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

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ABSTRACT

BACKGROUND: Inappropriate use of antibiotics for upper respiratory tract infections (URTIs) in Chinese children is rampant. Parents' decision-making processes with respect to treatment choices and antibiotic use for paediatric URTIs were investigated to identify key constructs for effective interventions that target the public.

METHODS: Data were collected between June 2017 and April 2018 from a random cluster sample of 3188 parents of children aged 0-13 years across three 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: A total of 1465 (46.0%) children of the 3188 parents who self-diagnosed their children with a URTI were given antibiotics, with or without prescription. Among these children, 40.5% were self-medicated with antibiotics by their parents and 56.1% obtained further antibiotic prescriptions at healthcare facilities. About 70% of children (n=2197) with URTI symptoms sought care; of these, 54.8% obtained antibiotic prescriptions and 7.7% asked for antibiotic prescriptions, with 79.4% successfully obtaining them. Those perceiving antibiotics as effective for treating the common cold and fever (adjusted odds ratio [aOR]=1.82[95% confidence interval, 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.

CONCLUSIONS: Multifaceted, context-appropriate interventions are vital to untangle the perpetual problem of self-medication, over-prescription and ill-informed demands for antibiotics. The findings in this study emphasise the need to prioritise interventions that enhance clinical training, neutralise the pressure from patients for antibiotics, educate on appropriate home care, discourage antibiotic self-medication and improve antibiotic dispensing.

1. Introduction

Acute, uncomplicated, upper respiratory tract infections (URTIs) are often benign, self-limiting and untreatable by antibiotics. These infections are diagnosed based on symptomatology and treatments are mainly symptomatic rather than focusing on changes in viral titres in the airway or viral shedding [1]. URTIs are considered the most common infectious disease among humans, and the

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most common cause of primary care visits and unnecessary use of antibiotics in children globally, particularly in China [2-4]. This has contributed to the rise in antimicrobial resistance (AMR), an imminent global health threat. Antibiotic-resistant pathogens, such as *Streptococcus pneumonia*, have been reported in children across China [5,6]. 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 [7,8]. Given the long-term consequences of antibiotic therapy on immune system development and that children may experience URTIs an average of 7-10 times per year [1], misuse of antibiotics in children is particularly harmful. Nevertheless, 48.2% of urban parents [9] and 62% of rural parents [10] in China were reported to have self-medicated children with antibiotics outside of clinical settings within the last six months.

Understanding the underlying reasons why parents decide to use antibiotics for paediatric URTIs without professional guidance is important for developing strategies to reduce antibiotic misuse. Most public-targeted health behaviour research and interventions on antibiotic use have centred on knowledge-attitudes-practice (KAP), with the assumption that individuals would make more risk-conscious choices if they were informed of the risks of AMR – an approach that has long been criticised for its overemphasis on personal responsibility [11]. When faced with an acute infection in themselves or a loved one, individuals may focus disproportionately on the immediate outcome of curing the illness (i.e., perceived antibiotic efficacy), and discount long-term risks such as AMR [12]. Therefore, parents' decision-making for treating URTIs might not be as rational or as informed as a KAP approach would suggest. 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. This study in children with self-diagnosed URTI symptoms investigated the extent and risk factors associated with the likelihood of (1) self-medication with non-prescription antibiotics by parents; (2) healthcare seeking; and (3) parental requesting for antibiotics and unnecessary prescriptions by healthcare providers.

2. Methods

2.1. Study population

Data were assessed from a survey of parents with children aged 0-13 years between June 2017 and April 2018. Three Chinese provinces representing different geographical areas and stages of economic development [13] were chosen: Zhejiang (East, ranked 5th of 31 in the 2017 provincial gross domestic product [GDP] ranking of economic development), Shaanxi (Central-Northwest, ranked 12th), and Guangxi (Southwest, ranked 26th). A multistage, random clustering, sampling design was applied. The four-stage sampling units were provinces, prefecture-level cities, urban and rural areas, and local sites: primary schools (age 6-13 years), kindergartens (age 3-5 years) and community health centres (age 0-2 years), where most children received vaccination [14]. Parents were identified and recruited through their children from all selected sites. The parents were asked to complete a structured questionnaire that was tailored to the Chinese sociocultural context informed by literature review [10,15,16] and formative/qualitative interviews with stakeholders and experts. The questionnaire comprised 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 to complete and an internet protocol (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, a pilot study was conducted with 315 respondents to evaluate potential sources of response error and improve the instrument. The questionnaire was completed by 9526 parents, with a response rate of 89%. Of those, 33.5% (n=3188) 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 [1].

