cultural, and doctor-patient relationship	-	None	Community and healthcare providers	Physician education (parent education pamphlets, parent information sheets, a sample letter, "prescription pad", CDC fact sheets	Public education materials: programs, pamphlets and posters, presentations and "Cold kits"	4.1 4.2 5.1 8.2 12.5	4.1 4.2 5.1 8.2 12.5	Education	-	Yes	Yes	Yes	Community	Partially reported	NR	NR	4 months	Medical records + self reports, lab testing	-
Belongia, 2005	not specified	USA	December 2003	Community	Knowledge (including awareness)	Wisconsin Antibiotic Resistance Network	"There's no excuse for overuse!" and "Get smart about antibiotics!"	Community and healthcare providers	Physician education (mailings, susceptibility reports, practice guidelines, satellite conferences, and presentations)	Mass media campaign (television, radio, newspapers, press conference; paid ad); Patient education materials	4.1 4.2 5.1 12.5	4.1 4.2 5.1 12.5	Education	-	Yes	Yes	Yes	Community	Yes	Access expired	NR	5 years	Medical records	-
Bernier, 2014	Not specified	France	December2010	Community	Knowledge (including awareness)	-	"Antibiotics Are Not Automatic!" and "Antibiotics, Used Unnecessarily, Lose Their Potency!"	Community	guidelines, seminars, academic detailing, letters	Pamphlets and posters, print media, radio, television, website	4.1 4.2 5.1 12.5	4.1 4.2 5.1 12.5	Education	-	NR	NR	Yes	Community	NR	NR	NR	6 months (ongoing)	Medical records	-
Cebotarenco, 2008	RTIs	Moldova	March 2004	School setting	Knowledge (including awareness) peer	-	None	Community - Students and guardians	-	Peer-education, parents' meetings, booklet, vignette video, newsletter, poster and poster contest	-	4.1 4.2 6.1 12.2	Education	Social Cognitive Theory	Yes	Yes	Yes	Community	Yes	Yes	NR	1 year	Self reports	-

Finkelstein, 2001	RTIs	USA	December, 1998	Community & Primary care setting	Knowledge (including awareness), doctor-patient relationship, peer leader	-	-	Community and healthcare providers	Guideline dissemination, small-group education, educational materials, and prescribing feedback.	Educational materials for parents by mail and in primary care practices, pharmacies, and childcare settings	2.2 3.2 4.1 4.2 5.1 8.2 9.1	4.1 4.2 5.1 8.2 9.1	Education	-	Yes	Yes	Yes	Community	NR	NR	NR	1 year	Medical records	189
Finkelstein, 2008	RTIs	USA	August 2003	Community	Knowledge (including awareness), doctor-patient relationship	Reducing Antibiotics for Children in Massachusetts (REACH Mass)	None	Community and healthcare providers	Guideline dissemination, small-group education, educational materials, "prescription pad", and prescribing feedback.	Educational materials for parents by mail and in primary care practices, pharmacies, and childcare settings	2.2 3.2 4.1 4.2 5.1 8.2	4.1 4.2 5.1 8.2	Education	Social marketing	Yes	Yes	Yes	Community	Partially reported	NR	NR	3 winters (Oct-March)	Medical records	189
Formoso, 2013	RTIs	Italy	March 2012	Community	Knowledge (including awareness), cultural, and doctor-patient relationship	Antibiotics, solution or problem	"Antibiotics, solution or problem?"	Community and healthcare providers	a newsletter on local AMR. Campaign materials (highlighting how to deal with patients' expectations, occurrence of AMR and of side effects.)	mass media spaces (television, radio, newspapers) written materials (brochures, posters, newsletters)	4.1 4.2 5.1 5.2 12.5	4.1 4.2 5.1 5.2 12.5	Education/persuasion	Social marketing	Yes	Yes	Yes	Community	Partially reported	Access expired	$60,800	4 months	Medical records + self reports	-
Fuertes, 2010	not specified	Canada	December 2008	Community	Knowledge (including awareness)	Do Bugs Need Drugs?	None	Community and healthcare providers	Television campaign	Television campaign	4.1 4.2 5.1 5.2 8.2	4.1 4.2 5.1 5.2 8.2	Education	-	NR	Yes	Yes	Community	NR	NR	NR	5 months	Medical records	-
Gonzales, 2004	RTIs	USA	February 2002	Community & Primary care setting	Knowledge (including awareness) and doctor-patient relationship	Minimizing Antibiotic Resistance in Colorado	Be SMART about Antibiotics	Community and healthcare providers	antibiotic prescribing profiles and practices guidelines	Waiting room materials, examination room posters; Mailing campaign packets: Household- and office-based patient education materials	1.3 12.5	4.1 4.2 5.1 9.1 12.5	Education	-	Yes	Yes	Yes	Community	Access expired	Access expired	NR	1 year	Medical records	248
Gonzales, 2005	RTIs	USA	February 2002	Community & Primary care setting	Knowledge (including awareness) and doctor-	Minimizing Antibiotic Resistanc	Be SMART about Antibiotics	Community and healthcare providers	antibiotic prescribing profiles and practices guidelines	Waiting room materials, examination room	1.3 12.5	4.1 4.2 5.1 9.1 12.5	Education	-	Yes	Yes	Yes	Community	Access expired	Access expired	$63,745	1 year	Medical records	(See Gonzales, 2004)

					patient relationship	e in Colorado				posters; Mailing campaign packets: Household - and office-based patient education materials															
Gonzales, 2008	not specified	USA	December 2003	Community	Knowledge (including awareness)	Minimizing Antibiotic Resistance in Colorado	"Get Smart: Use Antibiotics Wisely." And *"Use antibio´ticos solo si un doctor se lo receta"*	Community and healthcare providers	Primary care physicians	Mass media campaign, educational events and written educational materials	4.1 4.2 5.1 12.5	4.1 4.2 5.1 12.5	Education	Social marketing	Yes	Yes	Yes	Community	Yes	Yes	$196,710	4 months	Medical records + self reports	-
Hennessy, 2002	RTIs	USA	December 2000	Community	Knowledge (including awareness)	-	-	Community and healthcare providers	Workshops and follow-up visits	Printed information and newsletters	4.1 4.2	4.1 4.2 5.1	Education	-	Yes	Yes	Yes	Community	Access expired	Access expired	NR	6 months	Medical records + lab testing + self reports	-
Kliemann, 2016	not specified	Brazil	December 2012	Community	Socioeconomic determinants; Access to non-prescription antibiotics	-	-	Community and healthcare providers	Restriction on sale of antibiotics without prescription	Restriction on sale of antibiotics without prescription	12.1	12.1	Restriction, environmental restructuring	-	NA	Yes	Yes	Community	NA	NA	NA	Ongoing	Medical records	-
Lambert, 2007	RTIs	UK	February 2005	Community	Knowledge (including awareness)	-	Antibiotics – tracking down the trust	Community and healthcare providers	professional education and prescribing support	Mass media with printed materials	4.1 8.2 12.5	4.1 8.2 12.5	Education	-	NR	Yes	Yes	Community	NA	Partially reported	£25,000	2 winters	Medical records + self reports	-
Lee, 2017	RTIs	Singapore	Not specified	Primary care setting	Knowledge (correcting misconceptions)	--	-	Community - patients	-	Educational pamphlets and verbal counselling	-	4.1 4.2	Education	-	NR	NR	Yes	Individual	NR	NR	NR	2 weeks	Medical records	-
Mainous, 2009	not specified	USA	June 2008	Community	Knowledge (including misconceptions); cultural	"Solo Con Receta" (only with a prescription)	-	Community	-	Culturally-sensitive community intervention with multiple media sources	-	4.1 5.1	Education	-	NR	Yes	Yes	Community	Partially reported	NR	NR	9 months	Medical records + self reports	-
McNulty, 2010	RTIs	UK	January 2009	Community & Primary care setting	Knowledge (correcting misconceptions)	--	-	Community - patients	NICE guidance on the primary care management of common, acute, self-limiting RTIs	three posters displayed in magazines and newspapers	4.1 4.2 8.2	4.1 4.2	Education	-	NR	NR	Yes	Individual	NR	Yes	NR	2 months	self reports	249

Perz, 2002	RTIs	USA	April 1999	Community	Knowledge (including awareness); peer	-	Antibiotics and Your Child	Community and healthcare providers	Educating peer leader presentations	Public education via printed material	4.1 4.2	4.1 4.2 8.2	Education	-	Yes	Yes	Yes	Community	Partially reported	Partially reported	NR	1 year	Medical records	-
Sabuncu, 2009	RTIs	France	December 2007	Community	Knowledge (including awareness)	Keep Antibiotics Working	‘‘Les antibiotiques c’est pas automatique’’ (‘‘Antibiotics are not automatic’’)	Community	guidelines, seminars, academic detailing, letters	Pamphlets and posters, print media, radio, television, website	4.1 4.2 5.1 12.5	4.1 4.2 5.1 12.5	Education	-	NR	NR	Yes	Community	NR	NR	NR	5 years	Medical records	(see Bernier, 2014)
Santa-Ana-Tellez, 2013	Not specified	Brazil and Mexico	June 2012	Community	Access to non-prescription antibiotics	-	-	Community and healthcare providers	Restriction on sale of antibiotics without prescription in pharmacies, and introduction of fine on owners of pharmacies for non-compliance.	Restriction on sale of antibiotics without prescription	12.1 14.2 (only Mexico)	12.1	Restriction, coercion, environmental restructuring	-	NA	Yes	Yes	Community	NA	NA	NA	Ongoing	Medical records	220-222,250
Santa-Ana-Tellez, 2015	Not specified	Brazil and Mexico	March 2012	Community	Access to non-prescription antibiotics	-	-	Community and healthcare providers	Restriction on sale of antibiotics without prescription in pharmacies, and introduction of fine on owners of pharmacies for non-compliance.	Restriction on sale of antibiotics without prescription	12.1 14.2 (only Mexico)	12.1	Restriction, coercion, environmental restructuring	-	NA	Yes	Yes	Community	NA	NA	NA	Ongoing	Medical records	(see Santa-Ana-Tellez, 2013)
Taylor, 2005	RTIs	USA	April 2002	Primary care setting	Knowledge, Doctor-patient relationship	-	Puget Sound Paediatric Research Network	Community - parents and children	-	educational pamphlets and a video	-	4.1 9.1	Education	-	Yes	Yes	Yes	Community	NR	NR	NR	1 year	Medical records	-
Trepka, 2001	RTIs	USA	August 1998	Community & Primary care setting	Knowledge (including awareness), cultural, and doctor-patient relationship	-	Your Child and Antibiotics	Community and healthcare providers	“Grand rounds” presentations, small-group academic detailing, and distribution of written materials (clinical practice guidelines, clinical fact sheets, and samples of patient education materials.)	Public education materials: programs, pamphlets and posters, presentations and newspapers	4.1 4.2 5.1 8.2 12.5	4.1 4.2 5.1 8.2 12.5	Education	-	Yes	Yes	Yes	Community	Partially reported	NR	NR	4 months	self reports	-

Wirtz, 2013	Not specified	Chile, Colombia, Venezuela, Mexico	September 2009	Community	Access to non-prescription antibiotics	-	-	Community and healthcare providers	Restriction on sale of antibiotics without prescription	Restriction on sale of antibiotics without prescription	12.1	12.1	Restriction, coercion, environmental restructuring	-	NA	Yes	Yes	Community	NA	NA	NA	Ongoing	Medical records	220-222,250
Wutzke, 2007	RTIs	Australia	August 2004	Community & Primary care setting	Knowledge, Doctor-patient relationship; peer	The NPS common colds community campaign	'Common colds need common sense: they don't need antibiotics'.	Community and healthcare providers	Prescription pads, patient information leaflets, prescribing software. Newsletters,. Prescribing feedback, educational visiting, clinical audit with feedback and case studies (paper and peer group discussion).	Mass media activity using billboards, television, radio and magazines and small grants to promote local community education	2.2 3.1 4.1 4.2 8.2 12.5	4.1 4.2 8.2 12.5	Education/ persuasion	-	Yes	Yes	Yes	Community	Partially reported	Yes	NR	6 years	Medical records + self reports	-
Demand of brand name drugs																								
Beshears, 2013	not specified	USA	October 2014	Community	Knowledge (including awareness), Peer influence	-	-	Community - Union members	-	Informational letters with or without a Testimonial from person with/without shared union affiliation	-	8.2 9.1 10.1 10.2	Education, persuasion	-	NR	Yes	Yes	Individual	Partially reported	NR	NR	1 letter	Medical records	-
O'Malley, 2006	not specified	USA	December 2003	Community	Knowledge (including awareness), Incentives	-	-	Community and healthcare providers	Free generic drug samples, physician financial incentives	Member mailings, advertising campaigns	3.2 4.1 8.2 10.1 10.2 12.5	4.1 8.2 10.1 10.2 12.5	Education, incentivization	-	NR	Yes	Yes	community	NR	NR	NR	4 years	Medical records	-
Sedjo, 2009	not specified	USA	December 2007	Community	Knowledge (including awareness), Incentives	-	-	Community – health plan enrollees	-	Targeted messaging to raise awareness regarding lower-cost generic alternatives (a phone call and quarterly letters)	-	4.1 8.2 10.1 10.2	Education, incentivization	-	NR	Yes	Yes	Individual	NR	NR	NR	1 call and quarterly mails	Medical records	-

Vallès, 2003	not specified	Spain	February 2000	Primary care setting	Knowledge (including awareness)	-	-	chronic disorders patients who attended general practices	-	Verbal information and handout materials on advantages and disadvantages of generic equivalents and brand-name drugs	-	4.1 8.2 9.2	Education	-	NR	Yes	Yes	Individual	NR	NR	NR	1 session	Medical records	-
Non-medical use of prescription drugs																								
Hasak 2018	Pain management (short-term	USA	September, 2017	Community	Knowledge (including awareness), enabling	-	-	-	-	information brochure, website		4.1 4.2 5.1 5.2 12.1	Education; enablement	-	Yes	Yes	Yes	Individual	Yes	Yes	NR	2 times	self reports	251
Lawrence, 2019	Pain management (short-term	USA	January 2019	Community	Knowledge (including awareness), enabling	-	-	-	-	information brochure, video, Deterra bags		4.1 4.2 5.1 5.2 12.1 12.5	Education; enablement; environmental restructuring;	-	Yes	Yes	Yes	Individual	Yes	Yes	Partially reported ($5-7 per bag)	1 time	Medical records, self reports	252
Maughan, 2016	Pain management (short-term	USA	October 2015	Community	Knowledge (including awareness), enabling	-	-	-	-	information brochure, study hotline		4.1 4.2 5.1 5.2 12.1 12.5	Education; enablement; environmental restructuring;	-	NR	Yes	Yes	Individual	Yes	NR	NR	1 time	self reports	
Rose, 2016	Pain management (short-term	Canada	April 2015	Community	Knowledge (including awareness), enabling	-	-	-	-	information brochure		4.1 4.2 5.1 5.2 12.1	Education; enablement	-	Yes	Yes	Yes	Individual	Yes	Yes	NR	1 time	self reports	
Spoth, 2008	not specified	USA	December 2002	School setting	Enhance protective factors Family dynamics	Strengthening Families Program (ISFP) and Life Skills Training (LST)	-	Community - Students	-	Universal preventive interventions implemented during middle school (strengthening families program and life skills training)	-	3.1 12.2	Education; enablement; environmental restructuring;	social development model	NR	Yes	Yes	Individual	NR	NR	NR	6 2-hr sessions + 1 family follow up + boosters (cohort)	self reports	202,203,253-256
Spoth, 2013	not specified	USA	December 2011	School setting	Enhance protective factors Family dynamics	Strengthening Families Program (ISFP)	-	Community - Students	-	Universal preventive interventions implement	-	3.1 12.2	Education; enablement; enviro	social development model	NR	Yes	Yes	Individual	NR	NR	NR	6 2-hr sessions + 1 family follow	self reports	(see Spoth, 20080)

						and Life Skills Training (LST)				ed during middle school (strengthening families program and life skills training)		nmental restructuring;								up + boosters (cohort Study 1:1993-2008; study 2: 1998-2011)		
Elective Caesarean Section												-		-									
Eden, 2014	experienced previous caesarean birth	USA	May 2007	Community & Primary care settings	Knowledge (including awareness), enabling	-	-	Community - Pregnant women with one previous caesarean birth	-	Evidence-base information brochure or facilitated decision analysis	-	4.1 5.1 9.2	Education; enablement	-	Yes	Yes	Yes	Individual	NR	NR	NR	1 session	Medical records + self reports	-
Fraser, 1997	experienced previous caesarean birth	Canada	November 1994	Primary care setting	Knowledge (including awareness), Predisposing, enabling and reinforcing factors	-	-	Community - Pregnant women with one previous caesarean birth	-	Educational pamphlet, prenatal education and peer support program	-	3.3 4.1 5.1	Education; enablement	The PRECEDE-PROCEED model	NR	Yes	Yes	Individual	NR	NR	NR	2 sessions	Medical records + self reports	-
Hassani, 2016	not specified	Iran	**NR**	Primary care setting	Knowledge (including awareness	-	-	Community - Primiparous Pregnant women	-	Instructional sessions in the form of speech, group discussions, questions and answers, and presentations		4.1	Education	Health belief model	NR	Yes	Yes	Individual	NR	NR	NR	6 sessions - 50-60 minutes /session	self reports	-
Montgomery, 2007	experienced previous caesarean birth	UK	August 2006	Primary care setting	Knowledge (including awareness), enabling	-	-	Community - Pregnant women with one previous caesarean birth	-	Information program and facilitated decision analysis	-	4.1 5.1 9.2 9.2	Education; enablement	-	Yes	Yes	Yes	Individual	NR	NR	NR	10 weeks	Medical records + self reports	186-188,191,192
Navaee, 2015	fear of childbirth	Iran	NR	Primary care setting	Knowledge (including awareness), Emotions	-	-	Community - Primiparous Pregnant women	-	Education through role play about advantages and disadvantages	-	4.1 4.2 6.1 9.2	Education; modelling	-	NR	Yes	Yes	Individual	NR	NR	NR	1 session - 90 minutes	self reports	-

Sharifirad, 2013	Primiparous Pregnant women	Iran	NR	Primary care setting	Knowledge (including awareness), Family dynamics	-	-	Community – spouses of primiparous Pregnant women	-	Educational session about mechanism of natural vaginal and caesarean deliveries as well as their advantages and disadvantages.	-	3.1 4.1 5.1 9.2	Education; enablement	-	NR	Yes	Yes	Individual	NR	NR	NR	1 session - 90 minutes	self reports	-
Shorten, 2005	experienced previous caesarean birth	Australia	May 2003	Primary care setting	Knowledge (including awareness), enabling	-	-	Community - Pregnant women with one previous caesarean birth	-	Information materials and facilitated decision analysis	-	4.1 5.1 9.2	Education; enablement	-	Yes	Yes	Yes	Individual	NR	NR	NR	1 session	Medical records + self reports	190
Valiani, 2014	Primiparous Pregnant women	Iran	NR	Primary care setting	Knowledge (including awareness)	-	-	Community - Primiparous Pregnant women	-	childbirth workshops	-	4.1 4.2 5.1 6.1 9.2	Education; enablement	-	NR	Yes	Yes	Individual	NR	NR	NR	3 x 4hr/ week	Medical records	-

Note: NR = not reported; RTIs=Respiratory tract infections; GP = General Practitioner; CS=Elective Caesarean Section.

Table 2. Summary of findings of included studies measuring changes behavioural outcomes

First Author, Year	Study design		Study population	Study sample size	Primary outcome(s)	Change in intervention group	Change in control group	Effect size (95% CI)	P value	Effective in changing public behaviors	Quality Appraisal
Belongia, 2001	NCT	Longitudinal	Physicians and public	111 facilities, 664 children	Paediatric antibiotic prescribing in child care facilities	Baseline: 57.6%; post-intervention: 59.5% of initial visits	Baseline: 60.1%; post-intervention 61.5% of initial visits	NR	Baseline: P = 0.56.; Post-intervention: P = 0.66	No	WEAK
Belongia, 2005	CPP	Longitudinal	parents and primary care clinicians	4,115 primary care physicians	Change in annual antimicrobial prescribing rate	- 20.4%	- 19.8%	-0.6%	NR	No	MODERATE
Bernier, 2014	ITS	Longitudinal	French citizens covered by NHI	Not reported	change in antimicrobial prescribing rate	NA	NA	-30% (-36.3% to -23.8%)	P<0.001	Mixed	STRONG
Cebotarenco, 2008	CPP	Cross-sectional	Students and parents	~6302 people	No antibiotic use for cold and flu	Students: a 33.7% net increase in no antibiotic use; Adults: a 38.0% net increase in no use	students -0.4%; adults +0.1%	Students 3.694 (CI 2.516 to 5.423); adults 5.541 (CI 4.559 to 6.733)	P<0.0001	Yes	WEAK
Finkelstein, 2001	RCT	Longitudinal	Physicians and parents	8815 children	Antibiotics dispensed per person-year of observation among children	3 to <36mon (-18.6%), 36 to <72 (-15.0%)	3 to <36mon (-11.5%), 36 to <72 (-9.8%)	3 to <36mon (-16%), 36 to <72 (-12%)	3 to <36mon (P<0.001), 36 to <72 (P<0.001)	Yes	STRONG
Finkelstein, 2008	RCT	Longitudinal	Physicians and parents	223,135 person/years	Antibiotics dispensed per person-year of observation among children	3 to <24mon (-20.7%), 24 to <48 (-10.3), 48 to <72 (-2.5)	3 to <24mon (-21.2), 24 to <48 (-14.5), 48 to <72 (-9.3)	3 to <24mon (-0.5), 24 to <48 (-4.2), 48 to <72 (-6.7)	3 to <24mon (p=0.69), 24 to <48 (p<0.01), 48 to <72 (p<0.0001)	Mixed	STRONG
Formoso, 2013	NCT	Longitudinal	Modena and Parma, Emilia-Romagna region	1,150,000 residents	Antibiotic prescription rate	-11.9	-7.4	-4.3% (−7.1% to −1.5%)	P=0.008	Yes	STRONG
Fuertes, 2010	ITS	Longitudinal	Population in British Columbia, Canada	Not reported	Antibiotic utilization rate	-5.8%	NA	NR	NR	No	STRONG
Gonzales, 2004	NCT	Longitudinal	Medicare enrollees with acute respiratory tract infections (ARIs)	4,270 patient visits	Decreased antibiotic prescription rates	-5%	-2%	NR	p=0.79	No	MODERATE
Gonzales, 2005	NCT	Longitudinal	Children with pharyngitis and adults with acute bronchitis	Baseline:101 28 patients Study:9586 patients	Decreased antibiotic prescription rates	Children:-4% Adults: -24%	Children:-2% at local control; 1% at distant control; Adults:-10% at local control; -6% at distant control	NR	Children: P=0.18,p=0.48 compared with distant and local control; Adults: p<0.002 and p=0.006, for distant and local control	Mixed	MODERATE
Gonzales, 2008	NCT	Longitudinal	mothers of young children and primary care physicians	922 households, 1.38+ million antibiotic prescriptions	Net change in antibiotic dispensed per 1000 persons	–	–	−3.8% in retail pharmacy antibiotic dispenses and -8.8% in managed care organization (MCO) associated dispenses	P=0.30 for public, P=0.03 for MOC members	Mixed	STRONG
Hennessy, 2002	NCT	Longitudinal	Medical providers and community	10,809	Antibiotic utilization	-31% (P≤0.01)	-10% (p≥0.05)	-21%	NR	Mixed	MODERATE
Kliemann, 2016	ITS	Longitudinal	Residents of Sao Paulo	41,262,199	Antibiotic utilization	-1.616 DID	NA	NR	p = 0.002	Yes	MODERATE
Lambert, 2007	CPP	Longitudinal	Communities in North East of England	Not reported	per person, per clinic visit	Initial: -31% Expanded: -35%	NA	NR	p< 0.01	Mixed	WEAK
Lee, 2017	RCT	Cross-sectional	Adult patients	914 patients	antibiotic prescriptions	20.6%	17.7%	1.20 (0.83-1.73)	P=0.313	No	WEAK
Mainous, 2009	QE (controlled post test)	Cross-sectional	Latino adults	500 adults	Use of non-prescription antibiotics	1.3%	3.2%	NR	P=0.90	No	WEAK

McNulty, 2010	CPP	Cross-sectional	Adult ≥15	Pre= (1999); post (1830)	Antibiotic use without professional advice	-0.5%	0%	NR	NR	No	WEAK
Perz, 2002	CPP	Longitudinal	Children <15	464200 person-years	Antibiotic prescription rates	Year 3:19%	Year 1: 8%	11% (8%- 14%)	p<0.001	Yes	MODERATE
Sabuncu, 2009	ITS	Longitudinal	French citizens covered by NHI	Not reported	Change in winter antibiotic prescribing rate (Oct to Mar)	NA	NA	−26.5% (−33.5% to −19.6%)	< 0.0001	Yes	STRONG
Santa-Ana-Tellez, 2013	ITS	Longitudinal	Populations in Mexico and Brazil	Not reported	OTC antibiotics consumption	Brazil = -1.35; Mexico = -1.17	NA	NR	Brazil p<0.01; Mexico p<0.001	Mixed	STRONG
Santa-Ana-Tellez, 2015	ITS	Longitudinal	Populations in Mexico and Brazil	Not reported	Seasonal variation in total Penicillin use	Brazil = 0.077; Mexico = -0.359	NA	Brazil = 0.077 (-1.142 to 1.297); Mexico = -0.359 (-0.613 to -0.105)	Brazil p>0.05; Mexico p<0.01	Mixed	STRONG
Taylor, 2005	RCT	Cross-sectional	Parent/child dyads	499 children	Total no. of prescriptions for antibiotics	2.2 ±2.6	2.5 ± 2.9	NR	P=0.23	No	WEAK
Trepka, 2001	CPP	Cross-sectional	Physicians and public	365 children	expected an antibiotic for their child and did not receive one and brought their child to another physician because they did not receive an antibiotic	expected an antibiotic for their child and did not receive one: -5.1% brought their child to another physician because they did not receive an antibiotic: -2.9%	expected an antibiotic for their child and did not receive one: 3.2% brought their child to another physician because they did not receive an antibiotic: 1.6%	expected an antibiotic for their child and did not receive one: -8.4% (-13.9 to -2.8); brought their child to another physician because they did not receive an antibiotic: -4.5% (-8.0 to –0.9) they did not receive an antibiotic: 1.6%	expected an antibiotic for their child and did not receive one: p=0.003 brought their child to another physician because they did not receive an antibiotic: p=0.02	Yes	WEAK
Wirtz, 2013	ITS	Longitudinal	Chile, Colombia, Venezuela, Brazil	Not reported	OTC antibiotics consumption	Colombia: -2.4DID; Chile: -3.8DID; Venezuela: +5.39DID and Mexico: -2.4DID	NA	Colombia: --1.00; Chile: -5.56; Venezuela: opposite impact; Mexico: no difference	Colombia: p = 0.001; Chile: p < 0.05	Mixed	MODERATE
Wutzke, 2007	ITS	Longitudinal	Australian community	Not reported	change in use of antibiotics	-3.40%	NA	1.3–5.5	<0.05	Yes	MODERATE
Beshears, 2013	RCT	Cross-sectional	union members	5,498 adults	Conversion rate to lower-cost alternatives	Unaffiliated Testimonial Group 11.3%; Affiliated Testimonial Group 11.7%	12.20%	NR	NR (insignificant)	No	MODERATE
O'Malley, 2006	QE (matched controlled)	Longitudinal	Adult patients	9790064 claims	Generic dispensing rate	Mailing: -4.94; Advertising: -0.13; Generic sampling: -0.02; physician incentive: -0.33	Doubling co-payment for brand-name drugs: 8.60	NR	p>0.05	No	MODERATE
Sedjo, 2009	QE	Longitudinal	Consumer-Directed Health Care Enrolees	4026 people	Conversion rate to lower-cost alternatives	0.30%	9.30%	29.82 (4.41–201.93)	p<0.05	Yes	MODERATE
Vallès, 2003	RCT	Longitudinal	Patients taking medications for chronic disorders	4620 patients	Evolution of the percentage of generic prescribing	5.10% (1999-2000)	1.90% (1999-2000)	NR	p<0.001	Yes	STRONG
Hasak 2018	QE	Cross-sectional	postoperative patients	258 patients	Self-reported proper opioid disposal	28 (22)	14 (11)	NR	P=0.02	Yes	WEAK
Lawrence, 2019	RCT	Cross-sectional	Parents of postoperative patients	202 caregivers	Self-reported proper opioid disposal	66 (71.7)	50 (56.2)	15.5 (1.7 to 29.3)	P = 0.03.	Yes	MODERATE
Maughan, 2016	RCT	Cross-sectional	postoperative patients	79 patients	Self-reported proper opioid disposal	52% (16/31)	30% (8/27)	NR	p = 0.11.	No	WEAK
Rose, 2016	QE	Cross-sectional	postoperative patients	87 patients	Self-reported proper opioid disposal	12 (27%)	2 (5%)	22% (5 to 38)	P = 0.005	Yes	WEAK
Spoth, 2008	RCT	Longitudinal	Late adolescents	2651 (study 2 on	Self-reported lifetime	11th graders: 3.9%;	11th graders: 7.7%;	NR	11th graders: p<0.01;	Yes	WEAK

			and young adults	prescription drugs)	prescription drug misuse overall	12th graders: 7.7%	12th graders: 10.5%		12th graders: p<0.1		
Spoth, 2013	RCT	Longitudinal	Late adolescents and young adults	Study 1: 667 students; Study 2: 2127 students	Self-reported lifetime prescription drug misuse overall	Study1- 5.4; Study2- 2.5 in age 21, 4.4 in age 22, 6.3 in age25.	Study1- 15.5; Study2- 6.5 in age 21, 8.9 in age 22, 9.4 in age25.	Study 1:65%; Study 2: 62% in age 21, 51% in age 22, 33% in age 25.	Study 1- p<0.01; Study 2- age 21 p=0.015, age 22, p=0.019, age 25 p=0.064	Yes	WEAK
Eden, 2014	RCT	Cross-sectional	Pregnant women with previous caesarean	131 women	MoD (vaginal)	41%	37%	NR	p =0.724	No	WEAK
Fraser, 1997	RCT	Cross-sectional	Pregnant women with previous caesarean section	1,275 women	MoD (vaginal)	53%	49%	1.1 (1.0 to 1.2)	p>0.05	No	WEAK
Hassani, 2016	QE	Cross-sectional	Primiparous women	60 women	MoD (vaginal)	30%	10%	NR	NR	Yes	WEAK
Montgomery, 2007	RCT	Cross-sectional	Pregnant women with previous caesarean section	742 women	MoD (vaginal)	Decision analysis group: 37%; Info:29%	Usual care:30%	Info v. usual care:0.93(0.61,1.41) Decision v. usual care:1.42(0.94,2.14)	p>0.9 p=0.22	No	STRONG
Navaee, 2015	RCT	Cross-sectional	Primiparous women	67 women	MoD (vaginal)	62.9%	43.8%	NR	P=0.117	No	WEAK
Sharifirad, 2013	RCT	Cross-sectional	Pregnant women and partners	88 women and partners	MoD (vaginal)	71.5%	50.0%	NR	p<0.05	Yes	WEAK
Shorten, 2005	RCT	Cross-sectional	Pregnant women with previous caesarean section	227 women	MoD (vaginal)	VD: 49.2%	CS: 50.8%	NR	NR	No	WEAK
Valiani, 2014	RCT	Cross-sectional	Pregnant women and partners	180 women and partners	MoD (vaginal)	Mothers alone intervention = 60%; Couples =56.7%	26.7%	NR	P=0.017	Yes	WEAK

Notes: CS=Elective Caesarean Section; CPP= controlled pre- and post-study; NA = not applicable; NR=not reported; PDMO = Prescription drug misuse overall; NCT=Nonrandomised controlled trial; OTC= over-the-counter purchases; MoD= Mode of delivery; RCT=randomised controlled trial; VD= Normal vaginal delivery;

Table 3. Features of included interventions

First Author, Year	Gov't support	Policy	PROFESSIONAL TARGET						PUBLIC TARGET															Multilingual
			Letters to doctors	Educational meetings (academic detailing)	Written materials	clinical practice guidelines	prescribing feedback	physician financial incentives	TV	Video	Newsletters/mails	Poster	radio	Press conferences	Newspapers or Advertisements (including Bill boards, bus signs)	Websites	Informational written materials (including Pamphlets/brochures)	Education meetings	Mascots	School program (including Peer-education)	Family & friends	Decision-aid/Enabling Tools	Other MassMedia campaign activities	
Belongia, 2001	Yes		X	X	X	X						X					X	X						NR
Belongia, 2005	Yes		X	X	X	X			X		X	X	X	X	X	X	X	X	X				X	Yes
Bernier, 2014	Yes		X	X	X	X			X		X	X	X	X	X	X	X	X					X	NR
Cebotarenco, 2008	No									X		X			X		X	X		X	X		X	NR
Finkelstein, 2001	Yes			X	X	X	X				X					X	X							NR
Finkelstein, 2008	Yes			X	X	X	X				X					X	X	X		X	X		X	NR
Formoso, 2013	Yes		X						X			X	X		X	X	X							NR
Fuertes, 2010	Yes								X							X								NR
Gonzales, 2004	Yes				X	X					X	X				X	X				X			Yes
Gonzales, 2005	Yes				X	X					X	X				X	X				X			Yes
Gonzales, 2008	Yes		X									X	X		X	X	X						X	Yes
Hennessy, 2002	Yes			X							X					X	X	X						NR
Kliemann, 2016	Yes	X																						NA
Lambert, 2007	Yes								X			X	X		X		X		X				X	NR
Lee, 2017	No																X	X						Yes
Mainous, 2009	No												X		X		X							Yes
McNuty, 2010	Yes		X		X	X						X			X		X							NR
Perz, 2002	Yes			X	X	X			X		X	X			X		X	X					X	NR
Sabuncu, 2009	Yes		X	X	X	X			X		X	X	X	X	X	X	X	X					X	NR
Santa-Ana-Tellez, 2013	Yes	X																						NA
Santa-Ana-Tellez, 2015	Yes	X																						NA
Taylor, 2005	Yes									X							X							NR
Trepka, 2001	Yes		X	X	X	X						X			X		X	X						NR
Wirtz, 2013	Yes	X																						NA
Wutzke, 2007	Yes		X	X	X		X		X			X	X	X	X	X	X	X					X	NR
Beshears, 2013	Yes										X													NR
O'Malley, 2006	No			X				X			X		X	X	X	X							X	NR
Sedjo, 2009	No			X							X						X							NR
Vallès, 2003	No																X	X						NR
Hasak, 2018	No															X	X							NR
Lawrence, 2019	No									X							X					X		NR
Maughan, 2016	No																X					X		NR
Rose, 2016	No																X							NR
Spoth, 2008	No															X				X	X			NR
Spoth, 2013	No															X				X	X			NR
Eden, 2014	No																X					X		Yes

Fraser, 1997	Yes																X	X			X			Yes
Hassani, 2016	No																	X						NR
Montgomery, 2007	No															X						X		NR
Navaee, 2015	No																X	X			X			NR
Sharifirad, 2013	No																X	X			X			NR
Shorten, 2005	No																X					X		NR
Valiani, 2014	No																X	X			X			NR

NR=not reported

Table 4. Behaviour change techniques and number of interventions targeting health care consumers and included specific behaviour change techniques, Behaviour Change Techniques Taxonomy Volume 1 (BCTTv1) hierarchical clusters, and intervention content examples

BCT	BCTTv1 hierarchical clusters	Examples extracted from descriptions of the interventions	Frequency
3.1 Social support (unspecified)	**3. Social support**	*Educational programs for husbands of pregnant women that aimed to provide social support of husbands, which consequently reduces the rate of elective cesarean section.*	3
3.3 Social support (emotional)	**3. Social support**	*A resource person will provide peer influence during decision making process about mode of delivery*	1
4.1 Instruction on how to perform the behavior	**4. Shaping knowledge**	*Information about when antibiotics are and are not needed (eg, rarely for bronchitis, not for colds).*	34
4.2 Information about Antecedents	**4. Shaping knowledge**	*Information about bacterial and viral infections*	22
5.1 Information about health consequences	**5. Natural consequences**	*Information about bacterial resistance or side effects of antibiotic use*	22
5.2 Salience of consequences	**5. Natural consequences**	*Emphasis on the consequences inappropriate use of antibiotics (eg. Antimicrobial resistance or side effects of antibiotic use)*	6
6.1 Demonstration of the behavior	**6. Comparison of behavior**	*Role play education to reduce the fear of childbirth*	3
8.2 Behavior substitution	**8. Repetition and substitution**	*Alternative remedies instead of antibiotics for colds*	11
9.1 Credible source	**9. Comparison of outcomes**	*Endorsement by CDC was designed to increase the credibility of key messages.*	4
9.2 Pros and cons	**9. Comparison of outcomes**	*Information about the differences between generic and brand-name drugs in terms of advantages (high-quality bioequivalent formulations, health professionals' preferences, avoidance of confusions) and disadvantages (popularity, fidelity to branded products)*	8
10.1 Material incentive (behavior)	**10. Reward and threat**	*Switching to a lower-cost generic medication is cost-saving*	3
10.2 Material reward (behavior)	**10. Reward and threat**	*associated cost savings to the recipient from switching to each of these alternatives*	3
12.1 Restructuring the physical environment	**12. Antecedents**	*Restriction on sale of antibiotics without prescription*	8
12.2 Restructuring the social environment	**12. Antecedents**	*Interventions focused on empirically supported family risk and protective factors, such as parental nurturing, child management skills, improved parent–adolescent communication skills and adolescent prosocial skill development (e.g. managing conflict and stress, handling peer pressure, developing positive friendships)*	3
12.5 Adding objects to the environment	**12. Antecedents**	*Mass media strategies were undertaken including advertising using billboards, television, radio and magazines.*	12
15	**8**		143

Table 5. Behaviour change techniques and number of interventions targeting health care providers that included specific behaviour change techniques, Behaviour Change Techniques Taxonomy Volume 1 (BCTTv1) hierarchical clusters, and intervention content examples

BCT	BCTTv1 hierarchical clusters	Examples extracted from descriptions of the interventions	Frequency
1.3 Goal setting (outcome)	**1. Goals and planning**	*Provision of individual prescribing profiles depicting: (1) the proportion of adult bronchitis patients receiving antibiotic treatment (target 10 percent or less); (2) the proportion of these antibiotics belonging to a first-line group (erythromycin, doxycycline, tetracycline) (target 70 percent or more); and (3) the proportion of these antibiotics that are ineffective against proven bacterial causes of uncomplicated acute bronchitis (target 0 percent).*	1
2.2 Feedback on behavior	**2. Feedback and monitoring**	*Prescribing feedback, Clinical audit with feedback*	3
3.1 Social support (unspecified)	**3. Social support**	*Interventions that inform best practice prescribing and that support health professionals manage patient expectations*	1
3.2 Social support (practical)	**3. Social support**	*This intervention will (1) provide a range of patient education materials to physician offices without charge, (2) provide ongoing information about antibiotic-use rates and resistance in the community, (3) provide feedback about prescribing by practice, and (4) serve as a general resource on issues of antibiotic prescribing and resistance*	3
4.1 Instruction on how to perform the behavior	**4. Shaping knowledge**	*Academic detailing to promote appropriate antibiotic use; practice guidelines which included with the patient profiles for adults with bronchitis and children with pharyngitis were compatible with those produced by the Centers for Disease Control and Prevention (CDC)*	15
4.2 Information about Antecedents	**4. Shaping knowledge**	*Clinical practice guidelines for common respiratory illnesses*	13
5.1 Information about health consequences	**5. Natural consequences**	*a reference card providing easy-to-read facts about symptoms and treatments for ARIs*	9
5.2 Salience of consequences	**5. Natural consequences**	*Emphasis on AMR*	2
8.2 Behavior substitution	**8. Repetition and substitution**	*Prescription pads with explanations on symptoms and appropriate treatment options (to be given to patients instead of antibiotic prescriptions)*	9
9.1 Credible source	**9. Comparison of outcomes**	*Endorsement by CDC was designed to increase the credibility of key messages.*	1
10.1 Material incentive (behavior)	**10. Reward and threat**	*An intervention intends to reward physicians for reducing pharmacy costs for their patients, one component of which was to increase their prescribing of generic drugs*	1
10.2 Material reward (behavior)	**10. Reward and threat**	*Reward given to physicians for reducing pharmacy costs for their patients, one component of which was to increase their prescribing of generic drugs*	1
12.1 Restructuring the physical environment	**12. Antecedents**	*Waiting room materials (CDC posters and patient reference cards)*	4
12.5 Adding objects to the environment	**12. Antecedents**	*Mass media strategies were undertaken including advertising using billboards, television, radio and magazines.*	10
14.2 Punishment	**14. Scheduled consequences**	*Regulations that require prescriptions for antibiotics to be retained and registered in pharmacies, and imposes fines to the owners of the pharmacies for non-compliance.*	2
15	**10**		75

Appendix 1. Search Strategy

Database	*Search Strategy*	*Results*
PubMed	(((((((((AMR[tiab] OR antimicrobial resistance[tiab] OR antimicrobial[tiab] OR antibiotic*[tiab] OR caesarean Section*[mesh] OR C section[tiab] OR Caesarean[tiab] OR topical corticosteroid OR prescription drug* OR Drug Utilization[Mesh] OR generic drugs[Mesh] OR Anti-Bacterial Agents/therapeutic use*[Mesh] OR Opiate[tiab] OR opioid[tiab]))) AND ((behavior and behavior mechanisms[Mesh] OR choice behavior[Mesh] OR health knowledge, attitudes, practice*[Mesh] OR usage[tiab] OR use[tiab] OR consum*[tiab] OR behavior*[tiab] OR behavior*[tiab]))) AND ((education[tiab] OR campaign*[tiab] OR patient education as topic/methods[Mesh] OR health communication[Mesh] OR health education[Mesh] OR health promotion/utilization*[Mesh] OR social media[Mesh] OR communication[Mesh] OR communication[tiab] OR intervention*[tiab] OR strateg*[tiab] OR program*[tiab] OR media[tiab] OR mass media[Mesh] OR initiat*[tiab]))) AND ((((evidence-based Practice*[Mesh] OR Epidemiologic Methods[Mesh] OR evaluat*[tiab] OR assess*[tiab] OR effect*[tiab] OR empirical*[tiab] OR evidence[tiab] OR Evaluation Studies as Topic[Mesh] OR Program Evaluation*[Mesh] OR Evaluation Studies[pt] OR Randomized Controlled Trial[pt]) OR impact[tiab])))))) NOT ((((((((((animals[MeSH Terms]) OR depression[MeSH Terms]) OR economics[MeSH Terms]) OR intensive care units[MeSH Terms]) OR practice guidelines as topic[MeSH Terms]) OR inpatients[MeSH Terms]) OR mental disorders[MeSH Terms]) OR bacterial genome[MeSH Terms]) OR ((surge*[Title/Abstract] OR addiction[Title/Abstract] OR inject*[Title/Abstract]))))	1378
EMBASE	('evidence-based'/exp OR 'evidence-based' OR 'evidence'/exp OR 'evidence' OR 'empirical' OR 'evaluat*':ab,ti OR 'assess*':ab,ti OR 'effect*':ab,ti) AND ('health education'/exp OR 'interpersonal communication'/exp OR 'intervention study'/exp OR 'behavior'/exp OR 'awareness'/exp OR 'health promotion'/exp OR 'patient education'/exp OR 'social media'/exp OR 'attitude to health'/exp OR 'health communication'/exp OR 'campaign*':ab,ti OR 'strateg*':ab,ti) AND (('misuse':ab,ti OR 'overuse':ab,ti OR 'drug abuse':ab,ti) AND ('antibiotic agent'/exp OR 'antibiotic*':ab,ti OR 'opioid':ab,ti OR 'caesarean section':ab,ti OR 'topical corticosteroid':ab,ti OR 'prescription drug'/exp OR 'drug utilization'/exp) OR 'generic drug':ab,ti) NOT [animals]/lim NOT [medline]/lim AND [1-1-1900]/sd NOT [1-6-2019]/sd	1110
PsycINFO	(((((((MA evidence-based Practice* OR MA Epidemiologic Methods OR AB evaluat* OR AB assess* OR AB effect* OR AB empirical* OR AB evidence))) AND ((AB education OR AB campaign* OR MA patient education as topic/methods OR MA health communication OR MA health education OR health policy OR MA health promotion/ utilization* OR MA social media/ utilization OR MA communication OR AB communication OR intervention* OR strateg* OR program* OR MA access to information OR AB media OR MA mass media OR AB initiat*))) AND ((MA behavior and behavior mechanisms OR MA choice behavior OR MA health knowledge, attitudes, practice* OR AB usage OR AB use OR AB consum* OR AB behavior* OR AB behavior* OR AB "practice*"))) AND ((misuse OR overuse) AND (AB AMR OR AB antimicrobial resistance OR AB antibiotic*) OR MA caesarean Section* OR AB C section OR AB Caesarean OR AB topical corticosteroid OR AB prescription drug* OR MA Drug Utilization OR MA generic drugs OR MA anti-bacterial agents/therapeutic use* OR AB Opiate OR AB opioid))) NOT ((animal* OR AB surgery OR AB Surgical OR AB dental OR AB cancer* OR AB Chronic obstructive pulmonary disease OR AB COPD OR AB alcohol OR AB tobacco OR AB addiction OR AB depression OR AB disorder* OR AB adherence OR AB diabet* OR MA Inpatients* OR AB inpatient* OR MA Hospitals OR AB tertiary OR AB HIV OR AB tuberculosis OR MA Practice Guidelines as Topic OR emergency[ti] OR ED[tiab] OR MA Intensive Care Units OR MA Practice Patterns, Physicians' OR MA Economics OR AB steward* OR AB analgesic* OR MA Hospitalization OR MA Health Care Facilities OR MA Health Care Facilities OR MA Patient Care Management)) NOT PO animal) NOT Direct-to-consumer NOT AB inject	1557

Appendix 2. Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Type of inappropriate or unnecessary use of medical services or medicine	antibiotic use elective caesarean section nonmedical use of prescription drugs demand for brand-named drugs other types of inappropriate or unnecessary use of medical services or medicine	interventions based solely in clinical settings and relying on clinicians' participation
Language	All	none
Time period	inception of databases to May 2019	none
Population	general public children (age < 18 years) pregnant women	clinicians and other healthcare staff animal
Intervention	Non-clinical interventions that aim to change behaviors for the reduction of inappropriate medical services or medicine use on demand side, and were assessed with robust evaluation data	interventions that pertain to: behaviors of clinician, pharmacists, or prescribers treatments for impatient treatments for emergency services clinical guidelines stewardship programs targeting clinicians or providers dental setting cancer treatment addiction mental health tuberculosis clinical treatment HIV treatment direct-to-consumer advertisement alcohol or tobacco use substance abuse
Outcome	Reduction in: antibiotic use, the public's antibiotic-related behavior, or other types of inappropriate/unnecessary medical services or medicine use	outcomes that were not changes in consumption or behaviors outcomes that mainly focused on knowledge or attitudes, but not on behaviors.
Study Design	Randomized controlled trial (RCT) Cluster randomized controlled trial (CRT) Nonrandomised controlled trial (NCT) quasi-experiments: interrupted time series (with at least three data points before and three after the intervention) and controlled before-and-after studies	editorials or commentaries modelling study protocols reviews or literature reviews descriptive studies observational studies without evaluation data studies reported evaluation data but did not employ a control group and/or report baseline data Time series analysis that do not have a clearly defined point in time when the intervention occurred and at least three data points before and three after the intervention cost analysis or cost-effective analysis without behavioral data economy evaluation

Appendix 3. List of included studies

1. Belongia EA, Knobloch MJ, Kieke BA, Davis JP, Janette C, Besser RE. Impact of statewide program to promote appropriate antimicrobial drug use. *Emerg Infect Dis* 2005; **11**(6): 912-20.

2. Belongia EA, Sullivan BJ, Chyou PH, Madagame E, Reed KD, Schwartz B. A community intervention trial to promote judicious antibiotic use and reduce penicillin-resistant Streptococcus pneumoniae carriage in children. *Pediatrics* 2001; **108**(3): 575-83.

3. Bernier A, Delarocque-Astagneau E, Ligier C, Vibet MA, Guillemot D, Watier L. Outpatient antibiotic use in France between 2000 and 2010: after the nationwide campaign, it is time to focus on the elderly. *Antimicrobial agents and chemotherapy* 2014; **58**(1): 71-7.

4. Beshears J, Choi JJ, Laibson D, Madrian BC, Reynolds G. Testimonials do not convert patients from brand to generic medication. *The American journal of managed care* 2013; **19**(9): e314-31.

5. Cebotarenco N, Bush PJ. Reducing antibiotics for colds and flu: a student-taught program. *Health Educ Res* 2008; **23**(1): 146-57.

6. Eden KB, Perrin NA, Vesco KK, Guise JM. A randomized comparative trial of two decision tools for pregnant women with prior cesareans. *Journal of obstetric, gynecologic, and neonatal nursing : JOGNN* 2014; **43**(5): 568-79.

7. Finkelstein JA, Davis RL, Dowell SF, et al. Reducing antibiotic use in children: a randomized trial in 12 practices. *Pediatrics* 2001; **108**(1): 1-7.

8. Finkelstein JA, Huang SS, Kleinman K, et al. Impact of a 16-community trial to promote judicious antibiotic use in Massachusetts. *Pediatrics* 2008; **121**(1): e15-23.

9. Formoso G, Paltrinieri B, Marata AM, et al. Feasibility and effectiveness of a low cost campaign on antibiotic prescribing in Italy: community level, controlled, non-randomised trial. *Bmj* 2013; **347**: f5391.

10. Fraser W, Maunsell E, Hodnett E, Moutquin JM. Randomized controlled trial of a prenatal vaginal birth after cesarean section education and support program. Childbirth Alternatives Post-Cesarean Study Group. *American journal of obstetrics and gynecology* 1997; **176**(2): 419-25.

11. Fuertes EI, Henry B, Marra F, Wong H, Patrick DM. Trends in antibiotic utilization in Vancouver associated with a community education program on antibiotic use. *Canadian journal of public health = Revue canadienne de sante publique* 2010; **101**(4): 304-8.

12. Gonzales R, Corbett KK, Leeman-Castillo BA, et al. The "minimizing antibiotic resistance in Colorado" project: impact of patient education in improving antibiotic use in private office practices. *Health services research* 2005; **40**(1): 101-16.

13. Gonzales R, Corbett KK, Wong S, et al. "Get smart Colorado": impact of a mass media campaign to improve community antibiotic use. *Medical care* 2008; **46**(6): 597-605.

14. Gonzales R, Sauaia A, Corbett KK, et al. Antibiotic treatment of acute respiratory tract infections in the elderly: effect of a multidimensional educational intervention. *Journal of the American Geriatrics Society* 2004; **52**(1): 39-45.

15. Hasak JM, Roth Bettlach CL, Santosa KB, Larson EL, Stroud J, Mackinnon SE. Empowering Post-Surgical Patients to Improve Opioid Disposal: A Before and After Quality Improvement Study. *J Am Coll Surg* 2018; **226**(3): 235-40.e3.

16. Hassani L, Aghamolaei T, Ghanbarnejad A, Dadipoor S. The effect of an instructional program based on health belief model in decreasing cesarean rate among primiparous pregnant mothers. *J Educ Health Promot* 2016; **5**: 1.

17. Hennessy TW, Petersen KM, Bruden D, et al. Changes in antibiotic-prescribing practices and carriage of penicillin-resistant Streptococcus pneumoniae: A controlled intervention trial in rural Alaska. *Clin Infect Dis* 2002; **34**(12): 1543-50.

18. Kliemann BS, Levin AS, Moura ML, Boszczowski I, Lewis JJ. Socioeconomic Determinants of Antibiotic Consumption in the State of Sao Paulo, Brazil: The Effect of Restricting Over-The-Counter Sales. *PloS One* 2016; **11**(12): e0167885.

19. Lambert MF, Masters GA, Brent SL. Can mass media campaigns change antimicrobial prescribing? A regional evaluation study. *The Journal of antimicrobial chemotherapy* 2007; **59**(3): 537-43.

20. Lawrence AE, Carsel AJ, Leonhart KL, et al. Effect of Drug Disposal Bag Provision on Proper Disposal of Unused Opioids by Families of Pediatric Surgical Patients: A Randomized Clinical Trial. *JAMA pediatrics* 2019: e191695.

21. Lee MHM, Pan DST, Huang JH, et al. Results from a Patient-Based Health Education Intervention in Reducing Antibiotic Use for Acute Upper Respiratory Tract Infections in the Private Sector Primary Care Setting in Singapore. *Antimicrobial agents and chemotherapy* 2017; **61**(5).

22. Mainous AG, 3rd, Diaz VA, Carnemolla M. A community intervention to decrease antibiotics used for self-medication among Latino adults. *Annals of family medicine* 2009; **7**(6): 520-6.

23. Maughan BC, Hersh EV, Shofer FS, et al. Unused opioid analgesics and drug disposal following outpatient dental surgery: A randomized controlled trial. *Drug and alcohol dependence* 2016; **168**: 328-34.

24. McNulty CA, Nichols T, Boyle PJ, Woodhead M, Davey P. The English antibiotic awareness campaigns: did they change the public's knowledge of and attitudes to antibiotic use? *The Journal of antimicrobial chemotherapy* 2010; **65**(7): 1526-33.

25. Montgomery AA, Emmett CL, Fahey T, et al. Two decision aids for mode of delivery among women with previous caesarean section: randomised controlled trial. *Bmj* 2007; **334**(7607): 1305.

26. Navaee M, Abedian Z. Effect of role play education on primiparous women's fear of natural delivery and their decision on the mode of delivery. *Iranian journal of nursing and midwifery research* 2015; **20**(1): 40-6.

27. O'Malley AJ, Frank RG, Kaddis A, Rothenberg BM, McNeil BJ. Impact of alternative interventions on changes in generic dispensing rates. *Health services research* 2006; **41**(5): 1876-94.

28. Perz JF, Craig AS, Coffey CS, et al. Changes in antibiotic prescribing for children after a community-wide campaign. *Jama* 2002; **287**(23): 3103-9.

29. Rose P, Sakai J, Argue R, Froehlich K, Tang R. Opioid information pamphlet increases postoperative opioid disposal rates: a before versus after quality improvement study. *Canadian journal of anaesthesia = Journal canadien d'anesthesie* 2016; **63**(1): 31-7.

30. Sabuncu E, David J, Bernede-Bauduin C, et al. Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002-2007. *PLoS Med* 2009; **6**(6): e1000084.

31. Santa-Ana-Tellez Y, Mantel-Teeuwisse AK, Dreser A, Leufkens HG, Wirtz VJ. Impact of over-the-counter restrictions on antibiotic consumption in Brazil and mexico. *PLoS One* 2013; **8**(10): e75550.

32. Santa-Ana-Tellez Y, Mantel-Teeuwisse AK, Leufkens HG, Wirtz VJ. Seasonal variation in penicillin use in Mexico and Brazil: analysis of the impact of over-the-counter restrictions. *Antimicrobial agents and chemotherapy* 2015; **59**(1): 105-10.

33. Sedjo RL, Cox ER. The influence of targeted education on medication persistence and generic substitution among consumer-directed health care enrollees. *Health services research* 2009; **44**(6): 2079-92.

34. Sharifirad G, Rezaeian M, Soltani R, Javaheri S, Mazaheri MA. A survey on the effects of husbands' education of pregnant women on knowledge, attitude, and reducing elective cesarean section. *J Educ Health Promot* 2013; **2**: 50.

35. Shorten A, Shorten B, Keogh J, West S, Morris J. Making choices for childbirth: a randomized controlled trial of a decision-aid for informed birth after cesarean. *Birth (Berkeley, Calif)* 2005; **32**(4): 252-61.

36. Spoth R, Trudeau L, Shin C, et al. Longitudinal effects of universal preventive intervention on prescription drug misuse: three randomized controlled trials with late adolescents and young adults. *Am J Public Health* 2013; **103**(4): 665-72.

37. Spoth R, Trudeau L, Shin C, Redmond C. Long-term effects of universal preventive interventions on prescription drug misuse. *Addiction (Abingdon, England)* 2008; **103**(7): 1160-8.

38. Taylor JA, Kwan-Gett TS, McMahon EM, Jr. Effectiveness of a parental educational intervention in reducing antibiotic use in children: a randomized controlled trial. *The Pediatric infectious disease journal* 2005; **24**(6): 489-93.

39. Trepka MJ, Belongia EA, Chyou PH, Davis JP, Schwartz B. The effect of a community intervention trial on parental knowledge and awareness of antibiotic resistance and appropriate antibiotic use in children. *Pediatrics* 2001; **107**(1): E6.

40. Valiani M, Haghighatdana Z, Ehsanpour S. Comparison of childbirth training workshop effects on knowledge, attitude, and delivery method between mothers and couples groups referring to Isfahan health centers in Iran. *Iranian journal of nursing and midwifery research* 2014; **19**(6): 653-8.

41. Valles JA, Barreiro M, Cereza G, et al. A prospective multicenter study of the effect of patient education on acceptability of generic prescribing in general practice. *Health policy (Amsterdam, Netherlands)* 2003; **65**(3): 269-75.

42. Wirtz VJ, Herrera-Patino JJ, Santa-Ana-Tellez Y, Dreser A, Elseviers M, Vander Stichele RH. Analysing policy interventions to prohibit over-the-counter antibiotic sales in four Latin American countries. *Trop Med Int Health* 2013; **18**(6): 665-73.

43. Wutzke SE, Artist MA, Kehoe LA, Fletcher M, Mackson JM, Weekes LM. Evaluation of a national programme to reduce inappropriate use of antibiotics for upper respiratory tract infections: effects on consumer awareness, beliefs, attitudes and behaviour in Australia. *Health promotion international* 2007; **22**(1): 53-64.

Appendix 4. Summary of quality assessment of included studies

	Selection Bias	Study Design	Confounders	Blinding	Data Collection Methods	Withdrawal and Drop-outs	Overall Rating
Belongia, 2001	Weak	Moderate	Moderate	Weak	Strong	Weak	WEAK
Belongia, 2005	Weak	Moderate	Moderate	Moderate	Strong	Strong	MODERATE
Bernier, 2014	Strong	Moderate	Moderate	Moderate	Moderate	Moderate	STRONG
Cebotarenco, 2008	Moderate	Weak	Moderate	Weak	Weak	Weak	WEAK
Finkelstein, 2001	Moderate	Strong	Strong	Moderate	Strong	Strong	STRONG
Finkelstein, 2008	Moderate	Strong	Strong	Moderate	Strong	Strong	STRONG
Formoso, 2013	Moderate	Strong	Moderate	Moderate	Strong	Strong	STRONG
Fuertes, 2010	Strong	Moderate	Moderate	Moderate	Moderate	Moderate	STRONG
Gonzales, 2004	Weak	Moderate	Moderate	Moderate	Strong	Strong	MODERATE
Gonzales, 2005	Weak	Moderate	Moderate	Moderate	Strong	Strong	MODERATE
Gonzales, 2008	Moderate	Strong	Strong	Moderate	Strong	Strong	STRONG
Hennessy, 2002	Moderate	Strong	Weak	Moderate	Strong	Strong	MODERATE
Kliemann, 2016	Strong	Moderate	Weak	Moderate	Strong	Strong	MODERATE
Lambert, 2007	Moderate	Weak	Weak	Moderate	Moderate	Weak	WEAK
Lee, 2017	Weak	Strong	Weak	Weak	Moderate	Strong	WEAK
Mainous, 2009	Weak	Weak	Moderate	Weak	Weak	Weak	WEAK
McNulty, 2010	Moderate	Weak	Weak	Weak	Weak	Moderate	WEAK
Perz, 2002	Moderate	Moderate	Weak	Moderate	Strong	Strong	MODERATE
Sabuncu, 2009	Strong	Moderate	Moderate	Moderate	Moderate	Moderate	STRONG
Santa-Ana-Tellez, 2013	Strong	Moderate	Moderate	Moderate	Moderate	Moderate	STRONG
Santa-Ana-Tellez, 2015	Strong	Moderate	Moderate	Moderate	Moderate	Moderate	STRONG
Taylor, 2005	Weak	Weak	Weak	Moderate	Strong	Strong	WEAK
Trepka, 2001	Weak	Moderate	Moderate	Weak	Weak	Weak	WEAK
Wirtz, 2013	Strong	Moderate	Weak	Moderate	Strong	Strong	MODERATE
Wutzke, 2007	Strong	Moderate	Weak	Moderate	Moderate	Moderate	MODERATE
Beshears, 2013	Moderate	Moderate	Weak	Moderate	Strong	Strong	MODERATE
O'Malley, 2006	Moderate	Weak	Strong	Moderate	Strong	Strong	MODERATE
Sedjo, 2009	Moderate	Moderate	Weak	Moderate	Strong	Strong	MODERATE
Vallès, 2003	Moderate	Moderate	Strong	Moderate	Strong	Strong	STRONG
Hasak 2018	Weak	Weak	Weak	Weak	Weak	Moderate	WEAK
Lawrence, 2019	Moderate	Strong	Moderate	Weak	Moderate	Strong	MODERATE
Maughan, 2016	Weak	Moderate	Weak	Weak	Weak	Strong	WEAK
Rose, 2016	Weak	Weak	Weak	Weak	Weak	Moderate	WEAK
Spoth, 2008	Moderate	Moderate	Moderate	Weak	Moderate	Weak	WEAK
Spoth, 2013	Moderate	Moderate	Moderate	Weak	Moderate	Weak	WEAK
Eden, 2014	Weak	Moderate	Weak	Moderate	Strong	Moderate	WEAK
Fraser, 1997	Weak	Moderate	Weak	Moderate	Strong	Strong	WEAK
Hassani, 2016	Weak	Weak	Weak	Weak	Moderate	Strong	WEAK
Montgomery, 2007	Moderate	Moderate	Moderate	Moderate	Strong	Strong	STRONG
Navaee, 2015	Weak	Moderate	Weak	Moderate	Weak	Strong	WEAK
Sharifirad, 2013	Weak	Moderate	Weak	Weak	Weak	Strong	WEAK
Shorten, 2005	Weak	Moderate	Weak	Moderate	Strong	Moderate	WEAK
Valiani, 2014	Weak	Moderate	Weak	Weak	Weak	Strong	WEAK

CHAPTER FOUR

Contextualizing prevalent antibiotic misuse in children across China: a large-scale cross-sectional survey on parents' antibiotic use for common childhood illnesses in children

In this chapter, I report on secondary data analysis of a large-scale survey on antibiotic use for self-limiting illnesses among children under 13 across three provinces of different geographic regions and economic development stages in China. Data were collected from June 2017 to April 2018 by Zhejiang University. Institute of Social Medicine and Family Medicine.