2.2. 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 [17,18], the following potential risk factors were included in the 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 antibiotic 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 A flow diagram (Figure 1) was developed to illustrate the parental decision-making process of treatment and antibiotic use in their children for URTIs, from (non-clinical) household to (clinical) facility. The distributions of socio-demographic

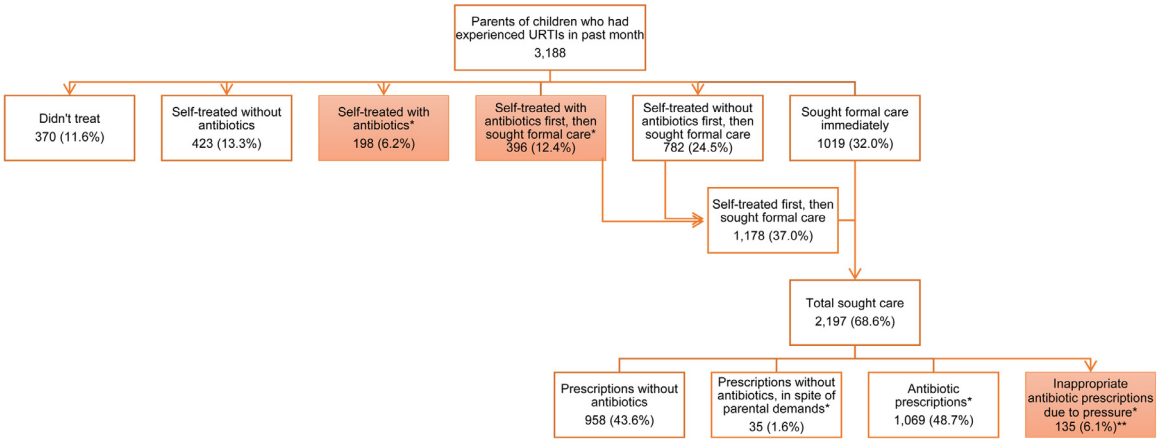

Figure 1. Antibiotic use for upper respiratory tract infections (URTIs) among Chinese children.
*Inappropriate antibiotic use for URTIs.
**170 parents asked for antibiotic prescriptions for URTI symptoms for their children, with a success rate of 79.4%.

characteristics and factors by treatment decision/behavioural outcomes were summarised. To examine the association between each factor and outcome, logistic regressions were applied to estimate the odds ratio (OR), 95% confidence interval (95% CI) for (1) 'self-medication with antibiotics' (vs. 'no self-medication with antibiotics') and (2) 'seeking healthcare' (vs, 'without seeking healthcare'). Factors considered included parental medical background, ability to identify antibiotics, perceived antibiotic efficacy for cold or fever, self-diagnosed severity, cues to action, and access to antibiotics. The associations with subgroups of antibiotic and healthcare use were explored, and multinomial logistic regressions were applied 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 care' (vs. 'no self-medication with antibiotics') and (2) 'sought care without requesting antibiotic prescriptions' and 'sought care and requested prescriptions' (vs. 'no seeking healthcare'). For parents who sought care for their children, RRR (95% CI) was estimated for 'receiving prescriptions without patients' request' and 'receiving prescriptions due to patients' request' (vs. 'without an antibiotic prescription'). For each outcome and risk factor, an unadjusted model was fitted then adjusted for the potential confounders to establish whether the association was independent of these socio-demographic characteristics. As different risk factors tend to co-occur all risk factors were mutually adjusted for simultaneously.

3. Results

Of the 3188 children who had URTI symptoms within the last month (see Table 1), 594 (18.6%) 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 care, of whom 54.8% (1204) obtained antibiotic prescriptions. A third of these prescriptions (33.9%) contained intravenous antibiotics, mostly combined with oral antibiotics. Patients or caregivers (i.e., the demand-side of the healthcare system) who were engaged in self-medication and who had 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).