I conducted the analysis plan design and analysis independently. The findings and results have been prepared as a draft of the manuscript, with comments on drafts from Professors James Hargreaves, Stephan Harbarth, Elizabeth Fearon, Xiaomin Wang, and Xudong Zhou. This manuscript has been submitted to the *Journal of Emerging Infectious Diseases* for publication consideration.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH1704488	**Title**	Ms.
First Name(s)	Leesa		
Surname/Family Name	Lin		
Thesis Title	Development of evidence-based behavioural interventions to reduce inappropriate use of antibiotics beyond clinical settings		
Primary Supervisor	Professor James Hargreaves		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Journal of Emerging Infectious Diseases
Please list the paper's authors in the intended authorship order:	Leesa Lin, James Hargreaves, Elizabeth Fearon, Stephan Harbarth, Xiaomin Wang, Xudong Zhou*
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Leesa Lin conducted the literature search, conducted data analysis and interpretation, and drafted and revised the manuscript. James Hargreaves and Elizabeth Fearon, supervised the data analysis and interpretation, and contributed to the first draft and following revisions of the manuscript. Stephan Harbarth contributed to data interpretation, and commented on the initial and following revisions of the manuscript. Xiaomin Wang contributed to data collection and interpretation, and commented on the initial and following revisions of the manuscript. Xudong Zhou conceived the study, led data collection, contributed to data interpretation, and commented on all drafts of this manuscript. All authors approved the final draft of this manuscript.

SECTION E

Student Signature	[redacted]
Date	09/09/2019

Supervisor Signature	[redacted]
Date	09/12/2019

Contextualizing prevalent antibiotic misuse in children across China: a large-scale cross-sectional survey on parents' antibiotic use on children for common childhood illnesses

SYNOPSIS

This study investigates antibiotic misuse behaviours among Chinese parents for their children. 9,526 parents of children (aged 0-13) across three Chinese provinces representing different geographical areas and economic development stages were surveyed. Antibiotic misuse was prevalent despite high levels of awareness of antimicrobial-resistance. 31.9% of children with self-limiting illnesses were self-medicated with antibiotics, with 70% of these antibiotics obtained from community pharmacies. Among children seeking care, 25.1% were administered antibiotics at home and 53.4% received antibiotic prescriptions, including 11.2% from parental demands. Parents with misconceptions about antibiotic efficacy and grandparents' input in child-care decisions were associated with antibiotic misuse in children. 48.1% of parents stored antibiotics at home leading to a higher likelihood of self-medication (aOR=4.98) while parental demands contributed to inappropriate prescriptions (aOR=3.43). The demand-side accounted for 40% of antibiotic use for childhood self-limiting illnesses. Context-appropriate multifaceted interventions are needed to improve antibiotic use for children.

INTRODUCTION

China, which accounts for half of global antibiotic consumption, has reportedly high rates of antibiotic misuse and antimicrobial resistance (AMR) [31,40], especially among Chinese children.[257,258] Parental knowledge and attitudes about common – and mostly self-limiting – childhood illnesses, such as the common cold and diarrhea, often lead parents to incorrectly conclude that antibiotics are necessary.[34,60,62,132,257,259-263] In a collective society like China that has experienced decades of one-child policy, childcare is the focus of not only parents, but extended family. Parents' antibiotic use for their children is influenced by multifaceted and interactive effects of personal and socio-environmental factors. A socio-ecological perspective[77,98] is needed to unpack this issue. To date, most interventions in China have been directed towards the supply-side of the healthcare system - prescribers and pharmacists - aimed at curbing over-prescribing, while demand-side factors such as inappropriate administration of antibiotics to children by parents or caregivers have barely been addressed. Few studies have been done to understand Chinese parental antibiotic use on children and available evidence is limited in scope to small-scale data in one geographic area, none of which considers the larger Chinese socio-cultural environment.[34,60,62,257,261-263]

This study aimed to (a) investigate antibiotic use for common childhood illnesses by parents across different geographical areas and economic development stages, (b) assess parental knowledge levels on antibiotic use and resistance for common childhood illnesses, (c) identify personal and socio-environmental factors of antibiotic misuse in children, and (d) estimate the impact of demand-side pressure for antibiotics on prescribing behaviours and the demand-side contribution to the overall use of antibiotics in Chinese children.

METHODS

Sites and population: This study used a cross-sectional survey, recruiting parents with children aged 0-13 years across three purposefully-selected Chinese provinces, between June 2017 and April 2018. China has 34 provinces, cities, and autonomous regions with wide regional inequality. We purposefully selected Zhejiang (East, ranked 5th in the 2017 provincial GDP ranking of economic development), Shaanxi (Central-Northwest, ranked 12th), and Guangxi (Southwest, ranked 26th) provinces.[264] The survey was administered to the parent identified as the primary person responsible for decision-making for the child.

Sampling: Parents were identified and recruited through their children. We anticipated the prevalence of common childhood illnesses within the last month to be 35% among young children. To ensure an adequate sample size for the planned subgroup analyses, the team aimed to achieve a valid sample size per province of ca. 3000 parents (i.e. 1500 per urban and rural area). Sample selection is stratified by urbanicity of residence (i.e. urban and rural) and by children's age groups (0-2, 3-5, and 6-13). Multistage stratified random cluster sampling was conducted in four stages, specifically provinces, prefecture-level cities, urban and rural areas, and lastly local sampling sites: primary schools (age 6-13), kindergartens (age 3-5), and community-based health centers (age 0-2, with a vaccination rate of 90% or higher[265]). Every prefecture-level city, its urban/rural areas, and the local sampling sites in the selected provinces had an equal chance of selection.

Questionnaire: This study used a systematically developed structured questionnaire. Questions were tailored to the Chinese sociocultural context, as informed by review of existing literature [62,261,266,267] and formative, qualitative interviews with stakeholders and experts. The questionnaire was comprised of four sections: 1) parental socio-demographic information, 2) antibiotics-related

knowledge, 3) last episode of illnesses and symptoms experienced by the child, and 4) treatment and care-seeking behaviours for their child's illness, including the chemical or brand names of antibiotics obtained from clinics and retail pharmacies. Before the formal survey, we conducted a pilot study with 315 respondents to validate the questionnaire and to evaluate potential sources of response error and improve the instrument. The reliability and validity fit the requirements.

Data collection: The survey was developed using Wen Juan Xing (Chinese equivalent of Survey Monkey) – a popular web-based platform for professional electronic questionnaire design and data collection – and delivered via WeChat, China's most-used communication application. With assistance from administrators at the schools and health centers, parents were recruited via paper or face-to-face invitations with informed consent. Participants could complete the questionnaire by scanning a QR code via a mobile device or accessing it directly online. Paper copies were provided if preferred. To avoid survey fatigue, the survey took no more than ten minutes. For data quality control, measures (e.g. trap questions and IP address control) were in place to detect random responses or duplications. A consent form was presented at the first section of the questionnaire that was signed by all participants. Participants were informed that participation was confidential, voluntary, and could be terminated at any time.

2.4 Main outcomes and exposures:

Behaviour outcomes: for the purpose of this study, unsupervised, non-prescription use of antibiotics for self-limiting illnesses was considered as antibiotic misuse.[268] Four types of antibiotic misuse were measured: keeping antibiotics at home for children, giving children antibiotics prophylactically, self-medication with non-prescription antibiotics, and asking/pressuring doctors for antibiotics if not initially prescribed.

Exposures: Four individual-level personal and socio-environmental factors were included: age of children, parents' antibiotic-related knowledge, grandparents' involvement in treatment decisions, and health facilities used for care.

2.5 Statistical analysis

We first presented the descriptive analysis on key exposures and antibiotic misuse in children for common childhood illnesses across three Chinese provinces. Levels of parents' antibiotic-related knowledge were measured in three domains – AMR awareness, misconceptions around antibiotic efficacy, and the ability to identify antibiotics). Scores for AMR awareness and antibiotic ability to identify antibiotics were created by adding the number of correct answers whereas scores for misconceptions were calculated by adding incorrect answers. A score of 0-1 was categorized as a low level, 2-3 medium, and 4 or above high. The internal consistency of the instrument was measured using Cronbach's alpha.

Unadjusted, univariate analyses were conducted to examine the associations between exposures and antibiotic misuse behaviours. Multivariable logistic regression and likelihood ratio tests were employed for adjusted analyses, controlling for socio-demographic variables and perceived severity of the illness (measured by number of symptoms expressed). The total percentage of missing values was low (< 11%)—these values were missing completely at random and therefore participants with missing data were excluded from final analyses according to the diagnostic results. Analyses were performed with STATA v.13.0.

RESULTS

3.1 Sample characteristics (Figure 1 and Table 1)

A total of 9,526 parents completed and returned a valid survey, with a response rate of 89%. The sex ratio of the children represented was 108:100, male vs

female; 44.7% were from a rural area, and 48.8% were only-children. The mean and standard deviation age was 5.8±3.6years. 69.7% of the parents surveyed reported that grandparents were involved in the care decisions for their children. Among the respondents, approximately 37.6% (n=3,579) self-reported that their children experienced a minor illness within a month, of whom 82.1% reported that it was a common cold, 47.7% sore throat, 31.0% fever, 12.5% diarrhea, and 3.3% otitis media with some overlap between symptoms. Profound regional differences were observed in parental socioeconomic composition, antibiotic use practices, and medical facilities used when children were ill.

3.2 Antibiotics-related knowledge and misconceptions (Table 2)

Respondents were assessed on their antibiotics-related knowledge. The overall Cronbach's alpha including all items was 0.92, with subscales ranging from 0.83-0.89. Three quarters of surveyed parents (72.5-78.5%) reported they were aware of the danger that overuse of antibiotics poses to the country. Yet, more than half (52.8%) had a high level of misconception. Less than 20% of parents correctly stated that antibiotics were not anti-inflammatory drugs and did not work for viruses. Although 62-64% knew that antibiotics are not appropriate for children with a cold, three out of five were unsure or wrongly stated that antibiotics might help expedite recovery or alleviate symptoms. Overall, a majority of parents had a high level of AMR awareness and ability to identify antibiotics (Table 1: n=5,832, 61.2% and n=5,137, 53.9%, respectively).

3.3 Antibiotic misuse in Chinese children outside of clinical settings (Tables 3 and 4)

More than half of the participating parents who reported an illness in their child treated their children (54.3%, n=1,944); among them, 31.9% (n=621) self-reported to have self-medicated with antibiotics (SMA). A majority of the antibiotics

for SMA came from a local pharmacy (57.0%) and one-third from a personal stock (33.3%), which mostly had come from leftover prescriptions (63.1%) and leftover purchases from a local pharmacy (35.3%) – in other words, community pharmacies accounted for roughly 70% of SMA for children. After adjusting for confounders, parents with higher scores in AMR awareness, ability to identify antibiotics and misconceptions about antibiotic efficacy were more likely to store antibiotics for their children's use (aOR=1.48 95%CI 1.28-1.71, aOR=3.01, 95%CI 2.61-3.47 and aOR=1.86, 95%CI 1.62-2.12, respectively) and to administer antibiotics prophylactically (aOR=1.22 95%CI 1.02-1.44, aOR=1.48, 95%CI 1.26-1.75 and aOR=3.44 95%CI 2.82-4.18, respectively). Parents with high ability to identify antibiotics and misconceptions were also more likely to self-treat their children with antibiotics when children were ill (aOR=1.84, 95%CI 1.28-2.63 and aOR=4.55 95%CI 3.21-6.46, respectively). When grandparents were involved in the childcare decisions, parents were more likely to keep antibiotics at home (aOR=1.21, 95%CI 1.10-1.33) and give them to children prophylactically (aOR=1.24, 95%CI 1.10-1.39). Those who kept antibiotics at home were more likely to give their children antibiotics for preventive use and when children were ill (aOR=3.28, 95%CI 2.69-4.01 and aOR=4.98, 95%CI 3.85-6.43 - see Supplement Tables A and B).

3.4 Determinants and results of healthcare-seeking (Table 5)

In total, parents of 70% of children (n=2,478) who were ill in the past month sought care for their children. A majority of parents brought their child to the doctor when otitis media or fever was present (57.1% and 51.0%, respectively), and one in three were prompted by a runny/stuffed nose, a cough (30.8%), or a sore throat (34.9%). Before seeing a doctor, 16.5% (n=410) of children had already been medicated with antibiotics at home; moreover, among them, 15.4% of parents admitted to having then asked for more antibiotics at the facility. Among those who

sought care after SMA, 83.9% (n=344, p<0.0001) were prescribed with antibiotics and 17.2% (n= 59) were due to further parental demands with a success rate of 93.7%. The majority of children whose parents pressured doctors for antibiotics were prescribed with infusion or a combination of infusion and oral antibiotics (51%, p<0.0001). Parents were found to be more likely to ask for antibiotics for their children in lower level hospitals than in tertiary hospitals. Parents with high levels of ability to identify antibiotics and misconceptions about antibiotic efficacy were more likely to receive antibiotic prescriptions (aOR=2.27, 95%CI 1.73-2.99 and aOR=2.03, 95%CI 1.56-2.66, respectively) and to ask doctors for antibiotics (aOR=2.38, 95%CI 1.38-4.10 and aOR=2.86, 95%CI 1.50-5.43, respectively), which led to a more than three-fold increase in being prescribed antibiotics (aOR=3.43, 95%CI 2.34-5.03 – see Supplement Table C), all of which were deemed to be inappropriate prescriptions.

Overall, 53.4% of children (n=1,323) for whom care was sought were prescribed antibiotics. The most commonly prescribed antibiotic classes were penicillins, macrolides, and cephalosporins – either alone or in combination. Differences emerge in antibiotic prescription rates by healthcare facilities used, ranging from 47.4% in tertiary hospitals to 56.0% in county hospitals. More than one in three children were administered intravenous antibiotics (injections/infusions) for self-limiting conditions, evenly across all developmental stages, and about half of those infusions were combined with oral antibiotics. As children grow older, parents became more likely to demand antibiotics.

Our data showed that, out of the 3,579 Chinese children who had self-limiting conditions in the prior month, 1639 (45.8%) had used antibiotics at least once; among them, 621 were self-administered nonprescription antibiotics while 1323 obtained a prescription, with 148 of those deemed inappropriate due to patient

pressure. Therefore, we estimated the demand-side contributed 40% [(148+621)/(1323+621)] of antibiotic use on Chinese children for self-limiting illnesses, compared with 60% on the supply-side. Though some doctors' prescriptions (supply-side) might be considered appropriate, all antibiotic demands and non-prescription uses from the demand-side were misuse.

DISCUSSION

Our findings demonstrate that the prevalence of antibiotic misuse in children is high across China. 31.9% of parents self-medicated their children with antibiotics when a common minor childhood ailment was presented. Of 2,478 children who sought care, 53.4% resulted in antibiotic prescriptions - a majority of which were for self-limiting illnesses and deemed inappropriate - and 25.1% had already received antibiotics at home before the visit. The high prevalence of antibiotic misuse in Chinese children is influenced by both parents' misconception about antibiotic efficacy for minor ailments and their surrounding social (e.g. family dynamics), healthcare (e.g. prescribing practice and doctor-patient interactions) and political contexts (e.g. laws and enforcement). Contrary to a previous study stating antibiotics abuse in China is not driven by patients actively demanding antibiotics,[56] here we quantified the impact of the demand-side pressure on pediatric outpatient antibiotic prescribing: parents who self-reported to have pressured for antibiotics were more likely to be prescribed with antibiotics than parents who did not. Chinese parents are responsible for the majority (40%) of antibiotic misuse on self-limiting childhood illnesses. Keeping antibiotics at home increases the odds of prevention use in children by three times and the odds of SMA when ill by five times. Consistent with other studies,[45,60] non-prescription sales of antibiotics at Chinese community pharmacies were found to be prevalent in all sampled sites. We estimated retail

pharmacies accounted for 70% of SMA in children. Although the Chinese Ministry of Health (MOH) issued an antimicrobial stewardship policy in 2012 limiting outpatient prescriptions with antibiotics to 20% for county hospitals and above and 30% for township hospitals, and the Chinese Food and Drug Administration (FDA) regulations have forbidden non-prescription sales at retail pharmacies since 2004,[269,270] the impact of these policies has evidently been limited.

The strength of this study is that we focused on common childhood illnesses with access to prescriptions across all levels of the health system in China. This is the first large-scale study that shows Chinese parents' knowledge, attitudes and practices of antibiotic use for children in their socio-cultural environmental context across different geographical areas and economic development stages, where antibiotic misuse was found in parents' chronic drug use habits, pre-visit medication for children, and demand for antibiotic prescriptions during visits. We demonstrated how parental antibiotic use in children is influenced by a set of complex and interactive socio-ecological factors. We acknowledge several limitations in our study. First, this is a cross-sectional survey and therefore cannot establish causal conclusions and is subject to recall bias. However, we limited the healthcare-seeking behaviours to a month prior - though it required a larger sample size – which helped to reduce the potential for bias. Second, the antibiotic consumption was estimated by a snapshot survey and not by prescriptions or visits; therefore, the true magnitude of misuse in children may be well-underestimated because repeated visit and use data were not included. Given young children present up to ten times a year with acute respiratory infections,[14,271] the situation of misuse is expected to be much more severe than presented here. Lastly, because the samples were clustered, the estimated standard errors used in significance tests may be biased. Specifically, the estimated standard errors might be under-estimated because the similarities between

individuals within clusters are greater than those among individuals in a random sample drawn from the population. As such, significance levels reported might have been over-reported or underreported. However, in our case, samples were drawn from three provinces of different development levels and then from the rural and urban areas within each province; the differences among these provinces and/or between rural and urban areas might be greater than those between individuals drawn from a random sample across the country. Variations at the provinces and/or urbanicity levels were accounted for in the analyses.

Compared with the estimate regarding university students,[45] parents appeared to be more cautious, but still drove 40% of antibiotic misuse in children. Overuse of medical care for self-limiting illnesses combined with a high prescription rate and the population size of the country drove the overall high antibiotic consumption in China. In our data, about 77.3% of children with common cold symptoms in the past month sought care, which was more than twice as many as those in UK (34-40%).[272] The possibility of receiving an antibacterial prescription for such symptoms was around 33% in UK,[273,274] compared to 53% in our survey. As such, we estimated that an average Chinese child consumes more than three times the amount of antibiotics as their peers in UK or other European countries.[273,275-277] The gap is even wider for Chinese children in infancy and early childhood, as they have higher usage of medical care than older children. This estimate is alarming considering it did not account for non-prescription use antibiotics in Chinese children. Our data indicates one in four Chinese children (n= 2,464, 25.9%) has self-medicated with antibiotics at least once in the past year - either for prevention use or treating minor ailments, which is 10 times higher than that of some European countries.[275-277] The true magnitude of this problem is underestimated because repeated use was not included in the calculation. This estimate is consistent with a survey conducted in 1995 and

demonstrates that Chinese parental antibiotic misuse for their children has not improved over the past two decades.[278] Such persistent, high levels of misuse should be understood through the lens of China's socio-ecological context.[279,280]

At the intrapersonal level, our data suggested the link between knowledge and behaviours is not straightforward, and may even at times appear counter-intuitive. Previous studies also identified this predicament – despite having a high level of knowledge, a majority of people still expect to get antibiotic prescriptions for self-limiting illnesses.[276,281] We found misconceptions about antibiotic efficacy played a more determining role in respect to actual antibiotic misuse behaviours than did other types of antibiotics-related knowledge, such as AMR awareness, which showed a limited impact on improving antibiotic use. Interventions which aim to correct these misconceptions might be more effective than a general AMR awareness campaign. This phenomenon might be explained by the "negative externality" associated with antibiotic use, where the parent focus is on the immediate alleviation of their own child's illness with little regard for the burden this behaviour places on society in the long run.[282] We also found that Chinese consumers often confused antibiotics for anti-inflammatory drugs, and were confused by their various types and efficacy, and by their chemical components, brand names and/or drug labels. Without adequate knowledge about care for illnesses and antibiotic efficacy, our data indicated that those with high ability to identify antibiotics might be more likely to seek out and misuse antibiotics. Studies have shown previous recommendations from a physician for similar symptoms and prior successful experiences with antibiotics could lead to higher use, including SMA.[160,283,284] Therefore, reverse causality is also likely, where high usage of antibiotics led to higher ability to identify antibiotics about the drugs. Operating in such a context, interventions that aim to increase AMR awareness and ability to

identify antibiotics alone but do not address local misconceptions might be counterproductive and may actually increase public demand for antibiotics. This paradox was also recently reported in the UK and Greece.[276,285,286] To effectively reduce antibiotic misuse in China, interventions should aim to educate the public about antibiotic efficacy, care for childhood illnesses, and correct local misconceptions.

Interpersonally, our data highlighted the importance of understanding how local culture influences healthcare decision making, including interactions with health care providers. Education interventions to improve children's antibiotic use must also target families as a whole, especially grandparents. Contrary to a previous finding,[56] we found that caregivers' high expectations of antibiotics for symptom relief and recovery for their children, coupled with the peculiar doctor-patient relationship in China,[287] may increase pressures (i.e. negative externality) on doctors to inappropriately overprescribe.[35,160] This might be further fueled by a local belief shared among Chinese medical professionals and the public that antibiotics act as a panacea for most illnesses.[31] Realigning such deep-rooted beliefs requires a multifaceted antibiotic stewardship program that both enhances prudent prescribing and improves doctor–patient communication.

Finally, consistent with previous findings, Chinese county hospitals were found to have the highest antibiotic prescription rates[36] and, similar to other countries, community pharmacies and leftovers are the most common sources of non-prescription antibiotics.[60,288] This study identified an immediate need to strengthen policy interventions at a structural level to enforce the restrictions on non-prescription sales and over-prescribing rates at lower level hospitals,[270] to implement a dose-based antibiotic dispensing system, and to encourage safe disposal or take-back of leftover antibiotics. Chinese parents were more careful with antibiotic use in

infants, but more likely to misuse antibiotics on older children. A preference for IV infusion for children is still prevalent among Chinese parents. This phenomenon is a product of Chinese hospitals' financial incentives, as well as the expectations of consumers for rapid recovery. It is also fueled by widespread accepting attitudes towards the use of needles in Chinese society,[289] influenced by the concept of acupuncture - an ancient traditional Chinese medical treatment. Since 2012, many Chinese hospitals have made an effort to limit or stop outpatient infusion treatments,[270] yet these regulations have not been adopted by most lower level hospitals and exclude pediatric patients. Furthermore, over-prescription in rural China may be due to deficits in diagnostic knowledge among providers;[126] improving their professional capacity is necessary.

CONCLUSION

This study has provided a comprehensive picture of overall antibiotic misuse in children and contextualized the underlying issues related to parents' routine medication practices and attitudes towards childhood illnesses and antibiotic use, intertwined with inadequate government oversight on retail sales and clinicians' prescribing behaviours. Context-tailored interventions that aim to correct misconceptions about antibiotic efficacy should be taken as a priority; otherwise AMR awareness and ability to identify antibiotics will continue to be linked to antibiotic misuse. Demand-side factors played a critical role in children's antibiotic misuse in China. Physicians' prescribing behaviour was significantly influenced by parents' expectations and demand of antibiotics. This study addressed a national priority in China and called for culturally grounded approaches to reducing AMR and antibiotic misuse, especially in children.

Table 1. Sample characteristics, by province (N=9526)

Province Region, National GDP ranking n (%)	**Zhejiang** East, 5th 2,924 (30.69)		**Shaanxi** Central-Northwest, 12th 3,355 (35.22)		**Guangxi** Southwest, 26th 3,247 (34.09)		**Total** 9526 (100%)
	Urban	Rural	Urban	Rural	Urban	Rural	
	1715 (58.65)	1209 (41.35)	1940 (57.82)	1415 (42.18)	1610 (49.58)	1637 (50.42)	
Sex of children							
Male	888 (51.78)	623 (51.53)	967 (49.85)	716 (50.60)	874 (54.29)	875 (53.45)	4,943 (51.89)
Female	827 (48.22)	586 (48.47)	973 (50.15)	699 (49.40)	736 (45.71)	762 (46.55)	4,583 (48.11)
Age of children							
0-2 Infancy	271 (15.80)	262 (21.67)	368 (18.97)	373 (26.36)	440 (27.33)	274 (16.74)	1,988 (20.87)
3-8 early childhood	934 (54.46)	556 (45.99)	1056 (54.43)	724 (51.17)	847 (52.61)	830 (50.70)	4,947 (51.93)
9-11 middle childhood	412 (24.02)	348 (28.78)	429 (22.11)	288 (20.35)	288 (17.89)	447 (27.31)	2,212 (23.22)
12-13 adolescence	98 (5.71)	43 (3.56)	87 (4.48)	30 (2.12)	35 (2.17)	86 (5.25)	379 (3.98)
Average household income (RMB, monthly)							
<=3,000 ($461)	28 (1.63)	95 (7.86)	296 (15.26)	457 (32.30)	283 (17.58)	943 (57.61)	2,102 (22.07)
3,001-5,000 ($462-$769)	187 (10.90)	332 (27.46)	724 (37.32)	570 (40.28)	575 (35.71)	501 (30.60)	2,889 (30.33)
5,001-10,000 ($770-$1538)	538 (31.37)	495 (40.94)	710 (36.60)	330 (23.32)	520 (32.30)	156 (9.53)	2,749 (28.86)
>10,001 (>$1539)	962 (56.09)	287 (23.74)	210 (10.82)	58 (4.10)	232 (14.41)	37 (2.26)	1,786 (18.75)
Parents' education level							
Primary school or below	15 (0.87)	41 (3.39)	60 (3.09)	50 (3.53)	69 (4.29)	200 (12.22)	435 (4.57)
Middle school	137 (7.99)	378 (31.27)	484 (24.95)	569 (40.21)	369 (22.92)	826 (50.46)	2,763 (29.00)
High school	272 (15.86)	333 (27.54)	631 (32.53)	499 (35.27)	513 (31.86)	420 (25.66)	2,668 (28.01)
College or above	1291 (75.28)	457 (37.80)	765 (39.43)	297 (20.99)	659 (40.93)	191 (11.67)	3,660 (38.42)
Parents with medical background							
No	1484 (86.53)	1095 (90.57)	1651 (85.10)	1268 (89.61)	1394 (86.58)	1512 (92.36)	8,404 (88.22)
Yes	231 (13.47)	114 (9.43)	289 (14.90)	147 (10.39)	216 (13.42)	125 (7.64)	1,122 (11.78)
Severity							
Low (1 symptom)	190 (30.69)	122 (30.35)	282 (38.06)	229 (41.41)	244 (36.15)	210 (35.65)	1,277 (35.68)
Medium (2 symptoms)	268 (43.30)	163 (40.55)	316 (42.65)	196 (35.44)	263 (38.96)	198 (33.62)	1,404 (39.23)
High (3 or more symptoms)	161 (26.01)	117 (29.10)	143 (19.30)	128 (23.15)	168 (24.89)	181 (30.73)	898 (25.09)
Type of primary caregiver							
Parents	1377 (80.29)	988 (81.72)	1640 (84.54)	1156 (81.70)	1327 (82.42)	1415 (86.44)	7,903 (82.96)
Grandparents	332 (19.36)	216 (17.87)	284 (14.64)	244 (17.24)	269 (16.71)	200 (12.22)	1,545 (16.22)
Other	6 (0.35)	5 (0.41)	16 (0.82)	15 (1.06)	14 (0.87)	22 (1.34)	78 (0.82)
Antibiotics-related knowledge							
AMR Awareness							
Low	96 (5.60)	191 (15.80)	281 (14.48)	311 (21.98)	326 (20.25)	556 (33.96)	1,761 (18.49)
Medium	225 (13.12)	252 (20.84)	411 (21.19)	360 (25.44)	343 (21.30)	342 (20.89)	1,933 (20.29)
High	1394 (81.28)	766 (63.36)	1248 (64.33)	744 (52.58)	941 (58.45)	739 (45.14)	5,832 (61.22)
Misconception							
Low	489 (28.51)	214 (17.70)	283 (14.59)	144 (10.18)	184 (11.43)	153 (9.35)	1,467 (15.40)
Medium	645 (37.61)	404 (33.42)	573 (29.54)	403 (28.48)	571 (35.47)	429 (26.21)	3,025 (31.76)
High	581 (33.88)	591 (48.88)	1084 (55.88)	868 (61.34)	855 (53.11)	1055 (44.45)	5,034 (52.84)
Ability to identify antibiotics							
Low	138 (8.05)	217 (17.95)	320 (16.49)	371 (26.22)	324 (20.12)	506 (30.91)	1,876 (19.69)
Medium	363 (21.17)	321 (26.55)	542 (27.94)	389 (27.49)	447 (27.76)	451 (27.55)	2,513 (26.38)
High	1214 (70.79)	671 (55.50)	1078 (55.57)	655 (46.29)	839 (52.11)	680 (41.54)	5,137 (53.93)
Grandparents' involvement in treatment decisions							
No	513 (29.91)	338 (27.96)	649 (33.45)	438 (30.95)	491 (30.50)	453 (27.67)	2,882 (30.25)
Yes	1202 (70.09)	871 (72.04)	1291 (66.55)	977 (69.05)	1119 (69.50)	1184 (72.33)	6,644 (69.75)
Children who were reported to be ill in the past month							
No	1096 (63.91)	807 (66.75)	1199 (61.80)	862 (60.92)	935 (58.07)	1048 (64.02)	5947 (62.43)
Yes	619 (36.09)	402 (33.25)	741 (38.20)	553 (39.08)	675 (41.93)	589 (35.98)	3579 (37.57)
Healthcare delivery system used (Urban/Rural)							
Tertiary hospital	40 (9.59)	26 (8.70)	76 (15.26)	38 (9.48)	145 (30.98)	42 (10.63)	367 (14.81)
Secondary/County hospital	327 (78.42)	151 (50.50)	162 (32.53)	159 (39.65)	114 (24.36)	144 (36.46)	1,057 (42.66)
Community Health Centers/Township hospital	47 (11.27)	120 (40.13)	157 (31.53)	111 (27.68)	131 (27.99)	153 (38.73)	719 (29.02)
Private Clinics/Village clinics	3 (0.72)	2 (0.67)	103 (20.68)	93 (23.19)	78 (16.67)	56 (14.18)	335 (13.52)
Keep antibiotics at home for children							
No	867 (50.55)	724 (59.88)	772 (39.79)	633 (44.73)	958 (59.50)	992 (60.60)	4946 (51.92)
Yes	848 (49.45)	485 (40.12)	1168 (60.21)	782 (55.27)	652 (40.50)	645 (39.40)	4580 (48.08)
Giving children antibiotics prophylactically							
No	1447 (84.37)	988 (81.72)	1417 (73.04)	1014 (71.66)	1339 (83.17)	1338 (81.73)	7543 (79.18)
Yes	268 (15.63)	221 (18.28)	523 (26.96)	401 (28.34)	271 (16.83)	299 (18.27)	1983 (20.82)
Self-treated children with antibiotics when being ill							
No	282 (78.99)	172 (85.15)	240 (57.28)	159 (55.23)	270 (73.77)	200 (61.92)	1,323 (68.06)
Yes	75 (21.01)	30 (14.85)	179 (42.72)	118 (44.77)	96 (26.23)	123 (38.08)	621 (31.94)
Asked doctors for antibiotics							
No	385 (92.33)	275 (91.97)	457 (91.77)	381 (95.01)	443 (94.66)	351 (88.86)	2292 (92.49)
Yes	32 (7.67)	24 (8.03)	41 (8.23)	20 (4.99)	25 (5.34)	44 (11.14)	186 (7.41)
Prescribed with antibiotics							
No	177 (42.45)	188 (62.88)	207 (41.57)	183 (45.64)	217 (46.37)	183 (46.33)	1155 (46.61)
Yes	240 (57.55)	111 (37.12)	291 (58.43)	218 (54.36)	251 (53.63)	212 (53.67)	1323 (53.39)

Table 2. Antibiotics-related knowledge among Chinese parents (N=9,526)

	Yes	No	Don't Know	alpha	Overall alpha
AMR Awareness				0.89	0.92
[Do you think the following statement is true (or not)?]					
The more frequently people use antibiotics, the harder it is to cure the bacteria infections	**6,902 (72.45)**	609 (6.39)	2,015 (21.15)		
Excessive use of antibiotics can lead to bacterial antibiotic resistance	**7,475 (78.47)**	267 (2.80)	1,784 (18.73)		
Excessive use of antibiotics is a serious problem in China	**7,420 (77.89)**	175 (1.84)	1,931 (20.27)		
Bacterial antibiotic resistance in China will become a serious problem	**6,999 (73.47)**	190 (1.99)	2,337 (24.53)		
Misconception				0.83	
[Do you think the following statement is true (or not)?]					
Antibiotics are anti-inflammatory drugs	5,764 (60.51)	**1,824 (19.15)**	1, 938 (20.34)		
Antibiotics are effective for children's viral infections.	5,416 (56.85)	**1,934 (20.30)**	2,176 (22.84)		
Antibiotics is appropriate when your child has [Sore throat]	2,356 (24.73)	**5,911 (62.05)**	1,259 (13.22)		
Antibiotics is appropriate when your child has [Cold/Runny or stuffy nose]	2,210 (23.20)	**6,186 (64.94)**	1,130 (11.86)		
Using antibiotics can speed up your child's cold recovery	3,547 (37.23)	**4,062 (42.64)**	1,917 (20.12)		
Using antibiotics can alleviate your child's cold symptoms	3,824 (40.14)	**3,636 (38.17)**	2,066 (21.69)		
Ability to recognise antibiotics				0.86	
[Do you think the following drug is an antibiotic (or not)?]					
Penicillin (amoxicillin)	**7,103 (74.56)**	897 (9.42)	1,526 (16.02)		
Cephalosporin (cefaclor, ceftriaxone sodium)	**7,179 (75.36)**	788 (8.27)	1,559 (16.37)		
Nonsteroidal anti-inflammatory drugs (ibuprofen, aspirin)	3,792 (39.81)	**3,086 (32.40)**	2,648 (27.80)		
Steroidal (Dexamethasone, Prednisone)	2,833 (29.74)	**2,725 (28,61)**	3,968 (41.65)		
Quinolones (norfloxacin, ofloxacin)	**4,626 (48.56)**	1,704 (17.89)	3,196 (33.55)		
Macrolides (azithromycin, roxithromycin)	**6,234 (65.44)**	831 (8.72)	2,461 (25.83)		

*Correct answers are in bold.

Table 3. Factors of habitual nonprescription antibiotic use on children among Chinese parents (N=9526)

	N=9526	Keep antibiotics at home for children (n=4,580, 48.08%)				Giving children antibiotics prophylactically (n=1,983, 20.82%)			
	N (%)	n (%)	OR (95%CI)	aOR (95%CI)	p-value[b]	n (%)	OR (95%CI)	aOR (95%CI)	p-value[b]
Individual Factors:									
Age of children					<0.0001				<0.001
0-2 Infancy	1,988 (20.87)	717 (36.07)	Reference	Reference		349 (17.56)	Reference	Reference	
3-8 early childhood	4,947 (51.93)	2,669 (53.95)	**2.08 (1.87-2.31)**	**1.86 (1.65-2.08)**		1,075 (21.73)	**1.30 (1.14-1.49)**	**1.31 (1.14-1.51)**	
9-11 middle childhood	2,212 (23.22)	1,035 (46.79)	**1.56 (1.38-1.76)**	**1.55 (1.36-1.78)**		489 (22.11)	**1.33 (1.14-1.55)**	**1.33 (1.13-1.56)**	
12-13 adolescence	379 (3.98)	159 (41.95)	**1.28 (1.02-1.60)**	**1.28 (1.01-1.63)**		70 (18.47)	1.06 (0.80-1.41)	1.09 (0.81-1.46)	
Antibiotics-related Knowledge									
AMR Awareness					<0.0001				<0.0005
Low	1,761 (18.49)	531 (30.15)	Reference	Reference		322 (18.29)	Reference	Reference	
Medium	1,933 (20.29)	912 (47.18)	**2.07 (1.81-2.37)**	**1.30 (1.11-1.51)**		476 (24.62)	**1.46 (1.25-1.71)**	**1.36 (1.14-1.62)**	
High	5,832 (61.22)	3,137 (53.79)	**2.70 (2.41-3.02)**	**1.48 (1.28-1.71)**		1,185 (20.32)	**1.14 (0.99-1.31)**	**1.22 (1.02-1.44)**	
Misconception					<0.0001				<0.0001
Low	1,467 (15.40)	679 (46.28)	Reference	Reference		137 (9.34)	Reference	Reference	
Medium	3,025 (31.76)	1,446 (47.80)	1.06 (0.94-1.20)	**1.32 (1.15-1.51)**		546 (18.05)	**2.14 (1.75-2.61)**	**2.08 (1.69-2.54)**	
High	5,034 (52.84)	2,455 (48.77)	1.10 (0.98-1.24)	**1.86 (1.62-2.12)**		1,300 (25.82)	**3.38 (2.80-4.07)**	**3.44 (2.82-4.18)**	
Ability to identify antibiotics					<0.0001				<0.0001
Low	1,876 (19.69)	487 (25.96)	Reference	Reference		325 (17.32)	Reference	Reference	
Medium	2,513 (26.38)	1,203 (47.87)	**2.62 (2.30-2.98)**	**2.26 (1.95-2.61)**		592 (23.56)	**1.47 (1.26-1.71)**	**1.51 (1.28-1.79)**	
High	5,137 (53.93)	2,890 (56.26)	**3.67 (3.26-4.12)**	**3.01 (2.61-3.47)**		1,066 (20.75)	**1.25 (1.09-1.43)**	**1.48 (1.26-1.75)**	
Interpersonal Factors									
Grandparents' involvement in treatment decisions					0.0001				<0.0005
No	2,882 (30.25)	1,305 (45.28)	Reference	Reference		525 (18.22)	Reference	Reference	
Yes	6,644 (69.75)	3,275 (49.29)	**1.17 (1.08-1.28)**	**1.21 (1.10-1.33)**		1,458 (21.94)	**1.26 (1.13-1.41)**	**1.24 (1.10-1.39)**	

OR, odds ratio; CI, confidence interval.

[a]Adjusted for children's sex, parents' education and medical background, primary carer, urban/rural residence, province, and household income.

[b]Likelihood ratio test

Table 4. Factors of self-treated children with antibiotics who were ill in the past month (N=1944)

	N=1944	Self-treated children with antibiotics who were ill in the past month (n= 621, 31.94%)			
	N (%)	n (%)	OR	aOR (95%CI)	p-value[b]
Individual Factors:					
Age of children					0.005
0-2 Infancy	360 (18.52)	99 (27.50)	Reference	Reference	
3-8 early childhood	1,238 (63.68)	398 (32.15)	1.25 (0.96-1.62)	**1.41 (1.06-1.87)**	
9-11 middle childhood	310 (15.95)	119 (38.39)	**1.64 (1.19-2.27)**	**1.51 (1.05-2.18)**	
12-13 adolescence	36 (1.85)	5 (13.89)	0.43 (0.16-1.12)	0.42 (0.15-1.16)	
Antibiotics-related Knowledge					
AMR Awareness					0.15
Low	223 (11.47)	72 (32.29)	Reference	Reference	
Medium	328 (16.87)	130 (39.63)	1.38 (0.96-1.97)	1.39 (0.93-2.08)	
High	1,393 (71.66)	419 (30.08)	0.90 (0.67-1.22)	1.09 (0.75-1.60)	
Misconception					<0.0001
Low	344 (17.70)	52 (15.12)	Reference	Reference	
Medium	628 (32.30)	153 (24.36)	**1.81 (1.28-2.56)**	**1.90 (1.32-2.74)**	
High	972 (50.00)	416 (42.80)	**4.20 (3.05-5.79)**	**4.25 (2.98-6.07)**	
Ability to identify antibiotics					<0.005
Low	249 (12.81)	70 (28.11)	Reference	Reference	
Medium	495 (25.46)	163 (32.93)	1.26 (0.90-1.75)	**1.60 (1.10-2.32)**	
High	1,200 (61.73)	388 (32.33)	1.22 (0.90-1.65)	**1.91 (1.32-2.76)**	
Interpersonal Factor:					
Grandparents' involvement in treatment decisions					0.22
No	524 (26.95)	181 (34.54)	Reference	Reference	
Yes	1420 (73.05)	440 (30.99)	0.85 (0.69-1.05)	0.86 (0.68-1.09)	

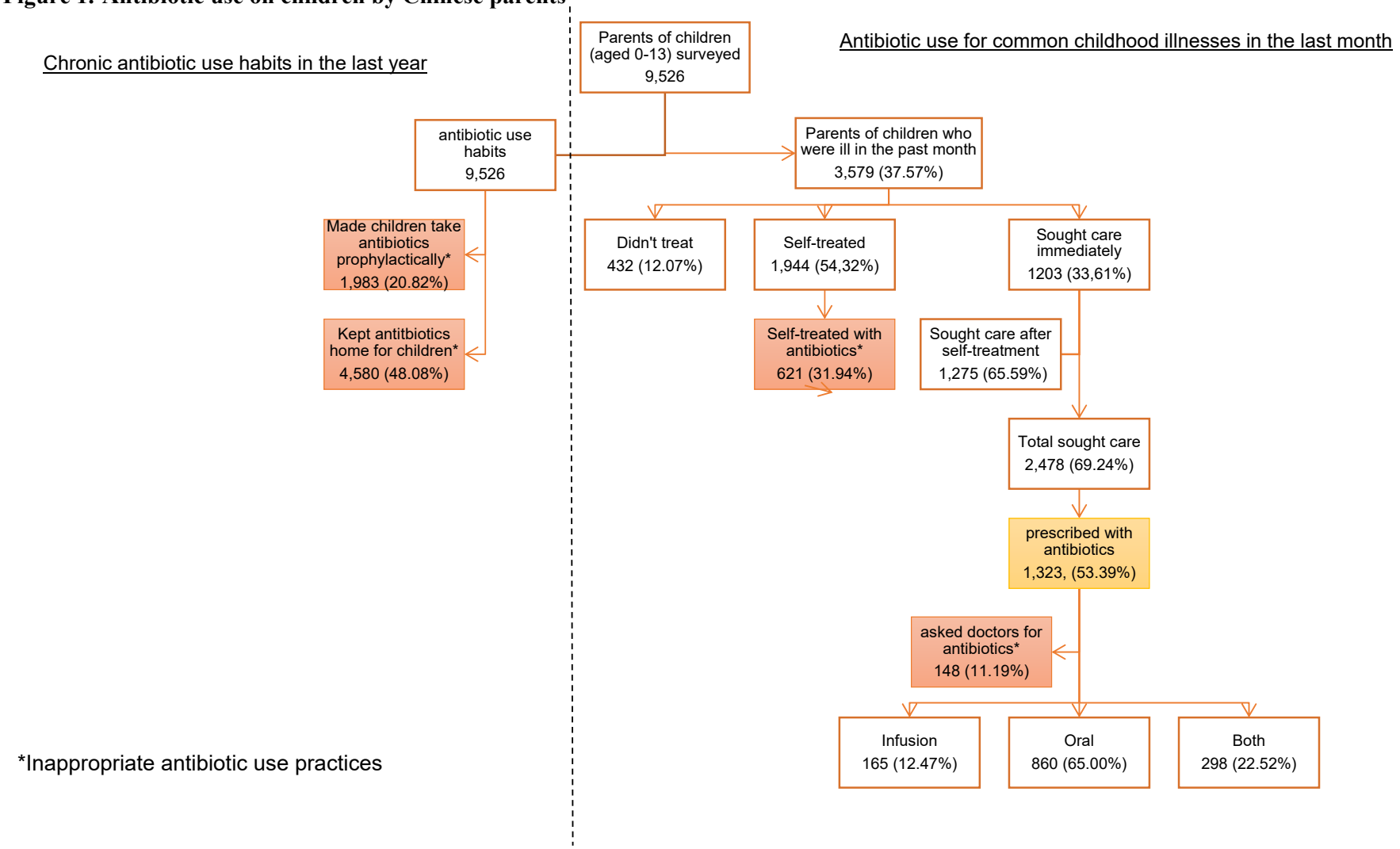
OR, odds ratio; CI, confidence interval.
[a]Adjusted for children's sex, perceived severity, parents' education and medical background, primary carer, urban/rural residence, province, and household income.
[b]Likelihood ratio test

Table 5. Factors of antibiotic prescriptions for children who were ill in the past month (N=2478)

	N=2478	**Prescribed with antibiotics (n= 1,323, 53.39%)**				**Asked doctors for antibiotics (n=186, 12.19%)**			
	N (%)	n (%)	OR	aOR (95%CI)	p-value[b]	n (%)	OR	aOR (95%CI)	p-value[b]
Individual Factors:									
Age of children					<0.01				0.005
0-2 Infancy	603 (24.33)	281 (46.60)	Reference	Reference		26 (4.31)	Reference	Reference	
3-8 early childhood	1,448 (58.43)	816 (56.35)	**1.48 (1.22-1.79)**	1.23 (0.99-1.52)		108 (7.46)	**1.79 (1.15-2.77)**	**1.75 (1.10-2.79)**	
9-11 middle childhood	371 (14.97)	206 (55.53)	**1.43 (1.10-1.86)**	1.16 (0.87-1.54)		46 (12.40)	**3.14 (1.91-5.18)**	**2.53 (1.39-4.32)**	
12-13 adolescence	56 (2.26)	20 (35.71)	0.64 (0.36-1.13)	**0.49 (0.27-0.90)**		6 (10.71)	**2.66 (1.05-6.77)**	**2.53 (1.23-6.70)**	
Antibiotics-related Knowledge									
AMR Awareness					0.01				0.01
Low	402 (16.22)	161 (40.05)	Reference	Reference		34 (8.46)	Reference	Reference	
Medium	488 (19.69)	262 (53.69)	**1.74 (1.33-2.27)**	**1.45 (1.08-1.95)**		51 (10.45)	1.26 (0.80-1.99)	1.09 (0.66-1.81)	
High	1588 (64.08)	900 (56.68)	**1.96 (1.57-2.45)**	**1.52 (1.15-2.03)**		101 (6.36)	0.74 (0.49-1.10)	**0.62 (0.37-1.02)**	
Misconception					<0.0001				<0.0005
Low	356 (14.37)	165 (46.35)	Reference	Reference		12 (3.37)	Reference	Reference	
Medium	783 (31.60)	401 (51.21)	**1.22 (0.95-1.56)**	**1.39 (1.06-1.81)**		44 (5.62)	1.71 (0.89-3.27)	1.64 (0.84-3.20)	
High	1339 (54.04)	757 (56.53)	**1.51 (1.19-1.90)**	**2.03 (1.56-2.66)**		130 (9.71)	**3.08 (1.69-5.64)**	**2.86 (1.50-5.43)**	
Ability to identify antibiotics					<0.0001				<0.005
Low	447 (18.04)	170 (38.03)	Reference	Reference		24 (5.37)	Reference	Reference	
Medium	651 (26.27)	341 (52.38)	**1.79 (1.40-2.29)**	**1.62 (1.24-2.13)**		60 (9.22)	**1.79 (1.10-2.92)**	**2.42 (1.42-4.13)**	
High	1,380 (55.69)	812 (58.84)	**2.33 (1.87-2.90)**	**2.27 (1.73-2.99)**		102 (7.39)	1.41 (0.89-2.22)	**2.38 (1.38-4.10)**	
Interpersonal Factor:									
Grandparents' involvement in treatment decisions					0.54				0.01
No	690 (27.85)	375 (54.35)	Reference	Reference		40 (5.80)	Reference	Reference	
Yes	1788 (72.15)	948 (53.02)	0.95 (0.79-1.13)	0.94 (0.78-1.14)		146 (8.17)	**1.44 (1.01-2.07)**	**1.61 (1.10-2.35)**	
Structural Factor:									0.08
Healthcare delivery system used (Urban/Rural)					<0.01				
Tertiary hospital	367 (14.81)	174 (47.41)	Reference	Reference		13 (3.54)	Reference	Reference	
Secondary/County hospital	1,057 (42.66)	592 (56.01)	**1.41 (1.11-1.79)**	**1.56 (1.20-2.03)**		89 (8.42)	**2.50 (1.38-4.54)**	**2.04 (1.09-3.80)**	
Community Health Centers/Township hospital	719 (29.02)	373 (51.88)	**1.20 (0.93-1.54)**	**1.29 (0.98-1.70)**		63 (8.76)	**3.14 (1.42-4.82)**	**2.87 (0.99-3.54)**	
Private Clinics/ Village clinics	335 (13.52)	184 (54.93)	**1.35 (1.00-1.82)**	**1.38 (1.00-1.92)**		21 (6.27)	2.66 (0.90-3.70)	1.40 (0.67-2.95)	

OR, odds ratio; CI, confidence interval.
[a]Adjusted for children's sex, perceived severity, parents' education and medical background, primary carer, urban/rural residence, province, and household income.
[b]Likelihood ratio test

Figure 1. Antibiotic use on children by Chinese parents



Supplement Table A. Factors of prevention use of antibiotics on children among Chinese parents (N=9526)

	N=9526	Giving children antibiotics prophylactically (n=1,983, 20.82%)			
	N (%)	n (%)	OR (95%CI)	aOR (95%CI)	p-value[b]
Individual Factors:					
Age of children					0.49
0-2 Infancy	1,988 (20.87)	349 (17.56)	Reference	Reference	
3-8 early childhood	4,947 (51.93)	1,075 (21.73)	**1.30 (1.14-1.49)**	0.93 (0.82-1.16)	
9-11 middle childhood	2,212 (23.22)	489 (22.11)	**1.33 (1.14-1.55)**	**1.04 (2.69-4.01)**	
12-13 adolescence	379 (3.98)	70 (18.47)	1.06 (0.80-1.41)	1.41 (0.78-2.54)	
Antibiotics-related Knowledge					
AMR Awareness					0.53
Low	1,761 (18.49)	322 (18.29)	Reference	Reference	
Medium	1,933 (20.29)	476 (24.62)	**1.46 (1.25-1.71)**	1.20 (0.87-1.64)	
High	5,832 (61.22)	1,185 (20.32)	**1.14 (0.99-1.31)**	1.12 (0.83-1.51)	
Misconception					<0.0001
Low	1,467 (15.40)	137 (9.34)	Reference	Reference	
Medium	3,025 (31.76)	546 (18.05)	**2.14 (1.75-2.61)**	**1.91 (1.36-2.68)**	
High	5,034 (52.84)	1,300 (25.82)	**3.38 (2.80-4.07)**	**3.09 (2.22-4.30)**	
Ability to identify antibiotics					0.78
Low	1,876 (19.69)	325 (17.32)	Reference	Reference	
Medium	2,513 (26.38)	592 (23.56)	**1.47 (1.26-1.71)**	**1.10 (0.82-1.47)**	
High	5,137 (53.93)	1,066 (20.75)	**1.25 (1.09-1.43)**	**1.03 (0.77-1.39)**	
Interpersonal Factors					
Grandparents' involvement in treatment decisions					<0.005
No	2,882 (30.25)	525 (18.22)	Reference	Reference	
Yes	6,644 (69.75)	1,458 (21.94)	**1.26 (1.13-1.41)**	**1.34 (1.09-1.66)**	
Keeping antibiotics at home					<0.0001
No	4946 (51.92)	595 (30.01)	Reference	Reference	
Yes	4580 (48.08)	1983 (20.82)	**3.18 (2.86-3.54)**	**3.28 (2.69-4.01)**	

OR, odds ratio; CI, confidence interval.
[a]Adjusted for children's sex, perceived severity, parents' education and medical background, primary carer, urban/rural residence, province, and household income.
[b]Likelihood ratio test

Supplement Table B. Factors of self-treated children with antibiotics who were ill in the past month (N=1944)

	N=1944	Self-treated children with antibiotics who were ill in the past month (n= 673, 34.60%)			
	N (%)	n (%)	OR	aOR (95%CI)	p-value[b]
Individual Factors:					
Age of children					0.06
0-2 Infancy	360 (18.52)	99 (27.50)	Reference	Reference	
3-8 early childhood	1,238 (63.68)	398 (32.15)	1.25 (0.96-1.62)	1.25 (0.93-1.70)	
9-11 middle childhood	310 (15.95)	119 (38.39)	**1.64 (1.19-2.27)**	1.36 (0.92-2.00)	
12-13 adolescence	36 (1.85)	5 (13.89)	0.43 (0.16-1.12)	0.43 (0.15-1.24)	
Antibiotics-related Knowledge					
AMR Awareness					0.07
Low	223 (11.47)	72 (32.29)	Reference	Reference	
Medium	328 (16.87)	130 (39.63)	1.38 (0.96-1.97)	**1.44 (0.94-2.21)**	
High	1,393 (71.66)	419 (30.08)	0.90 (0.67-1.22)	1.04 (0.69-1.55)	
Misconception					<0.0001
Low	344 (17.70)	52 (15.12)	Reference	Reference	
Medium	628 (32.30)	153 (24.36)	**1.81 (1.28-2.56)**	**1.83 (1.25-2.67)**	
High	972 (50.00)	416 (42.80)	**4.20 (3.05-5.79)**	**4.21 (2.90-6.09)**	
Ability to identify antibiotics					0.11
Low	249 (12.81)	70 (28.11)	Reference	Reference	
Medium	495 (25.46)	163 (32.93)	1.26 (0.90-1.75)	1.38 (0.93-2.05)	
High	1,200 (61.73)	388 (32.33)	1.22 (0.90-1.65)	**1.51 (1.02-2.23)**	
Interpersonal Factor:					
Grandparents' involvement in treatment decisions					0.05
No	524 (26.95)	181 (34.54)	Reference	Reference	
Yes	1420 (73.05)	440 (30.99)	0.85 (0.69-1.05)	0.78 (0.61-1.00)	
Keeping antibiotics at home					<0.0001
No	769 (39.56)	108 (14.04)	Reference	Reference	
Yes	1175 (60.44	513 (82.61)	4.74 (3.75-5.99)	**4.98 (3.85-6.43)**	

OR, odds ratio; CI, confidence interval.

[a]Adjusted for children's sex, perceived severity, parents' education and medical background, primary carer, urban/rural residence, province, and household income.

[b]Likelihood ratio test

Supplement Table C. Factors of antibiotic prescriptions for children who were ill in the past month (N=2478)

	N=2478	**Prescribed with antibiotics (n= 1,323, 53.39%)**			
	N (%)	n (%)	OR	aOR (95%CI)	p-value[b]
Individual Factors:					
Age of children					**<0.01**
0-2 Infancy	603 (24.33)	281 (46.60)	Reference	Reference	
3-8 early childhood	1,448 (58.43)	816 (56.35)	**1.48 (1.22-1.79)**	1.23 (0.99-1.52)	
9-11 middle childhood	371 (14.97)	206 (55.53)	**1.43 (1.10-1.86)**	1.16 (0.87-1.54)	
12-13 adolescence	56 (2.26)	20 (35.71)	0.64 (0.36-1.13)	**0.49 (0.27-0.90)**	
Antibiotics-related Knowledge					
AMR Awareness					**<0.01**
Low	402 (16.22)	161 (40.05)	Reference	Reference	
Medium	488 (19.69)	262 (53.69)	**1.74 (1.33-2.27)**	**1.36 (1.04-1.78)**	
High	1588 (64.08)	900 (56.68)	**1.96 (1.57-2.45)**	**1.92 (1.47-2.52)**	
Misconception					**<0.0001**
Low	356 (14.37)	165 (46.35)	Reference	Reference	
Medium	783 (31.60)	401 (51.21)	**1.22 (0.95-1.56)**	**1.36 (1.04-1.78)**	
High	1339 (54.04)	757 (56.53)	**1.51 (1.19-1.90)**	**1.92 (1.47-2.52)**	
Ability to identify antibiotics					**<0.0001**
Low	447 (18.04)	170 (38.03)	Reference	Reference	
Medium	651 (26.27)	341 (52.38)	**1.79 (1.40-2.29)**	**1.53 (1.16-2.02)**	
High	1,380 (55.69)	812 (58.84)	**2.33 (1.87-2.90)**	**2.15 (1.63-2.84)**	
Interpersonal Factor:					
Grandparents' involvement in treatment decisions					0.34
No	690 (27.85)	375 (54.35)	Reference	Reference	
Yes	1788 (72.15)	948 (53.02)	0.95 (0.79-1.13)	0.91 (0.75-1.10)	
Structural Factor:					
Healthcare delivery system used (Urban/Rural)					**0.02**
Tertiary hospital	367 (14.81)	174 (47.41)	Reference	Reference	
Secondary/County hospital	1,057 (42.66)	592 (56.01)	**1.41 (1.11-1.79)**	**1.51 (1.16-1.96)**	
Community Health Centers/Township hospital	719 (29.02)	373 (51.88)	**1.20 (0.93-1.54)**	**1.25 (0.95-1.65)**	
Private Clinics/ Village clinics	335 (13.52)	184 (54.93)	**1.35 (1.00-1.82)**	**1.37 (0.99-1.90)**	
Pressure for antibiotic prescriptions					**<0.0001**
No	2,292 (92.49)	1,175 (88.81)	**3.70 (2.57-5.34)**	Reference	
Yes	186 (7.51)	148 (11.19)	**1.05 (0.97-1.14)**	**3.43 (2.34-5.04)**	

OR, odds ratio; CI, confidence interval.
[a]Adjusted for children's sex, perceived severity, parents' education and medical background, primary carer, urban/rural residence, province, and household income.
[b]Likelihood ratio test

CHAPTER FIVE

Large-scale survey of parental antibiotic use for paediatric upper respiratory tract infections in China: implications for stewardship programmes and national policy

In this chapter, I report on secondary data analysis of a large-scale survey on treatment decisions with respect to antibiotic use for upper respiratory tract infections among children across three provinces of different geographic regions and economic development stages in China. Data were collected from June 2017 to April 2018 by Zhejiang University. Institute of Social Medicine and Family Medicine. (See Appendix I: Letter of Support.)

I conducted the analysis plan design and analysis independently with close collaboration with Senior Lecturer, Leah Li at the University College London Institute of Child Health. The findings and results have been prepared as a draft of the manuscript, with comments on drafts from Professors Stephan Harbarth, James Hargreaves, Xudong Zhou, and Leah Li. This manuscript has been submitted to the *International Journal of Antimicrobial Agents* for publication consideration.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH1704488	**Title**	Ms.
First Name(s)	Leesa		
Surname/Family Name	Lin		
Thesis Title	Development of evidence-based behavioural interventions to reduce inappropriate use of antibiotics beyond clinical settings		
Primary Supervisor	Professor James Hargreaves		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	International Journal of Antimicrobial Agents
Please list the paper's authors in the intended authorship order:	Leesa Lin, Stephan Harbarth, James Hargreaves, Xudong Zhou*, Leah Li
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Leesa Lin conducted the literature search, created the figures and the conceptual framework, conducted data analysis and interpretation, and drafted and revised the manuscript. Stephan Harbarth and James Hargreaves contributed to data interpretation, and commented on the initial and following revisions of the manuscript. Xudong Zhou conceived the study, led data collection, contributed to data interpretation, and commented on all drafts of this manuscript. Leah Li led the study design, supervised the data analysis and interpretation, and contributed significantly to the first draft and following revisions of the manuscript. All authors approved the final draft of this manuscript.

SECTION E

Student Signature	[redacted]
Date	09/09/2019

Supervisor Signature	[redacted]
Date	09/12/2019

Large-scale survey of parental antibiotic use for paediatric upper respiratory tract infections in China: implications for stewardship programmes and national policy

SYNOPSIS

BACKGROUND Inappropriate use of antibiotics for upper respiratory tract infections among Chinese children is rampant. To identify key constructs for effective interventions targeting the public, we investigated parents' decision-making processes with respect to treatment choices and antibiotic use for paediatric URTIs.

METHODS Data were collected between June 2017-April 2018 from a cluster random sample of 3,188 parents of children aged 0-13 across three purposefully-selected Chinese provinces, representing different stages of economic development. Risk factors of parents' treatment choices and antibiotic use for paediatric URTIs were assessed, using binary and multinomial logistic regressions, adjusting for socio-demographic characteristics.

RESULTS Of the 3,188 parents who self-diagnosed their children with a URTI, 46.0% children were given antibiotics, with or without prescription (n=1465). Among these children, 40.5% were self-medicated with non-prescription antibiotics by parents and 56.1% obtained further antibiotic prescriptions at healthcare facilities. About 70% of children with URTI symptoms sought healthcare (n=2197); of them, 54.8% obtained antibiotic prescriptions and 7.7% asked for antibiotic prescriptions with a 79.4% success rate to obtain them. Those perceiving antibiotics as effective for treating common cold and fever (aOR=1.82[1.51-2.19] and 1.77[1.47-2.13], respectively), who had access to non-prescription antibiotics (aOR=5.08[4.03-6.39]), and with greater perceived severity of infection (aOR=2.01[1.58-2.56]), were more likely to use antibiotics for paediatric URTIs.

CONCLUSIONS Context-appropriate multifaceted interventions are vital to untangle the perpetual problem of self-medication, over-prescription and ill-informed demands for antibiotics. Our findings emphasize the need to prioritise interventions enhancing clinical training, neutralising the pressure from patients for antibiotics, educating on appropriate home care, discouraging antibiotic self-medication, and improving antibiotic dispensing.

INTRODUCTION

Acute, uncomplicated upper respiratory tract infections (URTIs) – often benign, self-limiting, and untreatable by antibiotics - are diagnosed on symptomatology and treatments are mainly symptomatic rather than focusing on changes in viral titres in the airway or viral shedding.[14] Considered the most common infectious disease among humans, URTIs are the most common cause of primary care visits and unnecessary use of antibiotics for children around the world, especially in China,[31,37,257] which has contributed to the rise of antimicrobial resistance (AMR), an imminent global health threat. Antibiotic-resistant pathogens, such as *streptococcus pneumonia*, have been reported in children across China.[259,290] Antibiotic treatment changes gut microbiota and adversely impacts the development of the immune system, making it difficult for children to recover from repeated antibiotic exposure.[291,292] Given the long-term consequences on human development and that children may experience URTIs seven to ten times on average annually,[14] misuse of antibiotics in children is particular harmful. Nevertheless, 48.2% of urban parents[60] and 62% of rural parents[65] in China reported to have self-medicated children with antibiotics outside of clinical settings within the last six months.

Understanding the underlying reasons that drive the parental decision to use antibiotics for paediatric URTIs without professional guidance is important for developing strategies to reduce antibiotic misuse. To date, most public-targeted health behaviour research and interventions on antibiotic use have centred on knowledge-attitudes-practice (KAP), with the underlying assumption that individuals would make more risk-conscious choices if informed of the risks of AMR – an approach has long been criticised for its overemphasis on personal responsibility.[293] When faced with an

acute infection in themselves or a loved one, individuals may disproportionately focus on the immediate outcome of curing the illness (i.e. perceived antibiotic efficacy), and discount long term risks such as AMR.[148] As such, parents' decision-making for treating URTIs might not be as rational or informed as a KAP approach would assume. To develop effective interventions to reduce unnecessary or inappropriate use of antibiotics for paediatric URTIs in the Chinese community, evidence is needed on parents' decision-making for care and how these decisions influence antibiotic use within or outside of clinical settings. Here, for children with self-diagnosed URTI symptoms, we investigated the extent and risk factors associated with the likelihood of (1) self-medication with non-prescription antibiotics by parents; (2) healthcare seeking; (3) parental requesting for antibiotics and unnecessary prescriptions by healthcare providers.

METHODS

Study population We used data from a survey of parents with children aged 0-13 years between June 2017 and April 2018. Three Chinese provinces, which represent different geographical areas and stages of economic development, [264] were chosen. These included Zhejiang (East, ranked 5th out of 31 in the 2017 provincial GDP ranking of economic development), Shaanxi (Central-Northwest, ranked 12th), and Guangxi (Southwest, ranked 26th) provinces. A multistage stage random clustering sampling design was applied. The four-stage sampling units are provinces, prefecture-level cities, urban and rural areas, and local sites: primary schools (age 6-13), kindergartens (age 3-5) and community health centres (age 0-2), where most children received vaccination.[265] Parents were identified and recruited through their children from all selected sites. They

were asked to complete a structured questionnaire, which was tailored to the Chinese sociocultural context informed by literature review[45,62,65] and formative/qualitative interviews with stakeholders and experts. The questionnaire was comprised of four sections: 1) parental socio-demographic information, 2) healthcare- and antibiotic-related knowledge and perceptions, 3) last episode of URTI symptoms experienced by the child within the past month, and 4) treatment and parental care-seeking process and behaviours for the child's illness (i.e. the chemical or brand names of antibiotics obtained from clinics and retail pharmacies). To minimise the burden for the parents and ensure high quality of the response data, the survey was designed to take no more than 10 minutes and an IP address control was put in place to detect random responses or duplications. Parents could complete the questionnaire on a mobile device, online, or using a paper version and they were informed that participation was confidential, voluntary and could be terminated at any time. A consent form was presented in the first section of the questionnaire and was signed by the participants. To validate the questionnaire, we conducted a pilot study with 315 respondents to evaluate potential sources of response error and improve the instrument. The questionnaire was completed by 9,526 parents, with a response rate of 89%. Of those, 33.5% (n=3,188) reported that their children had experienced symptoms of a URTI within a month prior to the survey, including cold (cough, runny/stuffy nose), fever, sore throat, headache, and flu, either alone or in combination[14].

Outcome variables Participating parents reported whether they (1) self-treated children with antibiotics: *did not use antibiotics, self-medication with antibiotics,* and *seeking formal care after self-medication with antibiotics at home*; (2) sought care and/or requested antibiotics: *did not seek care, sought care, and sought care and explicitly*

requested antibiotics for their children. In addition, parents also reported whether clinicians' prescribed antibiotics for their child: *no antibiotic prescription, antibiotic prescriptions without being prompted,* and *inappropriate antibiotic prescriptions due to parental demands.*

Exposure variables Informed by the Health Belief Model[92,93] and Social Ecological Model[100], we included the following potential risk factors in our analyses:

(1) Whether parents had a medical background (yes/no), as it is relevant to parents' self-efficacy for making healthcare decisions for their children.

(2) Parents' ability to identify antibiotics, measured by *number of commonly available drugs correctly identified by parents as antibiotics or non-antibiotics: low (0-1), medium (2-3), high (4 or higher);*

(3) Parents' perceptions: (a) perceived benefits of antibiotic use, measured by two factual statements about antibiotics' efficacy to treat the common cold or fever; and (b) perceived severity of the infection, measured by the number of self-diagnosed URTI symptoms the child experienced;

(4) Cues to action: included (a) presence of fever and (b) information sources for treatment decisions: medical advice, family, and media including social media.

(5) *Parents' access to antibiotics* (with or without prescriptions), including: (a) non-prescription antibiotics: parents' habits of *keeping antibiotics at homes for children* in the past year; and (b) antibiotic prescriptions: when a child received formal care, *point of care used for treatment* was assessed, including hospitals above county level, county hospitals, township hospitals, and local clinics.

Covariates: Socio-demographic characteristics were included as potential confounders for the association between each exposure and treatment decisions, including *sex and age of the child, household income, parental education, urbanicity* and *province*.

Statistical analysis We first developed a flow diagram (Figure 1) to illustrate parental decision-making process of treatment and antibiotic use in their children for URTIs, from (non-clinical) household to (clinical) facility. We summarised the distributions of socio-demographic characteristics and factors by treatment decision/behavioural outcomes. To examine the association between each factor and outcome, we applied logistic regressions to estimate the OR (95% CI) for (1) 'self-medication with antibiotics' (vs 'no self-medication with antibiotics') and (2) 'seeking healthcare' (vs 'without seeking healthcare'). Factors considered include parental medical background, ability to identify antibiotics, perceived antibiotic efficacy for cold or fever, self-diagnosed severity, cues to action, and access to antibiotics. We explored the associations with subgroups of antibiotic and healthcare use, and applied multinomial logistic regressions to estimate the relative risk ratio, RRR (95% CI) for (1) 'self-medication with antibiotics without seeking healthcare' and 'self-medication with antibiotics then sought healthcare' (vs 'no self-medication with antibiotics') and (2) 'sought healthcare without requesting antibiotic prescriptions' and 'sought healthcare and requested prescriptions' (vs 'no seeking healthcare'). For parents who sought healthcare for their children, we estimated RRR (95%CI) for "receiving prescriptions without patients' request' and 'receiving prescriptions due to patients' request' (vs 'without an antibiotic prescription'). For each outcome and risk factor, we first fitted an unadjusted model, and then adjusted for the potential confounders to establish whether the association was independent of these socio-demographic characteristics. Because

different risk factors tend to co-occur, as sensitivity analyses, we mutually adjusted for all risk factors simultaneously.

RESULTS

Out of 3,188 parents whose children had URTI symptoms within the last month, 594 (40.5%) were self-medicated by parents without medical prescription - 56% of these children further obtained antibiotic prescriptions at healthcare facilities. Approximately 70% of children with URTI symptoms (n=2197) sought healthcare; of them, 1204 (54.8%) obtained antibiotic prescriptions – a third of which (33.9%) contained intravenous antibiotics injected directly into the bloodstream, mostly combined with oral antibiotics. Patients or caregivers - the demand-side of the healthcare system – who are engaged in self-medication and who have demanded antibiotic prescriptions were estimated to have contributed to 41% of antibiotic use for paediatric URTIs [(594+135)/(594+1204)]. (See Table 2 and Figure 1.)

Self-medication with antibiotics for paediatric URTIs (Table 2)

Perceived antibiotic efficacy for common cold or fever (aOR=1.82[1.51-2.19] and aOR=1.77[1.47-2.13], respectively), presence of fever (aOR=1.46[1.20-1.77]), high perceived severity of infection (aOR=2.01[1.58-2.56]), obtaining health information from family for treatment decisions (aOR=1.80[1.49-2.16]), and keeping antibiotics at home (aOR=5.08[4.03-6.39]) were associated with increased odds of self-medication with antibiotics use by parents for URTIs in children, after adjusting for socio-demographic characteristics**.** Parents who obtained health information from media were associated with a reduced risk (aRRR=0.46[0.24-0.89]). High levels of perceived

severity of the infection and presence of fever in children were associated with increased risk of self-medication with antibiotics then seeking healthcare.

Healthcare seeking and parents request for antibiotic prescription (Table 3)

Parents who perceived antibiotics as effective for the common cold and fever, who had high levels of perceived severity of infection, or presence of fever in children were more likely to seek healthcare and request antibiotic prescriptions, compared to their respective counterparts. Parents who had a medical background, obtained health information from family, or kept antibiotics at home were less likely to seek healthcare for their children (aOR=0.65, 0.81, and 0.84, respectively). Among parents who sought healthcare for their children, keeping antibiotics at home was associated with increased risk of requesting antibiotic prescriptions (aRRR=3.63[2.54-5.17]).

Antibiotic prescriptions for the treatment of URTIs (Table 4)

Children whose parents could identify most antibiotics perceived antibiotics as efficacious for common cold or fever, perceived higher severity in their children, and kept antibiotics at home were more likely to receive antibiotic prescriptions, with a greater risk of receiving prescriptions by request. Regarding point-of-care used, seeking healthcare from county hospitals was associated with an increased risk of antibiotic prescriptions for paediatric URTIs and inappropriate prescriptions by parents' request (aRRR=1.48[1.11-1.96] and 2.52[1.23-5.18], respectively), compared with tertiary hospitals. Findings from sensitivity analyses showed that when all factors were mutually adjusted, most associations remained, though reduced slightly, with one exception that 'parental ability to identify antibiotics' became non-significant for all outcomes. All other factors did not change substantially (data not shown).

DISCUSSION

Main findings Of the 3,188 children experiencing URTIs, nearly half (46%) were given antibiotics either by parents or by clinicians, 69% sought care, and among them 55% were prescribed antibiotics (of these 28% had already self-treated with antibiotics at home). Caregivers account for at least 40% of outpatient antibiotic use. Antibiotic misuse for paediatric URTIs can be summarised into three forms: (1) self-medication among children by caregivers in the community; and in clinical settings from either (2) unnecessary prescriptions by doctors, or (3) inappropriate prescriptions due to parental demand. Parents' perception of antibiotics as efficacious for treating URTIs and the nearly non-existent barriers to antibiotics are key risk factors in antibiotic misuse behaviours, including self-medication children with antibiotics and the demand and receipt of antibiotic prescriptions. *Presence of fever* leads to formal care seeking and the demand and receipt of antibiotics prescriptions. Those mainly *taking advice from family members* are more likely to self-medicate children with antibiotics and less likely to seek care; when they do seek care, they are more likely to receive antibiotic prescriptions. A majority of parents (n=1,728, 54.2%) reported having kept antibiotics at home for their children for the possibility of a future cold. Pressuring doctors for antibiotic prescriptions occurred at all levels of healthcare facilities with a high success rate (79.4%).

Strengths and Limitations This study is based on a large survey conducted in geographical areas representing various stages of economic development in China. This is the first study to comprehensively examine parental treatment decisions with respect to antibiotic use in children in both rural and urban settings across China. Though the cross-sectional study design limited us from drawing causal relationships, it helped

generate causal hypotheses and offered several points for intervention. This study showed that the high childhood antibiotic consumption in China is largely driven by a combination of excessive use of formal care for URTIs, high prescription rates, and large population size. The actual antibiotic consumption in Chinese children is expected to be much more prevalent than what has been reported in this study, considering repeated infections throughout a year and non-prescription use at home.[41] We found, before the parent sought formal care, 18% of children with URTIs had already received antibiotics, without prescription. The samples were clustered and therefore the estimated standard errors used in significance tests may be biased. In our case, samples were drawn from three provinces of different development level and then from the rural and urban areas within each province; the differences between these provinces and/or between rural and urban areas might be greater than those among individuals drawn from a random sample across the country. We accounted for variations at the province and/or urbanicity levels in the analyses.

Interpretation of our findings Evidence generated from this study can be used to inform intervention design to reduce inappropriate or unnecessary antibiotic use for paediatric URTIs in the context of China and in other low- and middle-income countries (LMICs) where antibiotic consumption is rising [294] and which also share similar challenges related to unsupervised or inappropriate use of antibiotics.[295,296] First, this study highlighted the continued need to tackle the drivers of inappropriate prescribing behaviours, including poor diagnostic capacity and financial incentives,[52,125] especially in primary care and rural settings[44]. 55% of paediatric patients with non-complicated URTI symptoms were prescribed with antibiotics while roughly 80% of those who demanded antibiotics were prescribed antibiotics, accounting for an estimate of 45%

outpatient paediatric antibiotic use in the country. Further, the influence of doctor-patient encounters on antibiotic prescriptions might be more complex than verbal communication. Our data identified a surprisingly similar set of risk factors influencing antibiotic prescription outcomes for paediatrics URTIs between parents who explicitly demand antibiotics and those who did not. If Chinese doctors' prescribing behaviours for paediatrics URTIs are mainly driven by poor diagnostic capacity or financial incentives, as suggested by previous literature,[52,125] we would have expected no association between these risk factors of parents and doctors' prescription decisions. This phenomenon might be explained by possible non-verbal cues (whether true or not) that prescribers pick up from their interactions with parents who showed certain character traits or profiles during consultation that signalled to the prescribers that an antibiotic prescription was desired. This explanation is supported by a study that identified a misalignment between parents' reported expectations, their communication messages, and physicians' perceptions of parents' expectations and their reaction to those perceptions.[297] These data pointed to an urgent need to enhance clinician training focusing on 1) clinical guidelines and appropriate prescribing for paediatric URTIs and 2) doctor-patient communication skills that aimed to help clinicians (a) neutralise the perceived expectation on/pressure from parents' demand for antibiotics and (b) inquire about possible parental self-medication with antibiotics on children before reaching the facility to avoid multiple doses.

Secondly, context-tailored patient/caregiver education interventions on appropriate home care for paediatric URTIs and prudent antibiotic use are needed. Content should prioritise correcting *perceived antibiotic efficacy* for relieving or eradicating URTI symptoms and appropriate care for *self-diagnosed paediatric URTIs*

symptoms and *fever*, and be delivered by medical professionals or mass media - both were identified as effective channels for health information.

Lastly, we found antibiotic misuse in Chinese children was associated with parents' *access to antibiotics,* within or outside of a clinical setting. Household antibiotic storage mainly came from leftover antibiotics from previous prescriptions (60.6%) and over-the-counter purchases (37.5%). *Cephalosporines, Amoxicillins,* and *Azithromycins* were the most commonly used antibiotics to treat paediatric URTIs, both with and without a prescription (data not shown). These antibiotics, *Cephalosporines* especially, are broad-spectrum antibiotics effective against a wide range of bacteria, which kill more normal microorganisms in children's body compared with narrow-spectrum antibiotics, and should only be used under professional supervision on patients who are sick on presentation. Furthermore, participants from all regions reported to have obtained antibiotics from retail pharmacies. Currently, antibiotic prescriptions are fulfilled and dispensed by packs, often more than the prescribed doses, leading to leftover antibiotics for unsupervised self-medication at home later on. Therefore, in addition to improving responsible prescribing practice, interventions should address the loopholes in current Chinese antibiotic dispensing system, including (1) strengthening the enforcement of Chinese government's AMR policies[298] that ban over-the-counter purchases and cap antibiotic prescriptions (e.g. at 20% for county hospitals), and (2) enabling responsible dispensing antibiotics according to prescribed doses.

Policy implications Findings from this study suggest that context-appropriate multifaceted interventions are vital to untangle the perpetual problem of over-prescription and ill-informed demands for antibiotics. Simultaneously enhancing both prescribing guidelines, doctor-patient communication skills, and patient education

targeting the family as a unit is critical. A blanket antibiotic awareness campaign in China and in other low- and middle-income countries (LMICs) will likely not be effective unless it is rigorously adapted to local context. Interventions enhancing parental *self-efficacy* of healthcare decision-making, especially regarding care management for paediatric URTIs, and correcting *(mis-)perceptions around antibiotic efficacy for URTI symptoms*, might reduce misuse. Education interventions should prioritise urban parents with low socio-economic status in less developed regions and be disseminated via medical professionals or media in order to effectively cue parents to a proper response. Enforcing regulations regarding the sale of antibiotics and pack-based antibiotic dispensing systems to reduce household antibiotic stockpiling could curb the main sources of non-prescription antibiotics for self-medication use in Chinese children.

CONCLUSIONS

Our data pointed to an urgent need for context-appropriate multifaceted interventions to untangle the perpetual problem of over-prescription and ill-informed demands for antibiotics. Having effective stewardship programmes that improve adherence to clinical practice guidelines for antibiotic prescribing and enhance doctor-patient communication over antibiotic use in China is vital. Risk factors influencing caregivers' antibiotic use identified in this study can inform much-needed interventions addressing the challenges posed by both the supply- and demand-side of healthcare system in China. Our findings emphasize the need to prioritise interventions enhancing clinical training, neutralising the pressure from patients for antibiotics, educating on appropriate home care, discouraging antibiotic self-medication, and improving antibiotic dispensing.

ACKNOWLEDGMENTS

The authors appreciate the help from administrators and officials at the schools and health centres involved in disseminating this survey and coordinating the study.

FUNDING

The study was funded by Zhejiang University Zijin Talent Programme.

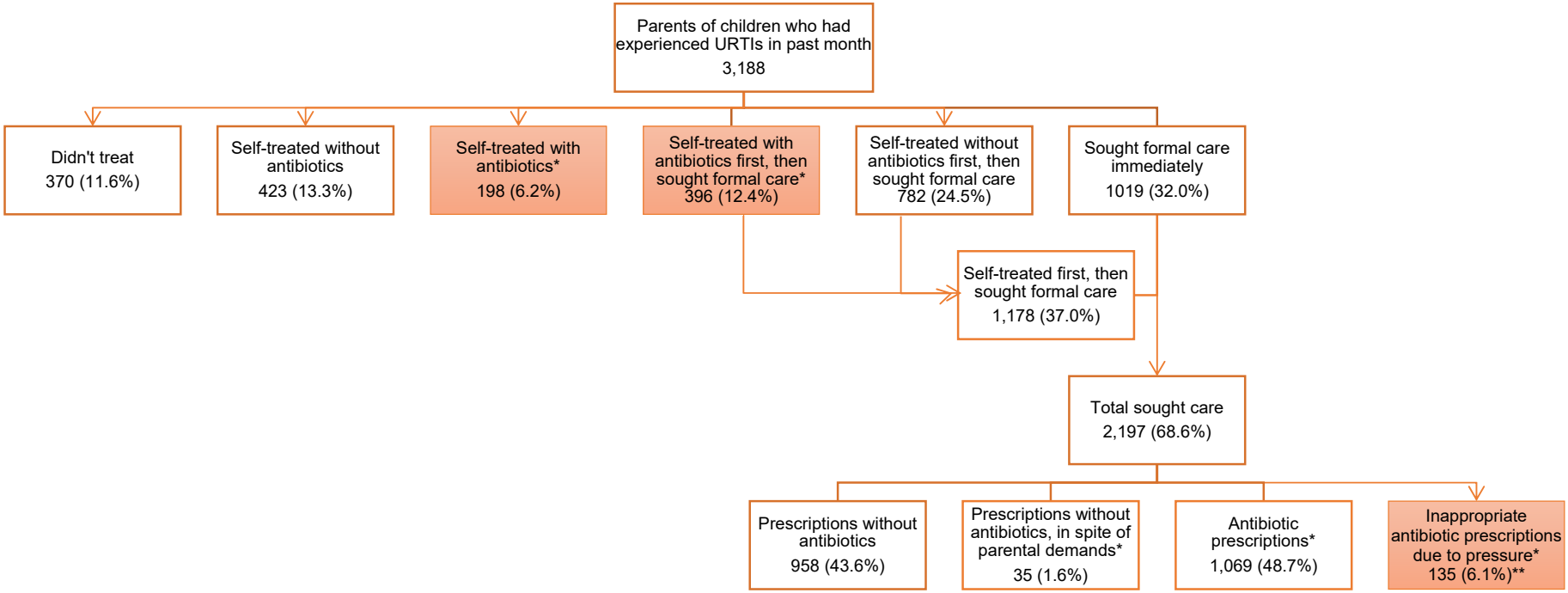
TRANSPARENCY DECLARATIONS

The authors have declared no conflict of interests related to this study.

ETHICS

The study protocol and survey were reviewed and exempted by the Institutional Review Board at the Zhejiang University School of Medicine (number ZGL201706-2) and London School of Hygiene & Tropical Medicine (number 14678).

Figure 1. Antibiotic use for upper respiratory tract infections (URTIs) among Chinese children



*Inappropriate antibiotic use for URTIs
**170 parents pressured doctors for antibiotic prescriptions for their children, with a success rate of 79.4%.

Table 1. Sample characteristics N (%) (N=3188)

	All children N (%)	Treated with antibiotics	Self-treated with antibiotics	Children who sought care
	3188	1,465 (46.0)	594 (18.6%)	2,197(68.9%)
Sex				
Boys	1,623 (50.9)	746 (50.9)	310 (52.2)	1,125 (51.2)
Girls	1,565 (49.1)	719 (49.1)	284 (47.8)	1,072 (48.8)
Age (years)				
0-3	1,025 (32.2)	441 (30.1)	163 (27.4)	735 (33.5)
4-6	1,109 (34.8)	539 (36.8)	214 (36.0)	762 (34.7)
7-9	673 (21.1)	331 (22.6)	147 (24.8)	462 (21.0)
10-13	381 (12.0)	154 (10.5)	70 (11.8)	238 (10.8)
Average household income (RMB, monthly)				
>5,000	1,520 (47.7)	655 (44.7)	232 (39.1)	1,023 (46.6)
3,001-5,000	1,032 (32.4)	498 (34.0)	220 (37.9)	718 (32.7)
<=3,000	636 (20.0)	312 (21.3)	142 (23.9)	456 (20.8)
Parents' education level				
College or above	1,365 (42.8)	603 (41.2)	228 (38.4)	889 (40.5)
High school or below	1,823 (57.2)	862 (58.8)	366 (61.6)	1,308 (59.5)
Province				
Zhejiang	885 (27.8)	346 (23.6)	94 (15.8)	612 (27.9)
Guangxi	1,152 (36.1)	516 (35.2)	209 (35.2)	793 (36.1)
Shaanxi	1,151 (36.1)	603 (41.2)	291 (49.0)	792 (36.1)
Hometown				
Rural	1,384 (43.4)	612 (41.8)	258 (43.4)	978 (44.5)
Urban	1,804 (56.6)	853 (58.2)	336 (56.6)	1,219 (55.5)
Parents with medical background				
No	2,785 (87.4)	1,290 (88.1)	516 (86.9)	1,960 (89.2)
Yes	403 (12.6)	175 (12.0)	78 (13.1)	237 (10.8)
Parents ability to identify antibiotics				
Low	530 (16.6)	183 (12.5)	68 (11.5)	387 (17.6)
Medium	829 (26.0)	384 (26.2)	154 (25.9)	579 (26.4)
High	1829 (57.4)	898 (61.3)	372 (62.6)	1,231 (56.0)
Parents perceptions				
Antibiotic efficacy				
Effective for common cold				
No/Don't know	1,842 (57.8)	728 (49.7)	266 (44.8)	1,233 (56.1)
Yes	1,346 (42.2)	737 (50.3)	328 (55.2)	964 (43.9)
Effective for fever				
No/Don't know	1,767 (55.4)	670 (45.7)	254 (42.8)	1,184 (53.9)
Yes	1,421 (44.6)	795 (54.3)	340 (57.2)	1,013 (46.1)
Self-diagnosed severity				
Low (1 symptom)	940 (29.5)	330 (22.5)	143 (24.1)	545 (24.8)
Medium (2)	1354 (42.5)	604 (41.2)	236 (39.7)	918 (41.8)
High (>=3)	894 (28.0)	531 (36.3)	215 (36.2)	734 (33.4)
Cues to action				
Presence of Fever				
No	2189 (68.7)	886 (60.9)	384 (64.7)	1383 (63.0)
Yes	999 (31.3)	579 (39.5)	210 (35.4)	814 (37.1)
Information sources				
Medical advice				
No	451 (14.5)	209 (14.3)	99 (16.7)	280 (12.7)
Yes	2,737 (85.9)	1,256 (85.7)	495 (83.3)	1,917 (87.3)
Family				
No	1,672 (52.5)	737 (50.3)	254 (2.8)	1,194 (54.4)
Yes	1,516 (47.6)	728 (49.7)	340 (57.2)	1,003 (45.6)
Media				
No	2,846 (89.3)	1,313 (89.6)	545 (91.8)	1,961 (89.3)
Yes	342 (10.7)	152 (10.4)	49 (8.3)	236 (10.7)
Antibiotics access				
Keeping antibiotics at home				
No	1,460 (45.8)	471 (32.2)	105 (17.7)	1,042 (47.4)
Yes	1,728 (54.2)	994 (67.9)	489 (82.3)	1,155 (52.6)

Table 2. Estimated odds ratio (OR, 95% CI) of 'self-treated with antibiotic' for URTIs among Chinese children and relative risk ratio (RRR, 95% CI) of 'self-treated with antibiotics only' and 'self-treated then thought care' (vs 'non-self-treated') for factors affecting parental treatment decisions (N=3188)

	Self-treated with antibiotics* (594, 18.6%)			Subgroup: Self-treated with antibiotics only (198, 6.2%)			Subgroup: Self-treated with antibiotics, then sought care (396, 12.4%)		
	%	OR (95%CI)	aOR (95%CI)	%	RRR (95%CI)	aRRR (95%CI)	%	RRR (95%CI)	aRRR (95%CI)
Parents with medical background									
No	18.5	-	-	5.8	-	-	12.7	-	-
Yes	19.4	1.06 (0.81-1.38)	1.04 (0.79-1.37)	8.9	**1.55 (1.06-2.27)**	1.47 (0.99-2.19)	10.4	0.83 (0.59-1.16`)	0.83 (0.59-1.18)
Parents ability to identify antibiotics									
Low	12.8	-	-	4.5	-	-	8.3	-	-
Medium	18.6	**1.55 (1.14-2.11)**	**1.67 (1.21-2.29)**	6.3	1.48 (0.90-2.44)	1.51 (0.91-2.51)	12.3	**1.59 (1.09-2.30)**	**1.75 (1.20-2.56)**
High	20.3	**1.73 (1.31-2.29)**	**2.03 (1.51-2.72)**	6.7	**1.61 (1.03-2.53)**	**1.73 (1.08-2.77)**	13.7	**1.80 (1.29-2.52)**	**2.20 (1.55-3.13)**
Parents perceptions									
Antibiotic efficacy									
Effective for common cold									
No/Don't know	14.4)	-	-	4.9	-	-	9.6	-	-
Yes	24.4	**1.91 (1.59-2.29)**	**1.82 (1.51-2.19)**	8.0	**1.86 (1.39-2.48)**	**1.81 (1.35-2.43)**	16.3	**1.94 (1.56-2.40)**	**1.88 (1.51-2.33)**
Effective for fever									
No/Don't know	14.3	-	-	4.8	-	-	9.5	-	-
Yes	24.0	**1.89 (1.58-2.26)**	**1.77 (1.47-2.13)**	8.0	**1.86 (1.39-2.50)**	**1.69 (1.26-2.28)**	16.1	**1.90 (1.54-2.36)**	**1.81 (1.45-2.25)**
Self-diagnosed severity									
Low (1 symptom)	15.2	-	-	6.7	-	-	8.5	-	-
Medium (2)	17.4	1.18 (0.94-1.48)	1.23 (0.97-1.55)	6.1	0.94 (0.67-1.32)	0.96 (0.68-1.35)	11.3	**1.36 (1.03-1.81)**	**1.44 (1.07-1.92)**
High (>=3)	24.1	**1.76 (1.40-2.23)**	**2.01 (1.58-2.56)**	5.8	0.97 (0.66-1.42)	1.09 (0.74-1.61)	18.2	**2.39 (1.80-3.18)**	**2.73 (2.04-3.66)**
Cues to action:									
Presence of Fever									
No	17.5	-	-	6.6	-	-	10.9	-	-
Yes	21.0	**1.25 (1.04-1.51)**	**1.46 (1.20-1.77)**	5.3	0.79 (0.58-1.09)	0.99 (0.71-1.38)	15.7	**1.52 (1.23-1.88)**	**1.74 (1.39-2.17)**
Information sources									
Medical advice									
No	22.0	-	-	8.2	-	-	13.8	-	-
Yes	18.1	**0.79 (0.62-1.00)**	0.79 (0.62-1.01)	5.9	**0.68 (0.47-0.99)**	0.69 (0.47-1.01)	12.2	0.85 (0.63-1.13)	0.85 (0.63-1.14)
Family									
No	16.9	-	-	5.2	-	-	10.0	-	-
Yes	23.6	**1.61 (1.35-1.93)**	**1.80 (1.49-2.16)**	7.3	**1.54 (1.15-2.06)**	**1.72 (1.28-2.31)**	15.1	**1.65 (1.34-2.05)**	**1.84 (1.48-2.29)**
Media									
No	19.2	-	-	6.6	-	-	12.5	-	-
Yes	14.3	**0.71 (0.51-0.97)**	**0.79 (0.57-1.10)**	2.9	**0.42 (0.22-0.80)**	**0.46 (0.24-0.89)**	11.4	0.86 (0.60-1.22)	0.97 (0.68-1.39)
Keeping antibiotics at home									-
No	7.2	-	-	2.5	-	-	4.7	-	
Yes	28.3	**5.09 (4.07-6.37)**	**5.08 (4.03-6.39)**	9.4	**4.92 (3.40-7.12)**	**4.63 (3.18-6.75)**	18.9	**5.18 (3.95-6.80)**	**5.31 (4.03-7.01)**

OR, odds ratio; RRR, relative risk ratio; CI, confidence interval.
*Reference group: parents who did not self-medicated children with antibiotics (n=2,594, 81.4%)
aAdjusted for sex, age, household income, parents' education, urbanicity and province.

Table 3. Estimated odds ratio (OR, 95% CI) of 'healthcare seeking' for URTIs among Chinese children and relative risk ratio (RRR, 95% CI) of 'seeking formal care without requesting for antibiotics' and 'Seeking antibiotic prescriptions' (vs 'no formal care') for factors affecting parental treatment decisions (N=3188)

	Healthcare seeking* (2,197, 68.9%)			Subgroup: Seeking formal care without requesting for antibiotics (2027, 63.6%)			Subgroup: Seeking antibiotic prescriptions (170, 5.3%)		
	%	OR (95%CI)	aOR (95%CI)	%	RRR (95%CI)	aRRR (95%CI)	%	RRR (95%CI)	aRRR (95%CI)
Parents with medical background									
No	70.4	-	-	64.9	-	-	5.5	-	-
Yes	58.8	**0.60 (0.48-0.74)**	**0.65 (0.52-0.81)**	54.3	**0.60 (0.48-0.75)**	**0.79 (0.67-0.93)**	4.5	**0.59 (0.35-0.99)**	0.91 (0.55-1.51)
Parents ability to identify antibiotics									
Low	73.0	-	-	68.7	-	-	4.3	-	-
Medium	69.8	0.86 (0.67-1.10)	0.92 (0.72-1.18)	63.6	0.83 (0.65-1.06)	1.12 (0.96-1.31)	6.3	1.29 (0.76-2.20)	**1.86 (1.14-3.10)**
High	67.3	**0.76 (0.61-0.94)**	0.87 (0.69-1.09)	62.1	**0.75 (0.60-0.93)**	**1.25 (1.08-1.44)**	5.2	0.99 (0.60-1.61)	**1.81 (1.12-2.91)**
Parents perceptions									
Antibiotic efficacy									
Effective for common cold									
No/Don't know	66.9	-	-	63.8	-	-	3.2	-	-
Yes	71.6	**1.25 (1.07-1.45)**	**1.27 (1.09-1.49)**	63.3	1.16 (0.99-1.35)	**1.22 (1.10-1.35)**	8.3	**3.08 (2.19-4.33)**	**3.10 (2.25-4.28)**
Effective for fever									
No/Don't know	67.0	-	-	63.4	-	-	3.6	-	-
Yes	71.3	**1.22 (1.05-1.42)**	**1.23 (1.06-1.44)**	63.8	1.16 (0.99-1.35)	**1.18 (1.07-1.31)**	7.5	**2.37 (1.69-3.31)**	**2.32 (1.69-3.18)**
Self-diagnosed severity									
Low (1symptom)	58.0	-	-	54.9	-	-	3.1	-	-
Medium (2 symptoms)	67.8	**1.53 (1.28-1.81)**	**1.60 (1.35-1.91)**	63.0	**1.50 (1.26-1.78)**	**1.58 (1.32-1.89)**	4.8	**2.03 (1.28-3.21)**	**2.04 (1.29-3.25)**
High (>=3 symptoms)	82.1	**3.32 (2.68-4.12)**	**3.43 (2.76-4.26)**	73.6	**3.15 (2.53-3.91)**	**3.25 (2.60-4.05)**	8.5	**6.47 (4.06-10.31)**	**6.63 (4.14-10.61)**
Cues to action:									
Presence of Fever									
No	63.2	-	-	59.3	-	-	3.9	-	-
Yes	81.5	**2.56 (2.14-3.08)**	**2.55 (2.12-3.07)**	73.1	**2.45 (2.04-2.95)**	**2.43 (2.02-2.93)**	8.4	**4.26 (3.03-5.98)**	**4.44 (3.14-6.28)**
Information sources									
Medical advice									
No	62.1	-	-	57.7	-	-	4.4	-	-
Yes	70.0	**1.43 (1.16-1.76)**	**1.43 (1.16-1.77)**	64.6	**1.42 (1.15-1.75)**	**0.82 (0.70-0.96)**	5.5	1.56 (0.95-2.57)	0.88 (0.55-1.41)
Family									
No	71.4	-	-	65.7	-	-	5.7	-	-
Yes	66.2	**0.78 (0.67-0.91)**	**0.81 (0.70-0.94)**	61.3	**0.79 (0.68-0.92)**	**1.22 (1.10-1.35)**	4.9	**0.72 (0.52-1.00)**	1.18 (0.86-1.61)
Media									
No	68.9	-	-	63.7	-	-		-	-
Yes	69.0	1.00 (0.79-1.28)	1.05 (0.82-1.34)	62.9	0.99 (0.77-1.27)	1.10 (0.93-1.30)	6.1	1.18 (0.71-1.94)	1.45 (0.91-2.33)
Keeping antibiotics at home									
No	71.4	-	-	68.4	-	-	3.0	-	-
Yes	66.8	**0.81 (0.70-0.94)**	**0.84 (0.72-0.98)**	59.5	**0.75 (0.64-0.87)**	**1.18 (1.07-1.31)**	7.4	**2.15 (1.49-3.11)**	**3.63 (2.54-5.17)**

OR, odds ratio; RRR, relative risk ratio; CI, confidence interval.
*Reference group: Parents who did not seek formal care for their children (n=991, 31.1%)
aAdjusted for sex, age, household income, parents' education, urbanicity and province.

Table 4. Clinicians' antibiotic prescriptions for URTIs for among Chinese children (N= 2,197): estimated relative risk ratio (RRR, 95% CI) of 'antibiotic prescriptions' and 'Inappropriate antibiotic prescriptions due to patients' demand' (vs 'no antibiotic prescription') for factors affecting parental treatment decisions

	Antibiotic prescriptions (1,069, 48.7%)			Inappropriate antibiotic prescriptions due to patients' demand (135, 6.1%)		
	%	RRR (95%CI)	**aRRR (95%CI)**	%	RRR (95%CI)	**aRRR (95%CI)**
Parents with medical background						
No	48.7	-	-	6.2	-	-
Yes	48.5	0.99 (0.75-1.30)	0.92 (0.69-1.22)	5.9	0.95 (0.53-1.71)	1.04 (0.57-1.91)
Parents ability to identify antibiotics						
Low	37.0	-	-	3.4	-	-
Medium	46.5	**1.62 (1.24-2.12)**	**1.66 (1.26-2.18)**	7.3	**2.72 (1.45-5.09)**	**3.16 (1.64-6.09)**
High	53.4	**2.15 (1.69-2.73)**	**2.25 (1.74-2.91)**	6.5	**2.82 (1.57-5.07)**	**3.37 (1.79-6.35)**
Parents perceptions:						
Antibiotic efficacy						
Effective for common cold						
No/Don't know	46.4	-	-	3.0	-	-
Yes	51.6	**1.47 (1.23-1.75)**	**1.49 (1.24-1.78)**	10.2	**4.48 (3.00-6.68)**	**4.17 (2.78-6.25)**
Effective for fever						
No/Don't know	43.1	-	-	3.7	-	-
Yes	55.2	**1.90 (1.59-2.27)**	**1.91 (1.60-2.29)**	9.0	**3.59 (2.45-5.26)**	**3.57 (2.43-5.26)**
Self-diagnosed severity						
Low (1 symptom)	42.8	-	-	3.7	-	-
Medium (2)	47.5	**1.29 (1.04-1.61)**	**1.34 (1.08-1.68)**	6.4	**2.78 (1.46-5.32)**	**1.99 (1.17-3.40)**
High (>=3)	54.5	**1.80 (1.43-2.27)**	**2.00 (1.58-2.54)**	7.6	**2.88 (1.57-5.28)**	**3.12 (1.81-5.38)**
Cues to action:						
Presence of Fever						
No	46.0	-	-	4.8	-	-
Yes	53.2	**1.48 (1.23-1.77)**	**1.64 (1.36-1.98)**	8.4	**2.20 (1.53-3.17)**	**2.44 (1.68-3.53)**
Information sources						
Medical advice						
No	51.4	-	-	5.4	-	-
Yes	48.3	0.89 (0.69-1.15)	0.88 (0.68-1.15)	6.3	1.11 (0.63-1.96)	1.07 (0.60-1.90)
Family						
No	45.4	-	-	6.5	-	-
Yes	52.5	**1.34 (1.12-1.59)**	**1.36 (1.14-1.63)**	5.8	1.04 (0.72-1.49)	1.11 (0.77-1.60)
Media						
No	48.5	-	-	6.0	-	-
Yes	50.0	1.10 (0.83-1.45)	1.12 (0.84-1.49)	7.2	1.27 (0.74-2.20)	1.44 (0.83-2.52)
Access to antibiotics						
No	38.1	-	-	2.1	-	-
Yes	58.2	**2.85 (2.38-3.41)**	**2.84 (2.36-3.41)**	9.8	**8.65 (5.38-13.90)**	**9.81 (6.04-15.94)**
Healthcare system used						
Tertiary hospital	45.5	-	-	3.3	-	-
Secondary/County hospital	50.5	**1.34 (1.03-1.75)**	**1.48 (1.11-1.96)**	7.0	**2.55 (1.28-5.09)**	**2.52 (1.23-5.18)**
Community Health Centres/Township hospital	45.9	1.08 (0.82-1.43)	1.16 (0.87-1.56)	6.6	**2.15 (1.05-4.39)**	1.89 (0.90-3.96)
Private Clinics/ Village clinics	52.2	1.37 (0.99-1.91)	1.27 (0.90-1.80)	5.1	1.83 (0.80-4.22)	1.42 (0.60-3.37)
ANTIBIOTIC USE						
No	38.6	-	-	2.2	-	-
Yes	70.0	**6.74 (4.95-9.19)**	**6.70 (4.89-9.23)**	14.1	**24.21 (13.24-44.25)**	**25.50 (13.62-47.74)**

OR, odds ratio; RRR, relative risk ratio; CI, confidence interval.
[*] Reference group: No antibiotic prescription (n=993, 45.2%)
[a]Adjusted for sex, age, household income, parents' education, urbanicity, province, and point-of-care used.

CHAPTER SIX

Decisions on antibiotic use for upper respiratory tract infections across China among university students: a large-scale cross-sectional survey

In this chapter, I report on secondary data analysis of a large-scale survey on treatment decisions with respect to antibiotic use for upper respiratory tract infections among young adults (university students) across six provinces of different geographic regions and economic development stages in China. Data were collected from September to November 2015 by the Zhejiang University Institute of Social Medicine and Family Medicine. (See Appendix I: Letter of Support.)

I conducted the analysis plan design and analysis independently. I employed two behavioural models - Health Belief Model and Social Ecological Model - for antibiotic use in the analysis and interpretation of the results. The findings and results have been prepared as a draft of the manuscript, with comments on drafts from Professors James Hargreaves, Stephan Harbarth, Elizabeth Fearon, Chunling Lu, Xiaomin Wang, and Xudong Zhou. This manuscript has been accepted by *BMJ Open*.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH1704488	**Title**	Ms.
First Name(s)	Leesa		
Surname/Family Name	Lin		
Thesis Title	Development of evidence-based behavioural interventions to reduce inappropriate use of antibiotics beyond clinical settings		
Primary Supervisor	Professor James Hargreaves		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	BMJ Open
Please list the paper's authors in the intended authorship order:	Leesa Lin, Elizabeth Fearon, Stephan Harbarth, Chunling Lu, Xudong Zhou*, James Hargreaves
Stage of publication	**In press**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Leesa Lin conducted the literature search, created the figures and theoretical framework, conducted data analysis and interpretation, and drafted and revised the manuscript. Elizabth Fearon, Stephan Harbarth, and Chunling Lu contributed to data interpretation, and commented on the initial and following revisions of the manuscript. Xudong Zhou conceived the study, led data collection, contributed to data interpretation, and commented on all drafts of this manuscript. James Hargreaves supervised the data analysis and interpretation, and contributed to the first draft and following revisions of the manuscript. All authors approved the final draft of this manuscript

SECTION E

Student Signature	[redacted]
Date	09/09/2019

Supervisor Signature	[redacted]
Date	09/12/2019

Decisions to use antibiotics for upper respiratory tract infections across China: a large-scale cross-sectional survey among university students

SYNOPSIS

BACKGROUND: Antibiotic misuse for upper respiratory tract infections (URTIs) is a global health challenge to efforts to contain antimicrobial resistance (AMR). The misuse is especially severe in China.

OBJECTIVES: We investigated the decision-making process of Chinese university students with respect to antibiotic use for URTIs.

METHODS: Data were obtained from a cluster random sample of 2834 university students across six Chinese regions, collected from September to November 2015. Using regular and multinomial logistic regression and adapted Health Belief Model, we identified and measured a number of variables as potential risk factors for antibiotic misuse behaviours in order to explain and predict people's treatment decisions and antibiotic use including knowledge, perceptions, access to antibiotics, and cues to action.

RESULTS: Of the 2834 university students who self-diagnosed a URTI, 947 (33.4%) self-reported having taken antibiotics; among them, 462 (48.8%) used non-prescription antibiotics, which came principally from leftover prescriptions (29.0%) and over-the-counter purchases at retail pharmacies (67.3%). One in four who sought care pressured their doctors for antibiotics; all received them. Those who perceived greater severity of the disease, had access to antibiotics, perceived benefits of using antibiotics, and were cued to action (e.g. seeing presence of fever or self-diagnosing their current infection as severe) were more likely to misuse antibiotics.

CONCLUSIONS: Misconceptions of antibiotic efficacy and easy access to antibiotics - with or without a prescription - were associated with antibiotic misuse

among Chinese university students, which calls for context-appropriate multifaceted interventions in order to effectively reduce antibiotic misuse.

INTRODUCTION

Acute upper respiratory tract infections (URTIs), widely known as "the common cold" and caused by several families of viruses, are the most common infectious diseases.[14] The use of antibiotics is unnecessary for treating URTIs, as most URTIs are viral whereas antibiotics neither expedite recovery from infections nor prevent complications.[7,299,300] Nevertheless, URTIs remain the most common reason for primary care seeking of antibiotics and antibiotic prescriptions in many countries, including China, which has one of the highest reported per-capita rates of antibiotics use globally at 138g/person.[32] Most Chinese antibiotic consumption occurs in outpatient settings, often unnecessarily for URTIs, which is a critical driver of inappropriate and excessive antibiotic use in China.[36,37] Despite the magnitude of antibiotic misuse in China, there is little evidence towards understanding how people make URTI treatment decisions, and little effort has been made to apply health behaviour theories towards understanding such decision-making.

An individual's medical decisions, such as antibiotic use for URTIs, are influenced by their attitudes and perceptions of the illness and treatment options while these attitudes and perceptions themselves are heavily influenced by socio-ecological context.[45,61,65] Adults may experience a URTI two to five times annually,[14] making it so well-recognised that, before consulting a physician, individuals commonly engage in self-diagnosis and decide a course of action – a majority of these self-recognized episodes were managed without seeking formal care.[301] To date, a majority of studies on antibiotic use behaviours examine the issues from a traditional, Knowledge-Attitudes-Practice (KAP) perspective, assuming people would make more 'risk-conscious' choices if informed of risks that could easily have been avoided (i.e. improved knowledge and awareness leads to changes in practice). However, decision scientists argue that, when people engage in

healthcare decision-making, they focus on attaining a goal – curing of an illness.[148] This thinking focuses on a positive rather than a negative outcome, where people accept the risks of drug resistance (for the immediate perceived benefits of antibiotic use) rather than intentionally taking risks.[148]

AMR stewardship programmes in China focused mostly on healthcare providers, i.e. prescribers[2,302], with very few targeting the public - the demand side of the healthcare system. In this study, we undertook a risk factor analysis for public's antibiotic misuse behaviours for informing effective intervention development. Risk factors were identified using the Health Belief Model with an aim to explain and predict health behaviours with respect to antibiotic use for URTIs. Specifically, with self-diagnosed URTIs cases, we aimed to assess Chinese university students' (1) antibiotic use, (2) treatment decisions regarding care-seeking and antibiotic use, and (3) prescription outcomes after seeking formal care, with a focus on antibiotic demands.

METHODS

Population Sample: We used a cluster random sampling method to recruit university students across six Chinese regions for a cross-sectional survey from September to November 2015. The single best comprehensive university[303] in each of six sampled provinces in each region was identified. Students attending these universities were eligible for enrolment. With assistance from school officials, class schedules were obtained the day prior to the survey. Classes were randomly selected from the timetable; every class had an equal chance of selection. All university students attending these classes were included. Over 95% of students in the selected classes completed the questionnaire; some students did not participate due to lacking a phone or laptop at the time of survey. Pilot tests indicated the prevalence of URTIs among Chinese university students in the past month to be 25-30%. To ensure an

adequate sample size for the planned subgroup analyses, we aimed to achieve a sample size per university of ca.1800 students. A total of 11,192 students completed the survey, with a response rate of 96%. Among participants, 25.32% (n=2834) self-reported experiencing symptoms of URTIs within the past month and such respondents were evenly distributed across all demographic groups. Further details on the survey's design and sampling methods have been previously described and published.[45,304]

Data collection: This study used a systematically developed questionnaire. Questions were tailored to the Chinese sociocultural context, as informed by literature review,[61,65,75,123] behavioural theories, and qualitative interviews with stakeholders and experts. A consent form was presented at the first section of the questionnaire and was signed by all participants, who were informed that participation was confidential, voluntary, could be terminated at any time, and that the questionnaire would take ~5 minutes to complete. The survey was developed using Wen Juan Xing – a popular web-based platform for professional electronic questionnaires and data collection – and delivered via WeChat, China's most used communication application. The survey was finalized after a pilot test with 254 respondents to evaluate potential sources of response error and improve the instrument. The reliability and validity fit the requirements.

Behavioural frameworks: We adapted the Health Belief Model[92,93] in the conceptual framework for analysis, as presented in Figure 1. The study aims to understand the impact of individuals' perception of illness and treatment on one's decisions for antibiotic use while accounting for the complex interplay between factors at different levels of socio-ecological environment[100] (i.e. individual, interpersonal, and societal). *Knowledge* relates to AMR awareness, ability to identify antibiotics, and misconceptions. Perceptions involve expectations about the

seriousness of the consequences of acquiring URTIs (i.e. *perceived severity*) or the benefits of antibiotic treatment for URTI symptoms (*perceived* antibiotic efficacy). *Cues to action* are external determinants of health behaviours *(e.g. presence of symptoms).*

Outcome variables: When responding to the question: *"During the most recent episode of sickness, what were the symptoms that you experienced?"*, participants who self-reported having symptoms of a URTI[14] - including cold (cough, runny/stuffy nose), fever, sore throat, headache, and flu, either alone or in combination - within a month prior to the survey were categorized into three subgroups with respect to their treatment decisions for using antibiotics: *no treatment or self-treated without antibiotics (reference group), self-treated with antibiotics, and sought formal care.* Diagnostic outcomes of care seeking were categorised into three subgroups with respect to doctors' prescribing decisions for antibiotics: *no antibiotic prescription (reference group), unnecessary antibiotic prescriptions for URTI symptoms,* and *inappropriate antibiotic prescriptions due to patients' demands.*

Exposure variables: We included the following potential risk factors in our analyses:

(1) *Knowledge about antibiotics and resistance* were measured by a series of factual statements related to *AMR awareness (5 items), ability to identify antibiotics (7 items),* and *misconception about the antibiotics as* "*anti-inflammatory drugs" (1 item).*

(2) Perceived severity of URTIs was measured by knowing that URTIs are self-limiting and will dissipate naturally.

(3) Perceived antibiotic efficacy was measured by 5 factual statements about antibiotics' efficacy to treat URTIs.

(4) Cues to action: (a) *numbers of cold symptoms experienced* and (b) *presence of fever.*

(5) *Access to antibiotics* were measured by two yes/no questions: (a) *keeping antibiotics at home in the past year,* and (b) *over-the-counter purchase of non-prescription antibiotics in the past year.*

Additionally, considering the Chinese socioecological environment regarding healthcare decisions, data on (6) *point of care* used for care seeking was collected, ranging from hospitals above county level, county level hospitals, township hospitals, and private clinics.

Covariates: Socio-demographic characteristics were included as potential confounders for the association between each exposure and treatment decisions, including age, sex, household income, urbanicity, university major in medicine, having at least one parent with medical background, and region/province.

Statistical analysis: First, we described and summarised participants' sociodemographic characteristics and modifying factors by treatment decision/behavioural outcomes. Second, we developed a flow diagram to show pathways of different medical decision outcomes with respect to antibiotic use for URTIs. Third, we described responses to different domains of knowledge about antibiotic use and resistance. Fourth, to examine the association between each risk factor and outcome, we applied logistic regressions to estimate the OR (95% CI) for 'treatment with antibiotic for URTIs' (vs 'no antibiotic use'). Last, we explored the associations with subgroups of antibiotic use for URTIs by self-medication and via formal care, and applied multinomial logistic regressions to estimate the relative risk ratio, RRR (95% CI) for (1) 'self-treatment with antibiotics' and 'sought healthcare' (vs 'no treatment or self-medication without antibiotics'). For students who sought healthcare, we estimated RRR (95%CI) for (2) "receiving (unnecessary)

prescriptions without request' and 'receiving (inappropriate) prescriptions due to patients request' (vs 'without an antibiotic prescription'). For each outcome and exposure, we first fitted an unadjusted model, and then a full model adjusted for potential confounders. These confounders - identified via published studies[61,65,75,123] on public's antibiotic use - include: *age*, *sex, household income, urbanicity, being a medical student or having at least one parent with a medical background, and hometown region of residence (university/province).*

RESULTS

Distributions of decisions for treatment and antibiotic use for URTIs (Figure 2)

When the 2834 university students with self-diagnosed URTIs were asked about their choice of treatment, 20.4% decided against treatment (n=579), 54.5% decided to self-treat (with or without antibiotics, n=1545), and a quarter sought formal care (n= 710, 25.1%). A total of 947 students self-reported having taken antibiotics for URTIs symptoms: 462 (48.8%) used non-prescription antibiotics and the rest obtained a prescription. Non-prescription antibiotics came principally from leftover prescriptions (29.0%) and over-the-counter purchases from pharmacies (67.3%). One out of every four respondents who sought formal care admitted to pressuring their doctors for antibiotics (n=123, 25.4%), with a 100% success rate.

Knowledge and perceptions about antibiotic use and resistance (Table 1)

Respondents were assessed on their knowledge about antibiotic use and resistance and perceptions on antibiotic efficacy and URTIs as a health threat. The overall Cronbach's alpha, including all items, was 0.81, with subscales of 0.71 (for AMR awareness) and 0.81 (for ability to identify antibiotics). Three quarters of participants (74.2-88.5%) reported being aware of the dangers posed by overuse of antibiotics. A majority of participants (63.0%) had trouble distinguishing cold medicine (e.g. Tylenol, Contac NT or Gankang) from antibiotics. 36.5% were

unaware antibiotics were not anti-inflammatory drugs; more than 60% had an incorrect perception of antibiotic efficacy for URTIs, either being unsure or wrongly stating that antibiotics might expedite recovery or alleviate symptoms.

Factors associated with antibiotic use for URTIs (Table 2)

Compared with those who did not use antibiotics for treatment of URTIs, *ability to identify antibiotics* (aOR=1.51, 95%CI:1.17-1.94)*, perceived antibiotics to be effective for the common cold* (aOR=2.55, 95%CI:1.93-3.38) or as *anti-inflammatory drugs* (aOR=1.35, 95%CI:1.12-1.63)*, not knowing that the common cold is self-limiting* (aOR=1.35, 95%CI:1.12-1.62)*, presence of fever* (aOR=2.05, 95%CI:1.62-2.60)*, multiple symptoms experienced* (aOR=1.86, 95%CI:1.41-2.45)]*, keeping antibiotics at home* (aOR=2.27, 95%CI:1.83-2.81), and *access to over-the-counter antibiotics* (aOR=2.00, 95%CI:1.63-2.45) were associated with a higher likelihood of antibiotic use for URTIs.

Factors associated with the treatment decisions for URTIs and antibiotic use (Table 3)

Relative to those who did nothing or self-treated without antibiotics for URTIs (reference group), participants who self-medicated with antibiotics were more likely to have *perceived antibiotic efficacy for URTIs* (aRRR=3.03, 95%CI:2.10-4.38)*, mistake antibiotics as anti-inflammatory drugs* (aRRR=1.40, 95%CI:1.10-1.77)*, not know that the common cold is self-limiting* (aRRR=1.34, 95%CI:1.05-1.71))*, experience multiple cold symptoms* (aRRR=1.96, 95%CI:1.36-2.84), *kept antibiotics at home* (aRRR=4.68, 95%CI:3.24-6.74), and *purchased over-the-counter antibiotics* (aRRR=3.21, 95%CI:2.34-4.41). Those who sought formal care were more likely to have a *high level of AMR awareness* (aRRR=0.61, 95%CI:0.42-0.89), have *not known that URTIs are self-limiting* (aRRR=1.66, 95%CI:1.36-2.02), *experienced multiple cold symptoms* (aRRR=1.64, 95%CI:1.21-

2.21), and had *presence of fever* (aRRR=2.98, 95%CI:2.32-3.83)]. Participants who had *perceived antibiotics to be effective for the common cold* (aRRR=1.89, 95%CI:1.38-2.57)*, kept antibiotics at home* (aRRR=1.24, 95%CI:1.00-1.54), and *purchased over-the-counter antibiotics* (aRRR=1.22, 95%CI:0.99-1.51) were also more likely to seek formal care.

Factors associated with the antibiotic prescriptions for the treatment of URTIs (Table 4)

Participants who sought care and had high levels of *AMR awareness* had lower risks of demanding antibiotics. Relative to those who sought formal care but did not get an antibiotics prescription (reference group), participants who had *high ability to identify antibiotics* (aRRR=6.35, 95%CI:2.85-14.13)*, perceived antibiotics to be effective for the common cold* (aRRR=3.67, 95%CI:1.61-8.39) or *as anti-inflammatory drugs* (aRRR=1.92, 95%CI:1.11-3.33)*, presence of fever* (aRRR=3.24, 95%CI:1.70-6.18)*, kept antibiotics at home* (aRRR=2.46, 95%CI:1.33-4.56), and made *over-the-counter purchase* (aRRR=3.69, 95%CI:1.97-6.91) had a higher likelihood of demanding antibiotic prescriptions. Evidence of structural differences was observed in antibiotic prescribing outcomes in *point of care.* 54.3% of patients who sought care at tertiary hospitals and 52.7% at township hospitals were prescribed antibiotics for URTIs, whereas 43.2% of county hospitals and 43.1% of local clinics gave antibiotic prescriptions for URTIs. All patients who demanded antibiotic prescriptions from a doctor received them.

DISCUSSION

We found that 33.4% of young Chinese educated in top universities (n=947) with URTIs used antibiotics; among them, 462 (48.8%) used non-prescription antibiotics and additionally, a quarter of prescriptions originated from patients' demands (n=123, 25.4%). We therefore estimated that the demand side is

responsible for 61.8% of antibiotic use for URTIs [(462+123)/947]. Surprisingly, high *ability to identify antibiotics* was linked to higher likelihoods of antibiotic use, especially antibiotic prescriptions. Mistaking antibiotics as anti-inflammatory drugs, perceiving antibiotics as efficacious for treating URTIs, and access to non-prescription antibiotics were strongly associated with antibiotic misuse, including self-medication with antibiotics and demands for antibiotic prescriptions. We found non-prescription antibiotics are easily accessible in China: 68.2% of participants kept antibiotics at home at the time of the survey and 64.2% made over-the-counter purchases at least once within the past year. At health facilities, roughly 70% of clinicians prescribed antibiotics – most deemed as inappropriate and unnecessary – for URTI symptoms, and there was practically no barrier to accessing antibiotic prescriptions from a doctor.

Strengths and limitations: This study is guided by the adapted Health Belief Model for analysis in explaining and predicting patients' treatment decisions and antibiotic use for URTIs. We found perceived infection severity, efficacy of antibiotic use for URTIs, barriers/access to antibiotics, and cues to action are determinants of higher likelihoods of antibiotic use for URTIs, with or without prescriptions. In the Chinese context, our data further identified the demands of the health system – rather than supply – as the driving force for outpatient antibiotic use for URTIs, with a 1.6:1 ratio [62% vs 38%], and that access to antibiotics, with or without a prescription, was extremely easy. This model can guide the design and development of behavioural change interventions which aim to reduce antibiotic misuse in the community, with a focus on the complex interplay between individual/interpersonal/societal factors and individuals' decisions on treatment and antibiotic use for URTIs.

Though the cross-sectional study design limited us from drawing causal relationships between knowledge and practice of antibiotic misuse, it helped to generate causal hypotheses and offered several points for intervention. Experiments, longitudinal studies, or behavioural data are needed in the near future to avoid recall bias, an inherent limitation of self-reported survey data. Considering people may have multiple infections during the year and because our target population consisted of university students, who are generally younger and healthier than the general population, we anticipate antibiotic misuse among the Chinese general population to be more prevalent and severe than what has been presented here. Lastly, because the samples were clustered therefore the estimated standard errors used in significance tests may be biased. In our case, samples were drawn from six universities across China, from provinces of different development levels; the differences among these provinces might be greater than those among individuals drawn from a random sample across the country. We have accounted for such variation at the province/university level in the analyses.

Interpretation of Findings: First, we found that, at the individual level, awareness of the danger of AMR was high among students, yet such awareness did not translate into prudent antibiotic use. This might imply the existence of an externality associated with antibiotic use for treating infections; despite a high awareness of AMR, the risks AMR imposes on others are unlikely to be felt directly or immediately by either the consumer or the supplier of treatment. Findings from this study identified a significant positive correlation between ability to identify antibiotics and self-medication, prescriptions, and demand for antibiotics. Some scholars have suggested many Chinese users make decisions on antibiotics without fully understanding the package insert, and that an inability to identify antibiotics may be a barrier to appropriate antibiotic use in China; as such, education

interventions to improve ability to identify antibiotics seem warranted.[62,67,75] However, studies demonstrated "successful experiences" in the past for "curing" a similar illness, and knowledge of the previously prescribed antibiotics could lead to improved ability to identify antibiotics and SMA.[75,283,305-307] Most KAP studies[113,308] tested antibiotics-related knowledge, attitudes, and beliefs and sometimes, even practice, as one coherent category - for example, grouping them into scores – but according to our findings, these measures might be inappropriate. Specifically, our data suggest heterogeneity exists in the "domain" of knowledge about antibiotics and its relationship with antibiotic practices for URTIs. Without sufficient knowledge about correct antibiotic efficacy, appropriate care for URTIs, and using antibiotics only under professional supervision, simply improving the public's ability to identify antibiotics alone could potentially cause greater misuse. Therefore, the common current practice of grouping multiple aspects of antibiotics- or AMR-related knowledge, attitudes and beliefs, and even practices into one score might not fully capture the complexity of their various associations with antibiotic use behaviours. It also means that a blanket awareness campaign or a simple intervention on clear labelling of antibiotics is likely to fail without adapting to the local context – a finding consistent with the recent assessment of WHO awareness campaign.[309] We found strong evidence showing that demanding antibiotic prescriptions was associated with household stockpiling and over-the-counter purchases of antibiotics. Interventions which target "demanders" and "heavy misusers" of antibiotics in the community and that correct the misperception of antibiotics' efficacy for URTIs or as anti-inflammatory drugs might reduce misuse.

Interpersonal relationships have a significant influence on individual's decisions regarding antibiotic use. All the participants who asked for antibiotics successfully received them. Even with good intentions,[35,38,62,257,261] unrealistic

patient expectations and pressure from patients or caregivers to prescribe antibiotics have been identified as major reasons why physicians prescribe antibiotics for self-limiting diseases.[35,279,310-312] This indicates an urgent need for further training to help clinicians improve clinical skills and doctor–patient communication skills. Because URTIs are self-resolving, the prescribers who treat them with antibiotics benefit from an apparently successful cure, promoting recommendations by patients and leading to a cycle of over-treatment.[140] In our case, clinicians' over-prescribing in China - incentivised by financial profits for health facilities[30] – might have helped shape and reinforce common public misperceptions of antibiotics as effective for URTIs, which, in turn, leads to patients' improved (or "learned") ability to identify antibiotics[307,313] and demand for antibiotics, further perpetuating misuse.

At the societal level, our data showed 68.2% of participants stored antibiotics, which mainly came from over-the-counter purchases and previous prescriptions. We found the effect of keeping antibiotics at home on antibiotic (mis)use in the community is as profound as the impact of unnecessary prescriptions for URTIs through formal care. Since 2011, China has implemented policies (such as banning over-the-counter purchases and capping antibiotic prescriptions at 20% for county hospitals and above and 30% for township hospitals) to control antibiotic misuse, but the success of such initiatives has been limited due to poor enforcement.[40,42,269,270,314,315] In our data, about 70% of URTIs patients who sought care were prescribed antibiotics; among them, over 50% of the patients received antibiotic prescriptions without prompting and close to 20% successfully obtained antibiotics through explicit requests. These data pointed to an urgent need for effective, context-tailored hospital stewardship programmes that improve adherence to clinical practice guidelines for antibiotic prescribing in China and enhance doctor-patient communication over antibiotic use. Consistent with other studies,[61,120,137,257]

over-the-counter sales of non-prescription antibiotics at community pharmacies were found across China. Societal normative influences on individual's antibiotic use in China are implied from the regional differences in antibiotic use, SMA and care seeking behaviours. Additionally, we identified a set of shared misconceptions in the community – even among the highly educated – such as viewing antibiotics as effective for URTIs and as anti-inflammatory drugs, which acted as drivers of antibiotic misuse in China.

Policy Implications

Customising strategies according to local needs and socio-ecological environments is fundamental to effective intervention. To date, most current AMR interventions in China focus on the supply side, such as stewardship programmes aiming to curb overprescribing. However, our findings point to an urgent need to complement these with context-specific and multilevel interventions targeting the demand-side of antibiotic misuse in China. To untangle the perpetual problem of over-prescription and ill-informed demands for antibiotics, interventions that include prescribing guidelines, communication skills, and patient education are necessary. Enforcing regulations regarding the sale of antibiotics, pack-based antibiotic dispensing systems, and public educational interventions to reduce consumer-driven prescriptions and leftover prescriptions could curb the main sources of antibiotics for self-medication use. Introducing interventions to reduce household storage of antibiotics, such as drugs/antibiotics take-back programmes, is necessary.

CONCLUSION

Determinants of medical decisions for antibiotic use and care seeking are complex. It is critical to consider the heterogeneity of culture, health systems, and social norms in the assessment and intervention of decision-making regarding antibiotic use. This study provided urgently needed evidence for future interventional studies to address

the challenges posed by the demand-side and to improve the Chinese general population's antibiotic use.

Acknowledgments

The authors appreciated the help from teachers and students involved in disseminating this survey and coordinating the study.

Ethics

The study protocol and survey were reviewed and exempted by the Institutional Review Board at the School of Public Health Zhejiang University (No. ZGL20160922) and London School of Hygiene & Tropical Medicine (No. 14678).

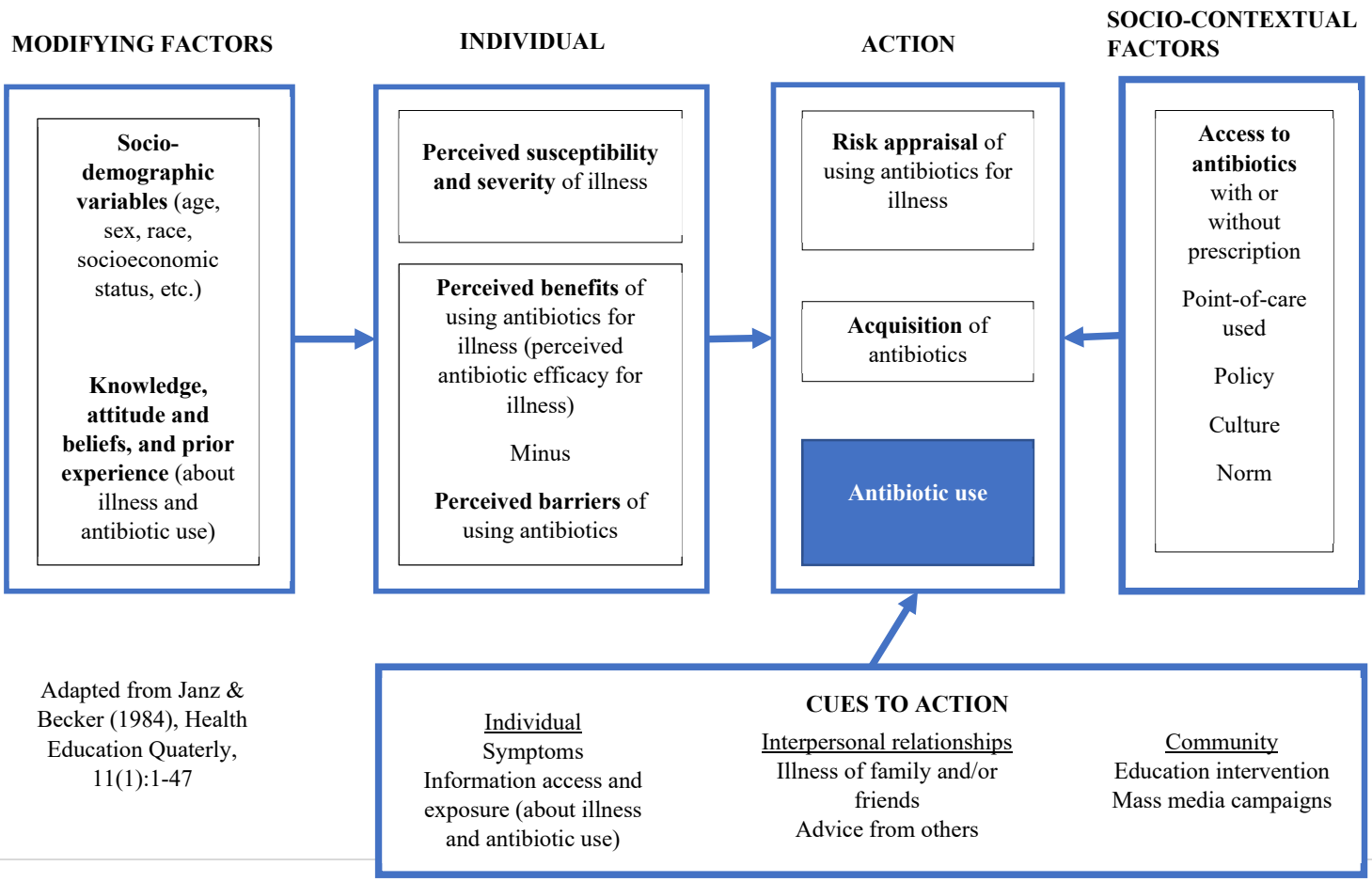
Funding

The study was funded by Zhejiang University Zijin Talent Programme.

Transparency declarations

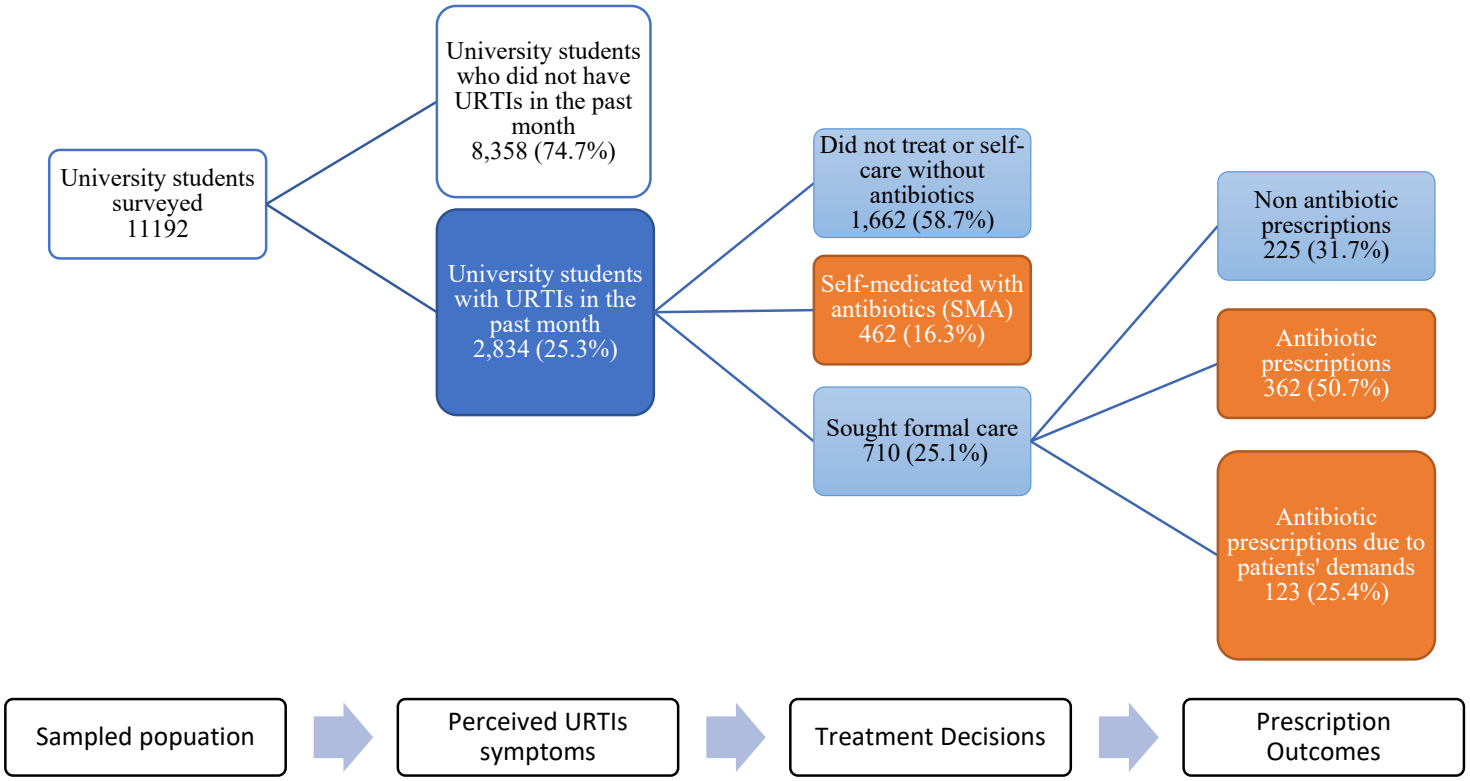
The authors have declared no conflict of interests related to this study.

Figure 1. Conceptual Framework



Adapted from Janz & Becker (1984), Health Education Quaterly, 11(1):1-47

Figure 2. Medical decisions about antibiotic use for upper respiratory tract infections among Chinese university students



Estimate of contribution to antibiotic misuse for URTIs

Demand side factors: (462 + 123)/(462+485) = 61.77%

Supply side factors: (485-123)/(462+485) = 38.23%

Table 1. Knowledge and perceptions about antibiotic use and resistance score distribution (n=2834)

	Yes n (%)	No n (%)	I don't know n (%)	**Alpha** **0.81**
AMR awareness				0.71
1. Antibiotic overuse is a serious problem in China.	**2168 (76.5)**	51 (1.8)	615 (21.7)	
2. The more frequently people use antibiotics; the more difficult it will be to treat bacterial infections.	**2270 (80.1)**	262 (9.2)	302 (10.7)	
3. Antibiotic overuse may increase antibiotic resistance.	**2509 (88.5)**	184 (6.5)	141 (5.0)	
4. Antibiotic resistance will become a serious problem in China.	**2102 (74.2)**	61 (2.2)	646 (23.7)	
5. We will have few antibiotics to use in the future if we don't use antibiotics properly.	**2367 (83.5)**	222 (7.8)	245 (8.7)	
Ability to identify antibiotics				0.81
1. Penicillin (amoxicillin)	**2263 (79.9)**	275 (9.7)	296 (10.4)	
2. Cephalosporin (cefaclor, ceftriaxone sodium)	**1969 (69.5)**	342 (12.1)	523 (18.5)	
3. Nonsteroidal Anti-inflammatory Drugs (ibuprofen, aspirin)	1129 (39.8)	**894 (31.6)**	811 (28.6)	
4. Quinolones (norfloxacin, ofloxacin)	**1306 (46.1)**	600 (21.2)	928 (32.8)	
5. Acetaminophen (Tylenol, Contac NT, Gankang)	799 (28.2)	**1049 (37.0)**	986 (34.8)	
6. Macrolides (azithromycin, roxithromycin)	**1669 (58.9)**	331 (11.7)	834 (29.4)	
7. Steroids (Dexamethasone, Prednisone)	762 (26.9)	**820 (28.9)**	1253 (44.2)	
Misconception about antibiotics				
1. Antibiotics are anti-inflammatory drugs.	575 (20.3)	**1799 (63.5)**	460 (16.2)	
Perceived antibiotic efficacy on URTIs				
1. Antibiotics can speed up recovery from flu.	1250 (44.1)	**1081 (38.1)**	503 (17.8)	
2. Antibiotics can relieve the symptoms of cold.	1384 (48.8)	**943 (33.3)**	507 (17.9)	
3. Antibiotics are effective for sore throat.	978 (34.5)	**1620 (57.2)**	236 (8.3)	
4. Antibiotics are effective for treating common cold (cough, runny nose).	687 (24.2)	**1912 (67.5)**	235 (8.3)	
Perceived threat about URTIs				
1. Common cold is self-limiting and does not require medication as the symptoms will dissipate naturally	**1927 (68.0)**	725 (25.6)	182 (6.4)	

Table 2. Logistic regression to assess factors associated with antibiotic use for upper respiratory tract infections among Chinese university students (N=2,834)

	All students with URTIs (N=2,834)	Antibiotic use for URTIs (n= 947, 33.42%)			
	N (%)	n (%)	OR (95%CI:)	aOR (95%CI:)	[b]p-value
Knowledge about antibiotics					
AMR awareness					0.97
Low	181 (6.39)	73 (7.71)	Reference	Reference	
Medium	571 (20.16)	210 (22.18)	0.86 (0.61-1.21)	1.02 (0.70-1.50)	
High	2082 (73.47)	664 (70.12)	**0.69 (0.51-0.95)**	0.99 (0.70-1.42)	
Ability to identify antibiotics					**0.002**
Low	806 (28.44)	226 (23.86)	Reference	Reference	
Medium	1267 (44.71)	470 (49.63)	**1.51 (1.25-1.83)**	**1.37 (1.11-1.70)**	
High	761 (26.85)	251 (26.50)	**1.26 (1.02-1.57)**	**1.51 (1.17-1.94)**	
Perceived severity of the infection					
Common cold is self-limiting					**0.002**
Yes	1927 (68.00)	581 (61.35)	Reference	Reference	
No/I don't know	907 (32.00)	366 (38.65)	**1.57 (1.33-1.85)**	**1.35 (1.12-1.62)**	
Perceived antibiotic efficacy					
Perceived antibiotic efficacy for URTIs					**<0.0001**
No/Low	938 (33.10)	200 (21.12)	Reference	Reference	
Medium	1476 (52.08)	542 (57.23)	**2.14 (1.77-2.59)**	**1.71 (1.39-2.10)**	
High	420 (14.82)	205 (21.65)	**3.52 (2.75-4.50)**	**2.55 (1.93-3.38)**	
Antibiotics are anti-inflammatory drugs					**0.001**
No	1799 (63.48)	524 (55.33)	Reference	Reference	
Yes/I don't know	1035 (36.52)	423 (44.67)	**1.68 (1.43-1.97)**	**1.35 (1.12-1.63)**	
Cues to action					
Self-diagnosed Symptoms Experienced					**<0.0001**
Low	1488 (52.51)	395 (41.71)	Reference	Reference	
Medium	893 (31.51)	317 (33.47)	**1.52 (1.27-1.82)**	**1.37 (1.13-1.67)**	
High	453 (15.98)	235 (24.82)	**2.98 (2.40-3.71)**	**1.86 (1.41-2.45)**	
Fever					**<0.0001**
No	2235 (78.86)	638 (67.37)	Reference	Reference	
Yes	599 (21.14)	309 (32.63)	**2.67 (2.22-3.21)**	**2.05 (1.62-2.60)**	
Barriers/Access to Antibiotics					
Keeping antibiotics at home					**<0.0001**
No	900 (31.76)	179 (18.90)	Reference	Reference	
Yes	1934 (68.24)	768 (81.10)	**2.65 (2.20-3.20)**	**2.27 (1.83-2.81)**	
Over-the-counter purchase of non-prescription antibiotics in the past year					**<0.0001**
No	1015 (35.82)	202 (21.33)	Reference	Reference	
Yes	1819 (64.18)	745 (78.67)	**2.79 (2.33-3.34)**	**2.00 (1.63-2.45)**	
Socio-demographic characteristics					0.79
Age	21.13[c] (2.67)		1.02 (0.99-1.05)	1.00 (0.96-1.03)	
Sex					0.44
Male	1476 (52.08)	496 (52.38)	Reference	Reference	
Female	1358 (47.92)	451 (47.62)	0.98 (0.84-1.15)	1.07 (0.90-1.28)	
Urbanicity of Hometown					0.07
Rural	1644 (58.01)	505 (53.33)	Reference	Reference	
Urban	1190 (41.99)	442 (46.67)	**1.33 (1.14-1.56)**	1.20 (0.98-1.47)	
Average household income (RMB, monthly)					0.05
>10,000 (>$1538)	496 (17.50)	147 (15.52)	Reference	Reference	
3,001-10,000 ($462-$1538)	1503 (53.03)	470 (49.63)	1.08 (0.87-1.35)	0.92 (0.72-1.17)	
<=3,000 ($461)	835 (29.46)	330 (34.85)	**1.55 (1.22-1.97)**	1.21 (0.90-1.62)	
Major in Medicine					**0.02**
No	2396 (84.54)	835 (88.17)	Reference	Reference	
Yes	438 (15.46)	112 (11.83)	**0.64 (0.51-0.81)**	**0.73 (0.56-0.95)**	
Having at least one parent with medical background					0.47
No	2524 (89.06)	836 (88.28)	Reference	Reference	
Yes	310 (10.94)	111 (11.72)	1.13 (0.88-1.44)	1.11 (0.84-1.46)	
Region (University, Province)					**0.001**
North (NKU, Tianjin)	417 (14.71)	121 (12.78)	Reference	Reference	
East (ZJU, Zhejiang)	459 (16.20)	104 (10.98)	**0.72 (0.53-0.97)**	0.81 (0.58-1.14)	
Southwest (GZU, Guizhou)	493 (17.40)	223 (23.55)	**2.02 (1.53-2.66)**	**1.56 (1.15-2.13)**	
Northwest (LZU, Gansu)	528 (18.63)	203 (21.44)	**1.53 (1.16-2.01)**	1.29 (0.95-1.74)	
South (WHU, Hubei)	480 (16.94)	121 (12.78)	0.82 (0.61-1.11)	0.93 (0.67-1.28)	
Northeast (JLU, Jilin)	457 (16.13)	175 (18.48)	1.52 (1.14-2.02)	1.09 (0.79-1.49)	

[a]Adjusted for age, sex, household income, urbanicity, major in medicine, having at least one parent with medical background, and region/province.
[b]Likelihood ratio tests for antibiotic use for URTIs
[c]mean (SD)

Table 3. Multinomial regression model to assess factors associated with treatment decisions for upper respiratory tract infections with respect to antibiotic use among Chinese university students (N=2,834)

	Did not treat or self-treated without antibiotics (n=1,662, 58.65%)	Self-medicated with antibiotics (n=462, 16.30%)			Sought formal care (n=710, 25.05%)			
	n (%)	n (%)	RRR (95%CI:)	aRRR (95%CI:)	n (%)	RRR (95%CI:)	aRRR (95%CI:)	[b]p-value
Knowledge about antibiotics								
AMR awareness								**0.006**
Low	84 (5.05)	23 (4.98)	Reference	Reference	74 (10.42)	Reference	Reference	
Medium	302 (18.17)	94 (20.35)	1.14 (0.68-1.90)	1.34 (0.77-2.34)	175 (24.65)	**0.66 (0.46-0.95)**	0.80 (0.54-1.18)	
High	1276 (76.77)	345 (74.68)	0.99 (0.61-1.59)	1.38 (0.82-2.33)	461 (64.93)	**0.41 (0.29-0.57)**	**0.61 (0.42-0.89)**	
Ability to identify antibiotics								0.49
Low	488 (29.36)	108 (23.38)	Reference	Reference	210 (29.58)	Reference	Reference	
Medium	718 (43.20)	224 (48.48)	**1.41 (1.09-1.82)**	1.08 (0.82-1.43)	325 (45.77)	1.05 (0.85-1.30)	1.08 (0.86-1.36)	
High	456 (27.44)	130 (28.14)	1.29 (0.97-1.71)	1.20 (0.87-1.67)	175 (24.65)	0.89 (0.70-1.13)	1.27 (0.97-1.66)	
Perceived severity of the infection								
Common cold is self-limiting								**<0.0001**
Yes	1216 (73.16)	297 (64.29)	Reference	Reference	414 (58.31)	Reference	Reference	
No/I don't know	446 (26.84)	165 (35.71)	**1.51 (1.22-1.89)**	**1.34 (1.05-1.71)**	296 (41.69)	**1.95 (1.62-2.34)**	**1.66 (1.36-2.02)**	
Perceived antibiotic efficacy								
Perceived antibiotic efficacy for URTIs								**<0.0001**
No/Low	664 (39.95)	90 (19.48)	Reference	Reference	184 (25.92)	Reference	Reference	
Medium	813 (48.92)	267 (57.79)	**2.42 (1.87-3.14)**	**1.99 (1.50-2.64)**	396 (55.77)	**1.76 (1.44-2.15)**	**1.46 (1.17-1.82)**	
High	185 (11.13)	105 (22.73)	**4.19 (3.02-5.80)**	**3.03 (2.10-4.38)**	130 (18.31)	**2.54 (1.92-3.35)**	**1.89 (1.38-2.57)**	
Antibiotics are anti-inflammatory drugs								**0.02**
No	1123 (67.57)	249 (53.90)	Reference	Reference	427 (60.14)	Reference	Reference	
Yes/I don't know	539 (32.43)	213 (46.10)	**1.78 (1.44-2.20)**	**1.40 (1.10-1.77)**	283 (39.86)	**1.38 (1.15-1.66)**	1.12 (0.91-1.38)	
Cues to action								
Self-diagnosed Symptoms Experienced								**<0.001**
Low	974 (58.60)	217 (46.97)	Reference	Reference	297 (41.83)	Reference	Reference	
Medium	507 (30.51)	152 (32.90)	**1.35 (1.07-1.70)**	**1.30 (1.01-1.68)**	234 (32.96)	**1.51 (1.24-1.85)**	**1.29 (1.04-1.61)**	
High	181 (10.89)	93 (20.13)	**2.31 (1.73-3.08)**	**1.96 (1.36-2.84)**	179 (25.21)	**3.24 (2.54-4.14)**	**1.64 (1.21-2.21)**	
Fever								**<0.0001**
No	1432 (86.16)	359 (77.71)	Reference	Reference	444 (62.54)	Reference	Reference	
Yes	230 (13.84)	103 (22.29)	**1.79 (1.38-2.32)**	1.23 (0.89-1.72)	266 (37.46)	**3.73 (3.04-4.58)**	**2.98 (2.32-3.83)**	
Barriers/Access to Antibiotics								
Keeping antibiotics at home								**<0.0001**
No	628 (37.79)	38 (8,23)	Reference	Reference	234 (32.96)	Reference	Reference	
Yes	1034 (62.21)	424 (91.77)	6.78 (4.79-9.58)	4.68 (3.24-6.74)	476 (67.04)	1.24 (1.03-1.49)	1.24 (1.00-1.54)	
Over-the-counter purchase of non-prescription antibiotics in the past year								**<0.0001**
No	709 (42.66)	55 (11.90)	Reference	Reference	251 (35.35)	Reference	Reference	
Yes	953 (57.34)	407 (88.10)	**5.51 (4.09-7.42)**	**3.21 (2.34-4.41)**	459 (64.65)	**1.36 (1.13-1.63)**	**1.22 (0.99-1.51)**	
Socio-demographic characteristics								0.78
Age			1.03 (0.99-1.07)	1.01 (0.97-1.05)		0.99 (0.96-1.02)	0.99 (0.95-1.03)	
Sex								0.19
Male	876 (52.71)	243 (52.60)	Reference	Reference	357 (50.28)	Reference	Reference	
Female	786 (47.29)	219 (47.40)	1.00 (0.82-1.23)	1.22 (0.97-1.52)	353 (49.72)	1.10 (0.92-1.31)	1.12 (0.92-1.35)	
Urbanicity of Hometown								0.64
Rural	1000 (60.17)	273 (59.09)	Reference	Reference	371 (52.25)	Reference	Reference	
Urban	662 (39.83)	189 (40.91)	1.05 (0.85-1.29)	1.07 (0.83-1.39)	339 (47.75)	**1.38 (1.16-1.65)**	1.11 (0.89-1.38)	
Average household income (RMB, monthly)								0.14
>10,000 (>$1538)	307 (18.47)	83 (17.97)	Reference	Reference	106 (14.93)	Reference	Reference	
3,001-10,000 ($462-$1538)	907 (54.57)	239 (51.73)	0.97 (0.74-1.29)	0.82 (0.60-1.12)	357 (50.28)	1.14 (0.89-1.47)	1.07 (0.82-1.41)	
<=3,000 ($461)	448 (26.96)	140 (30.30)	1.16 (0.85-1.57)	0.97 (0.67-1.41)	247 (34.79)	**1.60 (1.22-2.09)**	1.37 (0.99-1.89)	
Self-efficacy for healthcare decisions								
Major in Medicine								**0.03**
No	1365 (82.13)	397 (85.93)	Reference	Reference	634 (89.30)	Reference	Reference	
Yes	297 (17.87)	65 (14.07)	0.75 (0.56-1.01)	0.89 (0.64-1.25)	76 (10.70)	0.55 (0.42-0.72)	0.68 (0.50-0.91)	
Having at least one parent with medical background								0.34
No	1488 (89.53)	395 (85.50)	Reference	Reference	641 (90.28)	Reference	Reference	
Yes	174 (10.47)	67 (14.50)	1.45 (1.07-1.96)	1.27 (0.91-1.78)	69 (9.72)	0.92 (0.69-1.23)	1.00 (0.72-1.37)	
Region (University, Province)								**<0.0001**
North (NKU, Tianjin)	276 (16.61)	81 (17.53)	Reference	Reference	60 (8.45)	Reference	Reference	
East (ZJU, Zhejiang)	310 (18.65)	38 (8.23)	**0.42 (0.27-0.63)**	**0.50 (0.32-0.79)**	111 (15.63)	**1.65 (1.16-2.35)**	**1.86 (1.27-2.73)**	
Southwest (GZU, Guizhou)	240 (14.44)	84 (18.18)	1.19 (0.84-1.69)	0.98 (0.66-1.44)	169 (23.80)	**3.24 (2.30-4.56)**	**2.49 (1.72-3.60)**	
Northwest (LZU, Gansu)	287 (17.27)	103 (22.29)	1.22 (0.88-1.71)	1.08 (0.75-1.56)	138 (19.44)	**2.21 (1.57-3.12)**	**1.92 (1.33-2.77)**	
South (WHU, Hubei)	297 (17.87)	50 (10.82)	**0.57 (0.39-0.85)**	**0.66 (0.43-1.00)**	133 (18.73)	**2.06 (1.46-2.91)**	**2.39 (1.66-3.45)**	
Northeast (JLU, Jilin)	252 (15.16)	106 (22.94)	1.43 (1.02-2.01)	1.10 (0.76-1.60)	99 (13.94)	**1.81 (1.26-2.60)**	1.37 (0.93-2.03)	

[a]Adjusted for age, sex, household income, urbanicity, major in medicine, having at least one parent with medical background, and region/province.

[b]Likelihood ratio tests for treatment decisions for URTIs

[c]mean (SD)

Table 4. Multinomial regression model to assess factors associated with diagnostic outcomes with respect to antibiotic prescriptions for upper respiratory tract infections among Chinese university students who sought care (N=710)

	All students who sought care (N=710)	No antibiotic prescription (n=225, 31.69%)	Prescribed with antibiotics (n=362, 50.99%)			Asked for antibiotics (n=123, 17.32%)			
	N (%)	n (%)	n (%)	RRR (95%CI:)	aRRR (95%CI:)	n (%)	RRR (95%CI:)	aRRR (95%CI:)	[b]p-value
Knowledge about antibiotics									
AMR awareness									**0.004**
Low	74 (10.42)	24 (10.67)	27 (7.46)	Reference	Reference	23 (18.70)	Reference	Reference	
Medium	175 (24.65)	59 (26.22)	84 (23.20)	1.27 (0.67-2.41)	1.18 (0.59-2.38)	32 (26.02)	0.57 (0.28-1.16)	**0.37 (0.16-0.87)**	
High	461 (64.93)	142 (63.11)	251 (69.34)	1.57 (0.87-2.83)	1.62 (0.82-3.19)	68 (55.28)	**0.50 (0.26-0.95)**	**0.40 (0.17-0.91)**	
Ability to identify antibiotics									**<0.0001**
Low	210 (29.58)	92 (40.89)	100 (27.62)	Reference	Reference	18 (14.63)	Reference	Reference	
Medium	325 (45.77)	79 (35.11)	180 (49.72)	**2.10 (1.42-3.09)**	**1.85 (1.20-2.84)**	66 (53.66)	**4.27 (2.34-7.79)**	**4.03 (2.01-8.11)**	
High	175 (24.65)	54 (24.00)	82 (22.65)	1.40 (0.90-2.18)	1.48 (0.88-2.46)	39 (31.71)	**3.69 (1.92-7.08)**	**6.35 (2.85-14.13)**	
Perceived Severity of the infection									
Common cold is self-limiting									0.25
Yes	414 (58.31)	130 (57.78)	209 (57.73)	Reference	Reference	75 (60.98)	Reference	Reference	
No/I don't know	296 (41.69)	95 (42.22)	153 (42.27)	1.00 (0.72-1.40)	0.89 (0.61-1.29)	48 (39.02)	0.88 (0.56-1.37)	0.64 (0.38-1.09)	
Perceived antibiotic efficacy									
Antibiotic efficacy									**0.04**
Low	184 (25.92)	74 (32.89)	91 (25.14)	Reference	Reference	19 (15.45)	Reference	Reference	
Medium	396 (55.77)	121 (53.78)	207 (57.18)	1.39 (0.95-2.03)	1.23 (0.80-1.87)	68 (55.28)	**2.19 (1.22-3.93)**	**2.17 (1.12-4.24)**	
High	130 (18.31)	30 (13.33)	64 (17.68)	**1.73 (1.02-2.95)**	1.56 (0.86-2.84)	36 (29.27)	**4.67 (2.32-9.40)**	**3.67 (1.61-8.39)**	
Antibiotics are anti-inflammatory drugs									0.07
No	427 (60.14)	152 (67.56)	219 (60.50)	Reference	Reference	56 (45.53)	Reference	Reference	
Yes/I don't know	283 (39.86)	73 (32.44)	143 (39.50)	1.36 (0.96-1.93)	1.26 (0.85-1.89)	67 (54.47)	**2.49 (1.59-3.91)**	**1.92 (1.11-3.33)**	
Cues to action									
Self-diagnosed Symptoms Experienced									0.18
Low	297 (41.83)	119 (52.89)	138 (38.12)	Reference	Reference	40 (32.52)	Reference	Reference	
Medium	234 (32.96)	69 (30.67)	122 (33.70)	**1.52 (1.04-2.24)**	**1.48 (0.97-2.25)**	43 (34.96)	**1.85 (1.10-3.13)**	1.65 (0.89-3.06)	
High	179 (25.21)	37 (16.44)	102 (28.18)	**2.38 (1.52-3.72)**	**1.77 (1.00-3.13)**	40 (32.52)	**3.22 (1.81-5.70)**	1.48 (0.67-3.28)	
Fever									**0.001**
No	444 (62.54)	165 (73.33)	224 (61.88)	Reference	Reference	55 (44.72)	Reference	Reference	
Yes	266 (37.46)	60 (26.67)	138 (38.12)	**1.69 (1.18-2.44)**	1.40 (0.87-2.25)	68 (55.28)	**3.40 (2.14-5.40)**	**3.24 (1.70-6.18)**	
Barriers/Access to Antibiotics									
Keeping antibiotics at home									**0.01**
No	234 (32.96)	93 (41.33)	116 (32.04)	Reference	Reference	25 (20.33)	Reference	Reference	
Yes	476 (67.04)	132 (58.67)	246 (67.96)	1.49 (1.06-2.11)	1.39 (0.93-2.07)	98 (79.67)	2.76 (1.65-4.61)	**2.46 (1.33-4.56)**	
Over-the-counter purchase of non-prescription antibiotics									**0.0001**
No	251 (35.35)	104 (46.22)	125 (34.53)	Reference	Reference	22 (17.89)	Reference	Reference	
Yes	459 (64.65)	121 (53.78)	237 (65.47)	**1.63 (1.16-2.29)**	**1.68 (1.14-2.48)**	101 (82.11)	**3.95 (2.32-6.71)**	**3.69 (1.97-6.91)**	
Point of care									**<0.01**
Tertiary hospital	116 (16.34)	28 (12.44)	63 (17.40)/54.3	Reference	Reference	25 (20.33)/21.6	Reference	Reference	
Secondary/County hospital	81 (11.41)	23 (10.22)	35 (9.67)/43.2	0.68 (0.34-1.35)	0.56 (0.26-1.21)	23 (18.70)/28.4	1.12 (0.51-2.47)	0.83 (0.32-2.14)	
Community Health Centres/Township hospital	448 (63.10)	159 (70.67)	236 (65.19)/52.7	0.66 (0.40-1.08)	**0.56 (0.32-0.98)**	53 (43.09)/11.8	**0.37 (0.20-0.70)**	**0.35 (0.17-0.74)**	
Private Clinics/ Village clinics	65 (9.15)	15 (6.67)	28 (7.73)/43.1	0.83 (0.38-1.79)	0.61 (0.26-1.43)	22 (17.89)/33.8	1.64 (0.70-3.84)	1.03 (0.37-2.89)	
Socio-demographic characteristics									0.49
Age				1.02 (0.95-1.09)	0.96 (0.89-1.04)		1.04 (0.96-1.13)	0.95 (0.85-1.04)	
Sex									0.36
Male	357 (50.28)	104 (46.22)	193 (53.31)	Reference	Reference	60 (48.78)	Reference	Reference	
Female	353 (49.72)	121 (53.78)	169 (46.69)	0.75 (0.54-1.05)	0.78 (0.54-1.13)	63 (51.22)	0.90 (0.58-1.40)	0.96 (0.57-1.61)	
Urbanicity of Hometown									0.10
Rural	371 (52.25)	139 (61.78)	173 (47.79)	Reference	Reference	59 (47.97)	Reference	Reference	
Urban	339 (47.75)	86 (38.22)	189 (52.21)	**1.77 (1.26-2.48)**	**1.52 (1.00-2.31)**	64 (52.03)	**1.75 (1.12-2.73)**	1.69 (0.93-3.06)	
Average household income (RMB, monthly)									0.49
>10,000 (>$1538)	106 (14.93)	42 (18.67)	49 (13.54)	Reference	Reference	15 (12.20)	Reference	Reference	
3,001-10,000 ($462-$1538)	357 ((50.28)	126 (56.00)	173 (47.79)	1.18 (0.73-1.89)	1.09 (0.65-1.82)	58 (47.15)	1.29 (0.66-2.51)	1.10 (0.50-2.39)	
<=3,000 ($461)	247 (34.79)	57 (25.33)	140 (38.67)	**2.11 (1.26-3.52)**	1.59 (0.86-2.93)	50 (40.65)	**2.46 (1.22-4.95)**	1.67 (0.67-4.05)	
Major in Medicine									0.33
No	634 (89.30)	196 (87.11)	325 (89.78)	**Reference**	Reference	113 (91.87)	**Reference**	Reference	
Yes	76 (10.70)	29 (12.89)	37 (10.22)	**0.77 (0.46-1.29)**	0.65 (0.36-1.16)	10 (8.13)	**0.60 (0.28-1.27)**	0.62 (0.26-1.52)	
Having at least one parent with medical background									0.02
No	641 (90.28)	200 (88.89)	333 (91.99)	**Reference**	Reference	108 (87.80)	**Reference**	Reference	
Yes	69 (9.72)	25 (11.11)	29 (8.01)	**0.70 (0.40-1.22)**	0.87 (0.46-1.64)	15 (12.20)	**1.11 (0.56-2.20)**	1.02 (0.43-2.41)	
Region (University, Province)									0.07
North (NKU, Tianjin)	60 (8.45)	20 (8.89)	29 (8.01)	Reference	Reference	11 (8.94)	Reference	Reference	
East (ZJU, Zhejiang)	111 (15.63)	45 (20.00)	56 (15.47)	0.86 (0.43-1.71)	0.95 (0.45-2.01)	10 (8.13)	0.40 (0.15-1.10)	0.41 (0.13-1.27)	
Southwest (GZU, Guizhou)	169 (23.80)	30 (13.33)	101 (27.90)	**2.32 (1.15-4.68)**	1.87 (0.87-4.05)	38 (30.89)	2.30 (0.96-5.54)	1.31 (0.46-3.68)	
Northwest (LZU, Gansu)	138 (19.44)	38 (16.89)	72 (19.89)	1.31 (0.65-2.61)	1.23 (0.57-2.62)	28 (22.76)	1.34 (0.55-3.24)	0.68 (0.24-1.92)	
South (WHU, Hubei)	133 (18.73)	62 (27.56)	60 (16.57)	0.67 (0.34-1.31)	0.80 (0.39-1.67)	11 (8.94)	0.32 (0.12-0.86)	0.33 (0.11-1.01)	
Northeast (JLU, Jilin)	99 (13.94)	30 (13.33)	44 (12.15)	1.01 (0.49-2.11)	0.76 (0.34-1.72)	25 (20.33)	1.52 (0.61-3.75)	0.44 (0.15-1.32)	

[a]Adjusted for age, sex, household income, urbanicity, major in medicine, having at least one parent with medical background, and region/province.

[b]Likelihood ratio tests for prescribing outcomes for URTIs

[c]mean (SD)

CHAPTER SEVEN

Development of an antibiotic take-back programme to reduce non-prescription use and unsafe disposal in rural China: a mixed-methods approach

This thesis has reported on a series of research activities conducted between 2017 and 2019, with the aim of developing a behavioural change intervention to reduce antibiotic misuse through a focus on reducing unnecessary demand and increasing safe disposal beyond clinical settings. I investigated and identified the components of a new take-back programme for disposing of household's expired, unwanted, or unused (EUU) antibiotics in rural China.

I conducted the literature search, created the figures and the conceptual framework, developed study design and instruments, conducted data analysis and interpretation, and drafted and revised the manuscript. The development process and feasibility assessment of a novel evidence-based, theory-driven, community-based intervention has been prepared as a draft of the manuscript, with comments on drafts from Weiyi Wang, Professors James Hargreaves, Mark Petticrew, and Xudong Zhou. This manuscript has been submitted to *BMC Medical Research Methodology* for publication consideration.

An extended introduction of the development of the intervention.

In this chapter, I described the process of developing a community-based take-back programme for disposing of household's expired, unwanted, or unused (EUU) antibiotics in rural China. Below I present the respective evidence generated in each step prior to this chapter (presented in chapters two to six) that was used to inform intervention design:

Thesis structure	Key findings to inform intervention design	Implications for intervention design
Chapter two identifies non-clinical factors influencing the general public's and healthcare providers' antibiotic use in the Chinese community	a) Identification of factors and their potential pathways influencing public's antibiotic use and informing a conceptual framework for antibiotic use, which served as Theory of Change (See Figure 1) for the intervention development.	• Intervention design to address some of these factors/pathways. • The theory of change was later used to inform a logic model (Figure 2)
Chapter three identifies behavioural change techniques (BCTs) that may effectively reduce inappropriate use of medicines and medical procedures	b) Interventions consisting of health education messages (BCTs 4.1, 4.2, 5.1, 5.2), incentives (BCTs 10.1, 10.2), and a supporting environment (BCT 12.1, 12.5) that encourages the adoption of a new behaviour (BCT 8.2) are more likely to be successful.	• Intervention design to include *health education messages, recommended alternative behaviour, incentives,* and *a supporting environment*.
Chapter four assesses the prevalence of antibiotic misuse in children in the Chinese context	c) Almost half of the surveyed parents kept antibiotics at home for children d) Many Chinese parents self-medicated children with antibiotics (prophylactic or treatment) and before seeking formal care. e) Household antibiotics primarily came from leftover prescriptions and over-the-counter purchases (OTC).	• Household storage of antibiotics is a critical gap in current efforts to contain AMR in China (and most LMIC). • Health education messages to include awareness of the danger of AMR and non-prescription use of antibiotics. *Note: Issues around OTC were going to be addressed by other intervention components of the JGHT bid.*
Chapter five assesses the factors influencing Chinese parents' treatment decisions for paediatric URTIs.	f) Perceived antibiotic efficacy for URTIs symptoms is associated with an increased odds of self-medication with antibiotics and demand of antibiotic prescriptions. g) Parents who kept antibiotics at home for children were associated	• Health education message content selection (BCTs 4.1, 4.2, 5.1, 5.2) • Intervention design to reduce household storage of antibiotics. (BCTs 10.1, 10.2, 8.2, 12.1, 12.5) *Note: Issues around OTC were going to be addressed by other*

	with increased odds of self-medication with antibiotics for URTIs in children and over-the-counter purchases. h) Household antibiotics primarily came from leftover prescriptions and over-the-counter purchases (OTC).	*intervention components of the JGHT bid.*
Chapter six assesses the factors influencing Chinese young adults' treatment decisions for URTIs.	i) Not knowing URTIs are self-limiting and perceived antibiotic efficacy for URTIs symptoms are associated with increased odds of self-medication with antibiotics and demand of antibiotic prescriptions. j) Participants who kept antibiotics at home were associated with increased odds of self-medication with antibiotics. k) Household antibiotics primarily came from leftover prescriptions and over-the-counter purchases (OTC).	

Briefly, in chapter two, I identified factors and their potential pathways influencing public's antibiotic use, which informed a conceptual framework which served as Theory of Change (See Figure 1) for the intervention development. In chapter three, I found there had not been interventions that addressed inappropriate or unnecessary use of antibiotics in the community in LMIC including China. In chapters four to six, I found in China, household unsupervised use of antibiotics on adults and children alike has been a pervasive practice especially in the rural community. Many came from household storage, obtained from community pharmacies or leftover prescriptions. Keeping antibiotics at home led to a higher likelihood of self-medication. The demand-side of the health care system in China accounted for 40% of antibiotic use for childhood self-limiting illnesses and 60% for young adults in the country. I found that perception of antibiotics as effective for treating viral upper respiratory tract infections (URTIs) and access to non-prescription antibiotics were associated with inappropriate antibiotic use in the Children community.

Following Theory of Change, I aimed to develop a context-tailored, behavioural change intervention to improve antibiotic use in rural China that would 1) address the social-contextual factor of inappropriate community antibiotic use by removing access to non-prescription antibiotics storage at home to reduce the likelihood of unsupervised use of antibiotics in adults or children, and 2) implement a health education intervention (as a cue to action) to improve antibiotic literacy especially its (in-)efficacy for the common cold in target community. Specifically, the proposed intervention had two major components: a community-based bartering programme where residents were encouraged to bring household EUU antibiotics in for household items, and a health education campaign with messages on (a) prudent antibiotic use and antibiotic literacy, (b) care management for acute upper respiratory tract infection (URTI) symptoms, and (c) antibiotic take-back programme.

To recruit a pilot site for the development and adaptation of the intervention, I worked closely with local partners at Zhejiang University and identified/approached a rural village in Zhejiang Province. We followed a theory-based work stream plan (Table 1) in the adaptation, implementation and evaluation of this intervention, and developed a logic model (Figure 2) according to local characteristics and Theory of Change. A community advisory board consisting of researchers and community representatives was formed to guide the process. A mixed-methods formative evaluation was conducted, consisting of (1) quantitative surveying of a representative sample of 50 households in the target community and (2) qualitative semi-structured stakeholders' interviews to explore the design, development and adaptation, and implementation of the proposed intervention. Quantitative and qualitative data from a similar village – serving as a control - were also collected. The chosen communities had high social capital where everyone knows everyone

(Table 2). I reflected the collaborative knowledge translation process for evidence-based practice in the concept of implementation capital (Figure 3).

Working with local partners, I chose health education messages based on findings from chapters four to six, as presented in Figure 4, and adopted the manual on prudent antibiotic use, developed by China's National Health Commission (Appendix I), to train the community implementer of the take-back programme. Before implementing the pilot intervention, I made several key assumptions based on findings from the literature review and secondary data analyses about antibiotic use in rural China. As presented in Table 3, after the mixed-methods, baseline formative evaluation of 50 sampled households in the pilot village, some of these assumptions held unchanged, but some were adjusted as part of the local adaptation process. Qualitative data collected from the 50 households further informed the development of health education strategy (Table 4). Table 5 reported the intervention materials design and descriptions, developed for the pilot study.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH1704488	**Title**	Ms.
First Name(s)	Leesa		
Surname/Family Name	Lin		
Thesis Title	Development of evidence-based behavioural interventions to reduce inappropriate use of antibiotics beyond clinical settings		
Primary Supervisor	Professor James Hargreaves		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	BMC Medical Research Methodology
Please list the paper's authors in the intended authorship order:	Leesa Lin, Xiaomin Wang, Weiyi Wang, James Hargreaves, Xudong Zhou*
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Leesa Lin conducted the literature search, created the figures and the conceptual framework, developed study design and instruments, and contributed to data collection, analysis and interpretation. Leesa Lin drafted and revised the manuscript. Weiyi Wang contributed to data collection and analysis, and commented on revisions of the manuscript. James Hargreaves contributed to data interpretation, and commented on the initial and following revisions of the manuscript. Xudong Zhou conceived the study, led data collection, contributed to data interpretation, and commented on all drafts of this manuscript. All authors approved the final draft of this manuscript.

SECTION E

Student Signature	[redacted]
Date	09/09/2019

Supervisor Signature	[redacted]
Date	09/12/2019

Development of a take-back programme that reduces household antibiotic storage for unsupervised use in rural China: a mixed-methods approach

SYNOPSIS

BACKGROUND: Non-prescription use of antibiotics and unsafe disposal in communities may harm human and environmental health and contribute to the global threat of antimicrobial resistance. Currently, there is a lack of public-targeted behaviour change interventions to address this threat.

OBJECTIVE: This study describes the process of developing an evidence-based, theory-driven, community-based take-back programme for disposing of household's expired, unwanted, or unused (EUU) antibiotics in rural China.

METHODS: We incorporated and operationalised the RE-AIM framework, the community-based participatory research principles, 6SQuID model, and intervention mapping procedures in a theory-based work stream plan in the adaptation, implementation and evaluation of this intervention. A community advisory board consisting of researchers and community representatives was formed to guide the process. A mixed-methods formative evaluation was conducted, consisting of (1) quantitative surveying of a representative sample of 50 households in the target community and (2) qualitative semi-structured stakeholders' interviews to explore the design, development and adaptation, and implementation of the proposed intervention. Quantitative and qualitative data from a similar village – serving as a control - were also collected.

RESULTS: After knowledge syntheses of existing literature and primary research, the adaptation process underwent three steps: 1) model development; 2): collaboration and partnership for evidence-based intervention development; and 3) realist assessment (mixed-methods), which included forming a theory of change and logic model.

CONCLUSIONS: This study illustrates the potential efficacy of community-based antibiotic take-back programmes in China encouraging safe disposal and decreasing availability of EUU antibiotics in households for unsupervised use.

KEYWORDS: drug take-back; environment; community health, social marketing; drug abuse, prescription drugs, antimicrobial resistance (AMR), RE-AIM, community-based participatory research (CBPR), intervention mapping

BACKGROUND

Antimicrobial resistance (AMR) claims 700,000 lives annually, and AMR-related mortality is rising.[43] A majority of human antibiotic consumption occurs in community settings, especially in low-and-middle income countries (LMICs) where 40% of the population commonly self-medicate with antibiotics; half of such antibiotics come from household storage.[305] China is one of the world's largest producers and consumers of antibiotics and faces severe challenges from this crisis, with levels of per-capita antibiotic use and AMR-related health burden that are among the world's highest.[32] In the past decade, the Chinese government has enacted a series of measures to control the rate of antibiotic prescriptions, including the recent essential medicines scheme and zero-mark up policy,[51] which separates drug sales from medical treatment at public hospitals. Such policies may effectively remove inappropriate financial incentives from hospitals but, as presented in the 2019 BMJ review of China's 10-year progress on health system reform, largely ignores primary care and rural settings where the majority of people reside and outpatient dispensing takes place.[44] Few interventions aim to regulate communities' easy access to antibiotics.[269] Lord Jim O'Neill warned that, given the current trend, the associated global economic burden could reach US $100 trillion and cause 4.73 million deaths in the Asia-Pacific region alone by 2050.

Nationwide surveys demonstrate that over 70% of Chinese households store antibiotics, which are eventually self-administered without professional supervision.[41,68,305,316] Depending on the region, 40-50% report SMA without seeing a doctor,[61,64,75] and 20-30% had used antibiotics to prevent the common cold in the past year.[45] Sources of SMA come from leftover prescriptions and over-the-counter purchases in local pharmacies.[45,64] The practice of storing antibiotics at home for future self-medication persists even when Chinese migrate abroad.[119,317-319]

Furthermore, little attention has been paid to the danger of SMA and unsafe disposal in communities. Because there is no safe disposal programme for household medical waste, household antibiotics are disposed of as common trash and deposited in landfills, potentially becoming a hazard to environment, wildlife, and human health, especially in countries, like China, with poor waste management systems.[320]

Interventions, like drug take-back programs, for reducing household access to expired, unwanted, or unused (EUU) medications have been implemented in developed countries, including the United States and many European countries, e.g. Sweden and Germany, for over a decade and have had positive impacts on raising public awareness about and reducing misuse and abuse of drugs.[218,321-323] However, such practices are seldom seen in LMIC. In China, awareness and practices regarding safe disposal of antibiotics are non-existent. To date, no interventions have addressed non-prescription household antibiotic use or convenient and environmentally-responsible disposal methods for systemically removing or reducing household antibiotic stockpiles in China. The need for evidence-based, public-targeted interventions is pressing. In this study, we report on the implementation of science procedures translating available evidence into the development of an antibiotic take-back and disposal programme in rural China, where community antibiotic misuse is the most severe.[261,324]

METHODS

This paper details a series of research activities conducted between 2017 and 2019, with the overall aim of developing a behavioural change intervention to reduce antibiotic misuse beyond clinical settings in rural China.

Hypothesis and theory of change

The Health Belief Model[92,93] was developed in the early 1950s based on psychological and behavioural theory to understand people's responses to symptoms and adoption of disease prevention strategies and medical treatments. It suggests that an individual's course of action often depends on the person's perceptions of the benefits (i.e. the perceived efficacy of antibiotics) and barriers (i.e. access to antibiotics) related to health behaviour that can protect the person from a health threat. By examining these constructs, HBM will predict the likelihood the person will adopt the behaviour. Social Ecological Model[100], on the other hand, was developed to understand of the dynamic interrelations among various personal and environmental factors. Both models have been used to explain antibiotic use.[92,93,100] Accordingly, we developed a Theory of Change (ToC, see Figure 1) with a hypothesis that behaviour is influenced by context, personal knowledge and perceptions of benefits, barriers, and efficacy of actions. Specifically, the Theory of Change developed suggested that behavioural change would most likely occur in a social context with dynamic and reciprocal interactions between the person, community, and environment - both spatially and temporally - as an individual's behaviour is influenced by their past experiences through expectations and reinforcements. Whenever possible, the Theory of Change was applied to guide quantitative and qualitative data analyses to understand health behaviours in the target context, which led to the development of a simplified logic model (Figure 2) informing behavioural interventions.

Work stream plan of this project (presented in Table 1) integrates the community-based participatory research (CBPR) principles,[325,326] the RE-AIM (*Reach, Effectiveness, Adoption, Implementation, and Maintenance*) model,[327] and intervention mapping procedures[89,328] in the development, implementation and evaluation of an antibiotic take-back programme in rural China. CBPR is a

collaborative research approach that emphasises the importance of creating partnerships between researchers and knowledge users of the research. We followed the CBPR principles with a strong commitment to build on community strengths and resources and to facilitate collaborative partnerships in all phases of the research. A community advisory board (CAB) was formed as a coalition of researchers, government officials, and local partners to lead the adaptation, implementation and evaluation process. By integrating the RE-AIM model in the work stream plan for intervention development and feasibility assessment, we ensure each key element of RE-AIM is considered at the beginning of the intervention design and throughout the entire process. Finally, we adopted the Intervention Mapping (IM) procedures - from program objective-setting to generating evaluation plans - as a roadmap and guideline for knowledge translation for the development of theory- and evidence-based behavioural change interventions. As shown in the work stream plan, steps taken in the development of behavioural change interventions were iterative and cumulative, as we fluctuated between tasks, while each step built on previous steps. These steps have been closely aligned with the Six Essential Steps for Quality Intervention Development (6SQuID) model,[91]a pragmatic evidence-based guide to maximise likely effectiveness.

Setting and sample

Formative data (pre-intervention) for the intervention came from a representative community panel of 50 households from each of the two selected rural villages – one intervention and one control - in Zhejiang, China, conducted prior to the implementation of an antibiotic take-back programme in June 2019. All households in the two villages were eligible for inclusion and those agreeing to participate gave informed consent. Due to the intervention design and local context, we targeted self-identified female heads of household. If identified female heads of

household were unavailable after the second attempt, their spouse/partner was invited to participate. The 21 stakeholders from the intervention village were purposively selected, prior to the intervention or immediately after implementation, for interviews via the snowballing technique and included a representative sample of characteristics relevant to the study setting in terms of age, gender, socio-economic status, and community roles.

Data collection and management

Face-to-face household surveys with the community panel consisted of quantitative and qualitative items assessing antibiotic use and disposal behaviours, exposure to and participation in the programme, and cognitive measures of programme effects (risk appraisal, self-efficacy, normative influence, and public knowledge and perceptions). Inspections of household medical cabinets were conducted following each survey. Stakeholders, including residents, local government officials, community partners, potential implementers of the intervention, community pharmacies and clinicians, and others, were recruited for semi-structured interviews. An interview guide was developed with three main goals: (1) to assess the target population's beliefs, perceptions and behaviours in order to develop culturally appropriate interventions; (2) to describe the context in which these behaviours take place and understand the reasoning underlying such behaviours; and (3) to develop and test health education messaging regarding prudent antibiotic use in the community. The guide was piloted prior to full-scale interviews. Formative data - both quantitative and qualitative - were also collected from the control village with a similar sample. Qualitative interviews were audio-recorded, transcribed by an independent transcription company, checked for accuracy, anonymised and imported into Nvivo11 software to facilitate analysis.

Quantitative Measures

The primary objective was to describe antibiotic use and disposal behaviours. All respondents were asked whether, in the past month, they have: (a) kept antibiotics at home and (b) participated in the take-back programme. Relevant antibiotic use knowledge, attitudes, and behaviour outcomes were also measured.

Data analysis

Descriptive statistics (frequencies, means and standard deviations) were calculated for all quantitative variables to assess baseline antibiotic use behaviour patterns. Qualitative data were analysed using framework analysis. Priori codes were drawn from the interview topic guide, study objectives, and feasibility evaluation framework. LL conducted quantitative analysis and was the primary coder for qualitative data, along with ZXD and WWY. Consensus on themes and key findings were reached through discussion.

RESULTS

Intervention development, implementation, and feasibility testing

Through discussion and consensus with the community advisory board, we defined the desired intervention outcomes of interest as reductions in expired, unwanted, or unused (EUU) antibiotics in households in rural China. The immediate outcome for the pilot intervention was to reduce household storage of antibiotics and inappropriate disposal. The long-term outcome was to reduce self-medication with antibiotics and improve awareness and norms around antibiotic use and safe disposal. From literature review and our pre-intervention assessment, we found most household antibiotics came from leftover prescriptions unintentionally stored at home; we therefore chose “the use of bartering market for antibiotic-take back” as our target behaviour, and the reduction of household antibiotic storage as our primary outcome.

Intervention adaptation methods: antibiotic take-back programme

The intervention presented herein is adapted from U.S. National Take-Back Days events,[20] which aim to increase public awareness of prescription drug abuse and promote safe disposal of expired, unwanted, or unused (EUU) prescription medicine by collecting leftover prescription drugs or unused controlled substances in the community.[218,320,323,329] Supported by the Drug Enforcement Administration (DEA), since 2010, take-back events have been implemented across the United States, with more than 2,000 official collection sites biannually,[329] and consist of two main components: drug collection and an awareness campaign. Unfortunately, few details have been reported on the development of the events and the rationale and design behind each intervention component, and their respective evaluations tend to be weak in design and effectiveness.[323,329,330] Following the work stream plan, the community advisory board adapted the take-back event based on available evidence[218,320,323,329] and the Theory of Change. The adapted intervention was mainly composed of two constituents: antibiotic take-back programme and health education messages, presented below. The main objective of the programme is to reduce household antibiotic storage for unsupervised use of antibiotics in the community. A feasibility study (reported in another manuscript) established the acceptability and usability of our intervention.

Development of intervention adaptation Table 2 presents the socio-demographic characteristics of the samples for formative study. Fifty (50) households were randomly sampled for pre-intervention evaluation in June 2019. 29 out of 50 households (59.0%) self-reported to have antibiotics stored at home during baseline investigation. Of those who used antibiotics in the past month (n=20), 5 (25.0%) self-reported having self-medicated with antibiotics without a prescription. 82.4% reported being aware of the potential danger of self-medication with antibiotics; 78.4% were aware of the danger of unsafe disposal of antibiotics on

human and environmental health. 62.7% knew that antibiotics should not be discarded in the bin with other regular garbage. However, when asked about disposal practices, a majority of respondents (54.9%) had disposed of antibiotics as regular waste, followed by household storage (23.5%) - either unintentionally or purposefully for future use, and other methods (15.7%) including flushing down the toilet, burying in fields or feeding chickens. A total of 393 minutes of qualitative data were collected; each interview lasted approximately 10-34 minutes. Evidence generated in systematic reviews of existing evidence and primary research (aims 1-2) was used to inform key assumptions for developing intervention elements, which were further verified by the quantitative data and modified during the adaptation process (Table 3).

Antibiotic take-back programme: Formative data identified platforms and partners to removing household antibiotics leftover in the community. A solution readily identified by the community advisory board was for the garbage sorting and recycling programme (implemented in all rural villages in Zhejiang province since 2016) to utilise for providing the infrastructure for antibiotic take-back/removal. This programme includes a bartering market in which community members are compensated for recycled goods (e.g., through provision of common household items customised with health education messages). Additionally, we identified several common, popular household items for provision through the bartering market.

Health messages: A community-based health education campaign, as well as the appropriate materials and dissemination strategy, were required to promote high levels of engagement with this programme. A panel consisting of experts in behavioural science, psychology, communication, health promotion, public health and community partners was created to inform the development of health education

strategies. Informed by findings from Aims 1-2 and formative data, content of the communication messages focused on: (a) risks of inappropriate antibiotic use and antibiotic disposal, (b) awareness of AMR, and (c) promotion of the antibiotic take-back programme. The channels of dissemination included: (1) posters and pamphlets in public gathering areas: community centres, bartering markets, health clinics and township hospital outpatient departments, bus stops, community pharmacies; and (2) WeChat education campaigns. The design of health education materials came from a crowdsourcing campaign conducted by the Zhejiang University Centre of Health Communication in 2016, and was then tailored to improve the local community's antibiotic literacy around prudent use. Figure 4 presented selected sample health education materials and design covering (1) how to identify antibiotics, (2) how to safely dispose antibiotics, (3) how to safely use antibiotics, especially when individuals and/or family members have a common cold, and (4) information of the antibiotic take-back programme. Cognitive testing was conducted with 30 residents prior to implementation (See Table 4).

Formative data also identified a training need for the Women's Federation in the intervention village, with a focus on identification of antibiotics and risks of inappropriate use or disposal of antibiotics. To meet this need, we adopted the training materials on prudent antibiotic use developed by China's National Health Commission (Appendix I. Training materials and design) In the standard of care village (control), the Women's Federation and its bartering market would continue their usual practices.

Design of feasibility study

Guided by the work stream plan, formative data were used to guide the design of a pilot study conducted in two villages in Zhejiang testing the acceptability and feasibility of an antibiotics take-back programme with respect to:

Reach - the community engagement approach: CAB and Women's Federation will lead the outreach effort. Channels of dissemination will include traditional media, such as posters and pamphlets, and WeChat groups and other social networks.

Effectiveness: Measures of feasibility and process evaluation data were adapted from evaluation studies on take-back programmes[322,323,329-332] and their validity and reliability were retested in the target population during the pre-intervention assessment.

Adoption: Our formative data suggested that, although prescription drug diversion in the U.S. might be viewed as a type of behavioural disorder carrying potential social stigma,[333] in China keeping antibiotics at home for future use is a socially acceptable common practice.[60,334] While awareness of the danger of prescription drug abuse for non-medical purposes is high in the U.S., awareness of the risks of self-medication with antibiotics is relatively low in China.[60,334] However, Zhejiang recently implemented a series of environmental protection programmes at the community level; therefore, awareness and social norms around environmental protection are high in the area. The pilot intervention therefore included messages about the dangers of non-prescription antibiotic use and inappropriate antibiotic disposal to human, community, and environmental health. The pilot will also test the appropriate/effective incentives for rural residents to turn in leftover antibiotics.

Implementation: The local Women's Federation, which runs a WeChat (social media) group, includes female members of all households for health promotion and communication purposes and is responsible for the recycling programme, bartering markets for recyclables. As such, they were well-positioned to be the implementer of the intervention.

Maintenance (Sustainability): Studies indicate that inconvenience, a dearth of readily available programmes, reduced motivation from perceived future need, and lack of economic incentives were major reasons for non-participation in drug take-back events.[323,329,335] CAB therefore designed the intervention to be embedded into existing infrastructure, allowing the antibiotic take-back programme to potentially be a permanent, on-going public health initiative. The existing town-run bartering market for recyclables was deemed the most appropriate site, allowing participating residents to give antibiotics directly to bartering market personnel in exchange for small household items. This was intended to incentivise users to bring in antibiotics, generate awareness, enhance a sense of local ownership of the programme, and, in the long run, create a new norm around antibiotic take-back for safe disposal.[329]

Programme implementation and process evaluation. Within the first month of pilot testing, a total of 50 households participated in the antibiotic take-back programme at the town centre. We found a much greater proportion of antibiotics returned belonging to narrow-spectrum antibiotic groups (penicillin, amoxicillin, erythromycin), and a lower proportion of antibiotics belonging to more expensive, second-generation macrolides (azithromycin, clarithromycin). The total budget to conduct the household intervention and evaluation was 10,000.00 RMB for 800 households, $1.78 per household in 2019 dollars. The cost of materials for health education intervention was approximately 1200.00 RMB ($172.00) per campaign. Details of the intervention design and materials were reported in Table 5. Figures 4 and 5 presented sample training and health education materials demonstrating wording, colour, and font size.

DISCUSSION

This study addresses drivers of antibiotic misuse that are currently unexplored and unaddressed in both the literature and existing stewardship programmes across China

and most low-and-middle-income countries (LMIC): access to expired, unwanted, or unused (EUU) antibiotics in the household and unawareness of the associated danger on human and environmental health if not safely disposed. It contributes to the growing body of evidence in implementation research that seeks to understand what interventions do and do not work, how and why implementation succeeds or fails, and how improvements can be made. We described the process of developing and adapting an intervention from one context to another (U.S. to China) to address a relevant but different health concern (prescription drugs abuse to antibiotic misuse and antibiotic resistance) and factors affecting implementation, including the process of implementation. Findings from aim 1 identified a critical knowledge gap of rigorous studies on the development of public-targeted behavioural change interventions that recognise the complex, interactive social and behavioural influences on antibiotic use in the community. Intervention content, design, development and implementation strategies are rarely presented in sufficient detail, with limited evidence on the rationale and theory behind intervention components.

Strengths of this study include utilisation of a mixed-methods approach to achieve the study aims. Employing both quantitative and qualitative methods allowed identification of key components of the intervention and evaluation. Both qualitative and quantitative data and their integration were drawn on throughout various research activities. The quantitative results helped to 1) investigate social determinants of inappropriate antibiotics use in the context of China, 2) identify the specifications for the development of a behavioural intervention, e.g. target inappropriate antibiotic practices among the target population (e.g. urban/rural, high/low socioeconomic status, or various age groups), and 3) test hypotheses. Qualitative results informed hypotheses and explored the acceptability and feasibility of proposed interventions.

Our study sites embodied the characteristics of "small worlds" [336] – where "everyone knows everyone else," as described by Watts and Strogatz. The small worlds networks in these tight-knit communities allowed us to capitalise on two distinct forms of social capital - bonding and bridging – which coexist at the setting level and concurrently influence individual behaviours.[336] In both the intervention and control villages, over 90% of the residents knew the chairwomen of the Women's Federation, as well as at least half of the village officials, and agreed that their communities were tight-knit, where the residents maintained good relationships and were helpful to one another. Through the lens of the implementation framework, Neal and Neal viewed these two types of social capital as resources, namely "implementation capital."[337] In practice, we identified five key dimensions of implementation capital that determined the success of the knowledge translation process, which were *bonding social capital, bridging social capital, human capital, financial capital* and *contextual capital.* [Figure 3] The "bonding social capital" facilitates a sense of community and reinforces community norms. The "bridging social capital" connects researchers and villagers who are otherwise unfamiliar with each other. The former two constructs relate to whether evidence-based interventions can be successfully introduced to a community. We additionally identified "financial capital" (e.g. monetary or in-kind goods and services to run the bartering market and push out health messages), "human capital" (e.g. education, training or tools that could improve Women Federation's capacity and capability), and "contextual capital," which we defined as existing opportunity structures that make the chosen community a suitable location for certain activities. These latter three types of capital are necessary conditions in actualising the implementation of the proposed evidence-based practice.

In our case, the local Chinese Women's Federation - the most influential non-governmental organisation (NGO) in rural China – served as a gatekeeper and information broker for the community. By engaging them as the implementer of the intervention, we harnessed their bonding and bridging capital and gained entrance to introduce a new idea into the community. As implementers, the Women's Federation not only improved the implementation of EBP by influencing individual perceptions and behaviours (bonding social capital),[337,338] it guided us as researchers in navigating local social networks (bridging social capital). Equally important, recent health policy reforms and the existing environmental policies set a solid foundation, the *contextual capital,* for the proposed intervention. Zhejiang province has adopted a national environment policy since 2010 and instituted a series of province-wide environmental protection programmes, including a comprehensive water governance policy -"Five Water Treatment (五水共治 Wǔ shuǐ gòng zhì) – and a recycling programme. Our formative data indicated participation in household waste sorting programme for environmental protection is around 65% and the bartering market for recyclables is 25%. The selected study sites had historical legacies of community infrastructure (physically and societally) for an action-oriented health education strategy to recycle left-over antibiotics as an environmental pollutant and biohazard.

The aims of the proposed intervention were well-aligned with the national and local policies and the mission of Women's Federation, which is to advocate for the rights, protection, and health of women, children and the environment. In fact, the antibiotic take-back programme initially proposed placing containers alongside other recycling bins across the community following an awareness campaign, similar to an approach for prescription drugs take-back tested in New Jersey.[339] However, local Women's Federation, who ran the local recycling programme, bartering markets, and the WeChat groups for female villagers, advised adapting the

intervention design to better utilise existing platforms and fit local context and networks, which allowed us to reduce the required "financial capital" and "human capital" for implementing the project. This way, the Women's Federation helped develop solutions to tackle cross-context implementation barriers and determined the best way to introduce innovations into the local system. This adaptation overcame implementation barriers within the specific local context and improved the sustainability and scalability of the proposed intervention, given that most towns in Zhejiang province have a bartering market run by their respective local chapter of Women's Federation. Therefore, within the five dimensions, one aspect of implementation capital might facilitate or offset the other. For example, without project funding to support the bartering market, even with bridging social capital, the intervention idea may remain in the discussion phase between researchers and potential implementers but never make it to implementation. Conversely, leadership commitment (contextual capital) may lead to more financial support from the government or community in the form of subsidies or donations. In this particular intervention, with high implementation capital, we anticipate high intervention feasibility and acceptability. Furthermore, interactions exist among the five domains of implementation capital. For example, contextual capital, such as leadership commitment, could be leveraged to mobilise social capital along with other resources to support the implementation of evidence-based practices. Though we mainly kept the proposed project grassroots and locally run, in practice, commitment from the township government helped open the door to potential study sites where local community leaders welcomed researchers.

Our formative data demonstrated residents' concerns over antibiotics as pollutants to the environment (78.4%). Future studies should explore how public concerns can be leveraged as contextual capital and engage communities in a "One

Health" intervention aiming to increase prudent antibiotic use and disposal. Future research on social networks may expand on the "small worlds" theory and generate additional insight regarding the diffusion of innovations for reducing antibiotic misuse.

CONCLUSION

This study fills the knowledge gap by describing systematic steps taken to adapt a theory-driven, community-based intervention for a new context and a new health risk. There is a lack of environmentally safe disposal guidelines and take-back services for the proper disposal of antibiotics in China. In this study, we described the steps we took to employ the theory-based work stream plan to guide the development and assessment of community-based interventions. Evidence established that exposure to the educational messages is insufficient to overcome the influence of past behaviours of antibiotic use.[207] This proposed intervention served a dual-purpose: (a) to reduce access to unnecessary antibiotics in the household, and (b) to promote safe disposal. The intervention addresses a critical need of a public-targeted behavioural change intervention to decrease inappropriate antibiotic use in the community. This study also illustrated the critical role five-dimensional implementation capital plays in facilitating the knowledge translation process from evidence to an intervention that aims to tackle antibiotic misuse in the community setting in the local context.

Funding

Funding to develop and implement the intervention was supported by the Zhejiang University Zijin Talent Programme. The authors received no financial support for the feasibility research, authorship, and/or publication of this article.

Disclosure statement

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors have no conflicts of interest or financial interests in any product or service discussed in the manuscript.

Acknowledgments

We acknowledge the financial support from Zhejiang University. We thank the Jiangshan government officials, Women's Federation and personnel at the bartering market for offering their time, expertise, and providing support throughout the study.

Human Participant Protection

Ethics approval was obtained from Research Ethics Committees at Zhejiang University (Ref: ZGL201901-1) and the LSHTM (Ref: 16261). Written informed consent was obtained from participants.

Table 1. Work stream plan

Aims	Alignment with 6SQuID[91]	Methods/Tasks	Activities	Products
Aim 1: Synthesise existing evidence about the problem and explore possible solutions	Step 1. defining and understanding the problem and its causes; Step 2. identifying which causal or contextual factors are modifiable: which have the greatest scope for change and who would benefit most;	Systematic Reviews	1) Systematic review (SR1) on determinants of antibiotic misuse in the community, including primary care and hospital outpatient clinics in the Chinese context. 2) Systematic review (SR2) on public-targeted behavioural change interventions to reduce inappropriate, unnecessary, and non-essential use of medicines or medical procedures. 3) SR1 and thematic synthesis of qualitative studies of views, attitudes and experiences of health care providers and users (i.e. health professionals, patients, and caregivers) about treatment choices and antibiotic use for self-limiting illnesses in the Chinese context. 4) Synthesis of SR1 and SR2 to identify knowledge gaps where determinants of antibiotic misuse in the community are insufficiently addressed.	Key assumptions about the problem
Aim 2:Assess problems in the context and form assumptions	Step 2. identifying which causal or contextual factors are modifiable: which have the greatest scope for change and who would benefit most; Step 3. deciding on the mechanisms of change;	Quantitative Research	1) Large-scale surveys on knowledge, attitudes and practice of treatment choice and antibiotic use among young adults (university students) regarding self-limiting illnesses in the Chinese context. 2) Large-scale surveys on knowledge, attitudes and practice of treatment choices and antibiotic use among young parents (with children under 13) with respect to self-limiting illnesses in the Chinese context.	Key assumptions about the problem
Aim 3: Develop and adapt intervention	Step 4. clarifying how these will be delivered;	Mixed-methods	**3a. Theoretical Model Development** 1) Development of a Theory of Change (ToC). 2) Formation of key assumptions for intervention development.	Theory of Change (Figure 1-5)
			3b: Preparation for Knowledge Translation 1) Scoping and stage-setting • Identify pilot sites • Introduce proposed project aims and explain rationale for an intervention • Confirm presence of problems identified and needs • Introduce intervention adaptation process • Establish partnership and collaboration 2) Preparation for adaptation of knowledge to local context • Define desired aim and the behavioural target of this intervention • Explore and identify intervention components • Discuss how the intervention may or may not address the problems and needs • Discuss how the intervention may or may not address key planning and evaluation issues: *reach, effectiveness, adoption, implementation, maintenance* **(RE-AIM).** • Identify areas for intervention adaption • Map resources needed to implement a pilot intervention and assess available ***Implementation Capital for evidence-based practice*** • Form logic model	Logic model
	Step 5. testing and adapting the intervention		**Implementation (pilot)**	
			3c: Realist assessment of problems and needs of local context and appropriateness of proposed intervention 1) Conduct pre-intervention (baseline) evaluation, which consists of face-to-face surveys with quantitative and qualitative components, to assess problems and needs in local context. 2) Interview stakeholders to assess appropriateness, acceptability and feasibility of the proposed intervention. 3) Evidence synthesis of findings from Aims 1-2 and realist assessments with target population and stakeholders: • Identify the objectives, content, and channels for delivery of key health messages for the proposed intervention. • Pilot-test health messages. 4) Critically synthesise mixed-methods findings revising the logic model and finalising the adapted intervention	Finalised logic model Finalised intervention design for feasibility study
Aim 4: Evaluation: Assess feasibility and acceptability of the intervention	Step 5. testing and adapting the intervention (Note: for this project, I only conducted feasibility evaluation)	Mixed-methods	1) Develop feasibility study design 2) Conduct endpoint and follow-up evaluations 3) Conduct process evaluation 4) Analyse evaluation outcomes 5) Address 14 methodological issues of feasibility research for full-scale intervention development 6) Identify strengths, limitations and next steps	Finalised intervention design for pilot study

Table 2. Sample characteristics

	INTERVENTION		CONTROL
Number of Household	**916**		**447**
Population size	**3015**		**1624**
Data collection methods	**Household Survey n (%)**	**Stakeholders Interviews, n (%)**	**Household Survey n (%)**
Sample size	**n=50**	**n=21**	**n=50**
Sex			
Woman	42 (84.0)	19 (90.5)	36 (72.0)
Man	8 (16.0)	2 (9.5)	14 (28.0)
Age			
Minimum	23	24	22
Mean (sd)	45.5 (10.0)	40.6 (9.1)	49.3 (15.1)
Maximum	65	54	72
Highest Attainment Education			
College or above (> 12 years)	3 (6.0)	3 (14.3)	7 (14.0)
High school (10-12 years)	11 (22.0)	5 (23.8)	10 (20.0)
Middle school (6-9 years)	24 (48.0)	10 (47.6)	17 (34.0)
Primary school or less (=<6 years)	12 (24.0)	3 (14.3)	16 (32.0)
Income			
>10000	3 (6.0)	0	8 (16.0)
5001-10000	16 (32.0)	6 (28.6)	9 (18.0)
3001-5000	17 (34.0)	12 (57.1)	16 (32.0)
<3000	14 (28.0)	3 (14.3)	17 (34.0)
Employment			
Yes	21 (42.0)	9 (42.3)	11 (22.0)
No	29 (58.0)	12 (57.1)	39 (78.0)
Children in the household			
Yes	47 (94.0)	19 (90.5)	33 (66.0)
No	3 (6.0)	2 (9.5)	17 (34.0)
Social Capital			
I think my village is a tight-knit community; people are very helpful			
Agree	40 (80.0)		43 (86.0)
Neutral	10 (20.0)		7 (14.0)
Disagree	0 (0.0)		0 (0.0)
Do you know the chairwoman of Women's Federation			
Yes	48 (96.0)		46 (92.0)
No	2 (4.0)		4 (8.0)
People is my village keep frequent contact with each other			
Agree	29 (58.0)		31 (62.0)
Neutral	16 (32.0)		9 (18.0)
Disagree	5 (10.0)		10 (20.0)
If I have to make be away for a couple of days with short notice, I can ask neighbours to look after my family			
Agree	34 (68.0)		20 (40.0)
Neutral	10 (20.0)		13 (26.0)
Disagree	6 (12.0)		17 (34.0)
Knowledge and attitudes			
Excessive use of antibiotics will lead to antibiotic resistance rendering antibiotics to be ineffective in the future			
Agree	38 (76.0)		36 (72.0)
Neutral	6 (12.0)		11 (22.0)
Disagree	6 (12.0)		3 (6.0)
One should always obtain a medical prescription when using antibiotics			
Agree	41 (82.0)		40 (80.0)
Neutral	5 (10.0)		4 (8.0)
Disagree	4 (8.0)		6 (12.0)
Unsafe disposal of antibiotics might cause environmental hazard			
Agree	39 (78.0)		35 (70.0)
Neutral	5 (10.0)		10 (20.0)
Disagree	6 (12.0)		5 (10.0)
I know when and how to use antibiotics when I am/my family is sick			
Agree	9 (18.0)		10 (20.0)
Neutral	13 (26.0)		4 (80.0)
Disagree	28 (56.0)		36 (72.0)
Antibiotic use and disposal behaviours			
Household antibiotic storage in the past year			
Yes	29 (58.0)		23 (46.0)
No	21 (42.0)		27 (54.0)
Taken antibiotics in the past month			
Yes	20 (40.0)		14 (28.0)
No	30 (60.0)		36 (72.0)
Self-medication with antibiotics in the past month	**(N=20)**		**(N=14)**
Yes	5 (25.0)		2 (14.3)
No	15 (75.0)		12 (85.7)
Methods to dispose expired, unwanted, unused (EUU) antibiotics			
Stored in the house	5 (10.0)		1 (2.0)
Thrown into garbage bin	28 (56.0)		44 (88.0)
Flushed in the toilet	4 (8.0)		1 (2.0)
Buried in the field	3 (6.0)		1 (2.0)
Fed chicken	2 (4.0)		0 (0.0)
Ingestion	2 (4.0)		1 (2.0)
Others	6 (12.0)		2 (4.0)

Table 3. Key assumptions and adaptation of intervention strategy

Key assumptions about the pilot community	Initial Assumption	Formative data to verify the assumptions	Adaptation
1. Prevalence of household storage of antibiotics	High	Unchanged	In additional to the current AMR awareness messages, intervention strategy should focus on: (1) defining appropriateness of antibiotic disposal (2) discouraging household storage of antibiotics (3) promoting the antibiotic take-back programme at the bartering market as a preferred platform for EUU antibiotics (4) appealing to the public concern over environmental health
2. Prevalence of self-medication with antibiotics	High	Unchanged	
3. Awareness of the danger of unsafe antibiotic disposal to the environment	Low	High	
4. Awareness of the danger of AMR on human health	Low	High	
5. Likelihood to use a drug take-back service	Residents would be more likely to use a drug take-back service if offered compensation and/or if the collection site was in a frequently visited location	Unchanged	

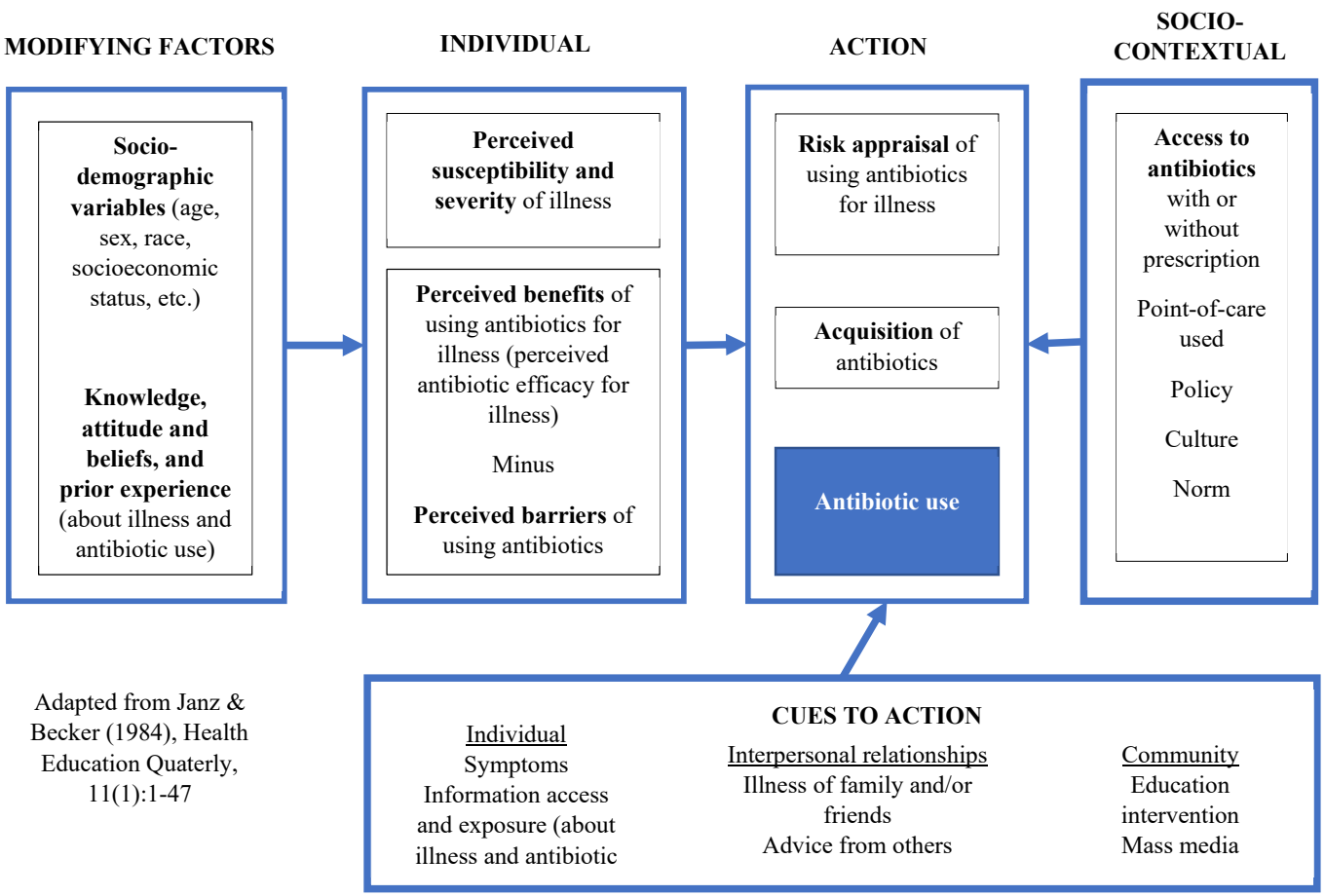
Table 4. Development of health education strategy

	Qualitative data to inform the development of health education strategy (selected quotations)	Key decisions for the health education strategy
Content	Note: content for health education was informed by findings from Aims 1 and 2 (existing literature and primary research data) where we focused on improving awareness of the danger of self-medication with antibiotics and unsafe disposal.	Expert panel evaluated the content validity Cognitive testing with residents of a village of similar characteristics
Format/Dissemination Channels	• *"If you send us a WeChat message, I will read it very diligently."* • *"The broadcast can actually be heard. Everyone heard it when they were buying something on this street."* • *"News passes quickly from mouth to mouth: everyone will know it".* • *"WeChat is very good. If it is sent during breakfast, lunch and dinner, definitely someone will see it."* • *"WeChat is fine. I've just been too busy recently looking after the store, so I didn't have time to look at it. Nevertheless, if I know there is such a thing, I will pay attention to it. "*	WeChat, posters, pamphlets, radio (public announcements), social networks
Frequency/Timing	• *"If we are sent a message, it is best to send it after 7 or 8 in the evening or during our break at noon. Otherwise, we will miss and not be able to read it, and even when we are not busy, we will forget about it."* • *"WeChat is very good. If it is sent during breakfast, lunch and dinner, definitely someone will see it."*	Lunch time (12-1pm) Dinner time or right after (6-9 pm)
Target audience	• *I received the WeChat message and read it seriously, but I still need to use the medicine myself.* • *I think the acceptance rate of the youth should still be good.*	Young adults Residents with an active WeChat account
Messengers	CAB meetings: Women's Federation is connected with all female adults in the households and runs the bartering market for recyclables. Our baseline data showed 96% (n=48/50) of the residents know the chairwoman of the Women's Federation.	Women's Federation

Table 5. Intervention materials design and descriptions

	Target	Sessions	When	Where	Materials	Description
Health education						
Programme implementer	Women's Federation (n=1)	45-minute briefing and training	May 2019	Village health centre	20-page training guide	Manual including project description and study aims, pre-tested health education messages, and guidelines (See Figure 4 & Appendices I)
Target population	Village women (n= est. 600 households)	Four health education messages	June 2019	mobile	pre-tested health education messages	Pre-tested health education campaign emphasizes four primary messages (antibiotics do not help colds and flu, colds and flu are not caused by viruses, antibiotics do not kill viruses, do not take antibiotics for colds and flu)
Recycling programme						
Programme implementer	Women's Federation (n=1)	45-minute briefing and training	May 2019	Village health centre	Feedback form and a worksheet for antibiotic recycling programme	A monitoring and evaluation form to record antibiotic returned to the programme and items in exchange.
Target population	Villager residents	Entire project period	June 2019	Village clinics: (n=1) Recycling programme (n=1) Mail: n=800	Pamphlet	Pamphlet: 21 x 29.7 cm (A4), colour-print, triple fold with Zhejiang University logo; emphasizes four primary messages (antibiotics do not help colds and flu, colds and flu are not caused by viruses, antibiotics do not kill viruses, do not take antibiotics for colds and flu) (See Figure 4)
Target population	Villager residents	Entire project period	June 2019	Bus stop: (n=8) Village clinics: (n=1) Recycling programme (n=1)	Poster	Poster: 60.96 x 91.44 cm; colour; photos of parents not to take antibiotics for colds and flu (See Figure 4)

Figure 1. Theory of Change



Adapted from Janz & Becker (1984), Health Education Quaterly, 11(1):1-47

Figure 2. Logic Model: antibiotic take-back programme in rural China

Inputs	Outputs		Outcomes – Impact			Impact
	Activities	*Participation*	*Short-term*	*Intermediate term*	*Long-term*	
Implementation capital of the community advisory board and Women's Federation Funding State-run environmental initiatives: • "Five Water Treatment" • "Waste Sorting and Recycling" programme Health education materials from the Zhejiang University crowdsourcing campaign Women's Federation's WeChat platform connecting female villagers Town-run bartering market for recyclables	Number of health education materials distributed Number of health education messages disseminated Number of households reached Number of work hours by Women's Federation which runs the bartering market Number of household items exchanged at the bartering market Number and type of dispose expired, unused, unwanted (EUU) antibiotics returned	Residents Women's Federation Community advisory board	Increase in awareness of the danger of self-medication with antibiotics without professional advice Increase in awareness of the danger of unsafe disposal of antibiotics Increase in number of residents using the bartering market to dispose expired, unused, unwanted (EUU) antibiotics Increase in number of residents reporting greater satisfaction using the bartering market	Reduction in number of residents storing antibiotics at home Reduction in number of residents engaging in unsafe disposal of antibiotics Reduction in number of residents engaging in self-medication of antibiotics without professional advice	Improving in norm discouraging self-medication with antibiotics Improving in norm encouraging safe disposal of antibiotics Improving in prudent use of antibiotics in the community	Reduction in prevalence of antibiotic resistance in the community

Figure 3. Implementation Capital for Evidence-Based Practice

Figure 4. Sample health education materials and design

(a) poster (I) – antibiotic literacy:

Attention!!!

The drugs above are all antibiotics. You should not use them without professional guidance nor store them at home. Keeping antibiotics at home is associated with an increased risk of self-medication with antibiotics; irresponsible disposal of antibiotics leads to environmental pollution.

Please bring your household antibiotic stock to the antibiotic take-back site in the village. In exchange, you will receive a small household item provided by Zhejiang University for your participation and support.

[Developed by Zhejiang University Research Team on Prudent Antibiotic Use]

(b) poster II: care management for children with the common cold or flu

Do not give antibiotics to children for the common cold or flu.

Please consult your doctor regarding how to alleviate the cold symptoms experienced by your children.

Please do not ask doctors for antibiotics (oral antibiotics or IV)

Antibiotics are not effective to treat the common cold, to alleviate cold symptoms, or to expedite cold recovery, caused by a virus. Rather, antibiotics might have an adverse impact on children's health. The best tips for getting over the common cold are to drink plenty of fluids and get plenty of rest.

[Developed by Zhejiang University Research Team on Prudent Antibiotic Use]

(c) pamphlet: prudent use of antibiotics

• Antibiotics can save lives, but not a cure all • If you don't use antibiotics responsibly, not only does it not benefit your children, but might have an adverse impact • Antibiotics can be effective for bacterial infections, but not for viral infections • Antibiotics can eliminate bacteria, but not virus. • When children are sick, antibiotics are not the only option. If it is necessary to use antibiotics, IV is saved for more severe cases.	Please let doctors determine children's antibiotic use. Please do not ask doctors for antibiotics (oral antibiotics or IV)	Please use antibiotics responsibly. You should learn antibiotic literacy. Please do not give antibiotics to children for the common cold or stuffy/runny nose.

[Developed by Zhejiang University Research Team on Prudent Antibiotic Use]

Appendix I. Training materials and design

Manual on prudent antibiotic use	**Table of Contents**
Protect your own health. Please use antibiotics responsibly. Edited by the National Health Commission Peking University Medical Press	1. What are antibiotics? 2. How to recognise antibiotics? 3. What is inappropriate use of antibiotics? 4. Why do antibiotics lose their efficacy? 5. The damage of antibiotic abuse 6. What to do? **7.** What not to do?

CHAPTER EIGHT

Cleaning up China's medicine cabinet – an antibiotic take-back programme to reduce unsafe use and disposal of household antibiotics in rural China: a mixed-methods feasibility study

This chapter presents the results of a pilot study conducted in two villages in rural Zhejiang – one intervention and one control - in June 2019 testing the acceptability and feasibility of an antibiotic take-back programme with respect to: the community engagement approach; the appropriate/effective incentives for rural residents to turn in household antibiotics; the appropriateness and literacy level of health education messages.

My local partners at Zhejiang University funded and implemented the pilot study on the proposed behavioural change intervention. I designed and led the feasibility evaluation for the proposed intervention that aimed to remove household storage of antibiotics in the community. Assisted by in Zhejiang University, fifty (50) households from the intervention village were randomly sampled for pre- and post-assessment; fifty (50) households with similar characteristics from different village served as control group. The intervention components were found to be feasible, appropriate, and acceptable, with high scalability. The findings and results have been prepared as a draft of the manuscript, with comments on drafts from Weiyi Wang, Professors James Hargreaves, Mark Petticrew, and Xudong Zhou. This manuscript has been accepted by *Antibiotics*.

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT

T: +44 (0)20 7299 4646
F: +44 (0)20 7299 4656
www.lshtm.ac.uk

RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	LSH1704488	**Title**	Ms.
First Name(s)	Leesa		
Surname/Family Name	Lin		
Thesis Title	Development of evidence-based behavioural interventions to reduce inappropriate use of antibiotics beyond clinical settings		
Primary Supervisor	Professor James Hargreaves		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*	Choose an item.	Was the work subject to academic peer review?	Choose an item.

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	Antibiotics
Please list the paper's authors in the intended authorship order:	Leesa Lin, Weiyi Wang, James Hargreaves, Xudong Zhou*
Stage of publication	**In press**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Leesa Lin conducted the literature search, created the figures and the conceptual framework, developed study design and instruments, and contributed to data collection, analysis, and interpretation. Leesa Lin drafted and revised the manuscript. Xiaomin Wang and Weiyi Wang contributed to data collection and analysis, and commented on revisions of the manuscript. James Hargreaves contributed to data interpretation, and commented on the initial and following revisions of the manuscript. Xudong Zhou conceived the study, led data collection, contributed to data interpretation, and commented on all drafts of this manuscript. All authors approved the final draft of this manuscript.

SECTION E

Student Signature	[redacted]
Date	09/09/2019

Supervisor Signature	[redacted]
Date	09/12/2019

ABSTRACT

BACKGROUND: Antibiotic misuse and unsafe disposal harm the environment and human health and contribute to the global threat of antimicrobial resistance. Unsupervised use and careless disposal of medications is a common practice in China and most low- and middle-income countries (LMICs). This study assesses the feasibility of an evidence-based, theory-informed, community-based take-back programme for disposing household's expired, unwanted, or unused antibiotics in rural China.

METHODS: Guided by the Medical Research Council's (MRC) framework for the evaluation of complex interventions and the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework, this mixed-methods research design comprised a controlled pre–post quantitative component and embedded qualitative component. The study methodology's feasibility was examined using following data : 1) quantitative surveying of a representative community panel of 50 households, and 2) qualitative semi-structured stakeholders' interviews. Specifically, quantitative data from three implementation phases (i.e. pre-intervention, intervention, and post-intervention) were used to assess recruitment, retention, follow-up measure response rates, missing follow-up measure data, and usage data. Qualitative data were gathered to assess acceptability. Data from a similar village – serving as a control – were also collected.

RESULTS: All a priori feasibility objectives were met: conversion to consent was 100.0% (100 screened, approached, recruited and consented). All participants completed the pre-intervention assessment, and 44/50 households in the intervention village completed the post-intervention assessment. The programme, embedded in existing social and physical infrastructure for dissemination, directly reached over 68.2% (30/44) of its target audience. Fourteen implementation research methodological

issues for future full-scale trials (e.g. sample size calculation, eligibility, recruitment, etc.) were critically examined and summarised.

CONCLUSION: This feasibility study presents an overall favourable public response toward a theory-driven, community-based bartering market for antibiotic-take-back as a feasible, acceptable, and appropriate intervention, warranting the expansion of the pilot programme. It filled the knowledge gap by describing systematic steps taken to adapt community-based interventions for a new context and a new health risk, and to conduct feasibility studies. This study illustrates the feasibility, acceptability, and potential efficacy of community-based antibiotic take-back programmes to encourage safe antibiotic use and disposal in the rural community.

KEYWORDS: drug take-back; environment; community health; drug abuse; prescription drugs; antimicrobial resistance (AMR)

BACKGROUND

The effectiveness of antibiotics has been undermined by decades of antibiotic misuse constituting a global health threat - antimicrobial resistance (AMR) - that might threaten human survival.[43,340] A majority of human antibiotic consumption occurs in community settings outside of clinical facilities, especially in low-and-middle income countries (LMICs) where antibiotic self-medication is close to 40%; half of these antibiotics come from household storage.[305] China, one of the world's largest producers and consumers of antibiotics, faces among the most severe challenges of this crisis, with antibiotic residues and resistance genes detectable in surface water, waste water treatment plants, soil, vegetable produce, and animals.[32,42,341,342] Since 2011, the Chinese government has implemented a series of measures to contain this problem; however, most of these stewardship programmes focus on regulating prescriptions in hospitals and few address the easy access to antibiotics available in communities.[269] Nationwide surveys demonstrated that over 70% of Chinese households stored antibiotics that were eventually self-administered without professional supervision.[41,68,305,316]

Recent reviews showed expired, unwanted, or unused (EUU) medicines were either stored unintentionally as leftovers or kept purposefully to treat similar conditions in the future (33%); among those who disposed of unused medicines, 50% used a take-back programme and 42% disposed the medicines in the trash or toilet.[320,329,343,344] The improper disposal of unused antibiotics can harm the health of the environment, wildlife, and humans, especially in countries, like China, with poor waste management systems.[320] The awareness and concern over the presence of pharmaceuticals in drinking water and the threat of misuse posed by EUU medications has led to interventions like drug take-back programs for the removal of household access in

developed countries (e.g. the United States, Sweden, and Germany) in the past decade.[330,344] Evaluations of take-back events demonstrated their positive effect on raising awareness about and reducing misuse or abuse of drugs.[218,321-323] The attention on ecopharmacovigilance (EPV) in China is recent, which focuses on minimization of environmental risks posed by pharmaceutical residues and the needs to guard against and control the pharmaceutical pollution source.[345-348] However, despite being one of the largest producers and consumers of antibiotics, discussions about safely disposing of antibiotics are practically non-existent in China. No interventions to date have attempted to address non-prescription household antibiotics use. There are few convenient and environmentally responsible disposal methods for systemically removing or reducing household antibiotic stockpiles in China, and public-targeted interventions are a pressing need.

In this study, we employed a mixed-methods approach to assess the feasibility and acceptance of an antibiotic take-back and disposal programme in rural China where antibiotic misuse in the community is the most severe.[65,324]

METHODS

This study aims to determine the feasibility and acceptability of the proposed intervention, an antibiotic take-back programme in rural China. The proposed intervention consists of two components: a community-based antibiotic take-back programme and health education. We first pre-tested intervention materials and implementation methods with experts and potential users for validity and appropriateness. Second, we explored stakeholders' views on potential facilitators and barriers to the intervention. Last, utilising a mixed-methods design, we assessed the feasibility, acceptability, and scalability of a pilot intervention and explored its

effectiveness. The study design and process of adapting existing interventions to new populations and settings are reported in detail elsewhere.

Feasibility study design

Guided by the Medical Research Council's (MRC) framework for the evaluation of complex interventions[349] and the RE-AIM (*Reach, Effectiveness, Adoption, Implementation, and Maintenance*) framework,[327] this mixed-methods research design comprised a controlled pre–post quantitative component and embedded qualitative component. The study methodology's feasibility was first examined using the following quantitative data: *recruitment, retention, follow-up measure response rates, missing follow-up measure data, and usage data*. The study design and intervention's feasibility and acceptability were then explored using qualitative semi-structured interviews with stakeholders. We noted that this pilot study was designed to test the feasibility of one intervention component of a large trial on complex intervention, not the efficacy or effectiveness of the new intervention, which is the aim of a full scale randomized controlled trial (RCT).[350] Lastly, we systematically explored and addressed the 14 potential methodological issues of feasibility studies identified by Bugge et al and Shanyinde et al.[351,352]

Setting and sample

Feasibility data for the intervention came from a representative community panel of 50 households in two rural villages – one intervention and one control - in Zhejiang, China, conducted over the first 30 days of implementation of an antibiotic take-back programme in June 2019. All households in the villages were eligible for inclusion and those agreeing to participate gave informed consent. Due to the intervention design and the local context, we targeted the self-identified female heads of household. Qualitative

data came from 21 purposively-selected stakeholders of the community, who represented the characteristics relevant to the study setting in terms of age, gender, socio-economic status, and community roles.

Data collection and management

For baseline, intervention, and post-intervention evaluations with the community panel, face-to-face household surveys consisted of quantitative and qualitative items assessing antibiotic use and disposal behaviours, exposure to and participation in the programme, and public knowledge and perceptions about antibiotic use. Inspections of household medical cabinets were conducted at the end of each survey. Stakeholders, including residents, local government officials, community partners, potential implementers of the intervention, community pharmacies and clinicians, and local residents, were recruited for semi-structured interviews and to access process evaluation data in the pilot village. Baseline and final evaluation data - both quantitative and qualitative - were also collected from the control village with a similar sample. Stakeholders' interviews were audio-recorded, transcribed by an independent transcription company, checked for accuracy, anonymised and imported into Nvivo11 software to facilitate analysis.

Sample size

While a sample size was not calculated (outcomes of interest were intervention and study design feasibility and acceptability), previous studies have identified a minimum of 20 participants is required to identify 95% of usability problems.[353] Although there is current no published guidance as to the sample size required for a pilot or feasibility trial and that this pilot study employed a controlled pre-and-post design (not a trial), we set the sample size to be 50 household per arm, which was higher than the median among the published UK pilot trials.[354] This intervention was delivered at the village,

rather than the individual, level. In a full-scale study, village- or township-level randomisation as part of a cluster trial would be appropriate. For this study, the feasibility of randomisation was not tested.

Measures

The intervention aimed to reduce household antibiotic storage and improve safe antibiotic disposal; this informed measure selection. The feasibility and acceptability of the selected study measures were assessed to determine those most appropriate for a future cluster trial.

Primary measures: The primary objective was to describe antibiotic storage and disposal behaviours. All respondents were asked whether, in the past month, they have: (a) kept antibiotics at home and (b) participated in the take-back programme.

Secondary measures included awareness and perceptions of the potential danger of "unsafe disposal" and "non-prescription antibiotic use" on human and environmental health.

Process evaluation: Routine data on programme utilisation, costs, and in-kind expenses were calculated. Returned antibiotics were stored in a pre-prepared bag with a pre-designed information sheet including details of each collection, e.g. types and amount of the drugs received and source of antibiotics, and user's satisfaction.

Data on participants' socio-demographic characteristics were also collected.

Data analysis

Descriptive statistics (frequencies, means and standard deviations) were calculated for all variables. Qualitative data were analysed using framework analysis. A priori codes were drawn from the interview topic guide, study objectives, and feasibility evaluation framework. LL was the primary coder and interpreted the data, along with two other

coders, ZXD and WWY. Consensus on themes and key findings were reached through discussion.

RESULTS

Table 1 reports the demographic and background characteristics of the study participants. A total of 412 minutes of qualitative stakeholders interview data were collected (n=21); each interview lasted approximately 10-34 minutes. 19 out of 21 respondents were female; all but three did not go to college. The mean age was 40.6 (±9.1) years. In the intervention village, 29 of the 50 households who completed the questionnaire in the baseline surveys self-reported having antibiotics stored at home prior to intervention; among them, seven (7) returned the antibiotics during the 30-day intervention period. 20 out of 50 reported having taken antibiotics within the month before the baseline survey; among them, five (5) took antibiotics without a prescription. 44 households in the intervention village and 39 households in the control village completed the post-intervention questionnaires with no missing data. Additionally, a month after the intervention, a follow-up assessment was conducted in pilot village to understand the change in awareness and perceptions of the potential danger of "non-prescription antibiotic use" and "unsafe disposal" on human and environmental health. Table 2 presented that 40 households in the intervention village completed the assessment with one household skipped several items (missing data). Due to the nature of the data and small sample size, these analyses are only useful for descriptive purposes.

Recruitment and retention: Fifty households in each study site were approached; all were eligible and recruited. The proportion of households approached who consented (conversion to consent) was 100% - well above the target set of 60.0%. Among them,

44 in the intervention village and 39 in the control village retained and completed the pre- and post-intervention questionnaires.

Reach is measured by the percentage of residents who were informed about the programme and were potential users. 30 out of 44 households in the community panel had heard of the antibiotic take-back programme. 13.3% had heard about it from WeChat and Women's Federation, over 90% from print materials.

Effectiveness is measured by project participation and increases in awareness of the danger of unsafe use or disposal of antibiotics. A total of 48 households used the bartering market (7 households from the community panel) and 34 said they would recommend other villages to adopt the antibiotic take-back programme in their bartering markets.

Adoption: No barriers to adoption were identified by implementers. Not knowing about the take-back programme, no household storage, and no time to bring antibiotics in were listed as the top three reasons for non-participation. Nevertheless, 38 households intended to participate in the future and 8 already recommended using the bartering market for antibiotic take-back to at least one other person in the past month.

Implementation of the programme, measured by *fidelity,* was delivered as intended. All eligible Women's Federation members were actively involved in intervention delivery. A total of 48 households used the bartering market for antibiotic take-back and disposal; all returned antibiotics were properly sorted and documented according to study protocol, reported in Table 2. Intervention adherence and participant compliance was achieved.

Maintenance concerns the long-term maintenance of behaviour change at the individual level, which is not assessed in this study. At the village level, the potential for the

antibiotic take-back programme to become a routine part of the culture is high. Among the 44 households who completed the post-intervention assessment, 40 interviewees thought the take-back programme should stay a part of the bartering market and be promoted to other villages, 4 stayed neutral, and none disagreed.

Acceptability and appropriateness: The acceptability and appropriateness of the intervention is high. Awareness around the environmental protection is high. The intervention was appropriate, acceptable and sustainable to the implementers, the Women's Federation. Data from the control group showed high acceptability for participating in an antibiotic take-back programme (31/36), which will indicate *scalability*.

Process evaluation outcomes are reported in Table 2. Respondents listed reasons to continue or expand the bartering market for antibiotic-take back: 34 said to protect the environment, 18 to prevent inappropriate use at home, and 12 because there is no other platform to safely dispose antibiotics, and 10 respondents felt incentivized by the household items at the bartering market.

Data that address 14 implementation research methodological issues for future full-scale trials are presented in Table 3.

DISCUSSION

This is one of the first feasibility studies in China and in low-and-middle income countries (LMIC) for a community-based behavioural change intervention to reduce antibiotic misuse and resistance. This study presents the high feasibility and acceptability of a community-based antibiotic take-back service offered at a local bartering market for recyclables. The overall positive feedback supports the need and warrants the continuation and expansion of the programme. There is a lack of

environmentally safe disposal guidelines and take-back services for the proper disposal of antibiotics in China. This proposed intervention served a dual-purpose: (a) to reduce access to unnecessary antibiotics in the household and the likelihood of self-medication with antibiotics without supervision, and (b) to promote safe disposal and protect the environment. Villagers confirmed the local town-run bartering market as a convenient site for an antibiotic disposal programme. Health education and removal of household antibiotic storage can reduce the likelihood of self-medication with antibiotics. Strengths of this study include utilisation of a mixed-methods approach and adoption of the RE-AIM and MRC evaluation frameworks to achieve the study aims. With RE-AIM constructs embedded in the study design since project inception, we were equipped to identify 'what works for whom, in what contexts, and how.' The findings from this study should be interpreted with several limitations. The small sample and use of one site may seem to limit the results' generalisability. Because data were collected from a representative sample of rural Chinese residents in the participating site, representing 5.5% (50/916) of the households, and from a control site (11.2%, 50/447) at three different time points, the general pattern of findings observed in this study is sufficiently robust for a feasibility study to alleviate concerns about potential spuriousness. This investigation offers needed empirical feasibility data on the antibiotic take-back programme for a large trial.

Interpretation of findings

This study identified a critical gap of current AMR strategy in the Chinese infrastructure where EUU antibiotics in the community are left unattended. There is a lack of knowledge of and platform for proper disposal and a strong interest in participating in take-back programmes. Formative data found that the local awareness

and concern over the presence of pharmaceuticals in drinking water and the threat of misuse were high in both intervention and control villages, yet self-medication with antibiotics were common among local residents who seemed to be unsure of what constitutes proper disposal and showed reluctance in giving up habits of household storage of antibiotics. We found individual's health decisions about antibiotic use to be complex and not entirely driven by their cognitive and rational characteristics - contextual factors, including access to antibiotics and interpersonal connections, are equally or more critical to healthcare decision-making processes. Evidence showed when information or time is limited and complexity of the situation is overwhelming, individuals often combine rationality with other sources of so-called tacit or experiential knowledge and utilise strategies such as trust, intuition and emotion to assist decision making.[238] Antibiotic misuse in China is driven by a complex set of factors embedded in its culture and beliefs, health system, and society.[30,41,44] Data from this project highlighted that increasing knowledge and raising awareness about the consequences of the inappropriate use and disposal alone is unlikely to enable the desired behaviour change. A complex intervention that also support prudent prescriptions, reduce over-the-counter purchases, improve dispensing system to reduce leftover prescriptions in addition to the proposed community-based intervention for an extended period of time will be necessary. Further clarifications about what constitutes "appropriate practices" in the given context should be included in the education intervention. In our sampled villages, respondents who engaged in misuse behaviours such as feeding children with antibiotics, burying them in the field, taking them before expiration, or not thinking antibiotics can "go bad" might consider their behaviour as "being completely appropriate." Changing the local social and infrastructure environments for appropriate

antibiotic use and disposal while providing actionable information about how and when/where to use and dispose antibiotics are key to cue people to action. Educating about how to care for common self-limiting illnesses and non-antibiotic alternatives for symptom relief will improve the likelihood for better use of antibiotics. Health education messages for the project should address these concerns during full scale implementation. This study also informed data collection strategy during full scale implementation. We found that many younger adults of a working age stayed away during the week for work, leaving only grandparents and children in the village; it was therefore best to reach them over weekends. This scenario has important implications on the planning of data collection when large sample size is involved as it restricts the number of days allowed for data collection. Furthermore, it is concerning that within 30 days, we saw a sharp decrease in the household antibiotic storage in the pilot village from 34.0% to 27.8% in the absence of an intervention. There might be several possible explanations for this phenomenon: first, a Hawthorne effect (also referred to as the observer effect) in which individuals modify their habits of storing antibiotic at home in response to their awareness of being observed. However, we ruled out this possibility because this effect was not seen in the intervention village which was also being observed. Also, formative data suggested that unlike prescription drug diversion in the U.S. which might be viewed as a type of behavioural disorder carrying a potential social stigma,[34] in China keeping antibiotics at home for future use is a socially acceptable common practice.[35,36] The concern over under-reporting of household storage of antibiotics is low. Furthermore, the quantity of household storage of antibiotics was verified by an inspection of the household medical cabinet onsite, leaving little room for error in reporting. A small sample size, a short study duration, or the timing of data

collection (e.g. flu season or not) may all also be variables in play. However, this speculation could not fully explain the sudden drop in the storage observed in the control village, which calls for further qualitative investigation. On the other hand, since there is currently no mechanism in place to remove the excess antibiotics from these households, the reduction in the storage can only be assumed to either have been consumed without a prescription or discarded inappropriately. This discovery was worrisome, especially considering the timing of the feasibility study (June) was not peak season for upper respiratory tract infections (URTI) and was low season for antibiotic consumption. Given this timing, compounded with easy access to antibiotics and the population size of 577 million rural residents, it is clear that the severity of misuse and mishandling of antibiotics in the community requires an urgent need for interventions. Nevertheless, during the 30-day period, this programme was able to reach a sizable portion (68.2%, 30/44) of the intended target audience with messages promoting the safe disposal of antibiotics, and among them, 26.7% (8/30) further spread this message, including people outside of the intervention villages. The frequent exchange of information between villages reported in this study also indicated that in a full-scale study, township-level randomisation - rather than village-level – would be appropriate as part of a cluster trial. Future research on social networks may be able to generate additional insight regarding the diffusion of innovations for reducing antibiotic misuse. Moreover, given the high levels of antibiotic residues in fresh water and soil in China, future studies should explore whether those more conscious about environmental protection are more likely to engage in prudent antibiotic use and disposal, which may inform a “One Health” approach. Finally, we recognise that although the proposed intervention will remove household antibiotic stockpiling, it will not address all the

challenges associated with antibiotic misuse in the community. A multifaceted intervention that also enforces regulations regarding the sale of antibiotics and pack-based antibiotic dispensing systems to reduce leftover antibiotic prescriptions is necessary to curb the main sources of non-prescription antibiotics for self-medication use.

To date, research reporting has mainly focused on effectiveness of interventions rather than the process of identifying and evaluating key components and the parameters within which they operate. Such lack of detail in the "contexts" and "mechanisms" that determine the effectiveness of interventions make replication and adaptation difficult, as it is hard to judge "what works for whom, in what contexts", and why and how. This study filled the knowledge gap by describing systematic steps taken to adapt community-based interventions for a new context and a new health risk, and to conduct feasibility studies. From a global health perspective, the results of this study demonstrate that a take-back programme can be a potentially effective instrument for decreasing the availability of unnecessary antibiotics and potential misuse in communities across China and around the world, especially in LMIC. As many rural Chinese towns have bartering markets, the proposed intervention has great potential for significance and scalability.

CONCLUSION

This feasibility study presents an overall favourable public response toward an antibiotic-take-back programme as a feasible, acceptable, and appropriate intervention, warranting the expansion of the pilot programme. The intervention can be an important component of a multifaceted AMR strategy to decrease inappropriate antibiotic use in the community, especially those in low-and-middle income countries including China.

List of abbreviations

AMR	Antimicrobial resistance
CBPR	Community-based participatory research
EPV	ecopharmacovigilance
EUU	expired, unwanted, or unused
LMICs	Low-and-middle income countries
MRC	Medical Research Council
RE-AIM	Reach, Effectiveness, Adoption, Implementation, and Maintenance
RCT	Randomized controlled trial
URTI	Upper respiratory tract infection

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from Research Ethics Committees at Zhejiang University (Ref: ZGL201901-1) and the LSHTM (Ref: 16261). Written informed consent was obtained from participants. A Project Advisory Group comprising researchers and stakeholders was established to discuss study findings and to inform the evaluation.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and/or analysed during the current study are not publicly available due to the likelihood of compromising the privacy of participating individuals given the small population size in the project sites; the study materials are available from the corresponding author upon reasonable request.

Competing interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors have no conflicts of interest or financial interests in any product or service discussed in the manuscript.

Funding

Funding to conduct the feasibility assessment of the proposed intervention was supported by the Zhejiang University Zijin Talent Programme. The authors received no

financial support for the feasibility research, authorship, and/or publication of this article.

Acknowledgments

We acknowledge the financial support from the Zhejiang University. We thank the Jiangshan government officials, Women's Federation and personnel at the bartering market for offering their time, expertise, and providing support throughout the study.

Table 1. Sample characteristics

	INTERVENTION		CONTROL
Population Size	3015		1624
No. of Household	916		447
	Baseline Survey	**Stakeholders Interview**	**Baseline Survey**
Sample size	**50**	**21**	**50**
Sex			
Woman	42 (84.0)	19 (90.5)	36 (72.0)
Man	8 (16.0)	2 (9.5)	14 (28.0)
Age			
Minimum	23	24	22
Mean (sd)	45.8 (10.0)	40.6 (9.1)	49.1 (15.2)
Maximum	65	54	72
Highest Attainment Education			
College or above	3 (6.0)	3 (14.3)	7 (14.0)
High school	11 (22.0)	5 (23.8)	10 (20.0)
Middle school	24 (48.0)	10 (47.6)	17 (34.0)
Primary school or less	12 (24.0)	3 (14.3)	16 (32.0)
Income			
>10000	3 (6.0)	0	8 (16.0)
5001-10000	16 (32.0)	6 (28.6)	9 (18.0)
3001-5000	17 (34.0)	12 (57.1)	16 (32.0)
<3000	14 (28.0)	3 (14.3)	17 (34.0)
Employment			
Yes	21 (42.0)	9 (42.3)	11 (22.0)
No	29 (58.0)	12 (57.1)	39 (78.0)
Children in the household			
Yes	47 (94.0)	19 (90.5)	33 (66.0)
No	3 (6.0)	2 (9.5)	17 (34.0)
Having an active WeChat account			
Yes	40 (80.0)		32 (64.0)
No	10 (20.0)		18 (36.0)
How often do you use WeChat?			
All the time	27 (67.50)		27 (87.38)
Frequent	9 (22.50)		2 (6.25)
Sometimes	2 (5.0)		1 (3.13)
Not frequent	1 (2.50)		2 (6.25)
Never	1 (2.50)		0 (0.0)
Do you participate in the waste sort and recycle initiatives?			
Yes	41 (82.0)		39 (78.0)
No	9 (18.0)		11 (22.0)
Have you ever used the bartering market for recyclables?			
Yes	11 (22.0)		4 (8.0)
No	39 (78.0)		46 (92.0)
Methods to dispose expired, unwanted, unused (EUU) antibiotics			
Stored in the house	5 (10.0)		1 (2.0)
Thrown into garbage bin	28 (56.0)		44 (88.0)
Flushed in the toilet	4 (8.0)		1 (2.0)
Buried in the field	3 (6.0)		1 (2.0)
Fed chicken	2 (4.0)		0 (0.0)
Ingestion	2 (4.0)		1 (2.0)
Others	6 (12.0)		2 (4.0)

Table 2. Awareness of the danger of antibiotic resistance and unsafe disposal and associated practices among community panels

	INTERVENTION VILLAGE n (%)			CONTROL VILLAGE n (%)	
INTERVENTION COMPONENTS	**PRE-** N=50	**POST-** N=44	**FOLLOW UP*** N=40	**PRE-** N=50	**POST-*** N=39
Health education strategy					
Knowledge and attitudes toward self-medication with and disposal of antibiotics					
Antibiotic overuse may increase antibiotic resistance					
Agree	33 (66.0)	35 (79.5)	30 (75.0)	37 (74.0)	27 (71.1)
Neutral	11 (22.0)	6 (13.6)	9 (22.5)	12 (24.0)	8 (21.1)
Disagree	6 (12.0)	3 (6.8)	1 (2.5)	1 (2.0)	3 (7.9)
Inappropriate disposal of antibiotics can harm the environment					
Agree	45 (90.0)	42 (95.4)	37 (92.5)	40 (80.0)	31 (81.6)
Neutral	4 (8.0)	2 (4.6)	2 (5.0)	5 (10.0)	6 (15.8)
Disagree	1 (2.0)	0	1 (2.5)	5 (10.0)	1 (2.63)
Inappropriate disposal of antibiotics can harm the environment, I will dispose it appropriately					
Agree	44 (88.0)	40 (90.9)	37 (92.5)	35 (70.0)	35 (89.8)
Neutral	10 (5.0)	4 (9.1)	2 (5.0)	10 (20.0)	2 (5.1)
Disagree	1 (2.0)	0	1 (2.5)	5 (10.0)	2 (5.1)
Inappropriate disposal of antibiotics can harm the environment, I know how to dispose it appropriately					
Agree	29 (58.0)	28 (63.6)	27 (67.5)	21 (42.0)	20 (51.3)
Neutral	13 (26.0)	6 (13.6)	5 (12.5)	13 (26.0)	6 (15.4)
Disagree	8 (16.0)	10 (22.7)	8 (20.0)	16 (32.0)	13 (33.3)
Self-medication with antibiotics might have an adverse impact on our health					
Agree	41 (82.0)	44 (100.0)	34 (85.0)	44 (88.0)	32 (84.2)
Neutral	7 (14.0)	0	5 (12.5)	3 (6.0)	4 (10.5)
Disagree	2 (4.0)	0	1 (2.5)	3 (6.0)	2 (5.3)
Self-medication with antibiotics might have an adverse impact on health, one should not take antibiotics without professional supervision					
Agree	42 (84.0)	42 (95.6)	31 (79.5)	38 (76.0)	29 (74.4)
Neutral	4 (8.0)	0	4 (10.3)	8 (16.0)	5 (12.8)
Disagree	4 (8.0)	2 (4.6)	4 (10.3)	4 (8.0)	5 (12.8)
Self-medication with antibiotics might have an adverse impact on our health, one should not store antibiotics at home					
Agree	24 (48.0)	30 (68.18)	18 (46.1)	26 (52.0)	24 (63.2)
Neutral	12 (24.0)	6 (13.6)	7 (18.0)	12 (24.0)	10 (26.3)
Disagree	14 (28.0)	8 (18.2)	14 (35.9)	12 (24.0)	4 (10.5)
Participation in the antibiotic take-back programme					
Household antibiotic storage at the time of survey					
Yes	25 (50.0)	22 (50.0)	18 (45.0)	17 (34.0)	8 (21.1)
No	25 (50.0)	22 (50.0)	22 (55.0)	33 (66.0)	30 (78.9)
Participation in the take-back programme					
Yes	-	7 (31.8)	6 (33.3)	-	-
No	-	15 (68.2)	12 (66.7)	-	-

*Some items had missing data from one household

Table 3. Process evaluation on the antibiotic take-back programme

Quantitative data	
Health education strategy	
No. of households in the intervention village completed post-evaluation	44 households
No. of households received the health education messages	30/44 households (68.2%)
No. of households further spread this message	8/30 households (26.7%)
Bartering market for household expired, unwanted, or unused (EUU) antibiotics	
No. of households participated in the bartering market (including those who are not in the community panel)	48 households
Antibiotics take-back via the bartering market Cephalosporin (cefaclor, ceftriaxone sodium) Penicillin (amoxicillin) Quinolones (norfloxacin, ofloxacin) Macrolides (Azithromycin) Nitroimidazoles (Tixiaozuo) Others (non-antimicrobials/non-antibiotics)	No. of box 10 11 2 7 1 19
Total no. of returned antibiotics (boxes)/total costs	50 boxes/RMB 592

Qualitative data: users' opinions on the feasibility of the bartering market		
	Participants	**Non-participants**
Acceptability of the bartering market	**1. I have seen health education materials and realized that overuse of antibiotics can cause harm to the human body.** • "*It is written on the leaflet that it is not good to take too much of it, so I brought it here.*" (Male, 65 years old, primary school) • *"In the past, I would put some medicine at home, and I would take it when I subsequently got sick. I think the doctors actually prescribe more or less the same medication, but after reading the leaflet, I felt these materials are very useful. It is bad to take too much of it, and you can't do this either. It has to be placed at the recycling point."* (Female, 42 years old, high school graduate)	**1. I saw the relevant materials but was too late to take them to the bartering market.** • *"Recently, it was really busy at home. I didn't have time to take it there. In the future, if I have time here, I will take it there. It [the bartering market] is just a stone's throw away, so it is very convenient."* (Male, 48 years old, high school graduate)
	2. Throwing antibiotics anywhere can pollute the environment. They are better handled by the bartering market. • *"The medicine is left at home, and it will be thrown away after a long period time. [I learned that] It will pollute the environment, so I brought it to the bartering market after seeing the ad."* (Male, 65 years old, primary school graduate) • *"It is not good to throw medicine as one pleases. You can't throw them away randomly. After reading the text messages carefully, I felt there was something to gain."* (Male, 62 years old, middle school graduate) • *"I saw a notice saying that throwing medicine along with other garbage would pollute the environment. The bartering market is very good and can be taken advantage of."* (Female, 40 years old, middle school graduate)	**2. There is no reserve of antibiotics at home.** • *"We are usually in Wenzhou; there are no antibiotics at home. I don't really like keeping too much medicine at home."* (Female, 29 years old, high school graduate) • *"We have no medicine at home, but after reading this material, I will be willing to take it there in the future."* (Male, 43 years old, high school graduate)
	3. There is no use keeping it at home. There are even gifts redeemable at the bartering market. • *"It is useless for me to keep medicine at home. The bartering market is quite good, and there are even redeemable gifts there, so they can be taken advantage of."* (Female, 40 years old, middle school graduate)	**3. No relevant health education materials were received.** • *"I didn't receive the text messages. It may be that there was something wrong with the mobile phone. We are already old, so we don't always check our mobile phones. I don't know where the leaflet was placed; it could no longer be found."* (Female, 49 years old, middle school graduate)
	4. I don't know how to handle it correctly myself. • *"I seemed to have set it up for a period of time before, but no one put it there. We usually just keep it at home, and I am worried that the children will take it randomly. If there is a recycling point, it will be more convenient because one can just put it directly there. Directly throwing antibiotics into an ordinary trash can doesn't seem too good either, but we don't know how to deal with it."* (Female, 33, high school graduate)	**4. If something remains, I can use it next time. I am not very willing to take it there.** • *"I also know that if it is just a small illness, one just needs to rest a few days even without taking medication to get well. But when one goes to work, they cannot rest for several days. I have to keep the medicine for use in the future. I don't want to buy medicine again. The symptoms are similar every time. And the medicine prescribed by the doctor is more or less the same. Just taking the same medicine as last time is enough; taking medicine makes one recover faster. And some medicines have one or two left, and I would be embarrassed to take them there in exchange for a gift."* (Male, 31 years old, college graduate)
Acceptability of the Incentives	• *"I think that ordinary soap, scented soap, toothpaste and other similar things can be used, it would be very good, I personally like it."* (Female, 42 years old, high school graduate) • *"As regards gifts, it's hard to say. Personal needs are different, and more choices are better."* (Female, 40 years old, middle school graduate)	• "Some medicines have one or two pieces left, and I would be embarrassed to take them there in exchange for a gift." (Male, 31 years old, college graduate)

Table 4. Summary of the findings against 14 methodological issues for feasibility research

METHODOLOGICAL ISSUES	FINDINGS	EVIDENCE
1. Did the feasibility study allow a sample size calculation for the main trial?	Yes	50 household approached 50 households eligible 50 households consent to participate in the study 48 households used the bartering market; 7 households were from the panel
2. What factors influenced eligibility and what proportion of those approached were eligible?	All households were eligible	All households were eligible
3. Was recruitment successful?	Yes	50/50 (100%) households agreed to participate in the panel
4. Did eligible participants consent?	Good conversion to consent	Fifty recruited out of 50 eligible, consent rate of 100.0%
5. Were participants successfully randomised and did randomisation yield equality in groups?	Not applicable in this study	Not applicable in this study
6. Were blinding procedures adequate?	Not applicable in this study	Not applicable in this study
7. Did participants adhere to the intervention?	Good adherence to the protocol	All take-back antibiotics were returned and documented according to the protocol.
8. Was the intervention acceptable to the participants?	acceptability explored in qualitative interviews	Residents from the intervention and control sites and the implementers found the intervention acceptable
9. Was it possible to calculate intervention costs and duration?	Yes	Costs for resource utilisation were assessed for participant use of antibiotic take-back programme and in-kind wage of implementors
10. Were outcome assessments completed?	There was no missing data from the take-back bartering market or from the household surveys.	There was no missing data as outcome data were collected in person.
11. Were outcomes measured those that were the most appropriate outcomes?	Outcome measures used did assess main outcomes of interest	Bartering market use data, household antibiotic stocks, and returned antibiotic were documented and analysed.
12. Was retention to the study good?	Good (88.0)	Response rates: Pre-intervention assessment (50/50) Post-intervention assessment (44/50)
13. Were the logistics of running a cluster randomised controlled trial addressed?	The buy-in from the Women's Federation on site positively influenced the logistical running of study	There were no difficulties identified in the various processes and the researcher's ability to implement them. Residents once recruited were readily identified.
14. Did all components of the protocol work together?	There were no difficulties identified in the various processes and the researcher's ability to implement them.	Residents and the implementer (i.e. the Women's Federation) found the intervention acceptable, feasible, and easy to implement.

CHAPTER NINE: DISCUSSION

9.1 Introduction

The aim of this PhD project was to develop a behaviour change intervention to reduce antibiotic misuse beyond clinical settings in China. I used a theory-based work stream plan to structure a synthesis of the findings from a workstream of research activities to inform the design of a complex intervention.

9.2 Research contributions

This PhD project has contributed to the generation of new evidence that addresses the pressing global health issue of antimicrobial resistance (AMR) and employs implementation research methods for the development, application, and feasibility assessment of a new behavioural change intervention in new contexts. These contributions are detailed in chapter nine and are summarised briefly here:

1) Identification of non-clinical determinants that influence antibiotic (mis)use in China. (Chapter two)
2) Identification of factors and their potential pathways influencing public's antibiotic use. (Chapter two)
3) Identification of behaviour change techniques (BCTs) that may be effective in reducing inappropriate or non-essential demand/use of medications or medical services. (Chapter three) This new knowledge has contributed to the development and selection of the community-based intervention components that aim not only to provide helpful information about the danger of AMR and unsafe disposal of antibiotic (BCTs 4.1, 4.2, 5.1, 5.2) but also to offer behaviour substitutes (8.2), incentives (10.1, 10.2), and improved environments (12.1, 12.5) that would reduce access to non-prescription antibiotics in rural Chinese households.

4) Prevalence of antibiotic misuse for self-limiting illnesses among Chinese children in the community, within and beyond clinical settings. (Chapter four)
5) Identification of risk factors influencing antibiotic use for URTIs in the Chinese community. (Chapters five and six) This new knowledge has contributed to the development and selection of the community-based intervention that aims to reduce access to non-prescription antibiotics in rural Chinese households.
6) Identification of the heterogeneity in the association between antibiotic use and various types of antibiotics-related knowledge, where the ability to identify antibiotics, perceived antibiotic efficacy for URTIs, and misconceptions about antibiotics as anti-inflammatory drugs were associated with increased odds of antibiotic use for URTIs. The findings suggested that raising public awareness about antibiotic resistance without tailoring the messages to local context may have unintended consequences. This new knowledge has contributed to the selection of the content of the health messages for AMR education interventions in the context of China and will be useful to future interventions of its kind. (Chapters five and six)
7) Development of a community-based intervention that reduces household antibiotic storage – the first one of its kind in China and low and middle-income countries (LMIC) which share the same challenges. There has not yet been an intervention that aims to reduce household storage of antibiotics. (Chapter seven)
8) Development of an intervention development and adaptation process, the theory-based work stream plan, which integrated the principles of RE-AIM, intervention mapping, and community-based participatory research (CBPR) to address methodological questions set out by the MRC guidelines and for the future implementation of the full trial. The work stream plans offers a theory-driven structure for the acquisition of feasibility-related evidence and for the translation

of research evidence into evidence-based practice into a new context. (Chapter seven)

9) Development of a public-targeted behaviour change intervention that recognises the social and behavioural influences on individual antibiotic use in the community. This is the first community-based AMR behavioural change intervention in China and low and middle-income countries (LMIC). (Chapters seven)
10) Development of the conceptual framework, implementation capital for evidence-based practice, for knowledge translation process. (Chapter seven)
11) Implementation of a feasibility study (first of its kind in China) for a community-based behavioural change intervention with an aim to reduce safe-medication and unsafe disposal of antibiotics in rural China. (Chapter eight)

9.3 Summary of main findings

I developed and showed that a theory-based work stream plan was effective in guiding the adaptation and development of an evidence-based practice (EBP) – an operationalising blend of the RE-AIM (*Reach, Effectiveness, Adoption, Implementation, and Maintenance*) framework,[327] community-based participatory research (CBPR) partnership principles,[325] and course of action of intervention mapping (IM)[89] and 6SQuID model, to guide and test the process of adapting existing interventions to new populations and settings. The review on non-clinical factors of antibiotic use in China (Chapter two, Aim 1) showed the majority of antibiotics for human use in China are consumed in the outpatient setting, often unnecessarily for viral URTIs - untreatable by antibiotics – especially in lower-level hospitals and health clinics.[33,36,37,57] Poor policy enforcement as well as loopholes in the current health system, permit inappropriate prescribing behaviours and access to antibiotics at retail pharmacies to continue in China, especially in primary care settings and in rural areas.[32,355] The review also identified limited data on the drivers of doctors' inappropriate prescribing behaviours and that current stewardship programmes may not address the root causes of the issue. I found there is an urgent need for behaviour change interventions directed at health system users in China to improve prudent antibiotic use. Findings from Chapter three (Aim 1) identified a critical knowledge gap of rigorous studies on the development of public-targeted behaviour change interventions that recognise the complex, interactive social and behavioural influences on antibiotic use in the community. Intervention content, design, development process, and implementation strategies are rarely presented in sufficient detail, with limited evidence offered on the rationale and theory behind the intervention components, making replicability difficult. The review showed that interventions consisting of both health education messages and a supporting

environment that encourages and incentivises the adoption of a new behaviour are more likely to be successful.

Figure 9.1 Intravenous infusion site at community health stations (photo credit: Leesa Lin)

In Chapters four to six (Aim 2), I presented an urgent need for an effective behavioural intervention to reduce demand for antibiotics for URTIs in the community beyond clinical settings, as lay people have formed a self-diagnostic process and response to URTIs that they often carry out prior to or in lieu of seeking clinical care. The quantitative data analyses showed the demand-side of the health system is driving roughly 70% of antibiotic use for URTIs in young adults and 40% in children under the age of 13 in China. Self-medication with antibiotics for URTI symptoms is highly prevalent, with a majority of patients or caregivers (55%) deciding to self-treat when self-diagnosed with URTIs; among them, about 35% used antibiotics. The success rates of patients or caregivers in requesting antibiotics from doctors for URTIs was extremely high: 100% for young adults and 70% for

caregivers - the majority received antibiotics via infusion. [See Figure 9.1] Non-prescription antibiotics are easily accessible in China; a majority of patients and caregivers reported having kept antibiotics at home for future use, with roughly 60% being leftover antibiotics from previous prescriptions and 40% from over-the-counter purchases in local retail pharmacies. Cephalosporine, Amoxicillin, and Azithromycin were the most commonly used antibiotics to treat URTIs, both with and without a prescription.

People's medical decisions and care-seeking behaviours for treating URTIs are shaped equally or more by individual and contextual factors than by clinical diagnoses. There is heterogeneity in the association between antibiotic use and various types of antibiotics-related knowledge, where the ability to identify antibiotics, perceived antibiotic efficacy for URTIs, and misconceptions about antibiotics as anti-inflammatory drugs were associated with increased odds of antibiotic use for URTIs. Interventions enhancing patients' or caregivers' self-efficacy for healthcare decision-making, especially regarding care management for URTIs, and correcting (mis-)perceptions around antibiotic efficacy for URTI symptoms, might reduce misuse. Context-appropriate multifaceted interventions are vital to untangling the perpetual problem of over-prescription and ill-informed demands for antibiotics. Simultaneously enhancing both prescribing guidelines and patient education targeting the family as a unit is critical. Education interventions should be disseminated via medical professionals or media in order to effectively cue people to a proper response. Enforcing regulations regarding the sale of antibiotics and pack-based antibiotic dispensing systems to reduce household antibiotic stockpiling could curb the main sources of non-prescription antibiotics for self-medication use in the community.

The formative data presented in Chapter seven (Aim 3) found that antibiotics are currently dispensed in packs, not by doses, which leads to leftover antibiotics in households which, in turn, become the main source of antibiotics for self-medication. Public awareness of the dangers that inappropriate use and disposal of antibiotics pose on the health of humans, the community or the environment is high, yet such high awareness does not translate into responsible antibiotic use and disposal. There is practically no safe disposal programme for household medical waste in the community, and as such, household antibiotics are disposed of as common trash bound for a landfill, potentially becoming an environmental hazard. Nevertheless, recent health policy reforms and existing environmental policies have set a solid foundation for the proposed intervention. An existing recycling programme and social network platform provided an opportunity in infrastructure (physically and societally) for an action-oriented health education strategy to take back left-over antibiotics as an environmental pollutant and biohazard. I described the process of development and adaptation of an intervention from one context to another (U.S. to China), to address a relevant but different global health concern (prescription drugs abuse to antibiotic misuse and antibiotic resistance) and factors affecting implementation and the process of implementation itself. Finally, in Chapter eight (Aim 4), a feasibility study established the acceptability and usability of the proposed intervention in which 14 implementation research methodological issues for future trials were carefully assessed.

9.4 Strengths and limitations of the study

The strengths of this study include 1) use of two sets of large-scale population survey data, with harmonised questions on antibiotic use-related knowledge and practice, among a new population for whom an existing drug take-back programme was adapted to reduce inappropriate or unnecessary antibiotic

consumption, 2) integration of practical reality and the inclusion of existing evidence, as well as both qualitative and quantitative data from primary research, and 3) adoption of participatory approach with commitment from the knowledge users. The work stream plan effectively allowed me to incorporate existing evidence into a theory-informed logic model developed within a given context. I integrated quantitative and qualitative findings to develop an evidence-based intervention that aligned with the needs and experiences of local partners and community members. Additionally, conducting interactive formative research in a community intervention helped foster a sense of ownership among participants towards the proposed intervention and positive attitudes towards researchers who demonstrated respect for local opinions. The collaborative aspect of the work stream plan, informed by a community-based participatory approach and intervention mapping procedures, is particularly important in the context of China, where interpersonal relationships are fundamental to collaborative activities and community leaders, including local officials, are viewed as gatekeepers of the community. The high feasibility, acceptability and sustainability were possible because of the high implementation capital the local partners in Zhejiang University and I were able to mobilise within a relatively short period of time, which allowed me and my colleagues to put together a grant application of a 30-town trial on a community-based complex intervention based on this project for the joint global health trial (call 9), which made it to the final stage.

The systematic review in chapter two found that there have not been consistent measures of antibiotic misuse behaviours in China and around the world, making comparisons of prevalence across studies and regions challenging. We did not find any national representative surveys on antibiotic use. In fact, the samples included in the secondary data analyses chapters four to six represented one of the

largest surveys conducted on this topic in the country. The participants represented healthcare decision-makers (for self or for children) of a population – young adults (university students) and young parents (with children under 13) – that are younger than the general public, which put constraints on the generalisability of the findings drawn from these data. These population are not only younger and better educated but also have had more exposure and presence on new media and technology (e.g. Weibo and WeChat) that emerged in the past decade, coincident with the Chinese government's efforts on tackling AMR and health reforms.

Although at least half of the sample in both datasets came from rural settings and/or with lower socio-economic positions, I expected them to have accessed and processed medical information differently than previous generations. As such, and considering people may have multiple infections during the year, I anticipate antibiotic misuse among the Chinese general population to be more prevalent and severe than what has been presented here. Longitudinal studies, behavioural data, or medical records such as prescriptions or clinical visits are needed in the near future to avoid recall bias, an inherent limitation of self-reported survey data.

Both surveys yielded high response rates above 85%. The high prevalence of antibiotic misuse recorded made (under-)responding bias less likely to be of a concern. However, when conducting the formal feasibility pilot study in rural Zhejiang (Aims 3 and 4), Zhejiang University and I decided to collect all data face-to-face due to low ability to recognise antibiotics levels of the targeted population. This operation highlighted the importance of an adequate translation and adaptation process from evidence generated from large scale surveys to practice in local context, especially in a country like China which has a large population that is diverse in culture and ethnicity, health systems, and development stages. In practice, it was critical to assess whether these knowledge, attitudes, practice (KAP) surveys

were valid or sufficient in capturing the local realities, especially among subpopulations that require further investigation. Furthermore, this conclusion echoes with the findings of systematic reviews (Aims 1) and the primary data collected for this study which indicated a need to investigate the effectiveness of current nation-wide AMR awareness campaigns in improving public's antibiotic use.

The limitations of this PhD project lie mainly in the secondary data from population-based surveys, generalisability of findings from each step laid out in the work stream plan, and translation from evidence to the development of the bartering market and health education materials to reduce antibiotic misuse, as there is currently no direct evidence regarding the mechanisms through which interventions work. First, because the samples were clustered the estimated standard errors used in significance tests may be biased. Specifically, the estimated standard errors might be under-estimated because the similarities between individuals within clusters are greater than those between individuals in a random sample drawn from the population. As such, significance levels reported might have been over-reported or underreported. However, in our case, samples of parents with young children (chapters four and five) were drawn from three provinces of different development levels (and from six provinces for university student data in chapter six) and then from the rural and urban areas within each province; the differences between these provinces and/or between rural and urban areas might be greater than those between individuals drawn from a random sample across the country. Variations at the province and/or urbanicity levels were accounted for in the analyses. Second, additionally, the models in chapter five (including adjusted models) did not include more than one of the key variables of interest because we were only interested in identifying factors for future interventions so the estimated effects would not be independent and could be confounded. Further, because I conducted multiple tests on

various factors of different URTI care and antibiotic use outcomes, there might be a possibility that the analysis gave a significant value when there in fact was none, which can be understood as the "role of chance". I, therefore, examined the full models with key factors adjusted for each other, controlling for sociodemographic factors, and found the conclusions remained unchanged.

Third, results from this study found that Chinese consumers often confused antibiotics for anti-inflammatory drugs, and were confused by their various types and efficacy, and by their chemical components, brand names and/or drug labels. Without adequate knowledge about care for illnesses and antibiotic efficacy, our data indicated that those with high ability to identify antibiotics might be more likely to seek out and misuse antibiotics. However, reverse causality is also likely, where high usage of antibiotics led to higher levels of knowledge about the drugs. Studies have shown previous recommendations from a physician for similar symptoms and prior successful experiences with antibiotics could lead to higher use, including SMA.[160,283,284] To effectively reduce antibiotic misuse in China, interventions should not only educate the public about antibiotics, but correct local misconceptions about care for childhood illnesses; otherwise, antibiotic resistance awareness campaigns about antibiotics might be counterproductive and may actually increase public demand for antibiotics.

Fourth, behavioural data that were gathered via survey instruments (chapters four to six) were by nature self-reported from health care consumers who may have been reluctant to report practices that could be considered inappropriate or may have been subject to recall bias, an inherent limitation of self-reported survey data. Experiments, longitudinal studies, or behavioural data are needed in the near future to avoid recall bias. Considering people may have multiple infections during the year and because our target population consisted of university students and parents of

young children, who are generally younger and have more knowledge about antibiotics and URTI care management than the general population, we anticipate antibiotic misuse among the Chinese general population to be more prevalent and severe than what has been presented in this thesis.

As for knowledge translation for the development of the intervention, the effectiveness of community-based interventions to reduce inappropriate use of medicines and medical interventions varies greatly. Furthermore, limited systematic research has been conducted to identify the design features (or the process to identify the design features) of health education materials and delivery strategies on prudent antibiotic use that are most likely to result in behavioural change. The evidence used to inform the two components of the intervention - the bartering market and health education – was clear and valid; in fact, my studies were the first to highlight heterogeneity within the knowledge domain of antibiotic use, resistance, and their association with antibiotic use behaviours. Working with local partners, we tailored the health education messages and strategy accordingly. However, relating to actual design and implementation, I struggled to find evidence from the literature that could guide the intervention design elements, such as layout, font and colour for print materials. Instead, I relied on elements identified in the previous crowdsourcing campaign on a similar topic, the community advisory board, expert opinions, and traditional testing with end-users to inform practical decisions involved in designing the intervention. Also, other than potential Hawthorne effects (observer bias) - a phenomenon in which individuals alter their behaviour in response to being observed, which usually refers to positive changes - there are a few obvious limitations to the available data. First, this study population reflected a narrow and generally less educated population sample in rural China, and thus our results may not be generalizable to other communities across China. Second, this was a single-

centre pilot study with a controlled before and after study design, and therefore I recognize that practices of antibiotic use and disposal, as well as practices for running the bartering markets, may differ amongst centres. That being said, the baseline rates of household storage of antibiotics between the two sites supported the notion that the proposed intervention has a high likelihood to be feasible, acceptable and appropriate to other rural villages. Third, its cross-sectional nature and the fact that estimates of health education message exposure and behavioural outcomes were limited to the past 30 days greatly complicated the task of estimating the true effect of the interventions on audiences. Community panels were approached at three different time points for feasibility assessments in a period of 6 weeks, which may have influenced their behaviours and/or induced a potential for a response bias in their reporting of results, as it became apparent to the interviewees what were the outcomes of interest. Fourth, as with any survey-based research, there exists the possibility of social desirability bias. Although the interviewers reassured all participants of their anonymity, face-to-face interviews relied on self-reporting, which may not accurately reflect patients' actual antibiotic use and disposal practices. Nevertheless, because important confounders were controlled for and a control village was included for the feasibility assessments, the general pattern of findings observed in this study is sufficiently robust to alleviate concerns about their potential spuriousness. Fifth, there might be a seasonal effect that was not observed. The prevalence of flu infections and cold is heavily affected by seasonality and the pilot was conducted in the summertime in China, during which the prevalence of the common cold was expected to be lower, which might have led to a lower rate of household antibiotic storage and unsupervised use. However, the aim of the feasibility study was to assess the likelihood of the proposed intervention to be feasible, acceptable and appropriate to Chinese rural villages; therefore, seasonality

was not a relevant consideration when implementing the pilot. Sixth, we found a high proportion of residents in the rural villages had employment outside their village and were only home during the weekends. As such, most of the assessment activities had to take place on the weekends, which might have had critical implications to budgeting of evaluation time and resources for the full trial. Seventh, validated tools for the take-back programmes are rarely available. As such, question items included in this project were identified from available publications on similar activities, such as the American Medicine Chest Challenge (AMCC) and other prescription drugs disposal programmes to address key variables, including disposal, storage, and awareness. Nonetheless, feasibility assessment results regarding the quantity of antibiotics returned, prevalence of self-medication with and household storage of antibiotics, awareness of the risks of unsupervised use of antibiotics and unsafe disposal, and the willingness of residents to respond to surveys regarding antibiotic use were informative for the design of a larger study. Eighth, it should be mentioned that the bartering market was a free service and the costs incurred for the pilot project were low - on average RMB10-12 per box of antibiotics and a very small incremental increase for the labour and time involved by the implementors. For a larger trial of multiple centres with a longer duration, honorariums might be appropriate for the implementors and survey respondents to recognise their commitment and contribution to the project. Ninth, as shown in our data, China is a vast country with great regional disparity. The site for the pilot study was located in Zhejiang province, a well-developed province whose residents generally share a higher awareness of the issues of environmental protection compared to other Chinese provinces with lower provincial GDP ranking; as such, the design, implementation, and feasibility evaluation findings from this pilot study (i.e. health education messages combined with antibiotic take-back programme) might not be

generalisable to rural areas in provinces with fewer resources or human capital. Tenth, the small sample and use of one site for the feasibility study may seem to limit the generalisability of the results. Because data were collected from a representative sample of rural Chinese residents in the participating site, representing 5.5% (50/916) of the households, and from a control site (11.2%, 50/447) at three different time points, the general pattern of findings observed in this study is sufficiently robust for a feasibility study to alleviate concerns about potential spuriousness. Lastly, the rural setting in which the pilot study was conducted was a "small world" where nearly everybody knows the chairwomen of the Women's Federation personally. In the anonymous setting of an urbanized area, people might be less willing to cooperate and to allow an evaluator to enter their homes for interviews and to investigate their medicine cabinet. As such, a formal acceptability assessment may be needed in other settings; even so, I do not anticipate significant differences in the household storage practices of people living in a big city.

From a public health perspective, the aim of this intervention is well-aligned with a newly emerging focus on ecopharmacovigilance (EPC), which aims to minimise the environmental risks posed by pharmaceutical residues and the need to guard against and control pharmaceutical pollution sources.[345-348] The results of this study confirm findings of previous studies in high income countries that drug take-back events have a strong potential to be an effective vehicle for decreasing the availability of prescription drugs (including antibiotics) for potential misuse in communities nationwide. Further research into this type of intervention seems warranted and should provide insight into its effectiveness in reducing unsafe medication use, intoxications, and waste.

9.5 Implications

Antibiotic use in community accounts for a significant part of the overall human use. In China, about half of antibiotic prescriptions take place at outpatient settings.[356] In Chapters four to six, we found that the health care consumers might be responsible for as high as 60% or 40% of community use (with or without prescription) for acute upper respiratory tract infections (URTIs) in adults and children, respectively. Compared with the estimate regarding university students,[45] parents appeared to be more cautious, but still drove 40% of antibiotic misuse in children. 7.7% of Chinese parents admitted to having asked doctors for antibiotics for paediatric URTIs, which is similar to what has been reported in some European countries.[357] Previous studies have shown that as high as 50% of the antibiotic prescriptions for URTIs were unnecessary.[356,358,359] Overuse of medical care for self-limiting illnesses combined with a high prescription rate and the population size of the country drove the high overall antibiotic consumption in China. Chinese children are particularly vulnerable. In our data, about 77.3% of children with common cold symptoms in the past month sought care, which was more than twice as many as those in UK (34-40%),[272] while the possibility of receiving an antibacterial prescription for such symptoms was around 33% in UK,[273,274] compared to 53% in our survey. As such, we estimated that an average Chinese child consumes more than three times the amount of antibiotics than is taken by their peers in UK or other European countries.[273,275-277] The gap is even wider for Chinese children in infancy and early childhood, as they have higher usage of medical care than older children. This estimate is alarming considering non-prescription use antibiotics in Chinese children was not included in this estimation. Our data indicates one in four Chinese children (n= 2,464, 25.9%) has self-medicated with antibiotics at least once in the past year - either for prevention use or treating minor ailments - which is 8-10 times

higher than that of the United States and some European countries.[153,275-277] The true magnitude of this problem is underestimated because repeated use was not included in the calculation. This estimate is consistent with a survey conducted in 1995 and demonstrates that Chinese parental antibiotic misuse for their children has not improved over the past two decades.[278] However, as shown in chapter three, as of 2019 there was not a public-target intervention addressing unsupervised use of antibiotics in the community in China or other low- and middle-income countries (LMIC), apart from a policy ban on over-the-counter purchases, which has had very limited impact in China. Even in high income countries, I have found very few interventions that addressed factors that drove antibiotic demand in community settings.

Therefore, the proposed pilot intervention to remove expired, unwanted, or unused (EUU) antibiotics from households was not only one of the first in China, but also in the LMIC. Evidently, the review findings in chapter two and survey data reported in chapters four to six have demonstrated that unnecessary and inappropriate use of antibiotics in China has been driven by a complex set of factors on both sides of the health care system for decades and has been embedded in the local culture of health care; as such, this PhD project aimed to develop and feasibility-test an evidence-based, context-tailored, community-based behavioural change intervention that can be integrated as a component in a complex intervention simultaneously targeting all factors of unnecessary and inappropriate use. The concept of such a complex intervention has been presented as a proposal of a 30-township community-based cluster-randomised trial in chapter one (1.8. Joint Global Health Trial (JGHT)). According to the review in chapter three, there were only a limited number of community-based intervention trials targeting the demand-side - the patients or the public in the United States,[103,360] and none in LMIC.

9.5.1 Implications for implementation research

To date, research reporting has mainly focused on effectiveness of interventions rather than the process of identifying and developing key components and the parameters within which they operate. Such lack of detail in the "contexts" and "mechanisms" that determine the effectiveness of interventions make replication and adaptation difficult, as it is hard to judge "what works for whom, in what contexts", and why and how.

This thesis explains study methodologies and explicit steps I undertook in intervention design, development and adaptation, and evaluation prior to piloting, and enables examination of any modifications and improvements I might make to the intervention design between feasibility and effectiveness studies. It contributes to the growing body of evidence in implementation research, which seeks to understand not only what is and isn't working, but how and why implementation does or does not work, and how to improve it. The iterative synthesis process defined in the work stream plan provides a method for the development of future complex interventions in the community using a theoretical framework and implementation research procedures combined with empirical findings from existing evidence and primary research. The model of implementation capital mapped out resources required to activate and operationalise the knowledge translation process. This study contributes to implementation science, an emerging field that has a great demand to address a critical knowledge gap. The INDEX study ('IdentifyiNg and assessing different approaches to DEveloping compleX interventions) has been funded by MRC to produce guidance on intervention development. In mid-2019, INDEX reported a systematic review of approaches to intervention development, which had identified the range of approaches available, and instructed how to synthesise the actions within these approaches. These efforts will help researchers to unpack effective

interventions that have been assessed and validated, develop complex interventions, and inform future guidance on intervention development.[361]

9.5.2 Implications for AMR research

Individual's health decisions are not entirely driven by their cognitive and rational characteristics. Contextual factors – including access to antibiotics and interpersonal connections – are equally or more critical to healthcare decision-making processes. Across China, among the educated (chapter 7 – survey data on university students) and less educated (chapters 2 and 8 – formative data on rural residents) alike, there exists a high level of awareness of the danger of AMR, which might have been the fruitful result of the Chinese government's recent AMR awareness campaign. Yet, alarmingly, evidence showed that such awareness did not translate into prudent antibiotic use. Such a phenomenon might be explained by two possible reasons. First, there exists an externality associated with antibiotic use for treating infections: despite a high awareness of AMR, the risks AMR imposes on others are unlikely to be felt directly or immediately by either the consumer or the supplier of treatment. Second, individuals use non-rational strategies to manage risk and uncertainty: in particular, when information or time is limited and the complexity of the situation is overwhelming, individuals often combine rationality with other sources of so-called tacit or experiential knowledge and utilise strategies such as trust, intuition, and emotion to assist decision-making.[238] As such, a blanket awareness campaign on prudent antibiotic use is insufficient to enable the desired behavioural change; an intervention has to include actionable knowledge that cues people to act. My findings are supported by a recent assessment of the public-funded antibiotic awareness campaigns (AAC) conducted since 2010.[309] The authors came to a similar conclusion that there has been limited evidence demonstrating the effectiveness of antibiotic awareness campaigns and that the adaptation of these

campaigns to local context was not systematic.[309] Key messages of future antibiotic awareness campaigns should be based rigorously on "scientific evidence, context specificities and behavioural change theory."[309]

Considering evidence from both rational and irrational strategies for health decision-making, the behavioural theories can be used to explain and predict antibiotic use and to inform behavioural change strategies that aim to reduce inappropriate use. Finally, heterogeneity exists in the "domain" of knowledge about antibiotics and its relationship with antibiotic practices for URTIs. Therefore, the common current practice of grouping multiple aspects of antibiotics- or AMR-related knowledge, attitudes and beliefs, and even practices into one score might not fully capture the complexity of their various associations with antibiotic use behaviours. Future research should explore various aspects of antibiotics- or AMR-related knowledge separately with respect to associated antibiotic use behaviours within the given context so as to inform AMR strategy.

The proposed intervention tackles antibiotic use behaviours that are un-explored or underexplored in both the literature and existing antibiotic stewardship programmes, specifically antibiotic use in the community which includes household storage of antibiotics and self-medication. It aimed to create an environment where household storage of antibiotics for self-medication and unsafe disposal are viewed negatively as irresponsible behaviours and are associated with adverse impacts on the health of humans, the community and the environment. By removing easy access to antibiotics from a household, we reduce the likelihood of self-medication with antibiotics without professional advice. However, similar to prescription drug take-back programmes in Europe and the United States, the intervention itself will not address all the fundamental root causes of overuse and misuse. I recognise that the intervention leaves the sources of household antibiotics –leftover antibiotic

prescriptions and over-the-counter purchases – largely unaddressed. To fully tackle the issue of inappropriate use of antibiotics at community level in China and other LMICs that face similar challenges, other avenues to unnecessary antibiotics must be addressed. The proposed intervention can inform a critical component of a multifaceted intervention that addresses all drivers of antibiotic misuse in the community, including at the population, regulatory, and policy levels.

9.5.3 Implications for AMR strategy in China

We conclude that prior successful experiences with antibiotics, including request of antibiotic prescription or self-medication with antibiotics, have largely contributed to antibiotic demand in China. After decades of excessive prescription of antibiotics - driven by financial incentives for the hospitals and prescribers[362] - the general public in China have "learned" to use antibiotics for self-limiting illnesses despite the fact that clinical conditions do not require them. This phenomenon further compounded - through easy access to antibiotics (with or without prescription) - the current tense doctor-patient relationship environment in China where workplace violence against healthcare professionals is frequently reported.[363,364] It also highlighted the inadequate diagnostic capacity of the prescribers and demonstrated that China's stewardship programmes, which mainly aim to change prescribing behaviours, have limited impact. The newly released BMJ review[44] on China's 10-year effort towards health reform highlighted the urgency of tackling the inappropriate use of antibiotics in primary care or rural settings, where most antibiotic use takes place. In 2015, Public Health England released a comprehensive literature review assessing the available evidence to support behavioural-science-based interventions that have the potential to drive more effective and sustained behaviour changes for reducing the risk of antibiotic resistance.[365] Lord Jim O'Neill suggested that tackling unnecessary antibiotic use

requires interventions that reach the general public. Interventions addressing the supply and demand sides of the health system are most likely to be effective in reducing antibiotic misuse and resistance in the community. In the context of China, this implies community-level complex interventions that simultaneously: (1) enhance clinical diagnostic and dispensing capacities, (2) improve clinician/parent communication, (3) dispense antibiotics by doses to reduce leftover antibiotics, (4) provide clinicians/pharmacists with alternate treatment actions that have the best chance of reducing antibiotic prescriptions in primary care for URTIs, (5) enforce regulations on over-the-counter purchases, (6) increase public awareness of the associated danger on human and environmental health, (7) improve the norms around self-medication and unsafe disposal of antibiotics, and (8) provide platforms to remove expired, unwanted, or unused (EUU) antibiotics from households. As a next step, research should focus on further optimising and testing feasibility of interventions that address unnecessary or inappropriate demand. It should prioritise the assessment of the design and development of each intervention component that contributes to an evidence-based, context-tailored complex intervention. Specifically, one should examine the (1) appropriateness and effectiveness of public education messages on safe use and disposal of antibiotics, (2) engagement and dissemination strategies that are tailored to different sub-communities in the Chinese context including the elderly, parents, migrants, and young adults, etc., and (3) adaption of the antibiotic take-back programme to the local context leveraging *implementation capital*. Interventions that foster effective communication between prescribers and consumers about prudent antibiotic use will help reduce unnecessary prescriptions, as well as requests of antibiotics from patients. Such interventions will also empower prescribers to adhere to clinical guidelines and make a prescribing decision based on their professional assessment. Each component of the complex

intervention should be tested for feasibility and acceptability, ideally before a full-scale randomised controlled trial of the complex intervention takes place. A pilot trial of a smaller scale should also be implemented to test effectiveness.

On a longer term basis, there is little evidence regarding the impact of optimised antibiotic use on rates of AMR in the community to date – a critical evidence gap in the field. Guillemot et al (2001, Pediatrics) and Belongia et al (2005, Clin Infect Dis) showed behavioural change interventions that last only several months might not be sufficient to show an impact on resistance rates. A multifaceted intervention that addresses both supply- and demand-side factors of antibiotic misuse in China is urgently needed. Findings from this thesis informed the design of a multi-year, community-based, multi-level behaviour change intervention, where each component of the trial is tailored to the social,[33] healthcare,[37] and political[355] context and has robust theoretical foundations for its mechanism of action. The proposed complex intervention has four components – (1) reduce pharmacy non-prescription sales, (2) improve hospital dispensing, (3) institute community recycling and health education, and (4) enforce doctor training and stewardship policies – which aim to remove the barriers at the structural, community, and individual levels that result in inappropriate antibiotic use in the community.

CONCLUSIONS

Following a theory-based work stream plan, I successfully integrated multiple studies into a critical synthesis of evidence to inform the development of a community-based behaviour change intervention. The formative procedures conducted for the development of the intervention consist of a combination of qualitative and quantitative data collection and analysis methods laid out from Aim 1 to Aim 4. Each aim allowed me to specify what the components should be as well as how they should be adapted to target population, suitable context, and potential pathways which they would be expected to work through for behavioural change. The review of assessed community-based behavioural interventions under Aim 1 allowed me to identify key programme parameters for cross-cultural adaptation, whereas the secondary data analyses of population surveys under Aim 2 aided in the identification of modifiable risk factors and helped pinpoint and prioritise key features relating to local perceptions and behaviours about antibiotics and treatment of self-limiting illnesses especially URTIs. Behavioural models including the Health Belief Model and Social Ecological Model were used to inform the conceptual framework to guide this study, especially the review findings and quantitative data analyses to identify risk factors for antibiotic use, which contributed to informing the elements in the feasibility study and process evaluation. Aim 3 developed theoretical models for evidence-based knowledge translation and established a collaborative partnership with local stakeholders of the potential pilot site. The qualitative approach supported theory generation, interpretation of quantitative findings, and allowed solutions to arise out of the data, therefore suggesting strategies that might be particularly effective with the target audience. The mixed-methods approach of the feasibility study in Aim 4 aided in better adapting the interventions to local conditions, which will lead to effectiveness in changing health behaviours for better outcomes. A showcase of the preliminary findings was awarded the best presentation at the Medical Research Foundation (MRF) National PhD Training Programme in Antimicrobial Resistance Research in August 2018. Findings from this study have successfully informed the design and development of a proposal for a multi-level, community-wide complex intervention to reduce inappropriate antibiotic use and antimicrobial resistance in Zhejiang province in China.

APPENDIX I. LETTER OF SUPPORT

ZHEJIANG UNIVERSITY
HANGZHOU 310058, CHINA

SCHOOL OF PUBLIC HEALTH

October 22, 2018

Department of Public Health, Environments and Society
Faculty of Public Health and Policy
London School of Hygiene & Tropical Medicine

Re: Confirmation of Collaboration with Leesa Lin and Permission of Data Use

We are pleased to provide this letter for Leesa Lin. We are writing to confirm our support of her proposed doctoral project as stated in her upgrading report. Ms. Lin has shared a preliminary copy of the report with us as an instrument of communication while we discuss the collaboration.

Zhejiang University has a strong track record of working with UK and US institutes such as University College London, Wellcome Trust, Harvard University and Yale University. Ms. Lin and our team have worked closely on two large-scale population surveys investigating antibiotic use behaviours of:

- university students (status: complete, sample size: 11,192),
- parents of children aged 0-13 (status: complete, sample size: 10,256.)

We have agreed to offer the said data to Ms. Lin to achieve Aim 2 where Ms. Lin will assess surveyed populations' medical decisions in relation to antibiotic use and treatments for the common cold. Findings from Aim 2 will be used to inform the development of an evidence-based, context-appropriate behavioural intervention to reduce inappropriate use in the community in China. We agree that Ms. Lin will be the first author of the manuscripts generated from the proposed analyses – one per dataset focused on medical decisions - and Zhejiang University will provide feedback on manuscripts when they are drafted and have co-authorship. The final author list will be agreed upon prior to publication according to contributions. In principle the following author list has been agreed as a starting point: Lin, xxx, xxx, Fearon, Zhou*, Hargreaves.

For the proposed field work under Aim 3, Zhejiang University would obtain an Institutional Review Board approval in compliance with local ethics guidelines and support the proposed activities, including facilitating the recruitment of project participants and collection of data according to the design.

We are interested in testing the effectiveness of Ms. Lin's proposed intervention and piloting the protocol developed under Aim 4 in addressing the challenge of antibiotic misuse in the Chinese communities. However, there is currently no plan and no timeline for doing so.

Should you have any questions, please do not hesitate to contact me at: zhouxudong@zju.edu.cn

Sincerely,

[redacted]

Xudong Zhou, Ph.D., Associate professor
Zhejiang University Institute of Social Medicine and Family Medicine
866 Yuhangtang Road, Hangzhou 310058, China
Email: zhouxudong@zju.edu.cn
Tel: +86 571 88208221

APPENDIX II. SAMPLE HEALTH EDUCATION MATERIALS

poster (I) – antibiotic literacy:

Attention!!!

The drugs above are all antibiotics. You should not use them without professional guidance nor store them at home. Keeping antibiotics at home is associated with an increased risk of self-medication with antibiotics; irresponsible disposal of antibiotics leads to environmental pollution.

Please bring your household antibiotic stock to the antibiotic take-back site in the village. In exchange, you will receive a small household item provided by Zhejiang University for your participation and support.

[*Developed by Zhejiang University Research Team on Prudent Antibiotic Use]

(b) poster II: care management for children with the common cold or flu

Do not give antibiotics to children for the common cold or flu.

Please consult your doctor regarding how to alleviate the cold symptoms experienced by your children.

Please do not ask doctors for antibiotics (oral antibiotics or IV)

Antibiotics are not effective to treat the common cold, to alleviate cold symptoms, or to expedite cold recovery, caused by a virus. Rather, antibiotics might have an adverse impact on children's health. The best tips for getting over the common cold are to drink plenty of fluids and get plenty of rest.

[*Developed by Zhejiang University Research Team on Prudent Antibiotic Use]

(c) pamphlet: prudent use of antibiotics

• Antibiotics can save lives, but not a cure all • If you don't use antibiotics responsibly, not only does it not benefit your children, but might have an adverse impact • Antibiotics can be effective for bacterial infections, but not for viral infections • Antibiotics can eliminate bacteria, but not virus. • When children are sick, antibiotics are not the only option. If it is necessary to use antibiotics, IV is saved for more severe cases.	Please let doctors determine children's antibiotic use. Please do not ask doctors for antibiotics (oral antibiotics or IV)	Please use antibiotics responsibly. You should learn antibiotic literacy. Please do not give antibiotics to children for the common cold or stuffy/runny nose.

[*Developed by Zhejiang University Research Team on Prudent Antibiotic Use]

APPENDIX III. SAMPLE TRAINING MATERIAL*

Manual on prudent antibiotic use	**Table of Contents**
Protect your own health. Please use antibiotics responsibly. Edited by the National Health Commission Peking University Medical Press	1. What are antibiotics? 2. How to recognise antibiotics? 3. What is inappropriate use of antibiotics? 4. Why do antibiotics lose their efficacy? 5. The damage of antibiotic abuse 6. What to do? 7. What not to do?

[*Developed by Zhejiang University Research Team on Prudent Antibiotic Use]

APPENDIX IV. ETHICS APPROVAL

The primary objective of this PhD study was to develop a behavioural intervention to reduce inappropriate antibiotic use in the community, and the purpose of the stakeholder interviews is to test its feasibility, appropriateness and acceptability in the local context. Therefore, no sensitive, private data were collected.

Ethical approval for various research activities was granted by Zhejiang University and then by the London School of Hygiene and Tropical Medicine:

Aim 2:

- Local approval for primary data collection by the School of Public Health Zhejiang University:
  - on university students: Reference number ZGL20160922 on 15th September 2015.
  - on parents of young children: Reference number ZGL201706-2 on 23rd June 2017.
- UK approval for **secondary data analysis** by London School of Hygiene and Tropical Medicine:
  - LSHTM Ethics Ref: 14678 on 12th March 2018.

Aims 3 and 4:

- Local approval for **primary data collection** by the School of Public Health Zhejiang University:
  - Qualitative study on factors influencing antibiotic use in China: Reference number ZGL201812-2 on 3rd January 2019
  - Pilot feasibility study on improving antibiotic use and disposal of rural residents in China through take-back of unused antibiotics: Reference number ZGL201901-1 on 29th January 2019
- UK approval for primary data collection by London School of Hygiene and Tropical Medicine
  - LSHTM Ethics Ref: 16261 on 17th May 2019.

Zhejiang University School of Public Health – Medical Ethics Committee

Scientific Research Project Ethics Review Application Form

ZUSPH Ethics Review No. *[ZGL201706-2]*

Name of Project	Knowledge, behaviours and their determinants of antibiotic use among parents of young children					
Applying Department	Department of Social Medicine	Project leader: ZHOU Xudong				
		Participating researchers: PENG Dandan				
Submitted Materials	Scientific Research Project Ethics Review Application Form ■ Problem Notification Form ☐ Research Plan and Project Summary ■ Informed Consent Form ■ Accompanying instructions ☐					
Review Assessment	Investigator eligibility: Meets national criteria ■ Does not meet criteria ☐				Resources: Self-funded	
	Means of obtaining Informed Consent Form: Appropriate ■ Inappropriate ☐					
	Experimentation plan: Appropriate ■ Inappropriate ☐					
Ethics Committee Member Names And Signatures	Name	Signature	Name	Signature	Name	Signature
	SHI Weixing		JIN Yongtang	*[signature]*	ZHU Shankuang	
	SHEN Yi	*[signature]*	XIA DAjing		WANG Wei	
	YE Huaizhuang		Song Yongxin			
Results:	Of the _2_ people who attended, _2_ people voted as follows: _2_ votes to approve; _0_ votes to approve after corrections(s); _0_ votes to reconvene and reassess after correction(s); _0_ votes to reject.					
Review Decision	Approve	Approve with minor changes	Reconvene and reassess after changes	Reject		
	✓					

Reviewer(s) comments:

Agree to implement.

Committee Chair (signature): *[signature and red-ink stamp]*

Zhejiang University School of Public Health – Medical Ethics Committee (seal):

June 23, 2017

List of Medical Ethics Committee Members, Zhejiang University School of Public Health

Ethics Committee position	Name	Sex	Specialty	Position	Work unit
Chair	SHI Weixing	Male	Medical ethics	Professor	Zhejiang University School of Public Health
Vice-chair	JIN Yongtang	Male	Occupational health and environmental hygiene	Professor	Zhejiang University School of Public Health
Committee member	ZHU Shankuan	Male	Nutrition and food hygiene	Professor	Zhejiang University School of Public Health
Committee member	XIA Dajing	Female	Health toxicology	Professor	Zhejiang University School of Public Health
Committee member	WANG Wei	Male	Mental illness and mental health	Professor	Zhejiang University School of Public Health
Committee member	SHEN Yi	Male	Medical statistics	Professor	Zhejiang University School of Public Health
Committee member	YE Huaizhuang	Male	Health inspection	Professor	Zhejiang University School of Public Health
Committee member	Song Yongxin	Male	Jurisprudence	Professor	Hangzhou Zijin Community

[red-ink stamp]

Secretary: MENG Fei

Address: Zhejiang University School of Medicine, Multifunctional Building 807 (866 Yuhang Tang Road, Hangzhou City, Zhejiang Province 310058)

Phone: 0571-88981319

Fax: 0571-88208099

Page Redacted

浙江大学公共卫生学院医学伦理委员会委员名单

伦理委员会职务	姓名	性别	专业	职称	工作单位
主任	施卫星	男	医学伦理学	教授	浙江大学公共卫生学院
副主任	金永堂	男	劳动卫生与环境卫生学	教授	浙江大学公共卫生学院
委员	朱善宽	男	营养与食品卫生学	教授	浙江大学公共卫生学院
委员	夏大静	女	卫生毒理学	教授	浙江大学公共卫生学院
委员	王伟	男	精神病与精神卫生学	教授	浙江大学公共卫生学院
委员	沈毅	男	医学统计学	教授	浙江大学公共卫生学院
委员	叶怀庄	男	卫生检验学	教授	浙江大学公共卫生学院
委员	宋永新	男	法律学	教授	杭州紫金社区

浙江大学公共卫生学院 医学伦理委员会

秘　　书：孟菲

地　　址：浙江大学医学部综合楼 807 室（浙江省杭州市余杭塘路 866 号　310058）

联系电话：0571-88981319

传　　真：0571-88208099

Zhejiang University School of Public Health – Medical Ethics Committee

Scientific Research Project Ethics Review Application Form

ZUSPH Ethics Review No. *ZGL20160922*

Name of Project	New media as interventions to improve prudent antibiotic use among university students nationwide					
Applying Department	Department of Social Medicine	Project leader: ZHOU Xudong				
		Participating researchers: WANG Xiaomin, PENG Dandan, WANG Weiyi				
Submitted Materials	Scientific Research Project Ethics Review Application Form ■ Problem Notification Form ☐ Research Plan and Project Summary ■ Informed Consent Form ■ Accompanying instructions ☐					
Review Assessment	Investigator eligibility: Meets national criteria ■ Does not meet criteria ☐			Resources: Self-funded		
	Means of obtaining Informed Consent Form: Appropriate ■ Inappropriate ☐					
	Experimentation plan: Appropriate ■ Inappropriate ☐					
Ethics Committee Member Names And Signatures	Name	Signature	Name	Signature	Name	Signature
	SHI Weixing		JIN Yongtang	*[signature]*	ZHU Shankuang	
	SHEN Yi	*[signature]*	XIA DAjing		WANG Wei	
	YE Huaizhuang		Song Yongxin			
Results:	Of the _2_ people who attended, _2_ people voted as follows: _2_ votes to approve; _0_ votes to approve after corrections(s); _0_ votes to reconvene and reassess after correction(s); _0_ votes to reject.					
Review Decision	Approve	Approve with minor changes	Reconvene and reassess after changes	Reject		
	✓					

Reviewer(s) comments:

Approve.

Committee Chair (signature): *[signature and red-ink stamp]*

Zhejiang University School of Public Health – Medical Ethics Committee (seal):

September 15, 2015

List of Medical Ethics Committee Members, Zhejiang University School of Public Health

Ethics Committee position	Name	Sex	Specialty	Position	Work unit
Chair	SHI Weixing	Male	Medical ethics	Professor	Zhejiang University School of Public Health
Vice-chair	JIN Yongtang	Male	Occupational health and environmental hygiene	Professor	Zhejiang University School of Public Health
Committee member	ZHU Shankuan	Male	Nutrition and food hygiene	Professor	Zhejiang University School of Public Health
Committee member	XIA Dajing	Female	Health toxicology	Professor	Zhejiang University School of Public Health
Committee member	WANG Wei	Male	Mental illness and mental health	Professor	Zhejiang University School of Public Health
Committee member	SHEN Yi	Male	Medical statistics	Professor	Zhejiang University School of Public Health
Committee member	YE Huaizhuang	Male	Health inspection	Professor	Zhejiang University School of Public Health
Committee member	Song Yongxin	Male	Jurisprudence	Professor	Hangzhou Zijin Community

[red-ink stamp]

Secretary: MENG Fei

Address: Zhejiang University School of Medicine, Multifunctional Building 807 (866 Yuhang Tang Road, Hangzhou City, Zhejiang Province 310058)

Phone: 0571-88981319

Fax: 0571-88208099

Page Redacted

浙江大学公共卫生学院医学伦理委员会委员名单

伦理委员会职务	姓名	性别	专业	职称	工作单位
主任	施卫星	男	医学伦理学	教授	浙江大学公共卫生学院
副主任	金永堂	男	劳动卫生与环境卫生学	教授	浙江大学公共卫生学院
委员	朱善宽	男	营养与食品卫生学	教授	浙江大学公共卫生学院
委员	夏大静	女	卫生毒理学	教授	浙江大学公共卫生学院
委员	王伟	男	精神病与精神卫生学	教授	浙江大学公共卫生学院
委员	沈毅	男	医学统计学	教授	浙江大学公共卫生学院
委员	叶怀庄	男	卫生检验学	教授	浙江大学公共卫生学院
委员	宋永新	男	法律学	教授	杭州紫金社区

浙江大学公共卫生学院 医学伦理委员会

秘　　书：孟菲

地　　址：浙江大学医学部综合楼 807 室（浙江省杭州市西湖区塘路 866 号　310058）

联系电话：0571-88981319

传　　真：0571-88208099

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Leesa Lin
LSHTM

12 March 2018

Dear Leesa

Study Title: Antibiotic misuse in China: a secondary analysis of cross-sectional survey data

LSHTM Ethics Ref: 14678

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type	File Name	Date	Version
Protocol / Proposal	Survey_Interventions to improve antibiotic use among university students	15/09/2015	1
Protocol / Proposal	Study Protocol_Interventions to improve antibiotic use among university students ?????????????????? - ??	15/09/2015	1
Consent form	Informed Consent_University Students ?????????_EN CH	15/09/2015	1
Local Approval	IRB Approval Letter_University Students ??????????_EN CH	15/09/2015	1
Protocol / Proposal	Study Protocol_Understanding factors influencing parents knowledge and practice of antibiotic use ?????????????????????-??	23/06/2017	1
Protocol / Proposal	Survey_Understanding factors influencing parents knowledge and practice of antibiotic use	23/06/2017	1
Consent form	Informed Consent_Parents ????????_EN CH	23/06/2017	1
Local Approval	IRB Approval Letter_Parents ?????????? EN CH	23/06/2017	1
Investigator CV	CV_LEESA K LIN_201801	01/01/2018	1
Covering Letter	Clarification Request_20180301	01/03/2018	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

Additional information is available at: www.lshtm.ac.uk/ethics

Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

Medical Ethics Committee, Zhejiang University School of Public Health

Ethics Approval for Research Project

(Zhe-Da-Gong-Wei) Lun-Yan-Pi No. (ZGL201812-2)

Project Name	Qualitative Study on Factors Influencing Antibiotic Use in China					
Department of Applicant	The Institute of Social Medicine and Family Medicine of Zhejiang University	Person Responsible for Project: Zhou Xudong Participants: Leesa Lin (Harvard University), Wang Xiaomin, Lu Jingjing, Xu Yannan				
Submitted Materials	Application form for ethics review ■ Project notification form ☐ Research program and project summary ■ Informed consent form ■ Related explanations ■					
Review	Qualifications of researchers: Meets requirements ■ Does not meet requirements ☐			Funding source: Self-funded		
	Method for obtaining informed consent: Appropriate ■ Not appropriate ☐					
	Testing method: Appropriate ■ Not appropriate ☐					
Signatures of Ethics Committee Members	Name of Committee Member	Signature	Name of Committee Member	Signature	Name of Committee Member	Signature
	Shi Weixing		Jin Yongtang	[signed]	Zhu Shankuan	
	Shen Yi		Xia Dajing		Wang Wei	
	Ye Huaizhuang	[signed]	Song Yongxin			
Result	In Attendance: 2; Votes: 2 Approved 2 votes; Approved after making necessary revisions 0 votes; Revise and resubmit 0 votes; Not approved 0 votes					
Outcome	Approved	Approved after minor revisions	Revise and resubmit	Not approved		
	✓					

Review comments:

Application Approved

Committee Director (Signature): [Signed]

Medical Ethics Committee, Zhejiang University School of Public Health (Stamp):

Medical Ethics Committee, Zhejiang University School of Public Health

January 3, 2019

List of Members of Medical Ethics Committee, Zhejiang University School of Public Health

Committee Position	Name	Sex	Expertise	Job title	Employer
Director	Shi Weixing	Male	Medical ethics	Professor	School of Public Health, Zhejiang University
Deputy Director	Jin Yongtang	Male	Occupational and Environmental Health	Professor	School of Public Health, Zhejiang University
Member	Zhu Shankuan	Male	Nutrition and Food Hygiene	Professor	School of Public Health, Zhejiang University
Member	Xia Dajing	Female	Health Toxicology	Professor	School of Public Health, Zhejiang University
Member	Wang Wei	Male	Psychiatry and Mental Health	Professor	School of Public Health, Zhejiang University
Member	Shen Yi	Male	Medical Statistics	Professor	School of Public Health, Zhejiang University
Member	Ye Huaizhuang	Male	Sanitary Inspection	Professor	School of Public Health, Zhejiang University
Member	Song Yongxin	Male	Law	Professor	Zijin Community, Hangzhou

Secretary: Meng Fei

Address: Room 807, Zonghe Building. Zhejiang University School of Medicine (310058 No. 866, Yuhangtang Road, Hangzhou City, Zhejiang Province)

Telephone: 0571-88981319

Fax: 0571-88208099

Medical Ethics Committee, Zhejiang University School of Public Health

Page Redacted

浙江大学公共卫生学院医学伦理委员会委员名单

伦理委员会职务	姓名	性别	专业	职称	工作单位
主任	施卫星	男	医学伦理学	教授	浙江大学公共卫生学院
副主任	金永堂	男	劳动卫生与环境卫生学	教授	浙江大学公共卫生学院
委员	朱善宽	男	营养与食品卫生学	教授	浙江大学公共卫生学院
委员	夏大静	女	卫生毒理学	教授	浙江大学公共卫生学院
委员	王伟	男	精神病与精神卫生学	教授	浙江大学公共卫生学院
委员	沈毅	男	医学统计学	教授	浙江大学公共卫生学院
委员	叶怀庄	男	卫生检验学	教授	浙江大学公共卫生学院
委员	宋永新	男	法律学	教授	杭州紫金社区

秘　　书：孟菲

地　　址：浙江大学医学部综合楼 807 室（浙江省杭州市余杭塘路 866 号　310058）
联系电话：0571-88981319
传　　真：0571-88208099

浙江大学公共卫生学院
医学伦理委员会

Medical Ethics Committee, Zhejiang University School of Public Health

Ethics Approval for Research Project

(Zhe-Da-Gong-Wei) Lun-Yan-Pi No. (ZGL201901-1)

Project Name	Pilot Feasibility Study on Improving Antibiotic Use and Disposal of Rural Residents in China through Take-back of Unused Antibiotics					
Department of Applicant	The Institute of Social Medicine and Family Medicine of Zhejiang University	Person Responsible for Project: Zhou Xudong Participants: Zhou Xudong, Wang Xiaomin, Wang Weiyi, Lu Jingjing, Yao Tingting, Cai Jingjing				
Submitted Materials	Application form for ethics review ■ Project notification form ☐ Research program and project summary ■ Informed consent form ■ Related explanations ■					
Review	Qualifications of researchers: Meets requirements ■ Does not meet requirements ☐		Funding source: Self-funded			
	Method for obtaining informed consent: Appropriate ■ Not appropriate ☐					
	Testing method: Appropriate ■ Not appropriate ☐					
Signatures of Ethics Committee Members	Name of Committee Member	Signature	Name of Committee Member	Signature	Name of Committee Member	Signature
	Shi Weixing		Jin Yongtang	[signed]	Zhu Shankuan	
	Shen Yi		Xia Dajing		Wang Wei	
	Ye Huaizhuang	[signed]	Song Yongxin			
Result	In Attendance: 2; Votes: 2 Approved 2 votes; Approved after making necessary revisions 0 votes; Revise and resubmit 0 votes; Not approved 0 votes					
Outcome	Approved	Approved after minor revisions	Revise and resubmit	Not approved		
	✓					

Review comments:

Application Approved

Committee Director (Signature): [Signed]

Medical Ethics Committee, Zhejiang University School of Public Health (Stamp):

Medical Ethics Committee, Zhejiang University School of Public Health

January 29, 2019

List of Members of Medical Ethics Committee, Zhejiang University School of Public Health

Committee Position	Name	Sex	Expertise	Job title	Employer
Director	Shi Weixing	Male	Medical ethics	Professor	School of Public Health, Zhejiang University
Deputy Director	Jin Yongtang	Male	Occupational and Environmental Health	Professor	School of Public Health, Zhejiang University
Member	Zhu Shankuan	Male	Nutrition and Food Hygiene	Professor	School of Public Health, Zhejiang University
Member	Xia Dajing	Female	Health Toxicology	Professor	School of Public Health, Zhejiang University
Member	Wang Wei	Male	Psychiatry and Mental Health	Professor	School of Public Health, Zhejiang University
Member	Shen Yi	Male	Medical Statistics	Professor	School of Public Health, Zhejiang University
Member	Ye Huaizhuang	Male	Sanitary Inspection	Professor	School of Public Health, Zhejiang University
Member	Song Yongxin	Male	Law	Professor	Zijin Community, Hangzhou

Medical Ethics Committee, Zhejiang University School of Public Health

Secretary: SiJia Wu

Address: Room 906, Zonghe Building. Zhejiang University School of Medicine (310058 No. 866, Yuhangtang Road, Hangzhou City, Zhejiang Province)

Telephone: 0571-88208098

Fax: 0571-88208099

Page Redacted

浙江大学公共卫生学院医学伦理委员会委员名单

伦理委员会职务	姓名	性别	专业	职称	工作单位
主任	施卫星	男	医学伦理学	教授	浙江大学公共卫生学院
副主任	金永堂	男	劳动卫生与环境卫生学	教授	浙江大学公共卫生学院
委员	朱善宽	男	营养与食品卫生学	教授	浙江大学公共卫生学院
委员	夏大静	女	卫生毒理学	教授	浙江大学公共卫生学院
委员	王伟	男	精神病与精神卫生学	教授	浙江大学公共卫生学院
委员	沈毅	男	医学统计学	教授	浙江大学公共卫生学院
委员	叶怀庄	男	卫生检验学	教授	浙江大学公共卫生学院
委员	宋永新	男	法律学	教授	杭州紫金社区

秘　　书：伍思佳

地　　址：浙江大学医学部综合楼 906 室（浙江省杭州市余杭塘路 866 号　310058）

联系电话：0571-88208098

传　　真：0571-88208099

London School of Hygiene & Tropical Medicine
Keppel Street, London WC1E 7HT
United Kingdom
Switchboard: +44 (0)20 7636 8636

www.lshtm.ac.uk

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Observational / Interventions Research Ethics Committee

Ms Leesa Lin
LSHTM

17 May 2019

Dear Ms Leesa Lin

Study Title: Antibiotic misuse in China - Development of evidence-based behavioural interventions to reduce inappropriate use of antibiotics beyond clinical settings

LSHTM Ethics Ref: 16261

Thank you for responding to the Observational Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

Approval is dependent on local ethical approval having been received, where relevant.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

The committee Suggest to the PI that they do some back translation of their information and consent forms

Document Type	File Name	Date	Version
Local Approval	Ethics Approval_Antibiotic use in the community_Zhejiang University_CH	03/01/2019	1
Local Approval	Ethics Approval_Antibiotic use in the community_Zhejiang University_EN translated	03/01/2019	1
Local Approval	Ethics Approval_Zhejiang University_Feasibility Study_CH	29/01/2019	1
Information Sheet	Interview Guide_CH_022019	29/01/2019	1
Information Sheet	Interview Guide_EN_022019	29/01/2019	1
Protocol / Proposal	Study Protocol_EN_201902	29/01/2019	1
Advertisements	Recruitment emails_CH	29/01/2019	1
Advertisements	Recruitment emails_EN	29/01/2019	1
Local Approval	Ethics approval_Zhejiang University Feasibility Study_EN	29/01/2019	1
Investigator CV	CV_Leesa Lin_2019	28/02/2019	1
Information Sheet	Antibiotic use in the community_China_Zhejiang University Consent_CH.pdf	01/04/2019	2
Information Sheet	Antibiotic use in the community_China_Zhejiang University Consent_EN.pdf	01/04/2019	2
Information Sheet	Revised Consent_042019_EN_highlighted changes	01/04/2019	2
Information Sheet	Revised Consent_042019_CH_highlighted changes	01/04/2019	2
Covering Letter	Response to ethics committee_30042019	30/04/2019	1

After ethical review

The Chief Investigator (CI) or delegate is responsible for informing the ethics committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the committee.

The CI or delegate is also required to notify the ethics committee of any protocol violations and/or Suspected Unexpected Serious Adverse Reactions (SUSARs) which occur during the project by submitting a Serious Adverse Event form.

An annual report should be submitted to the committee using an Annual Report form on the anniversary of the approval of the study during the lifetime of the study.

At the end of the study, the CI or delegate must notify the committee using an End of Study form.

All aforementioned forms are available on the ethics online applications website and can only be submitted to the committee via the website at: http://leo.lshtm.ac.uk

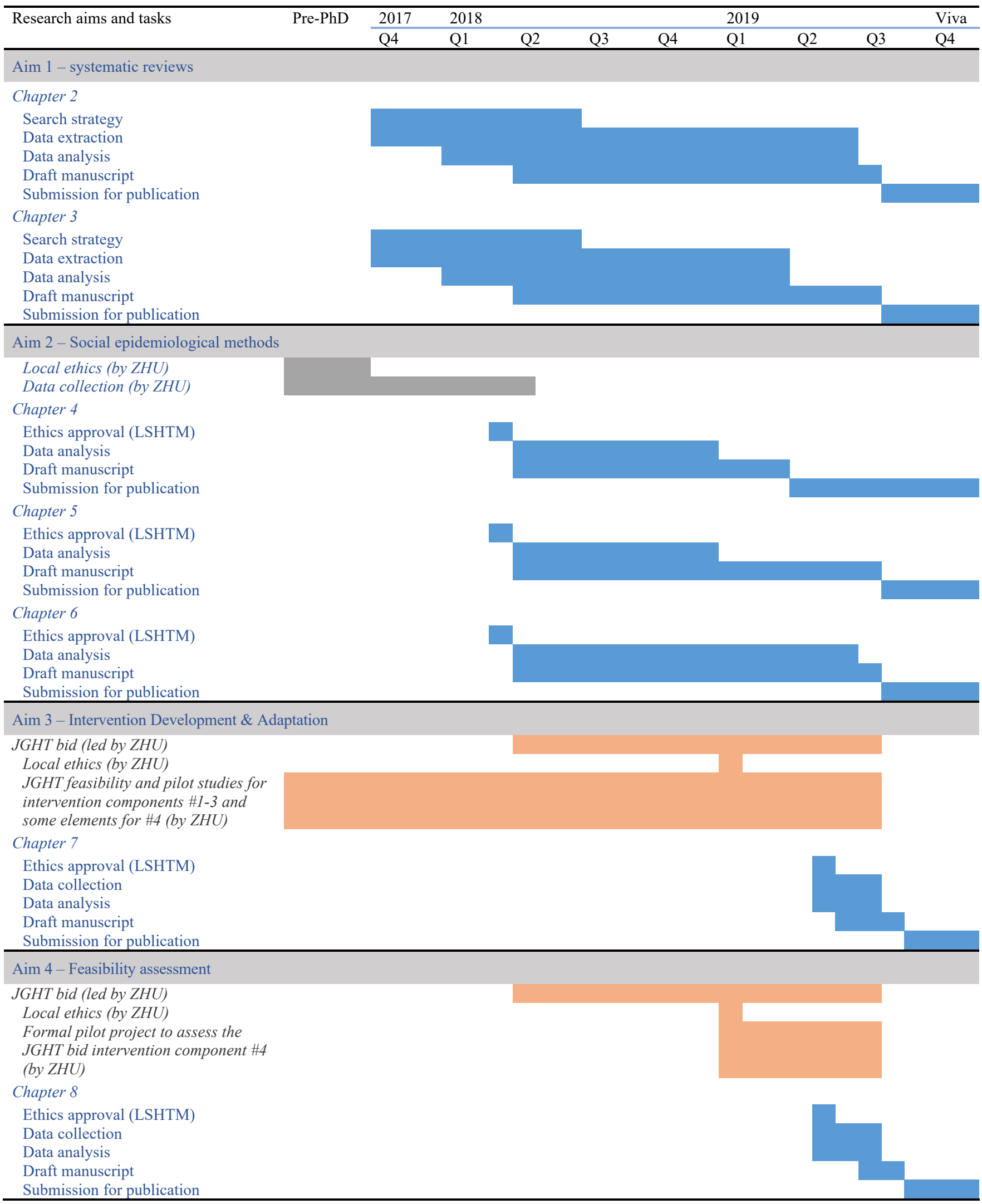
Additional information is available at: www.lshtm.ac.uk/ethics

[redacted]

Professor John DH Porter
Chair

ethics@lshtm.ac.uk
http://www.lshtm.ac.uk/ethics/

APPENDIX V. TIMETABLE



APPENDIX VI. DATA MANAGEMENT PLAN

All data files from this study have been de-identified. These files are managed, processed, and stored in a secure environment (i.e. lockable computer systems with passwords, firewall system in place, and virus/malicious intruder protection) and by controlling access to digital files with encryption and/or password protection.

Data Type	Study	Description of data acquisition	Format	Software
Literature reviews	Review of published non-clinical factors influencing antibiotic use in the community in China	Research Aim 1 – systematic literature review	Text and numerical data (.xls)	Microsoft Excel & STATA-15
	Review of quantitatively-assessed evidence-based behavioural change interventions to reduce inappropriate or unnecessary medical use	Research Aim 1 – systematic literature review	Text and numerical data (.xls)	Microsoft Excel & STATA-15
Quantitative	Large-scale cross-sectional population survey data on (a) university students and (b) parents of young children (<13-year-old)	Research Aim 2 – social epidemiological methods/secondary data analysis	Analysis (.dta)	STATA-15
	Quantitative data from the household panels and process evaluation data	Research Aims 3 & 4 – Face-to-face interviews, the bartering market usage records	Analysis (.dta)	STATA-15
Qualitative	In-depth interviews on antibiotic use in the community in the context of China	Interview notes	Form (.docx) Analysis (.nvp)	Microsoft Word Nvivo-11
	Semi-structured interviews on the feasibility and acceptability of a proposed behavioural intervention that is designed to reduce antibiotic misuse and unsafe disposal in the community	Research Aims 3 & 4 – interview notes or transcription of audio recording of stakeholders' interviews	Audio (.mp3) Form (.docx) Analysis (.nvp)	Microsoft Word Nvivo-11

APPENDIX VII. STUDY TOOLS INTERVIEW GUIDES

普通感冒用抗生素因素

[一般民众]

目的: 了解民众之于普通感冒和抗生素使用的相关医疗决策。

目标参与者: 干预小区居民. 访谈指南将根据受访者在家庭人口组成和其在家庭的角色进行调整 (例如:年幼子女的父母,多代同堂家庭).

社会人口特征

- 年龄_____
- 性别_____
- 教育水平_____
- 医疗背景_____
- 职业_____
- 每月家庭平均收入_____
- 家庭人口组成_____
- 您有孩子吗？年龄和性别 _ _ _ _ _ _ _ ？

第一部分– 自我健康管理和观点, 日常自我健康诊断和药物使用习惯

1. [自我健康认知]您如何描述您的健康状况？ 您每天做些什么来维护健康 (包括保养与调理)?
2. [药物的一般使用] 您是否定期服药或保健食品 (包括中医和维他命)？大多听谁的建议？
3. [信任] 当您觉得不舒服的时候, 您会怎么做？您去哪一家诊所？您相信医生建议吗？
4. [中医] 您对中医有什么看法？相信中医？怎么决定看西医或中医？
5. [健康咨询]如果您对您的健康有疑问, 您会去哪？[请排名反应按序列您是否信任医生、政府或家人和朋友提供的医疗保健建议？
6. [健康信息] 您通常从哪里获得健康信息？为什么？
   - 提示：您相信这些信息来源吗？微信呢？

- 提示：您是否曾分享、发送健康信息？那是什么健康信息？为什么, 如何分享、发送的?

7. [对于在家中有孩子的人] 孩子主要是谁在照顾？生病时，是谁决定怎么处里? 祖父母或其他人是否会参与孩子的医疗决定? 这和其他重要决定(例如教育) 类似吗, 还是不一样？关于孩子的健康问题，您的信息来源主要是哪里？您会和其他人谈论孩子的健康或医疗问题吗? (伴侣？朋友？家庭？教师？您最常听谁的意见？您最相信谁的意见？

社区

8. 谁是社区中有影响力或值得信赖的意见领袖？
9. 您周末还是下班后去哪里？社区成员都去哪里，聚集在哪里？
10. 您能告诉我现有的回收计划吗？您参加了吗？为什么？您认为这是什么目的？经验如何？
    - 提示：可持续回收计划的基础设施. 谁在您家里处理回收？

第二部分– 抗生素使用和常见感冒等医疗决策的社会规范

[普通感冒的自我诊断]

11. 您是否能正确诊断普通感冒的症状？如果是, 请大致描述？(注意关于"发炎"的用词)
    - 提示：
        - "我有信心, 我可以正确诊断自己的普通感冒的症状" [李克特量表, 1-7]
        - (如适用)"我有信心, 我可以正确诊断我的孩子的普通感冒的症状" [李克特量表, 1-7]
    - 提示: 如果是, 您是如何学会诊断他们？
    - 提示: 如果是, 普通感冒的症状是什么？ 一般您会怎么应对?
        - 让它自己好起来 – 为什么？会放任不管多久？
        - 寻求治疗 - 为什么？在哪里寻求治疗, 为什么？
        - 自我治疗 - 为什么？如何自我治疗, 为什么？
    - 提示: 如果没有, 如果您经历 [喉咙痛、咳嗽、鼻塞、流鼻涕、腹泻、发烧等], 您该怎么办？

- 提示: 据您所知，人们如何得到普通感冒？
- 提示: 家里其他人(如老年人或儿童)得了感冒后，怎么应对？
- 提示: 平均来说, 一年中您得几次普通感冒？

[最近一次普通感冒的经验]

12. 您最近一次感冒是什么时候？

- 提示: 谁决定怎么应对？
- 提示: 您做了什么？
    - 让它自己好起来 – 为什么？前后病了多久？
    - 寻求治疗-为什么？在哪里寻求治疗, 为什么？
        - 提示: 如果看了医生, 您去了哪里？医生做了什么？给您开了抗生素吗？您跟医生要过抗生素吗？
    - 自我治疗-为什么？如何自我治疗, 为什么？
        - 提示: 如果使用药物, 是什么药物？
        - 提示: 如果使用抗生素, 为什么？抗生素从哪来的？
- (如适用)您的孩子最近一次感冒是什么时候？

[普通感冒的管理]

13. 您会考虑其他选择吗？(例如中医？咳嗽药？观望几天？

- 提示: 如果医生告诉您, 普通感冒是一种自限性的疾病, 它自然会痊愈, 您会怎么应对？
- 提示: 如果医生建议您观察几天, 您会怎么应对？
- 提示: 如果医生没有为普通感冒开抗生素, 您会怎么应对？
- 提示: 您是否在当地药房购买了抗生素？
    - 如果是, 那是为了什么？
    - 您购买了抗生素用了处方了吗？如果是这样,处方是哪里来的？
    - 如果您不能在没有医生处方的情况下购买当地药房, 您会怎么应对？
- 提示: 在不使用 [抗生素] 的情况下, 您有没有信心自我管理普通感冒的症状？为什么？
    - "我相信我能自我处理普通感冒的症状"[李克特量表, 1-7]

- (如适用)"我相信我能自我处理我的孩子的普通感冒症状 "[李克特量表, 1-7]

[对抗生素的认知]

14. 您听说过 "抗生素" 吗？
    - 提示: 如果是, 抗生素是什么？您什么时候需要抗生素？
    - 提示: 如果是, 在哪里可以得到抗生素？抗生素的价格一般是多少？负担得起吗？

15. 这句话有什么看法: **"抗生素是消炎药"?**

16. 以下哪一项是抗生素？
    - 青霉素类药物, 如阿莫西林
    - 头孢类药物, 如头孢克洛/头孢曲松钠等
    - 非甾体药物, 如布洛芬/默林/阿司匹林等
    - 甾体类药物如地塞米松/泼尼松等
    - 喹诺酮类药物, 如氧氟沙星/诺氟沙星等
    - 大环内酯类药物, 如阿奇霉素/罗红霉素等

17. 您认为下面的语句怎么样？
    - 如果需要使用抗生素，应优先选用输液方式。
    - 病情一旦好转，应该立即停止使用抗生素。
    - 抗生素越贵越有效。
    - 新抗生素比老抗生素更有效。
    - 进口的抗生素比国产的有效。

18. 结构性因素–政策和访问:
    - 关于抗生素的销售和使用的现行政策是什么？
    - 您知道在哪里可以得到抗生素？

[使用抗生素进行自我治疗]

19. 在过去的一年里, 您有没有使用过抗生素而不先找医生？何时何地？
    - (如适用) 使用抗生素的方式与您平常服用的其他药物有不同吗？
    - 提示: 您用了哪种抗生素？为什么？
    - 提示: 您从哪儿弄来的抗生素？为什么？

- 提示: 您听从指示服用抗生素了吗？您按指示吃了整个疗程了吗？为什么？
- 提示: 您是否担心您可能服用了错误的药物？为什么？
- (如适用)在过去的一年里, 您有没有让您的孩子使用抗生素而不先找医生？为什么？您拿了什么抗生素？效果如何？
- 提示: 您 (或您的孩子) 是否经历过任何抗生素副作用不良影响？

[家中储备抗生素]

20. 您家目前是否有储备抗生素吗？
- 提示: 如果是, 请问有什么抗生素 [药物名称]?
- 提示: 如果是, 为什么？
- 提示: 如果是, 您在哪里买的？为什么？
- 提示: 如果是, 如何储备抗生素？
- 提示: 如果是, 您曾经给过别人抗生素吗？是什么抗生素? 和谁？为什么？结果如何？
- 提示: 如果是, 您是否在某个时候处理[丢弃]掉抗生素？如果是, 怎么处理的？为什么？
- 提示: 如果是, 并且使用过, 您怎么使用家中储备的抗生素？您怎么知道该怎么做？经验如何？
- 提示: [干预] 如果是, 如果政府鼓励 "回收"储备抗生素, 您会参加吗？您觉得怎么样？为什么？您认为政府为什么要 "回收" 抗生素？

[最近使用抗生素的经验]

21. 您最后一次服用抗生素是什么时候？
- 提示: 您用了什么抗生素？
- 提示: 为了什么目的？
- 提示: 您从哪儿弄来的抗生素？为什么？
- 提示: 如果您不能从当地药房得到它, 您会怎么应对？为什么？
- 提示: 您听从指示服用抗生素了吗？您完成整个疗程了吗？为什么？
- 提示: 您是否经历过任何副作用？

[抗生素耐药细菌认知]

22. 您听说过 "抗生素耐药性细菌" 这个词吗？如果是, 那是什么？听说了什么？

23. 您同意下列任何一项声明吗？

- 过度使用抗生素是中国的一个严重问题。
- 抗生素有效治疗病毒感染。
- 抗生素是有效的治疗细菌感染。
- 人们使用的抗生素越多, 以后治疗的难度就越大。
- 过量使用抗生素会导致细菌对抗生素产生抗药性。
- 中国的抗生素耐药性将是一个严重的问题。

[风险感知-感知严重性和感知敏感性]

24. 风险感知–

- 您认为您或您的家人会有多大可能感染上耐药性细菌感染？[李克特量表, 1-7]
- 您认为您社区里的人有多有可能感染上耐药性细菌感染？[李克特量表, 1-7]
- 如果您或您的家庭成员感染上耐药性细菌, 您认为会有多严重？？[李克特量表, 1-7]
- 如果您社区里的人感染上耐药性细菌, 您认为会有多严重？[李克特量表, 1-7]
- 如果自我使用抗生素, 您认为您或您的家人有多大可能会有不良反应？[李克特量表, 1-7]
- 如果自我使用抗生素, 您认为您社区里的人有多大可能会有不良反应？[李克特量表, 1-7]
- 如果自我使用抗生素, 您认为您或您的家人有不良反应的话，会有多严重？[李克特量表, 1-7]
- 如果自我使用抗生素, 您认为您社区里的人有不良反应的话，会有多严重？[李克特量表, 1-7]

[普通感冒和抗生素使用的社会规范]

25. 描述性规范–

- 如果您的朋友或邻居有普通感冒的症状, 您会给他们什么建议？您希望他们怎么应对？为什么？
- 您认为用上次使用剩下的抗生素可以吗？如果您发现您的朋友或邻居使用了剩余的抗生素, 您会怎么应对？为什么？
- 您认为向医生要求抗生素可以吗？如果您发现您的朋友或邻居问医生要抗生素, 您会怎么应对？为什么？
- 您认为用抗生素治疗常见的感冒症状可以吗？如果您的朋友或邻居用抗生素治疗感冒症状, 您会怎么应对？为什么？
- 当您感觉好些的时候, 您认为停止服用抗生素可以吗？如果您的朋友或邻居在感觉好些的时候停止服用抗生素, 您会怎么应对？为什么？

26. 限制性规范-

- 当您遇到感冒的症状时, 您的朋友或邻居会怎么反应？
- 当您有剩余的抗生素时, 您认为其他人希望您怎么处理？如果您使用剩余的抗生素, 您的朋友或邻居会如何反应？
- 如果您的朋友或邻居得知您向医生索取抗生素, 您会如何反应？
- 如果您的朋友或邻居得知您使用抗生素自我治疗感冒症状, 您会如何反应？
- 如果您在感觉好些的时候停止服用抗生素, 您的朋友或邻居会如何反应？

抗生素用于普通感冒-抗生素回收

利益相关者采访

目标：

- 理解可能干预措施的背景
- 评估可能干预措施的可接受性和可行性

目标参与者: 可能的干预站点中的利益干系人

1. 政策执行者 (如当地政府官员)
2. 干预执行者 (如妇女联合会)
3. 其他利益相关者 (如社区药房)
4. 目标人群 (如一般公众)

注意: 该指南可能根据利益干系人类型和相关性进行修改调整

.

社会人口特征

- 年龄_____
- 性别_____
- 教育水平_____
- 医疗背景_____
- 每月家庭平均收入_____
- 您有孩子吗？年龄和性别 _ _ _ _ _ _ _ ？
- 单位_____
- 职位_____
- 服务年限_____

单位

1. 请问您的单位主要负责什么业务、主要的工作内容、和优先事项是什么？
2. 您在这个单位中的角色是什么, 您主要的工作内容、和优先事项是什么？

抗生素的认知

1. 关于抗生素的销售和使用的现行政策是什么？
2. 您听说过 "抗生素耐药性" 吗？如果是, 那是什么？
3. [风险感知]-
   - 您认为您或您的家人会有多大可能感染上耐药性细菌感染？[李克特量表, 1-7]
   - 您认为您社区里的人有多有可能感染上耐药性细菌感染？[李克特量表, 1-7]
   - 如果您或您的家庭成员感染上耐药性细菌, 您认为会有多严重？？[李克特量表, 1-7]
   - 如果您社区里的人感染上耐药性细菌, 您认为会有多严重？[李克特量表, 1-7]
   - 如果自我使用抗生素, 您认为您或您的家人有多大可能会有不良反应？[李克特量表, 1-7]
   - 如果自我使用抗生素, 您认为您社区里的人有多大可能会有不良反应？[李克特量表, 1-7]
   - 如果自我使用抗生素, 您认为您或您的家人有不良反应的话，会有多严重？[李克特量表, 1-7]
   - 如果自我使用抗生素, 您认为您社区里的人有不良反应的话，会有多严重？[李克特量表, 1-7]
4. 您认为下面的语句怎么样？为什么？
   - 抗生素过度使用在中国是个严重的问题。
   - 抗生素耐药在中国将会成为一个严重的问题。
   - 人们使用抗生素越频繁，以后细菌感染就越难治好。
   - 过度使用抗生素会使细菌会对抗生素产生耐药性。
   - 如果不合理使用抗生素，将来有效的抗生素将越来越少。

健康教育信息评估

[提交健康教育信息]

5. 您觉得这文章/海报主要在说什么？
   - 提示： 您有什么反馈？

- 您最喜欢哪种格式？文章、海报、微信？
- 提示：您会分享这个 [健康信息] 吗？怎么分享和为什么？
- 提示：您会和谁分享这个 [健康信息]？怎么分享和为什么？
- 提示：如果您的医生和您分享这个[健康信息], 您会怎么应对？如果是当地的 CDC/亲戚/邻居/直系亲属呢？

可能行为干预的内容:

6. 谁是社区中有影响力或值得信赖的意见领袖？
7. 您通常从哪里获得健康信息？为什么？您相信这些信息来源吗？微信？
8. 您能告诉我关于现有的回收程序？
   - 您自己家里参与了吗？为什么？您认为这是什么目的？经验如何？
   - 目前社区内回收项目的基础设施程序
   - 您/您的机构是否参与抗生素 "收回"程序如果有的话？为什么？
   - 如果该现有回收程序要包括抗生素, 您认为原因是什么？您会参加吗？为什么？
   - 预期可能成本?

可行性

9. [可行性和可接受性] 想问问您的意见, 将现有回收计划纳入抗生素, 您觉得如何? 能与现行计划良好结合吗？可持续性？有这个需求吗?
10. [可实施性和实用性] 如果我们要实施一项健康教育运动, 鼓励抗生素 "回收" 您觉得可行吗?可以被小区接受吗？为什么？您个人会参加吗？为什么？
    - 提示: 谁应该实现它？谁应该参加这项活动？
    - 提示：您的单位是否可能参与其中？为什么？它是否符合您单位的业务目标？会给您的单位带来什么影响吗, 正面或负面的？
    - 提示: 需要哪些资源？会增加实施成本吗？
    - 提示: 您能想到任何风险吗？我们能降低抗生素滥用的风险吗？
    - 提示: 潜在的障碍或阻力？如何和为什么？有可能的解决方案？
11. 项目设计
    - 提示: 社区民众一般聚集在哪里？
    - 提示：周末还是下班后都去哪里？

- 提示: 传播和传播的渠道和格式呢? (例如社交媒体、广播和电视广告、海报、小册子和儿童保育演示文稿)中心/学校, 报纸, 新闻发布会, 传单和邮件, 社区领袖或学校教师, 和其他教育材料)?
- 提示: 什么是有效的或适当的实施渠道 (例如基于社区的组织、学校、社区中心, 加入政府赞助的活动)?

12. 评价

- 提示: 关于实施时间，有没有建议 (如与学校日历年度重合, 避免农历新年等主要节假日)?
- 提示: 关于干预的评估，可能使用什么样的行为数据，哪个单位会有的？

抗生素用于普通感冒-健康教育信息的测试

[一般民众]

目的: 测试和完善健康教育信息

健康教育信息测试

第一步: 干预前: 抗生素耐药细菌相关的知识评估和风险感知项目

第二步: [提供与 抗生素耐药细菌相关的健康教育信息–小册子、新闻文章、或 WHO/当地疾控中心/医生/学校教师的官方声明]:

- 在中国的环境中, 抗生素耐药细菌和抗生素滥用的危险因素。
- 如何管理常见的感冒症状。
- 如何负责任地使用抗生素。
- 如何正确处置抗生素。
- 抗生素可能改变肠道环境, 影响人的健康

第三步: 干预后: 抗生素耐药细菌相关的知识评估和风险感知项目

健康教育干预内容评价

1. 您觉得这文章/海报主要在说什么?
   - 提示： 您有什么反馈?
2. 创新传播
   - 提示：在您同意他说的吗?
   - 提示：您认为人们收到这条信息后会怎么应对?
   - 提示：如果您认识的人使用剩余的抗生素治疗感冒, 您会怎么应对, 为什么?
   - 提示：如果您认识的人自我使用抗生素治疗感冒, 您会怎么应对, 为什么?
3. 社交网络
   - 提示：您会分享这个 [健康信息] 吗？怎么分享和为什么?
   - 提示：您会和谁分享这个 [健康信息]？怎么分享和为什么?

- 提示：如果您的医生和您分享这个[健康信息], 您会怎么应对？如果是当地的 CDC/亲戚/邻居/直系亲属呢？

4. 健康教育成效
   - 这个 [健康信息] 是否会改变您如何应对常见感冒症状？如果是, 会有什么样的改变和为什么？如果不是, 为什么？
   - 您觉得这个 [健康信息] 会改变其他人应对常见感冒的症状吗？如果是, 会有什么样的改变和为什么？如果不是没有, 为什么？
   - 这个 [健康信息] 会改变您使用抗生素的方式 (例如, 自我治疗或向医生索要抗生素) 吗？如果是, 如何和为什么？如果不是, 为什么？
   - 这个 [健康信息] 是否会改变其他人使用抗生素的方式 (例如, 自我治疗或向医生索要抗生素)？如果是, 会有什么样的改变和为什么？如果不是, 为什么？

健康教育干预的实施

5. 您最喜欢哪种格式？文章、海报、微信？
6. 谁是社区中有影响力或值得信赖的意见领袖？
   - 提示：周末还是下班后都去哪里？
   - 提示：社区成员聚集在哪里？
7. 您能告诉我关于现有的回收程序？
   - 您自己家里参与了吗？为什么？您认为这是什么目的？经验如何？
   - 目前小区内回收项目的基础设施程序
   - 提示：如果该现有回收程序要包括抗生素, 您认为原因是什么？您会参加吗？为什么？

27. 您通常从哪里获得健康信息？为什么？
   - 提示：您相信这些信息来源吗？微信呢？
   - 提示：您是否曾分享、发送健康信息？
   - 提示：如果是, 那是什么健康信息？为什么, 如何分享、发送的?

ANTIBIOTIC USE FOR THE COMMON COLD

[general community members]

Aim: to understand local norms around medical decision-making for the common cold and antibiotic use.

Socio-demographic characteristics

- Age _____
- Gender _____
- Education Level _____
- Medical background_____
- Monthly household income_____
- Do you have children? _____ If so, age and sex_____?

Part I – Understand norms around medical decisions for antibiotic use and the common colds

[Health maintenance & TCM]

- Do you do anything in particular to stay healthy? [e.g. eating habits, vitamins, exercise, etc.]
- Have you ever seen a traditional Chinese medical doctor? [If yes, how often and why? If no, why?]
- Have you tried Chinese treatments, e.g. acupuncture, gua-sha, tui-na? [Why? How often?]
- Do you include Chinese herbs in your diet, e.g. ginseng, goji, siwu, etc.? [Why? How often?]
- What do you think of Chinese herb medicine, e.g. banlangen? Have you tried it? [Why? How often?]
- What do you think of infusion? How about the needle?
- What's inflammation?
- How often do you see a doctor?

[Self-diagnosis of the Common cold]

28. Can you recognise the symptoms of the common cold?

- Prompt:
    - "I am confident that I can diagnose correctly the symptoms of the common cold for myself" [a 7-point likert scale, 1-7]
    - (If applicable) "I am confident that I can diagnose correctly the symptoms of the common cold for my children" [a 7-point likert scale, 1-7]
- Prompt: If yes, how did you learn to recognise them?
- Prompt: If yes, what are they? What to do and why?
    - let it run its course – why? for how long and why?
    - seek treatment – why? Where to seek treatment and why?
    - self-treat – Why? How to self-treat and why?
- Prompt: If no, what do you do if you experience [sore throat, cough, stuffy nose, runny nose, diarrhea, fever, etc.]?
- Prompt: How do people get the common cold?
- Prompt: How about treatment options for family (e.g. the elderly or children?)?
- Prompt: On average, how often do you experience the common cold in a year?

[Recent experience with the Common Cold]

29. When was the last time that you had the common cold?

- Prompt: who was involved in the treatment decision?
- Prompt: what did you do?
    - let it run its course – why? for how long and why?
    - seek treatment – why? Where to seek treatment and why?
        - Prompt: If health services were used, where did you go? What did the doctor do? Were you prescribed antibiotics? Did you ask for antibiotics?
    - self-treat – Why? How to self-treat and why?
        - Prompt: If medicine was used, what was it?
        - Prompt: If antibiotics are used, why? Where did you get it?
- (If applicable) When was the last time that your child had the common cold?

[Management of the Common Cold]

30. Would you consider alternative options? (e.g. traditional Chinese medicine? Cough medicine? advice to watch and wait?)
    - Prompt: What would you do if doctors tell you that the common cold is a self-limiting illness and it would go away naturally?
    - Prompt: What would you do if doctors advise you to watch and wait?
    - Prompt: What would you do if doctors do not prescribe antibiotics for the common cold.
    - Prompt: Have you purchased antibiotics in a local pharmacy?
        - If so, what was it for?
        - Did you present a prescription? If so, where did you get the prescription?
        - What would you do if you cannot purchase a local pharmacy without a doctor's prescription.
    - Prompt: How confident are you to manage the symptoms of the common cold without using [antibiotics]? Why?
        - "I am confident that I can manage the symptoms of the common cold for myself" [a 7-point likert scale, 1-7]
        - (If applicable) "I am confident that I can manage the symptoms of the common cold for my children" [a 7-point likert scale, 1-7]

[What do people know about antibiotics?]

31. Have you heard of the medicine "antibiotics"?
    - Prompt: If yes, what are they? When would you need them?
    - Prompt: If yes, where can you get them? How much (price) do they cost? Are they affordable?
32. What do you think of the statement: "antibiotics are **anti-inflammatory drugs**"?
33. Which one(s) of the following are antibiotics?
    - Penicillin drugs such as amoxicillin
    - Cephalosporins such as cefaclor/ceftus sodium
    - Non-steroidal drugs such as ibuprofen/merlin/aspirin
    - Dexamethasone/prednisone and other steroids
    - Quinolones such as ofloxacin/norfloxacin
    - Macrolides such as azithromycin/roxithromycin
34. What do you think of the following statements?

- Infusion is more effective than oral antibiotics.
- Antibiotics should be stopped immediately when one's condition improves.

- The more expensive the antibiotics, the more Effective.
- New antibiotics are more effective than old Antibiotics.
- The imported antibiotics are more effective than domestic.

35. Structural factors – policy and access:
    - What are the existing policies regarding antibiotic access and use?
    - Where can you get the antibiotics?

[Self-medication with antibiotics]

36. Have you ever used antibiotics without seeking a doctor first in the past year? When and why?
    - Prompt: What did you take? Why?
    - Prompt: For what purpose?
    - Prompt: Where did you get them? Why?
    - Prompt: Did you follow the instructions? Did you complete the course? Why or why not?
    - Prompt: Were you concerned that you might have taken wrong medicine? Why or why not?*
    - (If applicable) Have you ever let you kid(s) use antibiotics without seeking a doctor first in the past year? When? Why? What did you take? How?
    - Prompt: Did you (or your children) experience any adverse effect?

[Keeping antibiotics at home]

37. Do you currently have antibiotics at home?
    - Prompt: if yes, please specify the name of the specific antibiotics
    - Prompt: if yes, why? What do you do with them?
    - Prompt: if yes, where did you get them? Why?
    - Prompt: if yes, how do you store them?
    - Prompt: if yes, did you ever share them with others? What? Whom? Why? How?
    - Prompt: if yes, do you dispose them at some point? If so, when and why?
    - Prompt: if yes and used them, what did you use them for? How did you know

what to do? How was the experience?

- Prompt: [Intervention] if yes, if the government encourages "take-back", would you participate in it? What do you think? Why? Why do you think the government wants to "take back" antibiotics?

[Recent experience with antibiotics]

38. When was the last time you took antibiotics?
    - Prompt: What did you take?
    - Prompt: For what purpose?
    - Prompt: Where did you get them? Why?
    - Prompt: What would you do if you cannot get it from a local pharmacy? Why?
    - Prompt: Did you follow the instructions? Did you complete the course? Why?
    - Prompt: Did you experience any adverse effect?

[AMR Awareness]

39. Have you heard of the term "antibiotic resistance"? If so, what is it? Where did you last hear about it?
40. Do you agree with any of the following statement?
    - Excessive use of antibiotics is a serious problem in China.
    - Antibiotics are effective in treating viral infections.
    - Antibiotics are effective in the treatment of bacterial infections.
    - The more antibiotics people use, the more difficult it is to cure them later.
    - Overuse of antibiotics can cause bacteria to become resistant to antibiotics.
    - Antibiotic resistance in China will be a serious problem.

[Risk perception - Perceived Severity and Perceived Susceptibility]

41. Risk Perception –
    - How likely do you think you or your family would be to contract drug-resistant bacterial infections？ [a 7-point likert scale, 1-7]
    - How likely do you think someone in your community would be to contract drug-resistant bacterial infections？ [a 7-point likert scale, 1-7]

- How serious would it be if you or your family member contracted a drug-resistant bacterial infection？[a 7-point likert scale, 1-7]
- How serious would it be if someone in your community contracted a drug-resistant bacterial infection？[a 7-point likert scale, 1-7]
- How likely do you think you or your family would be to experience adverse effect when self-medicating with antibiotics？[a 7-point likert scale, 1-7]
- How likely do you think someone in your community would be to experience adverse effect when self-medicating with antibiotics？[a 7-point likert scale, 1-7]
- How serious would it be if you or your family experienced an adverse effect when self-medicating with antibiotics？[a 7-point likert scale, 1-7]
- How serious would it be if someone in your community experienced an adverse effect when self-medicating with antibiotics？[a 7-point likert scale, 1-7]

[Social Norms around treating the common cold and antibiotic use]

42. Descriptive norm –
    - If your friend or neighbor experienced the symptoms of the common cold, what would you say to them? What do you expect them to do? Why?
    - Do you think it is okay to use leftover antibiotics? What would you say if you find out your friend or neighbor used leftover antibiotics? Why?
    - Do you think it is okay to ask doctors for antibiotics? What would you say if you find out your friend or neighbor asked doctors for antibiotics? Why?
    - Do you think it is okay to self-medicate with antibiotics for the common cold symptoms? What would you do if your friend or neighbor self-medicated with antibiotics for common cold symptoms? Why?
    - Do you think it is okay to stop taking antibiotics when you feel better? What would you do if your friend or neighbor stopped taking antibiotics when they feel better? Why?
43. Injunctive norms -
    - How would your friend or neighbor react when you experience the symptoms of the common cold?
    - What do you think others expect you to do when you have leftover antibiotics?

How would your friend or neighbor react if you used leftover antibiotics?

- How would your friend or neighbor react if they learned that you asked doctors for antibiotics?
- How would your friend or neighbor react if they learned that you self-medicated with antibiotics for the common cold symptoms?
- How would your friend or neighbor react if you stopped taking antibiotics when you felt better?

Part II – Explore local channels for communication

[Health Communication Channels]

44. Who are the influencers or trusted messengers in the community?
45. From where do you usually get health information? Why?
    - Prompt: Do you trust these information sources? How about WeChat?
    - Prompt: Do you share health information?
    - Prompt: If so, what was it? why, and how?
46. Where do you go on the weekend or after work? Where do community members gather?

STAKEHOLDERS' INTERVIEWS

Aims:

- To understand the context of the proposed intervention
- To assess the acceptability and feasibility of the proposed intervention

Socio-demographic characteristics

- Age _____
- Gender _____
- Education Level _____
- Medical background_____
- Do you have children? _____ If so, age and sex_____?
- Organisation _____
- Position _____

General

13. What are the existing policies regarding antibiotic access and use?
14. Have you heard about "antibiotic resistance"? If so, what is it?
15. [Risk perception] -
    - How likely do you think you or your family would be to contract drug-resistant bacterial infections? [a 7-point likert scale, 1-7]
    - How likely do you think someone in your community would be to contract drug-resistant bacterial infections? [a 7-point likert scale, 1-7]
    - How serious would it be if you or your family member contracted a drug-resistant bacterial infection? [a 7-point likert scale, 1-7]
    - How serious would it be if someone in your community contracted a drug-resistant bacterial infection? [a 7-point likert scale, 1-7]
    - How likely do you think you or your family would be to experience adverse effect when self-medicating with antibiotics? [a 7-point likert scale, 1-7]
    - How likely do you think someone in your community would be to experience adverse effect when self-medicating with antibiotics? [a 7-point likert scale, 1-7]
    - How serious would it be if you or your family experienced an adverse effect

when self-medicating with antibiotics？ [a 7-point likert scale, 1-7]

- How serious would it be if someone in your community experienced an adverse effect when self-medicating with antibiotics？ [a 7-point likert scale, 1-7]

16. What do you think of the following statements? Why?
    a) The more frequently people use antibiotics, the more difficult it will be to treat bacterial infections.
    b) Antibiotic overuse may increase antibiotic resistance.
    c) We will have few antibiotics to use in the future if we don't use antibiotics properly.
    d) Antibiotic overuse is a serious problem in China.
    e) Antibiotic resistance will become a serious problem in China.

Health Education Message Appraisal

[presenting health education messages]

17. What are the key messages here?
    - Prompt: What do you think about them?
    - Prompt: Which format do you like the best?
    - Prompt: Would you share this [health information]? Why or why not?
        - Prompt: If so, who would you share this [health information] with? How and why?

Content and contextual factors of the intervention:

18. Who are the influencers or trusted messengers in the community?
19. From where do you usually get health information? Why? Do you trust these information sources? How about WeChat?
20. Can you tell me about the existing recycling programme(s)?
    - Are you participating in it? Why or why not? What do you think is the purpose of this? How is the experience?
    - The infrastructure for a sustainable recycling programme
    - Would you/your agency participate in the antibiotics "take back" programme if there is one? Why or why not?
    - If the existing recycling programme to include antibiotics, what do you think the reasons are? Would you participate in it? Why or why not?

Implementation and evaluation

21. If we are to implement an education campaign which leads up to an antibiotic "take back" programme, what do you think? [feasibility and acceptability]
    - Prompt: Effectiveness: would it work? Why or why not?
    - Prompt: Can you think of any risks? Can we mitigate the risk?
    - Prompt: Potential barriers or resistance? How and why? Possible solutions?
22. Implementation
    - Prompt: Who should implement it? Who should participate in this?
    - Prompt: What would be the resources needed?
    - Prompt: Where do community members gather?
    - Prompt: Where do you go on the weekend or after work?
    - Prompt: What channels and formats for communication and dissemination (e.g. social media, radio and television advertisements, posters, pamphlets, and presentations at childcare centres/schools, newspaper, press conferences, flyers and mailings, community leaders or school teachers, and other educational materials)?
    - Prompt: What would be the effective or appropriate channels of implementation (e.g. community-based organisations, schools, community centres, joining government-sponsored events)?
23. Evaluation
    - Prompt: Timeline (e.g. coinciding with school calendar year, avoiding the major holidays such as the Chinese New Year)
    - Prompt: Behavioural data availability

ANTIBIOTIC USE FOR THE COMMON COLD – PILOT TESTING OF HEALTH EDUCATION MESSAGES

[general community members]

Aim: to test and refine health education messaging

Message comprehension

Step 1: Pre-intervention: AMR-related knowledge assessment (23 items, tested by Aim 2 large-scale surveys) and Risk Perception items

Step 2: [To Present AMR-related education information – a pamphlet, a news article, or an official statement from local CDC/doctors/school teachers]:

- The danger of AMR and antibiotic misuse in the context of China.
- How to manage the common cold symptoms.
- How to use antibiotics responsibly.
- How to dispose antibiotics properly.
- Antibiotics might change gut environment and affect one's health

Step 3: Post-intervention: AMR-related knowledge assessment (23 items, tested by Aim 2 large-scale surveys) and Risk Perception items

Appraisal

8. What are the key messages here?
    - Prompt: What do you think about them?
9. Diffusion of Innovation
    - Prompt: What do you think of this [health information]? Do you agree, why or why not?
    - Prompt: What do you think people would do after receiving this message?
    - Prompt: If someone you know use leftover antibiotics to treat the common cold, what would you do and why?
    - Prompt: If someone you know use self-medicate with antibiotics to treat the common cold, what would you do and why?
10. Social Network
    - Prompt: Would you share this [health information]? How and why?
    - Prompt: Who would you share this [health information]? How and why?

- Prompt: If your doctor share this [health information] with you, what would you do? How about local CDC/relatives/neighbors/immediate family members?

11. Perceived effectiveness
    - Would this [health information] change how you handle the symptoms of the common cold for your family? If so, how and why? If not, why?
    - Would this [health information] change how others handle the symptoms of the common cold for your family? If so, how and why? If not, why?
    - Would this [health information] change how you use antibiotics (e.g. self-medication or asking doctors for antibiotics)? If so, how and why? If not, why?
    - Would this [health information] change how others use antibiotics (e.g. self-medication or asking doctors for antibiotics)? If so, how and why? If not, why?

Delivery of the education intervention

12. Which format do you like the best?
13. Who are the influencers or trusted messengers in the community?
14. Where do you go on the weekend or after work?
    - Prompt: Where do community members gather?
15. Can you tell me about the existing recycling programme(s)?
    - Prompt: Are you participating in it? Why or why not? What do you think is the purpose of this? How is the experience?
    - Prompt: The infrastructure for a sustainable recycling programme
    - Prompt: Would you participate in the antibiotics "take back" programme if there is one? Why or why not?
    - Prompt: If the existing recycling programme to include antibiotics, what do you think the reasons are? Would you participate in it? Why or why not?

47. From where do you usually get health information? Why?
    - Prompt: Do you trust these information sources? How about WeChat?
    - Prompt: Do you share health information?
    - Prompt: If so, what was it? why, and how?

REFERENCES

1. The World Health Organization. Antimicrobial resistance: global report on surveillance 2014. http://www.who.int/drugresistance/documents/surveillancereport/en/ (accessed 8 March 2018). 2014.

2. Cui D, Liu X, Hawkey P, et al. Use of and microbial resistance to antibiotics in China: a path to reducing antimicrobial resistance. *J Int Med Res* 2017; **45**(6): 1768-78.

3. Sun HL, Wang H, Chen MJ, et al. [An antimicrobial resistance surveillance of gram-positive cocci isolated from 12 teaching hospitals in China in 2009]. *Zhonghua nei ke za zhi* 2010; **49**(9): 735-40.

4. Zhao C, Sun H, Wang H, et al. Antimicrobial resistance trends among 5608 clinical Gram-positive isolates in China: results from the Gram-Positive Cocci Resistance Surveillance program (2005-2010). *Diagn Microbiol Infect Dis* 2012; **73**(2): 174-81.

5. Liu W, Chen L, Li H, et al. Novel CTX-M {beta}-lactamase genotype distribution and spread into multiple species of Enterobacteriaceae in Changsha, Southern China. *J Antimicrob Chemother* 2009; **63**(5): 895-900.

6. Eccles R. Understanding the symptoms of the common cold and influenza. *The Lancet Infectious Diseases* 2005; **5**(11): 718-25.

7. Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. *Cochrane Database Syst Rev* 2013; (6): Cd000247.

8. Gulliford MC, Dregan A, Moore MV, et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. *BMJ Open* 2014; **4**(10): e006245.

9. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ (Clinical research ed)* 2010; **340**: c2096.

10. Dekker AR, Verheij TJ, van der Velden AW. Inappropriate antibiotic prescription for respiratory tract indications: most prominent in adult patients. *Fam Pract* 2015; **32**(4): 401-7.

11. Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. *Jama* 1997; **278**(11): 901-4.

12. Worrall G. Common cold. *Canadian family physician Medecin de famille canadien* 2011; **57**(11): 1289-90.

13. Allan GM, Arroll B. Prevention and treatment of the common cold: making sense of the evidence. *CMAJ : Canadian Medical Association Journal* 2014; **186**(3): 190-9.

14. Eccles R. Understanding the symptoms of the common cold and influenza. *The Lancet Infectious diseases* 2005; **5**(11): 718-25.

15. Pfeiffer WF. A multicultural approach to the patient who has a common cold. *Pediatrics in review* 2005; **26**(5): 170-5.

16. Thielmann A, Gerasimovska-Kitanovska B, Buczkowski K, et al. Self-Care for Common Colds by Primary Care Patients: A European Multicenter Survey on the Prevalence and Patterns of Practices-The COCO Study. *Evidence-based complementary and alternative medicine : eCAM* 2016; **2016**: 6949202.

17. Cherniack EP, Ceron-Fuentes J, Florez H, Sandals L, Rodriguez O, Palacios JC. Influence of race and ethnicity on alternative medicine as a self-treatment preference for common medical conditions in a population of multi-ethnic urban elderly. *Complementary therapies in clinical practice* 2008; **14**(2): 116-23.

18. Pachter LM, Sumner T, Fontan A, Sneed M, Bernstein BA. Home-based therapies for the common cold among European American and ethnic minority families: the interface between alternative/complementary and folk medicine. *Archives of pediatrics & adolescent medicine* 1998; **152**(11): 1083-8.

19. Baer RD, Weller SC, de Alba Garcia JG, Rocha AL. Cross-cultural perspectives on physician and lay models of the common cold. *Medical anthropology quarterly* 2008; **22**(2): 148-66.

20. Eccles R. Is the common cold a clinical entity or a cultural concept? *Rhinology* 2013; **51**(1): 3-8.

21. Meng Q, Mills A, Wang L, Han Q. What can we learn from China's health system reform? *BMJ (Clinical research ed)* 2019; **365**: l2349.

22. Sun Y, Gregersen H, Yuan W. Chinese health care system and clinical epidemiology. *Clin Epidemiol* 2017; **9**: 167-78.

23. Qian D, Lucas H, Chen J, Xu L, Zhang Y. Determinants of the use of different types of health care provider in urban China: a tracer illness study of URTI. *Health Policy* 2010; **98**(2-3): 227-35.

24. Wei X, Pearson S, Zhang Z, Qin J, Gerein N, Walley J. Comparing knowledge and use of health services of migrants from rural and urban areas in Kunming City, China. *J Biosoc Sci* 2010; **42**(6): 743-56.

25. Qingyue M HY, Wen C, Qiang S, Xiaoyun L. . People's Republic of China Health System Review. Vol.5 No.7. Manila: World Health Organization, Regional Office for the Western Pacific. 2015.

26. Sun Q, Santoro MA, Meng Q, Liu C, Eggleston K. Pharmaceutical policy in China. *Health affairs (Project Hope)* 2008; **27**(4): 1042-50.

27. Wenhui M, Wen C. Improving health system efficiency: China: the zero mark-up for essential medicines at primary level facilities. Geneva: World Health Organization, 2015.

28. World Health Organization. Regional Office for the Western P. People's Republic of China health system review. Manila : WHO Regional Office for the Western Pacific; 2015.

29. Chinese Academy of Sciences (2015). Ed. Chen, X. China Consumes Almost Half of World's Antibiotics. http://english.cas.cn/newsroom/mutimedia_news/201506/t20150623_149222.shtml (last accessed: March 2016). 2015.

30. Li Y. China's misuse of antibiotics should be curbed. *BMJ : British Medical Journal* 2014; **348**.

31. Tang Q, Song P, Li J, Kong F, Sun L, Xu L. Control of antibiotic resistance in China must not be delayed: The current state of resistance and policy suggestions for the government, medical facilities, and patients. *Bioscience trends* 2016; **10**(1): 1-6.

32. Qiao M, Ying GG, Singer AC, Zhu YG. Review of antibiotic resistance in China and its environment. *Environment international* 2018; **110**: 160-72.

33. Yin X, Song F, Gong Y, et al. A systematic review of antibiotic utilization in China. *J Antimicrob Chemother* 2013; **68**(11): 2445-52.

34. Hui L, Li XS, Zeng XJ, Dai YH, Foy HM. Patterns and determinants of use of antibiotics for acute respiratory tract infection in children in China. *The Pediatric infectious disease journal* 1997; **16**(6): 560-4.

35. Zhang Z, Zhan X, Zhou H, et al. Antibiotic prescribing of village doctors for children under 15 years with upper respiratory tract infections in rural China: A qualitative study. *Medicine (Baltimore)* 2016; **95**(23): e3803.

36. Zhang Z, Hu Y, Zou G, et al. Antibiotic prescribing for upper respiratory infections among children in rural China: a cross-sectional study of outpatient prescriptions. *Glob Health Action* 2017; **10**(1): 1287334.

37. Li J, Song X, Yang T, et al. A Systematic Review of Antibiotic Prescription Associated With Upper Respiratory Tract Infections in China. *Medicine (Baltimore)* 2016; **95**(19): e3587.

38. Sun Q, Dyar OJ, Zhao L, et al. Overuse of antibiotics for the common cold - attitudes and behaviors among doctors in rural areas of Shandong Province, China. *BMC Pharmacol Toxicol* 2015; **16**: 6.

39. Su N, Lin JT, Liu GJ, et al. [A survey of knowledge on common cold and its treatment situation among physicians from various levels of hospitals in mainland China]. *Zhonghua nei ke za zhi* 2012; **51**(4): 266-9.

40. Heddini A, Cars O, Qiang S, Tomson G. Antibiotic resistance in China--a major future challenge. *Lancet (London, England)* 2009; **373**(9657): 30.

41. Fang Y. China should curb non-prescription use of antibiotics in the community. *BMJ (Clinical research ed)* 2014; **348**: g4233.

42. Wang Z, Zhang H, Han J, Xing H, Wu MC, Yang T. Deadly Sins of Antibiotic Abuse in China. *Infection control and hospital epidemiology* 2017; **38**(6): 758-9.

43. O'Neill J. Tackling Drug-Resistant Infections Globally: final report and recommendations. (https://amr-review.org/Publications.html, accessed on September 25, 2017). 2016.

44. He P, Sun Q, Shi L, Meng Q. Rational use of antibiotics in the context of China's health system reform. *BMJ (Clinical research ed)* 2019; **365**: l4016.

45. Wang X, Peng D, Wang W, Xu Y, Zhou X, Hesketh T. Massive misuse of antibiotics by university students in all regions of China: implications for national policy. *Int J Antimicrob Agents* 2017; **50**(3): 441-6.

46. Xiao Y-H, Giske CG, Wei Z-Q, Shen P, Heddini A, Li L-J. Epidemiology and characteristics of antimicrobial resistance in China. *Drug Resistance Updates* 2011; **14**(4): 236-50.

47. Liu Y-Y, Wang Y, Walsh TR, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *The Lancet Infectious Diseases* 2016; **16**(2): 161-8.

48. Xiao Y, Zhang J, Zheng B, Zhao L, Li S, Li L. Changes in Chinese Policies to Promote the Rational Use of Antibiotics. *PLoS medicine* 2013; **10**(11): e1001556.
49. Mao W, Chen W. CHINA: The Zero Mark-up Policy for essential medicines at primary level facilities; 2015.
50. Zhou Z, Su Y, Campbell B, et al. The financial impact of the 'zero-markup policy for essential drugs' on patients in county hospitals in western rural China. *PLoS One* 2015; **10**(3): e0121630.
51. Wei X, Yin J, Walley JD, et al. Impact of China's essential medicines scheme and zero-mark-up policy on antibiotic prescriptions in county hospitals: a mixed methods study. *Trop Med Int Health* 2017; **22**(9): 1166-74.
52. Wei X, Zhang Z, Walley JD, et al. Effect of a training and educational intervention for physicians and caregivers on antibiotic prescribing for upper respiratory tract infections in children at primary care facilities in rural China: a cluster-randomised controlled trial. *The Lancet Global health* 2017; **5**(12): e1258-e67.
53. Zou G, Wei X, Hicks JP, et al. Protocol for a pragmatic cluster randomised controlled trial for reducing irrational antibiotic prescribing among children with upper respiratory infections in rural China. *BMJ Open* 2016; **6**(5): e010544.
54. Liu C, Zhang X, Wang X, Zhang X, Wan J, Zhong F. Does public reporting influence antibiotic and injection prescribing to all patients? A cluster-randomized matched-pair trial in china. *Medicine (Baltimore)* 2016; **95**(26): e3965.
55. Yang L, Liu C, Wang L, Yin X, Zhang X. Public reporting improves antibiotic prescribing for upper respiratory tract infections in primary care: a matched-pair cluster-randomized trial in China. *Health Res Policy Syst* 2014; **12**: 61.
56. Currie J, Lin W, Zhang W. Patient knowledge and antibiotic abuse: Evidence from an audit study in China. *Journal of health economics* 2011; **30**(5): 933-49.
57. Wang J, Wang P, Wang X, Zheng Y, Xiao Y. Use and prescription of antibiotics in primary health care settings in China. *JAMA Intern Med* 2014; **174**(12): 1914-20.
58. Xiao Y, Li L. Legislation of clinical antibiotic use in China. *The Lancet Infectious Diseases* 2013; **13**(3): 189-91.
59. Y. X. National action plan to contain Antimicrobial Resistance in China: 2016–2020. http://en.nhfpc.gov.cn/2016-08/26/c_70276.htm. (Last accessed: January 2018). 2016.

60. Chang J, Lv B, Zhu S, et al. Non-prescription use of antibiotics among children in urban China: a cross-sectional survey of knowledge, attitudes, and practices. *Expert review of anti-infective therapy* 2018; **16**(2): 163-72.

61. Lv B, Zhou Z, Xu G, et al. Knowledge, attitudes and practices concerning self-medication with antibiotics among university students in western China. *Trop Med Int Health* 2014; **19**(7): 769-79.

62. Ding L, Sun Q, Sun W, et al. Antibiotic use in rural China: a cross-sectional survey of knowledge, attitudes and self-reported practices among caregivers in Shandong province. *BMC Infect Dis* 2015; **15**: 576.

63. Cheng J, Coope C, Chai J, et al. Knowledge and behaviors in relation to antibiotic use among rural residents in Anhui, China. *Pharmacoepidemiol Drug Saf* 2018; **27**(6): 652-9.

64. Lei X, Jiang H, Liu C, Ferrier A, Mugavin J. Self-Medication Practice and Associated Factors among Residents in Wuhan, China. *International Journal of Environmental Research and Public Health* 2018; **15**(1): 68.

65. Yu M, Zhao G, Stålsby Lundborg C, Zhu Y, Zhao Q, Xu B. Knowledge, attitudes, and practices of parents in rural China on the use of antibiotics in children: a cross-sectional study. *BMC Infect Dis* 2014; **14**: 112.

66. McCartney M. Margaret McCartney: Blaming doctors won't reduce antibiotic overuse. *BMJ (Clinical research ed)* 2015; **351**: h4697.

67. Zhu X, Pan H, Yang Z, Cui B, Zhang D, Ba-Thein W. Self-medication practices with antibiotics among Chinese university students. *Public Health* 2016; **130**: 78-83.

68. Wang X, Lin L, Xuan Z, Li L, Zhou X. Keeping Antibiotics at Home Promotes Self-Medication with Antibiotics among Chinese University Students. *Int J Environ Res Public Health* 2018; **15**(4).

69. 李伊婷, 宋宇, 邵睿臻, et al. 南通市居民抗生素自我药疗行为及其影响因素. *中国卫生事业管理* 2016; **33**(01): 39-41.

70. 廖日炎. 家长抗生素认知水平对小学生自主使用抗生素的影响. *实用预防医学* 2013; **20**(01): 42-5.

71. 姚振江, 周俊立, 李颖, et al. 广州市幼儿园儿童抗生素自主使用情况分析. *中国公共卫生* 2013; **29**(10): 1485-7.

72. Lin L, Hargreaves J, Fearon E, Harbarth S, Wang X, Zhou X. Contextualizing prevalent antibiotic misuse in children across China: a large-scale

cross-sectional survey on parents' antibiotic use on children for common childhood illnesses (under review). *Emerging Infectious Diseases* 2019.

73. Lin L, Harbarth S, Hargreaves J, Zhou X, Li L. Parental treatment decisions for paediatric upper respiratory tract infections with respect to antibiotic use across China: a large-scale survey based on Socio-Ecological Health Belief Model (under review). *Lancet Global Health* 2019.

74. Lin L, Fearon E, Harbarth S, et al. Decisions on antibiotic use for upper respiratory tract infections across China among university students: a large-scale cross-sectional survey based on Socio-Ecological Health Belief Model (under review). *Journal of Antimicrobial Chemotherapy* 2019.

75. Pan H, Cui B, Zhang D, Farrar J, Law F, Ba-Thein W. Prior knowledge, older age, and higher allowance are risk factors for self-medication with antibiotics among university students in southern China. *PLoS One* 2012; **7**(7): e41314.

76. Yang K, Wu D, Tan F, et al. Attitudes and perceptions regarding antimicrobial use and resistance among medical students in Central China. *SpringerPlus* 2016; **5**(1): 1779.

77. Weissman J, Besser RE. Promoting appropriate antibiotic use for pediatric patients: a social ecological framework. *Semin Pediatr Infect Dis* 2004; **15**(1): 41-51.

78. CDC. U.S. Centers for Disease Control and Prevention (CDC). Get Smart: Know When Antibiotics Work in Doctor's Offices. https://www.cdc.gov/getsmart/community/improving-prescribing/program-development-eval/evaluation-manual/step2.html (Last accessed: September 4, 2017). 2015.

79. Theobald S, Brandes N, Gyapong M, et al. Implementation research: new imperatives and opportunities in global health. *Lancet (London, England)* 2018; **392**(10160): 2214-28.

80. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Implementation research: what it is and how to do it. *BMJ (Clinical research ed)* 2013; **347**: f6753.

81. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *International journal of nursing studies* 2013; **50**(5): 587-92.

82. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health* 1999; **89**(9): 1322-7.

83. Bowen DJ, Kreuter M, Spring B, et al. How we design feasibility studies. *American journal of preventive medicine* 2009; **36**(5): 452-7.
84. Peters DHT, N.T.; Adam, T. . Implementation Research in Health: A Practical Guide. Alliance for Health Policy and Systems Research, World Health Organizatio (WHO). Geneva, Switzerland. 2013.
85. Orsmond GI, Cohn ES. The Distinctive Features of a Feasibility Study: Objectives and Guiding Questions. *OTJR : occupation, participation and health* 2015; **35**(3): 169-77.
86. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC medical research methodology* 2010; **10**: 67.
87. Hagen NA, Biondo PD, Brasher PM, Stiles CR. Formal feasibility studies in palliative care: why they are important and how to conduct them. *Journal of pain and symptom management* 2011; **42**(2): 278-89.
88. Minary L, Trompette J, Kivits J, Cambon L, Tarquinio C, Alla F. Which design to evaluate complex interventions? Toward a methodological framework through a systematic review. *BMC medical research methodology* 2019; **19**(1): 92.
89. Kok G, Gottlieb NH, Peters GJ, et al. A taxonomy of behaviour change methods: an Intervention Mapping approach. *Health psychology review* 2016; **10**(3): 297-312.
90. Kok G, Schaalma H, Ruiter RA, van Empelen P, Brug J. Intervention mapping: protocol for applying health psychology theory to prevention programmes. *Journal of health psychology* 2004; **9**(1): 85-98.
91. Wight D, Wimbush E, Jepson R, Doi L. Six steps in quality intervention development (6SQuID). *Journal of Epidemiology and Community Health* 2016; **70**(5): 520.
92. Janz NK, Becker MH. The Health Belief Model: a decade later. *Health education quarterly* 1984; **11**(1): 1-47.
93. Ancillotti M, Eriksson S, Veldwijk J, Nihlen Fahlquist J, Andersson DI, Godskesen T. Public awareness and individual responsibility needed for judicious use of antibiotics: a qualitative study of public beliefs and perceptions. *BMC Public Health* 2018; **18**(1): 1153.
94. Tola HH, Shojaeizadeh D, Tol A, et al. Psychological and Educational Intervention to Improve Tuberculosis Treatment Adherence in Ethiopia Based on

Health Belief Model: A Cluster Randomized Control Trial. *PLoS One* 2016; **11**(5): e0155147.

95. Gebru T, Lentiro K, Jemal A. Perceived behavioural predictors of late initiation to HIV/AIDS care in Gurage zone public health facilities: a cohort study using health belief model. *BMC research notes* 2018; **11**(1): 336.

96. Grier S, Bryant CA. Social marketing in public health. *Annual review of public health* 2005; **26**: 319-39.

97. Smith WA. Social marketing: an overview of approach and effects. *Injury prevention : journal of the International Society for Child and Adolescent Injury Prevention* 2006; **12 Suppl 1**: i38-43.

98. Edgar T, Boyd SD, Palame MJ. Sustainability for behaviour change in the fight against antibiotic resistance: a social marketing framework. *J Antimicrob Chemother* 2009; **63**(2): 230-7.

99. Suarez-Almazor ME. Changing health behaviors with social marketing. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA* 2011; **22 Suppl 3**: 461-3.

100. Weissman J, Besser RE. Promoting appropriate antibiotic use for pediatric patients: a social ecological framework. *Seminars in Pediatric Infectious Diseases* 2004; **15**(1): 41-51.

101. Thabane L, Ma J, Chu R, et al. A tutorial on pilot studies: the what, why and how. *BMC medical research methodology* 2010; **10**: 1.

102. Gu D, Dong N, Zheng Z, et al. A fatal outbreak of ST11 carbapenem-resistant hypervirulent Klebsiella pneumoniae in a Chinese hospital: a molecular epidemiological study. *The Lancet Infectious diseases* 2017.

103. Belongia EA, Sullivan BJ, Chyou PH, Madagame E, Reed KD, Schwartz B. A community intervention trial to promote judicious antibiotic use and reduce penicillin-resistant Streptococcus pneumoniae carriage in children. *Pediatrics* 2001; **108**(3): 575-83.

104. Finkelstein JA, Huang SS, Kleinman K, et al. Impact of a 16-community trial to promote judicious antibiotic use in Massachusetts. *Pediatrics* 2008; **121**(1): e15-23.

105. Gonzales R, Corbett KK, Leeman-Castillo BA, et al. The "minimizing antibiotic resistance in Colorado" project: impact of patient education in improving

antibiotic use in private office practices. *Health services research* 2005; **40**(1): 101-16.

106. Shen X, Lu M, Feng R, et al. Web-Based Just-in-Time Information and Feedback on Antibiotic Use for Village Doctors in Rural Anhui, China: Randomized Controlled Trial. *J Med Internet Res* 2018; **20**(2): e53.

107. Hay SI, Rao PC, Dolecek C, et al. Measuring and mapping the global burden of antimicrobial resistance. *BMC medicine* 2018; **16**(1): 78.

108. WHO. World Health Organization. Antimicrobial resistance: global report on surveillance. (https://www.who.int/drugresistance/documents/surveillancereport/en/, last accessed: May 2019). 2014.

109. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet (London, England)* 2005; **365**(9459): 579-87.

110. BMJ Critical Appraisal Checklist For A questionnaire Study. https://www.bmj.com/content/suppl/2004/05/27/328.7451.1312.DC1.

111. The Critical Appraisals Skills Programme (CASP) Appraisal Checklists. https://casp-uk.net/casp-tools-checklists/.

112. Hu Y, Wang X, Tucker JD, et al. Knowledge, Attitude, and Practice with Respect to Antibiotic Use among Chinese Medical Students: A Multicentre Cross-Sectional Study. *Int J Environ Res Public Health* 2018; **15**(6).

113. Chai J, Coope C, Cheng J, et al. Cross-sectional study of the use of antimicrobials following common infections by rural residents in Anhui, China. *BMJ Open* 2019; **9**(4): e024856.

114. Peng D, Wang X, Xu Y, Sun C, Zhou X. Antibiotic misuse among university students in developed and less developed regions of China: a cross-sectional survey. *Glob Health Action* 2018; **11**(1): 1496973.

115. Wun YT, Lam TP, Lam KF, Sun KS. Comparison of the knowledge, attitudes and practice with antibiotic use between traditional Chinese medicine and western medicine usual attenders in Hong Kong. *Complement Ther Med* 2014; **22**(1): 99-106.

116. Jin Y, Lu Y, Lu P, et al. Influence of Demographic Characteristics on Antibiotics Use among Middle-Aged and Elderly People [in Chinese]. *Chin J Public Health* 2014; **30**(09): 1140-3.

117. Lam TP, Lam KF, Ho PL, Yung RW. Knowledge, attitude, and behaviour toward antibiotics among Hong Kong people: local-born versus immigrants. *Hong Kong medical journal = Xianggang yi xue za zhi* 2015; **21 Suppl 7**: S41-7.
118. Lam TP, Wun YT, Lam KF, Sun KS. Differences in antibiotic use between patients with and without a regular doctor in Hong Kong. *BMC Pharmacol Toxicol* 2015; **16**: 40.
119. Wun YT, Lam TP, Lam KF, Ho PL, Yung WH. Are There Differences in Antibiotic Use Between the Recent-Immigrants from Mainland China and the Local-Born in Hong Kong? *J Immigr Minor Health* 2015; **17**(4): 1177-84.
120. Wun YT, Lam TP, Lam KF, Ho PL, Yung WH. The public's perspectives on antibiotic resistance and abuse among Chinese in Hong Kong. *Pharmacoepidemiol Drug Saf* 2013; **22**(3): 241-9.
121. Liao CC, Chang YK, Chen HH, Lu CY, Huang LY, Sung FC. Knowledge and use of antibiotics among people in Taiwan. *Taiwan Journal of Public Health* 2006; **25**(2): 135-42.
122. Wang W, Wang X, Hu YJ, et al. The Misconception of Antibiotic Equal to an Anti-Inflammatory Drug Promoting Antibiotic Misuse among Chinese University Students. *Int J Environ Res Public Health* 2019; **16**(3).
123. Huang Y, Gu J, Zhang M, et al. Knowledge, attitude and practice of antibiotics: a questionnaire study among 2500 Chinese students. *BMC medical education* 2013; **13**: 163.
124. Huang Y, Chen R, Wu T, Wei X, Guo A. Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. *Br J Gen Pract* 2013; **63**(616): e787-94.
125. Currie J, Lin W, Meng J. Addressing Antibiotic Abuse in China: An Experimental Audit Study. *Journal of development economics* 2014; **110**: 39-51.
126. Xue H, Shi Y, Huang L, et al. Diagnostic ability and inappropriate antibiotic prescriptions: a quasi-experimental study of primary care providers in rural China. *J Antimicrob Chemother* 2019; **74**(1): 256-63.
127. Lam TP, Lam KF. What are the non-biomedical reasons which make family doctors over-prescribe antibiotics for upper respiratory tract infection in a mixed private/public Asian setting? *Journal of clinical pharmacy and therapeutics* 2003; **28**(3): 197-201.

128. Lam TP, Lam KF. Why do family doctors prescribe antibiotics for upper respiratory tract infection? *International journal of clinical practice* 2003; **57**(3): 167-9.
129. Liao R. Investigation on the Impact of Parents' Cognitive Level of Antibiotics on Self-directed Use of Antibiotics in Pupils [in Chinese]. *Practical Preventive Medicine* 2013; **20**(01): 42-5.
130. Yao Z, Zhou J, Li Y, et al. Prevalence of Self-Medication with Antibiotics in Kindergarten Children of Guangzhou City [in Chinese]. *Chin J Public Health* 2013; **29**(10): 1485-7.
131. Lv B, Yang D, Fang Y, et al. Studying on the Behaviors and Influencing Factors of Self-Medication with Antibiotics among University Students in China [in Chinese]. 2013 Annual Meeting of Pharmacy Management Professional Committee of Chinese Pharmaceutical Association and Academic Forum on "Medicine Safety and Scientific Development"; 2013 2013/08/01; Beijing, China; 2013. p. 6.
132. Li R, Xiao F, Zheng X, et al. Antibiotic misuse among children with diarrhea in China: results from a national survey. *PeerJ* 2016; **4**: e2668.
133. Li Y, Song Y, Shao R, et al. Determinants of Self-medication with Antibiotics among Residents in Nantong [in Chinese]. *The Chinese Health Service Management* 2016; **33**(01): 39-41.
134. Gu J, Zhao J, Huang Y, et al. Use of antibiotics by urban and rural residents in Heilongjiang Province, China: cross-sectional study. *Trop Med Int Health* 2015; **20**(12): 1815-22.
135. Tian L, Dong J, Zeng Y, Liu W, Chang P. Logistic Regression Analysis of Factors Affecting University Students' Antibiotics Self-Medication [in Chinese]. *Science Popularity (Science Education)* 2015; (06): 143.
136. Dyar OJ, Yin J, Ding L, et al. Antibiotic use in people and pigs: a One Health survey of rural residents' knowledge, attitudes and practices in Shandong province, China. *J Antimicrob Chemother* 2018; **73**(10): 2893-9.
137. You JH, Yau B, Choi KC, Chau CT, Huang QR, Lee SS. Public knowledge, attitudes and behavior on antibiotic use: a telephone survey in Hong Kong. *Infection* 2008; **36**(2): 153-7.
138. Chang J, Ye D, Lv B, et al. Sale of antibiotics without a prescription at community pharmacies in urban China: a multicentre cross-sectional survey. *J Antimicrob Chemother* 2017; **72**(4): 1235-42.

139. Jin C, Ely A, Fang L, Liang X. Framing a global health risk from the bottom-up: User perceptions and practices around antibiotics in four villages in China. *Health, Risk & Society* 2011; **13**(5): 433-49.
140. Reynolds L, McKee M. Factors influencing antibiotic prescribing in China: an exploratory analysis. *Health Policy* 2009; **90**(1): 32-6.
141. Lu T, Li X. A Study on the Knowledge, Attitude and Behavior of Antibiotic Use among Students in Five Universities in Nanjing [in Chinese]. *ACTA UNIVERSITATIS MEDICINALIS NANJING (Social Sciences)* 2016; **16**(04): 274-80.
142. Zhu E, Fors U, Smedberg A. Understanding how to improve physicians' paradigms for prescribing antibiotics by using a conceptual design framework: a qualitative study. *BMC Health Serv Res* 2018; **18**(1): 860.
143. Jiang H, Jin Y, Ye J, Zhang Y, Jiang C, Zheng W. An Analysis on Knowledge, Attitude and Practice Regarding Antibiotics Use among Community Residents in Hangzhou [in Chinese]. *Preventive medicine* 2017; **29**(10): 978-82.
144. Zhong M, Yang W, Gao G, Guan J. Analysis on Antibiotic Knowledge and Uses among the Residents of Guangdong [in Chinese]. *Chin J of PHM* 2018; **34**(05): 589-91.
145. Gong S, Qiu X, Song Y, et al. Effect of Financially Punished Audit and Feedback in a Pediatric Setting in China, within an Antimicrobial Stewardship Program, and as Part of an International Accreditation Process. *Frontiers in public health* 2016; **4**: 99.
146. Liu C, Zhang X, Wan J. Public reporting influences antibiotic and injection prescription in primary care: a segmented regression analysis. *Journal of evaluation in clinical practice* 2015; **21**(4): 597-603.
147. Wei X, Zhang Z, Hicks JP, et al. Long-term outcomes of an educational intervention to reduce antibiotic prescribing for childhood upper respiratory tract infections in rural China: Follow-up of a cluster-randomised controlled trial. *PLoS medicine* 2019; **16**(2): e1002733.
148. Brun KHTaW. Anticipating the future: appraising risk and uncertainty. In: Ray Crozier RR, Ola Svenson, ed. Decision Making: Cognitive Models and Explanations. 1 ed. London; : New York : Routledge; 1997.
149. Chan YH, Fan MM, Fok CM, et al. Antibiotics nonadherence and knowledge in a community with the world's leading prevalence of antibiotics resistance: implications for public health intervention. *Am J Infect Control* 2012; **40**(2): 113-7.

150. Guan X, Tian Y, Song J, Zhu D, Shi L. Effect of physicians' knowledge on antibiotics rational use in China's county hospitals. *Soc Sci Med* 2019; **224**: 149-55.

151. Liu C, Liu C, Wang D, Deng Z, Tang Y, Zhang X. Determinants of antibiotic prescribing behaviors of primary care physicians in Hubei of China: a structural equation model based on the theory of planned behavior. *Antimicrob Resist Infect Control* 2019; **8**: 23.

152. Wang J, Huang C, Li Z, et al. Knowledge and Behaviors of Antibiotic Use for Upper Respiratory Tract Infections among Parents of Young Children in Changsha City [in Chinese]. *Chin J Public Health* 2017; **33**(03): 415-8.

153. Belongia EA, Naimi TS, Gale CM, Besser RE. Antibiotic use and upper respiratory infections: a survey of knowledge, attitudes, and experience in Wisconsin and Minnesota. *Preventive medicine* 2002; **34**(3): 346-52.

154. Kurniawan, Posangi J, Rampengan N. Association between public knowledge regarding antibiotics and self-medication with antibiotics in Teling Atas Community Health Center, East Indonesia. *Medical Journal of Indonesia* 2017; **26**(1): 62-9.

155. Lum EPM, Page K, Nissen L, Doust J, Graves N. Australian consumer perspectives, attitudes and behaviours on antibiotic use and antibiotic resistance: a qualitative study with implications for public health policy and practice. *BMC Public Health* 2017; **17**(1): 799.

156. Scholl L SP, Kariisa M, Wilson N, Baldwin G. . Drug and Opioid-Involved Overdose Deaths – United States, 2013-2017. Morb Mortal Wkly Rep. ePub: 21 December 2018. https://www.cdc.gov/mmwr/volumes/67/wr/mm675152e1.htm?s_cid=mm675152e1_w (Last accessed: July 2019). 2018.

157. The L. Stemming the global caesarean section epidemic. *Lancet (London, England)* 2018; **392**(10155): 1279.

158. Boerma T, Ronsmans C, Melesse DY, et al. Global epidemiology of use of and disparities in caesarean sections. *Lancet (London, England)* 2018; **392**(10155): 1341-8.

159. Jones MR, Viswanath O, Peck J, Kaye AD, Gill JS, Simopoulos TT. A Brief History of the Opioid Epidemic and Strategies for Pain Medicine. *Pain and therapy* 2018; **7**(1): 13-21.

160. Pinder R, Sallis A, Chadborn T, Berry D. Behaviour Change and antibiotic prescribing in healthcare: A literature review and behavioural analysis. (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/405031/Behaviour_Change_for_Antibiotic_Prescribing_-_FINAL.pdf (Last accessed in November 2018). London: Public Health England 2015.

161. Johnson MJ, May CR. Promoting professional behaviour change in healthcare: what interventions work, and why? A theory-led overview of systematic reviews. *BMJ Open* 2015; **5**(9): e008592.

162. Chhina HK, Bhole VM, Goldsmith C, Hall W, Kaczorowski J, Lacaille D. Effectiveness of academic detailing to optimize medication prescribing behaviour of family physicians. *Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques* 2013; **16**(4): 511-29.

163. Forsetlund L, Bjørndal A, Rashidian A, et al. Continuing education meetings and workshops: effects on professional practice and health care outcomes. *The Cochrane database of systematic reviews* 2009; **2009**(2): Cd003030.

164. Tuti T, Nzinga J, Njoroge M, et al. A systematic review of electronic audit and feedback: intervention effectiveness and use of behaviour change theory. *Implementation science : IS* 2017; **12**(1): 61.

165. Arditi C, Rege-Walther M, Durieux P, Burnand B. Computer-generated reminders delivered on paper to healthcare professionals: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev* 2017; **7**: Cd001175.

166. Cheung A, Weir M, Mayhew A, Kozloff N, Brown K, Grimshaw J. Overview of systematic reviews of the effectiveness of reminders in improving healthcare professional behavior. *Systematic reviews* 2012; **1**: 36.

167. Ivers N, Jamtvedt G, Flottorp S, et al. Audit and feedback: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev* 2012; (6): Cd000259.

168. Van de Velde S, Heselmans A, Delvaux N, et al. A systematic review of trials evaluating success factors of interventions with computerised clinical decision support. *Implementation science : IS* 2018; **13**(1): 114.

169. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database Syst Rev* 2005; (4): Cd003539.

170. Cross EL, Tolfree R, Kipping R. Systematic review of public-targeted communication interventions to improve antibiotic use. *J Antimicrob Chemother* 2017; **72**(4): 975-87.
171. Huttner B, Goossens H, Verheij T, Harbarth S. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. *The Lancet Infectious diseases* 2010; **10**(1): 17-31.
172. Huttner B, Harbarth S, Nathwani D. Success stories of implementation of antimicrobial stewardship: a narrative review. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2014; **20**(10): 954-62.
173. Ryan R, Santesso N, Hill S, Lowe D, Kaufman C, Grimshaw J. Consumer-oriented interventions for evidence-based prescribing and medicines use: an overview of systematic reviews. *Cochrane Database Syst Rev* 2011; (5): Cd007768.
174. Ryan R, Santesso N, Lowe D, et al. Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. *Cochrane Database Syst Rev* 2014; (4): Cd007768.
175. de Kraker MEA, Abbas M, Huttner B, Harbarth S. Good epidemiological practice: a narrative review of appropriate scientific methods to evaluate the impact of antimicrobial stewardship interventions. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 2017; **23**(11): 819-25.
176. Michie S, van Stralen MM, West R. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. *Implementation Science* 2011; **6**(1): 42.
177. Michie S, Richardson M, Johnston M, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 2013; **46**(1): 81-95.
178. McParland JL, Williams L, Gozdzielewska L, et al. What are the 'active ingredients' of interventions targeting the public's engagement with antimicrobial resistance and how might they work? *Br J Health Psychol* 2018; **23**(4): 804-19.
179. Kebede MM, Liedtke TP, Mollers T, Pischke CR. Characterizing Active Ingredients of eHealth Interventions Targeting Persons With Poorly Controlled Type

2 Diabetes Mellitus Using the Behavior Change Techniques Taxonomy: Scoping Review. *Journal of medical Internet research* 2017; **19**(10): e348.

180. Presseau J, Ivers NM, Newham JJ, Knittle K, Danko KJ, Grimshaw JM. Using a behaviour change techniques taxonomy to identify active ingredients within trials of implementation interventions for diabetes care. *Implementation science : IS* 2015; **10**: 55.

181. Roque F, Herdeiro MT, Soares S, Teixeira Rodrigues A, Breitenfeld L, Figueiras A. Educational interventions to improve prescription and dispensing of antibiotics: a systematic review. *BMC Public Health* 2014; **14**: 1276.

182. Martins SS, Ghandour LA. Nonmedical use of prescription drugs in adolescents and young adults: not just a Western phenomenon. *World Psychiatry* 2017; **16**(1): 102-4.

183. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org., 2011.

184. Armstrong R, Waters E, J. D. Chapter 21: reviews in health promotion and public health. In: J Higgins, S Green, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.10. London: The Cochrane Collaboration, . 2011.

185. Valles JA, Barreiro M, Cereza G, et al. A prospective multicenter study of the effect of patient education on acceptability of generic prescribing in general practice. *Health Policy* 2003; **65**(3): 269-75.

186. Frost J, Shaw A, Montgomery A, Murphy DJ. Women's views on the use of decision aids for decision making about the method of delivery following a previous caesarean section: qualitative interview study. *BJOG : an international journal of obstetrics and gynaecology* 2009; **116**(7): 896-905.

187. Emmett CL, Shaw AR, Montgomery AA, Murphy DJ. Women's experience of decision making about mode of delivery after a previous caesarean section: the role of health professionals and information about health risks. *BJOG : an international journal of obstetrics and gynaecology* 2006; **113**(12): 1438-45.

188. Montgomery AA. The DiAMOND trial protocol: a randomised controlled trial of two decision aids for mode of delivery among women with a previous caesarean section [ISRCTN84367722]. *BMC pregnancy and childbirth* 2004; **4**(1): 25.

189. Stille CJ, Rifas-Shiman SL, Kleinman K, Kotch JB, Finkelstein JA. Physician responses to a community-level trial promoting judicious antibiotic use. *Annals of family medicine* 2008; **6**(3): 206-12.
190. Shorten A, Chamberlain M, Shorten B, Kariminia A. Making choices for childbirth: development and testing of a decision-aid for women who have experienced previous caesarean. *Patient education and counseling* 2004; **52**(3): 307-13.
191. Emmett CL, Murphy DJ, Patel RR, et al. Decision-making about mode of delivery after previous caesarean section: development and piloting of two computer-based decision aids. *Health expectations : an international journal of public participation in health care and health policy* 2007; **10**(2): 161-72.
192. Hollinghurst S, Emmett C, Peters TJ, et al. Economic evaluation of the DiAMOND randomized trial: cost and outcomes of 2 decision aids for mode of delivery among women with a previous cesarean section. *Medical decision making : an international journal of the Society for Medical Decision Making* 2010; **30**(4): 453-63.
193. Montgomery AA, Emmett CL, Fahey T, et al. Two decision aids for mode of delivery among women with previous caesarean section: randomised controlled trial. *BMJ (Clinical research ed)* 2007; **334**(7607): 1305.
194. Emmett CL, Montgomery AA, Murphy DJ. Preferences for mode of delivery after previous caesarean section: what do women want, what do they get and how do they value outcomes? *Health expectations : an international journal of public participation in health care and health policy* 2011; **14**(4): 397-404.
195. Belongia EA, Knobloch MJ, Kieke BA, Davis JP, Janette C, Besser RE. Impact of statewide program to promote appropriate antimicrobial drug use. *Emerg Infect Dis* 2005; **11**(6): 912-20.
196. Cebotarenco N, Bush PJ. Reducing antibiotics for colds and flu: a student-taught program. *Health education research* 2008; **23**(1): 146-57.
197. Gonzales R, Corbett KK, Wong S, et al. "Get smart Colorado": impact of a mass media campaign to improve community antibiotic use. *Medical care* 2008; **46**(6): 597-605.
198. McNulty CA, Nichols T, Boyle PJ, Woodhead M, Davey P. The English antibiotic awareness campaigns: did they change the public's knowledge of and attitudes to antibiotic use? *J Antimicrob Chemother* 2010; **65**(7): 1526-33.

199. Wutzke SE, Artist MA, Kehoe LA, Fletcher M, Mackson JM, Weekes LM. Evaluation of a national programme to reduce inappropriate use of antibiotics for upper respiratory tract infections: effects on consumer awareness, beliefs, attitudes and behaviour in Australia. *Health promotion international* 2007; **22**(1): 53-64.
200. Formoso G, Paltrinieri B, Marata AM, et al. Feasibility and effectiveness of a low cost campaign on antibiotic prescribing in Italy: community level, controlled, non-randomised trial. *BMJ (Clinical research ed)* 2013; **347**: f5391.
201. Fraser W, Maunsell E, Hodnett E, Moutquin JM. Randomized controlled trial of a prenatal vaginal birth after cesarean section education and support program. Childbirth Alternatives Post-Cesarean Study Group. *American journal of obstetrics and gynecology* 1997; **176**(2): 419-25.
202. Spoth R, Trudeau L, Shin C, et al. Longitudinal effects of universal preventive intervention on prescription drug misuse: three randomized controlled trials with late adolescents and young adults. *Am J Public Health* 2013; **103**(4): 665-72.
203. Spoth R, Trudeau L, Shin C, Redmond C. Long-term effects of universal preventive interventions on prescription drug misuse. *Addiction* 2008; **103**(7): 1160-8.
204. Hassani L, Aghamolaei T, Ghanbarnejad A, Dadipoor S. The effect of an instructional program based on health belief model in decreasing cesarean rate among primiparous pregnant mothers. *Journal of education and health promotion* 2016; **5**: 1.
205. Bernier A, Delarocque-Astagneau E, Ligier C, Vibet MA, Guillemot D, Watier L. Outpatient antibiotic use in France between 2000 and 2010: after the nationwide campaign, it is time to focus on the elderly. *Antimicrob Agents Chemother* 2014; **58**(1): 71-7.
206. Lambert MF, Masters GA, Brent SL. Can mass media campaigns change antimicrobial prescribing? A regional evaluation study. *J Antimicrob Chemother* 2007; **59**(3): 537-43.
207. Mainous AG, 3rd, Diaz VA, Carnemolla M. A community intervention to decrease antibiotics used for self-medication among Latino adults. *Annals of family medicine* 2009; **7**(6): 520-6.
208. Perz JF, Craig AS, Coffey CS, et al. Changes in antibiotic prescribing for children after a community-wide campaign. *Jama* 2002; **287**(23): 3103-9.

209. Sabuncu E, David J, Bernede-Bauduin C, et al. Significant reduction of antibiotic use in the community after a nationwide campaign in France, 2002-2007. *PLoS medicine* 2009; **6**(6): e1000084.
210. O'Malley AJ, Frank RG, Kaddis A, Rothenberg BM, McNeil BJ. Impact of alternative interventions on changes in generic dispensing rates. *Health services research* 2006; **41**(5): 1876-94.
211. Shorten A, Shorten B, Keogh J, West S, Morris J. Making choices for childbirth: a randomized controlled trial of a decision-aid for informed birth after cesarean. *Birth (Berkeley, Calif)* 2005; **32**(4): 252-61.
212. Eden KB, Perrin NA, Vesco KK, Guise JM. A randomized comparative trial of two decision tools for pregnant women with prior cesareans. *Journal of obstetric, gynecologic, and neonatal nursing : JOGNN* 2014; **43**(5): 568-79.
213. Taylor JA, Kwan-Gett TS, McMahon EM, Jr. Effectiveness of a parental educational intervention in reducing antibiotic use in children: a randomized controlled trial. *The Pediatric infectious disease journal* 2005; **24**(6): 489-93.
214. Lee MHM, Pan DST, Huang JH, et al. Results from a Patient-Based Health Education Intervention in Reducing Antibiotic Use for Acute Upper Respiratory Tract Infections in the Private Sector Primary Care Setting in Singapore. *Antimicrob Agents Chemother* 2017; **61**(5).
215. Sharifirad G, Rezaeian M, Soltani R, Javaheri S, Mazaheri MA. A survey on the effects of husbands' education of pregnant women on knowledge, attitude, and reducing elective cesarean section. *Journal of education and health promotion* 2013; **2**: 50.
216. Hasak JM, Roth Bettlach CL, Santosa KB, Larson EL, Stroud J, Mackinnon SE. Empowering Post-Surgical Patients to Improve Opioid Disposal: A Before and After Quality Improvement Study. *Journal of the American College of Surgeons* 2018; **226**(3): 235-40.e3.
217. Lawrence AE, Carsel AJ, Leonhart KL, et al. Effect of Drug Disposal Bag Provision on Proper Disposal of Unused Opioids by Families of Pediatric Surgical Patients: A Randomized Clinical Trial. *JAMA pediatrics* 2019: e191695.
218. Maughan BC, Hersh EV, Shofer FS, et al. Unused opioid analgesics and drug disposal following outpatient dental surgery: A randomized controlled trial. *Drug and alcohol dependence* 2016; **168**: 328-34.

219. Rose P, Sakai J, Argue R, Froehlich K, Tang R. Opioid information pamphlet increases postoperative opioid disposal rates: a before versus after quality improvement study. *Canadian journal of anaesthesia = Journal canadien d'anesthesie* 2016; **63**(1): 31-7.
220. Santa-Ana-Tellez Y, Mantel-Teeuwisse AK, Dreser A, Leufkens HG, Wirtz VJ. Impact of over-the-counter restrictions on antibiotic consumption in Brazil and Mexico. *PLoS One* 2013; **8**(10): e75550.
221. Santa-Ana-Tellez Y, Mantel-Teeuwisse AK, Leufkens HG, Wirtz VJ. Seasonal variation in penicillin use in Mexico and Brazil: analysis of the impact of over-the-counter restrictions. *Antimicrob Agents Chemother* 2015; **59**(1): 105-10.
222. Wirtz VJ, Herrera-Patino JJ, Santa-Ana-Tellez Y, Dreser A, Elseviers M, Vander Stichele RH. Analysing policy interventions to prohibit over-the-counter antibiotic sales in four Latin American countries. *Trop Med Int Health* 2013; **18**(6): 665-73.
223. Kliemann BS, Levin AS, Moura ML, Boszczowski I, Lewis JJ. Socioeconomic Determinants of Antibiotic Consumption in the State of Sao Paulo, Brazil: The Effect of Restricting Over-The-Counter Sales. *PLoS One* 2016; **11**(12): e0167885.
224. Neighborhoods and Health. Second Edition ed: Oxford Scholarship; 2018.
225. Salihu HM, Wilson RE, King LM, Marty PJ, Whiteman VE. Socio-ecological Model as a Framework for Overcoming Barriers and Challenges in Randomized Control Trials in Minority and Underserved Communities. *International journal of MCH and AIDS* 2015; **3**(1): 85-95.
226. Pellmar TC, Brandt EN, Jr., Baird MA. Health and behavior: the interplay of biological, behavioral, and social influences: summary of an Institute of Medicine report. *American journal of health promotion : AJHP* 2002; **16**(4): 206-19.
227. Finch RG, Metlay JP, Davey PG, Baker LJ. Educational interventions to improve antibiotic use in the community: report from the International Forum on Antibiotic Resistance (IFAR) colloquium, 2002. *The Lancet Infectious diseases* 2004; **4**(1): 44-53.
228. Beshears J, Choi JJ, Laibson D, Madrian BC, Reynolds G. Testimonials do not convert patients from brand to generic medication. *The American journal of managed care* 2013; **19**(9): e314-31.

229. Fuertes EI, Henry B, Marra F, Wong H, Patrick DM. Trends in antibiotic utilization in Vancouver associated with a community education program on antibiotic use. *Canadian journal of public health = Revue canadienne de sante publique* 2010; **101**(4): 304-8.
230. Cabral C, Horwood J, Hay AD, Lucas PJ. How communication affects prescription decisions in consultations for acute illness in children: a systematic review and meta-ethnography. *BMC family practice* 2014; **15**(1): 63.
231. Grant S, Mayo-Wilson E, Montgomery P, et al. CONSORT-SPI 2018 Explanation and Elaboration: guidance for reporting social and psychological intervention trials. *Trials* 2018; **19**(1): 406.
232. Moe-Byrne T, Chambers D, Harden M, McDaid C. Behaviour change interventions to promote prescribing of generic drugs: a rapid evidence synthesis and systematic review. *BMJ Open* 2014; **4**(5): e004623.
233. M. J. Information et informatisation en médecine générale. Inf.-G-Iciens. Namur (Belgium): Presses Universitaires de Namur; 1986. p. 193–209.
234. Kuehlein T SD, Visentin G, Gérvas J, Jamoulle M. Quaternary prevention: a task of the general practitioner. . *Prim Care* 2010; **10**: 350.
235. Brodersen J, Schwartz LM, Woloshin S. Overdiagnosis: how cancer screening can turn indolent pathology into illness. *APMIS : acta pathologica, microbiologica, et immunologica Scandinavica* 2014; **122**(8): 683-9.
236. Martins C, Godycki-Cwirko M, Heleno B, Brodersen J. Quaternary prevention: reviewing the concept. *Eur J Gen Pract* 2018; **24**(1): 106-11.
237. Kahneman D. Thinking, fast and slow: First edition. New York : Farrar, Straus and Giroux, 2011.; 2011.
238. Zinn JO. 'In-between' and other reasonable ways to deal with risk and uncertainty: A review article. *Health, risk & society* 2016; **18**(7-8): 348-66.
239. Kaplan WA, Ritz LS, Vitello M, Wirtz VJ. Policies to promote use of generic medicines in low and middle income countries: a review of published literature, 2000-2010. *Health Policy* 2012; **106**(3): 211-24.
240. Babar ZU, Kan SW, Scahill S. Interventions promoting the acceptance and uptake of generic medicines: a narrative review of the literature. *Health Policy* 2014; **117**(3): 285-96.
241. Malhotra S, Cheriff AD, Gossey JT, Cole CL, Kaushal R, Ancker JS. Effects of an e-Prescribing interface redesign on rates of generic drug prescribing: exploiting

default options. *Journal of the American Medical Informatics Association : JAMIA* 2016; **23**(5): 891-8.

242. Patel MS, Day S, Small DS, et al. Using default options within the electronic health record to increase the prescribing of generic-equivalent medications: a quasi-experimental study. *Annals of internal medicine* 2014; **161**(10 Suppl): S44-52.

243. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implementation science : IS* 2011; **6**: 42.

244. Lorencatto F, Charani E, Sevdalis N, Tarrant C, Davey P. Driving sustainable change in antimicrobial prescribing practice: how can social and behavioural sciences help? *J Antimicrob Chemother* 2018; **73**(10): 2613-24.

245. Langdridge D, Davis M, Gozdzielewska L, et al. A visual affective analysis of mass media interventions to increase antimicrobial stewardship amongst the public. *Br J Health Psychol* 2019; **24**(1): 66-87.

246. Davey P, Marwick CA, Scott CL, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev* 2017; **2**: Cd003543.

247. Charani E, Edwards R, Sevdalis N, et al. Behavior change strategies to influence antimicrobial prescribing in acute care: a systematic review. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2011; **53**(7): 651-62.

248. Gonzales R, Steiner JF, Lum A, Barrett PH, Jr. Decreasing antibiotic use in ambulatory practice: impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in adults. *Jama* 1999; **281**(16): 1512-9.

249. McNulty CA, Nichols T, French DP, Joshi P, Butler CC. Expectations for consultations and antibiotics for respiratory tract infection in primary care: the RTI clinical iceberg. *Br J Gen Pract* 2013; **63**(612): e429-36.

250. Dreser A, Vazquez-Velez E, Trevino S, Wirtz VJ. Regulation of antibiotic sales in Mexico: an analysis of printed media coverage and stakeholder participation. *BMC Public Health* 2012; **12**: 1051.

251. Gandhi T, Best K. Educate patients about proper disposal of unused Rx medications-for their safety. . *Current Psychiatry* 2015; **14**(4): 8.

252. Verde Technologies. Deterra Drug Deactivation System - Deterra System (https://deterrasystem.com/ Last accessed June 2019).

253. Spoth R, Trudeau L, Redmond C, Shin C. Replicating and extending a model of effects of universal preventive intervention during early adolescence on young adult substance misuse. *Journal of consulting and clinical psychology* 2016; **84**(10): 913-21.
254. Spoth R, Trudeau L, Guyll M, Shin C, Redmond C. Universal intervention effects on substance use among young adults mediated by delayed adolescent substance initiation. *Journal of consulting and clinical psychology* 2009; **77**(4): 620-32.
255. Spoth R, Trudeau L, Redmond C, Shin C. Replication RCT of early universal prevention effects on young adult substance misuse. *Journal of consulting and clinical psychology* 2014; **82**(6): 949-63.
256. Spoth RL, Redmond C, Trudeau L, Shin C. Longitudinal substance initiation outcomes for a universal preventive intervention combining family and school programs. *Psychology of addictive behaviors : journal of the Society of Psychologists in Addictive Behaviors* 2002; **16**(2): 129-34.
257. Quan-Cheng K, Jian-Guo W, Xiang-Hua L, Zhen-Zhen L. Inappropriate use of antibiotics in children in China. *Lancet (London, England)* 2016; **387**(10025): 1273-4.
258. Wang CQ, Wang AM, Yu H, et al. [Report of antimicrobial resistance surveillance program in Chinese children in 2016]. *Zhonghua er ke za zhi = Chinese journal of pediatrics* 2018; **56**(1): 29-33.
259. Wang H, Wang B, Zhao Q, et al. Antibiotic body burden of Chinese school children: a multisite biomonitoring-based study. *Environ Sci Technol* 2015; **49**(8): 5070-9.
260. Yang YH, Fu SG, Peng H, et al. Abuse of antibiotics in China and its potential interference in determining the etiology of pediatric bacterial diseases. *The Pediatric infectious disease journal* 1993; **12**(12): 986-8.
261. Yu M, Zhao G, Stalsby Lundborg C, Zhu Y, Zhao Q, Xu B. Knowledge, attitudes, and practices of parents in rural China on the use of antibiotics in children: a cross-sectional study. *BMC Infect Dis* 2014; **14**: 112.
262. Cheng J, Chai J, Sun Y, Wang D. Antibiotics use for upper respiratory tract infections among children in rural Anhui: children's presentations, caregivers' management, and implications for public health policy. *Journal of public health policy* 2019.

263. Li X, Fei YT, Zhang Y, et al. Parents' attitude toward antibiotics and traditional Chinese medicine use for cold in china: A cross-sectional study. *Journal of Alternative and Complementary Medicine* 2016; **22**(6): A118.

264. China. N. National Bureau of Statistics China http://data.stats.gov.cn/english/ (Last accessed in September 2018). 2017.

265. Xinhua. China maintains high vaccination rate: official http://www.xinhuanet.com/english/2019-02/25/c_137849510.htm (Last accessed in March 2019). *Xinhua News* 2019.

266. Cantarero-Arevalo L, Hallas MP, Kaae S. Parental knowledge of antibiotic use in children with respiratory infections: a systematic review. *Int J Pharm Pract* 2017; **25**(1): 31-49.

267. Wang XM, Zhou XD, Hesketh T. Massive misuse of antibiotics by university students in China: A cross-sectional survey. *The Lancet* 2016; **388**(SPEC.ISS 1): 94.

268. Kunin CM, Lipton HL, Tupasi T, et al. Social, behavioral, and practical factors affecting antibiotic use worldwide: report of Task Force 4. *Reviews of infectious diseases* 1987; **9 Suppl 3**: S270-85.

269. Xiao Y, Li L. Legislation of clinical antibiotic use in China. *The Lancet Infectious diseases* 2013; **13**(3): 189-91.

270. Wang L, Zhang X, Liang X, Bloom G. Addressing antimicrobial resistance in China: policy implementation in a complex context. *Globalization and health* 2016; **12**(1): 30.

271. Chen Y, Kirk MD. Incidence of acute respiratory infections in Australia. *Epidemiology and Infection* 2013; **142**(7): 1355-61.

272. Hay AD, Heron J, Ness A. The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): a prospective cohort study. *Fam Pract* 2005; **22**(4): 367-74.

273. Meropol SB, Chen Z, Metlay JP. Reduced antibiotic prescribing for acute respiratory infections in adults and children. *Br J Gen Pract* 2009; **59**(567): e321-8.

274. Easton G, Saxena S. Antibiotic prescribing for upper respiratory tract infections in children: how can we improve? *London journal of primary care* 2010; **3**(1): 37-41.

275. Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. *The Lancet Infectious diseases* 2011; **11**(9): 692-701.

276. Panagakou SG, Spyridis N, Papaevangelou V, et al. Antibiotic use for upper respiratory tract infections in children: a cross-sectional survey of knowledge, attitudes, and practices (KAP) of parents in Greece. *BMC pediatrics* 2011; **11**: 60.
277. Rousounidis A, Papaevangelou V, Hadjipanayis A, et al. Descriptive study on parents' knowledge, attitudes and practices on antibiotic use and misuse in children with upper respiratory tract infections in Cyprus. *Int J Environ Res Public Health* 2011; **8**(8): 3246-62.
278. Bi P, Tong S, Parton KA. Family self-medication and antibiotics abuse for children and juveniles in a Chinese city. *Soc Sci Med* 2000; **50**(10): 1445-50.
279. Harbarth S, Albrich W, Brun-Buisson C. Outpatient antibiotic use and prevalence of antibiotic-resistant pneumococci in France and Germany: a sociocultural perspective. *Emerg Infect Dis* 2002; **8**(12): 1460-7.
280. Deschepper R, Grigoryan L, Lundborg CS, et al. Are cultural dimensions relevant for explaining cross-national differences in antibiotic use in Europe? *BMC Health Serv Res* 2008; **8**: 123.
281. Al-Shawi MM, Darwish MA, Abdel Wahab MM, Al-Shamlan NA. Misconceptions of Parents about Antibiotic use in Upper Respiratory Tract Infections: A survey in Primary Schools of the Eastern Province, KSA. *Journal of family & community medicine* 2018; **25**(1): 5-12.
282. Leal JR, Conly J, Henderson EA, Manns BJ. How externalities impact an evaluation of strategies to prevent antimicrobial resistance in health care organizations. *Antimicrobial resistance and infection control* 2017; **6**: 53-.
283. Alhomoud F, Aljamea Z, Almahasnah R, Alkhalifah K, Basalelah L, Alhomoud FK. Self-medication and self-prescription with antibiotics in the Middle East-do they really happen? A systematic review of the prevalence, possible reasons, and outcomes. *Int J Infect Dis* 2017; **57**: 3-12.
284. Al-Kubaisi KA, De Ste Croix M, Vinson D, Ellis L, Sharif SI, Abduelkarem AR. What drives using antibiotic without prescriptions? A qualitative interview study of university students in United Arab Emirates. *Pharmacy practice* 2018; **16**(2): 1172.
285. Hallsworth M, Chadborn T, Sallis A, et al. Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial. *Lancet (London, England)* 2016; **387**(10029): 1743-52.

286. Roope LSJ, Tonkin-Crine S, Butler CC, et al. Reducing demand for antibiotic prescriptions: Evidence from an online survey of the general public on the interaction between preferences, beliefs and information, United Kingdom, 2015. *Eurosurveillance* 2018; **23**(25).
287. Wu D, Wang Y, Lam KF, Hesketh T. Health system reforms, violence against doctors and job satisfaction in the medical profession: a cross-sectional survey in Zhejiang Province, Eastern China. *BMJ Open* 2014; **4**(12): e006431.
288. Grigoryan L, Monnet DL, Haaijer-Ruskamp FM, Bonten MJ, Lundborg S, Verheij TJ. Self-medication with antibiotics in Europe: a case for action. *Curr Drug Saf* 2010; **5**(4): 329-32.
289. Reynolds L, McKee M. Serve the people or close the sale? Profit-driven overuse of injections and infusions in China's market-based healthcare system. *The International journal of health planning and management* 2011; **26**(4): 449-70.
290. Zhao C, Li Z, Zhang F, et al. Serotype distribution and antibiotic resistance of Streptococcus pneumoniae isolates from 17 Chinese cities from 2011 to 2016. *BMC Infect Dis* 2017; **17**(1): 804.
291. Francino MP. Antibiotics and the Human Gut Microbiome: Dysbioses and Accumulation of Resistances. *Front Microbiol* 2016; **6**: 1543-.
292. Ipci K, Altintoprak N, Muluk NB, Senturk M, Cingi C. The possible mechanisms of the human microbiome in allergic diseases. *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery* 2017; **274**(2): 617-26.
293. Short SE, Mollborn S. Social Determinants and Health Behaviors: Conceptual Frames and Empirical Advances. *Current opinion in psychology* 2015; **5**: 78-84.
294. Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci U S A* 2018; **115**(15): E3463-e70.
295. Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. *The Lancet Infectious Diseases* 2011; **11**(9): 692-701.

296. Wilkinson A, Ebata A, MacGregor H. Interventions to Reduce Antibiotic Prescribing in LMICs: A Scoping Review of Evidence from Human and Animal Health Systems. *Antibiotics (Basel)* 2018; **8**(1): 2.

297. Stivers T, Mangione-Smith R, Elliott MN, McDonald L, Heritage J. Why do physicians think parents expect antibiotics? What parents report vs what physicians believe. *The Journal of family practice* 2003; **52**(2): 140-8.

298. PRC. National Health and Family Planning Commission of the People's Republic of China. Guiding Principles of Clinical Application of Antibacterials. Beijing, 2015:7. 2015.

299. Alves Galvao MG, Rocha Crispino Santos MA, Alves da Cunha AJ. Antibiotics for preventing suppurative complications from undifferentiated acute respiratory infections in children under five years of age. *Cochrane Database Syst Rev* 2016; **2**: Cd007880.

300. Kim NN, Marikar D. Antibiotic prescribing for upper respiratory tract infections: NICE guidelines. *Archives of disease in childhood Education and practice edition* 2019.

301. Kleinman A, Eisenberg L, Good B. Culture, illness, and care: clinical lessons from anthropologic and cross-cultural research. *Annals of internal medicine* 1978; **88**(2): 251-8.

302. He P, Sun Q, Shi L, Meng Q. Rational use of antibiotics in the context of China's health system reform. *Bmj* 2019; **365**: l4016.

303. ShanghaiRanking Consultancy, Best Chinese Universities Ranking • Overall Ranking - 2015 (Last accessed June 2019: http://www.shanghairanking.com/chinese_universities_rankings/overall-ranking-2015.html). 2015.

304. Hu Y, Wang X, Tucker JD, et al. Knowledge, Attitude, and Practice with Respect to Antibiotic Use among Chinese Medical Students: A Multicentre Cross-Sectional Study. *International journal of environmental research and public health* 2018; **15**(6): 1165.

305. Ocan M, Obuku EA, Bwanga F, et al. Household antimicrobial self-medication: a systematic review and meta-analysis of the burden, risk factors and outcomes in developing countries. *BMC Public Health* 2015; **15**: 742.

306. Núñez M, Tresierra-Ayala M, Gil-Olivares F. Antibiotic self-medication in university students from Trujillo, Peru. *Medicina Universitaria* 2016; **18**(73): 205-9.

307. Nepal G, Bhatta S. Self-medication with Antibiotics in WHO Southeast Asian Region: A Systematic Review. *Cureus* 2018; **10**(4): e2428-e.
308. Huh K, Chung DR, Kim SH, et al. Factors affecting the public awareness and behavior on antibiotic use. *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology* 2018; **37**(8): 1547-52.
309. Huttner B, Saam M, Moja L, et al. How to improve antibiotic awareness campaigns: findings of a WHO global survey. *BMJ Glob Health* 2019; **4**(3): e001239.
310. Branthwaite A, Pechere JC. Pan-European survey of patients' attitudes to antibiotics and antibiotic use. *J Int Med Res* 1996; **24**(3): 229-38.
311. McCullough AR, Parekh S, Rathbone J, Del Mar CB, Hoffmann TC. A systematic review of the public's knowledge and beliefs about antibiotic resistance. *J Antimicrob Chemother* 2016; **71**(1): 27-33.
312. Fletcher-Lartey S, Yee M, Gaarslev C, Khan R. Why do general practitioners prescribe antibiotics for upper respiratory tract infections to meet patient expectations: a mixed methods study. *BMJ Open* 2016; **6**(10): e012244.
313. Cabral C, Ingram J, Lucas PJ, et al. Influence of Clinical Communication on Parents' Antibiotic Expectations for Children With Respiratory Tract Infections. *Annals of family medicine* 2016; **14**(2): 141-7.
314. Yip WC, Hsiao W, Meng Q, Chen W, Sun X. Realignment of incentives for health-care providers in China. *Lancet (London, England)* 2010; **375**(9720): 1120-30.
315. Li Y. China's misuse of antibiotics should be curbed. *Bmj* 2014; **348**: g1083.
316. Lescure D, Paget J, Schellevis F, van Dijk L. Determinants of Self-Medication With Antibiotics in European and Anglo-Saxon Countries: A Systematic Review of the Literature. *Frontiers in public health* 2018; **6**: 370.
317. Hu J, Wang Z. In-home antibiotic storage among Australian Chinese migrants. *Int J Infect Dis* 2014; **26**: 103-6.
318. Hu J, Wang Z. Bringing antibiotics from overseas and self-medication amongst Australian Chinese migrants. *Internet Journal of Infectious Diseases* 2015; **14**(1).

319. Hu J, Wang Z. Non-prescribed antibiotic use and general practitioner service utilisation among Chinese migrants in Australia. *Australian journal of primary health* 2016; **22**(5): 434-9.
320. Paut Kusturica M, Tomas A, Sabo A. Disposal of Unused Drugs: Knowledge and Behavior Among People Around the World. *Reviews of environmental contamination and toxicology* 2017; **240**: 71-104.
321. MacWhorter K. Educating the community of Powell, WY on drug take-back programs. *Journal of Investigative Medicine* 2018; **66**(1): 104-5.
322. Yanovitzky I. The American Medicine Chest Challenge: Evaluation of a Drug Take-Back and Disposal Campaign. *Journal of studies on alcohol and drugs* 2016; **77**(4): 549-55.
323. Yanovitzky I. A Multiyear Assessment of Public Response to a Statewide Drug Take-Back and Disposal Campaign, 2010 to 2012. *Health education & behavior : the official publication of the Society for Public Health Education* 2017; **44**(4): 590-7.
324. Do NTT, Nadjm B, Nguyen KV, van Doorn HR, Lewycka S. Reducing antibiotic overuse in rural China. *The Lancet Global health* 2018; **6**(4): e376.
325. Cacari-Stone L, Wallerstein N, Garcia AP, Minkler M. The promise of community-based participatory research for health equity: a conceptual model for bridging evidence with policy. *Am J Public Health* 2014; **104**(9): 1615-23.
326. Israel BA, Coombe CM, Cheezum RR, et al. Community-based participatory research: a capacity-building approach for policy advocacy aimed at eliminating health disparities. *Am J Public Health* 2010; **100**(11): 2094-102.
327. Gaglio B, Shoup JA, Glasgow RE. The RE-AIM framework: a systematic review of use over time. *Am J Public Health* 2013; **103**(6): e38-46.
328. Garba RM, Gadanya MA. The role of intervention mapping in designing disease prevention interventions: A systematic review of the literature. *PloS one* 2017; **12**(3): e0174438-e.
329. Buffington DE, Lozicki A, Alfieri T, Bond TC. Understanding factors that contribute to the disposal of unused opioid medication. *J Pain Res* 2019; **12**: 725-32.
330. DEA. Get smart about drugs (Last accessed, June 2019; https://www.getsmartaboutdrugs.gov/content/national-take-back-day). 2019.
331. Perry LA, Shinn BW, Stanovich J. Quantification of an ongoing community-based medication take-back program. *J Am Pharm Assoc (2003)* 2014; **54**(3): 275-9.

332. Yang CHJ, Doshi M, Mason NA. Analysis of Medications Returned During a Medication Take-Back Event. *Pharmacy (Basel)* 2015; **3**(3): 79-88.
333. Allen B, Harocopos A. Non-Prescribed Buprenorphine in New York City: Motivations for Use, Practices of Diversion, and Experiences of Stigma. *Journal of substance abuse treatment* 2016; **70**: 81-6.
334. Ye D, Chang J, Yang C, et al. How does the general public view antibiotic use in China? Result from a cross-sectional survey. *Int J Clin Pharm* 2017; **39**(4): 927-34.
335. Abrons J, Vadala T, Miller S, Cerulli J. Encouraging safe medication disposal through student pharmacist intervention. *J Am Pharm Assoc (2003)* 2010; **50**(2): 169-73.
336. Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. *Nature* 1998; **393**(6684): 440-2.
337. Neal JW, Neal ZP. Implementation capital: merging frameworks of implementation outcomes and social capital to support the use of evidence-based practices. *Implementation science : IS* 2019; **14**(1): 16.
338. Neal JW, Neal ZP, Kornbluh M, Mills KJ, Lawlor JA. Brokering the Research-Practice Gap: A typology. *American journal of community psychology* 2015; **56**(3-4): 422-35.
339. Egan KL, Gregory E, Sparks M, Wolfson M. From dispensed to disposed: evaluating the effectiveness of disposal programs through a comparison with prescription drug monitoring program data. *Am J Drug Alcohol Abuse* 2017; **43**(1): 69-77.
340. European Antibiotic Awareness Day provides platform for campaigns on prudent use of antibiotics for the fourth time. *Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin* 2011; **16**(46).
341. Hanna N, Sun P, Sun Q, et al. Presence of antibiotic residues in various environmental compartments of Shandong province in eastern China: Its potential for resistance development and ecological and human risk. *Environment international* 2018; **114**: 131-42.
342. Wang Z, Chen Q, Zhang J, et al. Characterization and source identification of tetracycline antibiotics in the drinking water sources of the lower Yangtze River. *Journal of environmental management* 2019; **244**: 13-22.

343. Maeng DD, Snyder RC, Medico CJ, Mold WM, Maneval JE. Unused medications and disposal patterns at home: Findings from a Medicare patient survey and claims data. *J Am Pharm Assoc (2003)* 2016; **56**(1): 41-6.e6.
344. Stergachis A. Promoting the proper disposal of unused, unwanted, or expired medications: Andy Stergachis. *Journal of the American Pharmacists Association* 2014; **54**(3): 226.
345. Chen D, Liu S, Zhang M, Li S, Wang J. Comparison of the occurrence of antibiotic residues in two rural ponds: implication for ecopharmacovigilance. *Environmental monitoring and assessment* 2018; **190**(9): 539.
346. Wang J, He B, Hu X. Human-use antibacterial residues in the natural environment of China: implication for ecopharmacovigilance. *Environmental monitoring and assessment* 2015; **187**(6): 331.
347. Wang J, He B, Yan D, Hu X. Implementing ecopharmacovigilance (EPV) from a pharmacy perspective: A focus on non-steroidal anti-inflammatory drugs. *The Science of the total environment* 2017; **603-604**: 772-84.
348. Yu X, Hu X, Li S, Zhang M, Wang J. Attitudes and Practice Regarding Disposal for Unwanted Medications among Young Adults and Elderly People in China from an Ecopharmacovigilance Perspective. *Int J Environ Res Public Health* 2019; **16**(8).
349. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ (Clinical research ed)* 2008; **337**: a1655.
350. Whitehead AL, Sully BG, Campbell MJ. Pilot and feasibility studies: is there a difference from each other and from a randomised controlled trial? *Contemporary clinical trials* 2014; **38**(1): 130-3.
351. Bugge C, Williams B, Hagen S, et al. A process for Decision-making after Pilot and feasibility Trials (ADePT): development following a feasibility study of a complex intervention for pelvic organ prolapse. *Trials* 2013; **14**: 353.
352. Shanyinde M, Pickering RM, Weatherall M. Questions asked and answered in pilot and feasibility randomized controlled trials. *BMC medical research methodology* 2011; **11**: 117.
353. Faulkner L. Beyond the five-user assumption: benefits of increased sample sizes in usability testing. *Behavior research methods, instruments, & computers : a journal of the Psychonomic Society, Inc* 2003; **35**(3): 379-83.

354. Billingham SA, Whitehead AL, Julious SA. An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC medical research methodology* 2013; **13**: 104.
355. Wang L, Zhang X, Liang X, Bloom G. Addressing antimicrobial resistance in China: policy implementation in a complex context. *Globalization and health* 2016; **12**(1): 30.
356. Li H, Yan S, Li D, Gong Y, Lu Z, Yin X. Trends and patterns of outpatient and inpatient antibiotic use in China's hospitals: data from the Center for Antibacterial Surveillance, 2012–16. *Journal of Antimicrobial Chemotherapy* 2019; **74**(6): 1731-40.
357. Rousounidis A, Papaevangelou V, Hadjipanayis A, et al. Descriptive study on parents' knowledge, attitudes and practices on antibiotic use and misuse in children with upper respiratory tract infections in Cyprus. *International journal of environmental research and public health* 2011; **8**(8): 3246-62.
358. Gonzales R, Malone DC, Maselli JH, Sande MA. Excessive antibiotic use for acute respiratory infections in the United States. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2001; **33**(6): 757-62.
359. Kronman MP, Zhou C, Mangione-Smith R. Bacterial prevalence and antimicrobial prescribing trends for acute respiratory tract infections. *Pediatrics* 2014; **134**(4): e956-65.
360. Guillemot D, Varon E, Bernede C, et al. Reduction of antibiotic use in the community reduces the rate of colonization with penicillin G-nonsusceptible Streptococcus pneumoniae. *Clin Infect Dis* 2005; **41**(7): 930-8.
361. O'Cathain A, Croot L, Sworn K, et al. Taxonomy of approaches to developing interventions to improve health: a systematic methods overview. *Pilot and Feasibility Studies* 2019; **5**(1): 41.
362. Li Y, Xu J, Wang F, et al. Overprescribing in China, driven by financial incentives, results in very high use of antibiotics, injections, and corticosteroids. *Health affairs (Project Hope)* 2012; **31**(5): 1075-82.
363. Li P, Xing K, Qiao H, et al. Psychological violence against general practitioners and nurses in Chinese township hospitals: incidence and implications. *Health and Quality of Life Outcomes* 2018; **16**(1): 117.

364. Yang SZ, Wu D, Wang N, et al. Workplace violence and its aftermath in China's health sector: implications from a cross-sectional survey across three tiers of the health system. *BMJ Open* 2019; **9**(9): e031513.
365. Pinder R, Berry D, Sallis A, Chadborn T. Antibiotic prescribing and behaviour change in healthcare settings: literature review and behavioural analysis. London, UK, 2015.