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

Perceived antibiotic efficacy for the common cold or fever (adjusted OR=1.82[95% CI, 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 the media were associated with a reduced risk (adjusted relative risk ratio [aRRR]=0.46[0.24-0.89]). High levels of perceived severity of infection and presence of fever in children were associated with increased risk of self-medication with antibiotics then seeking healthcare.

3.2. 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 with 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 care for their children, keeping antibiotics at home was associated with increased risk of requesting antibiotic prescriptions (aRRR=3.63[2.54-5.17]).

3.3. Antibiotic prescriptions for the treatment of URTIs (Table 4)

Children whose parents could identify most antibiotics, perceived antibiotics as efficacious for the 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).

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

SOCIO-DEMOGRAPHIC CHARACTERISTICS	All children N (%) 3188	Treated with antibiotics 1465 (46.0)	Self-treated with antibiotics 594 (18.6%)	Children who sought care 2197(68.9%)
Sex				
Male	1623 (50.9)	746 (50.9)	310 (52.2)	1125 (51.2)
Female	1565 (49.1)	719 (49.1)	284 (47.8)	1072 (48.8)
Age (years)				
0-3	1025 (32.2)	441 (30.1)	163 (27.4)	735 (33.5)
4-6	1109 (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)				
>5000	1520 (47.7)	655 (44.7)	232 (39.1)	1023 (46.6)
3001-5000	1032 (32.4)	498 (34.0)	220 (37.9)	718 (32.7)
≤3000	636 (20.0)	312 (21.3)	142 (23.9)	456 (20.8)
Parents' education level				
College or above	1365 (42.8)	603 (41.2)	228 (38.4)	889 (40.5)
High school or below	1823 (57.2)	862 (58.8)	366 (61.6)	1308 (59.5)
Province				
Zhejiang	885 (27.8)	346 (23.6)	94 (15.8)	612 (27.9)
Guangxi	1152 (36.1)	516 (35.2)	209 (35.2)	793 (36.1)
Shaanxi	1151 (36.1)	603 (41.2)	291 (49.0)	792 (36.1)
Hometown				
Rural	1384 (43.4)	612 (41.8)	258 (43.4)	978 (44.5)
Urban	1804 (56.6)	853 (58.2)	336 (56.6)	1219 (55.5)
RISK FACTORS				
Parents with medical background				
No	2785 (87.4)	1290 (88.1)	516 (86.9)	1960 (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)	1231 (56.0)
Parents' perceptions				
Antibiotic efficacy				
Effective for common cold				
No/Don't know	1842 (57.8)	728 (49.7)	266 (44.8)	1233 (56.1)
Yes	1346 (42.2)	737 (50.3)	328 (55.2)	964 (43.9)
Effective for fever				
No/Don't know	1767 (55.4)	670 (45.7)	254 (42.8)	1184 (53.9)
Yes	1421 (44.6)	795 (54.3)	340 (57.2)	1013 (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	2737 (85.9)	1256 (85.7)	495 (83.3)	1917 (87.3)
Family				
No	1672 (52.5)	737 (50.3)	254 (2.8)	1194 (54.4)
Yes	1516 (47.6)	728 (49.7)	340 (57.2)	1003 (45.6)
Media				
No	2846 (89.3)	1313 (89.6)	545 (91.8)	1961 (89.3)
Yes	342 (10.7)	152 (10.4)	49 (8.3)	236 (10.7)
Antibiotics access				
Keeping antibiotics at home				
No	1460 (45.8)	471 (32.2)	105 (17.7)	1042 (47.4)
Yes	1728 (54.2)	994 (67.9)	489 (82.3)	1155 (52.6)

4. Discussion

Main findings Of the 3188 children with URTIs, nearly half (46%) were given antibiotics by parents or clinicians, 69% sought care, and among them 55% were prescribed antibiotics (of these 28% had already self-treated with antibiotics at home). Caregivers accounted for at least 40% of outpatient antibiotic use. Antibiotic misuse for paediatric URTIs can be categorised 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 of 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

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 sought 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)**

(a)OR, (adjusted) odds ratio; (a)RRR, (adjusted) relative risk ratio; CI, confidence interval.
* Reference group: parents who did not self-medicate children with antibiotics (n=2594, 81.4%)[a]Adjusted 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* (2197, 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 (1 symptom)	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)**

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

Table 4
Clinicians' antibiotic prescriptions for URTIs among Chinese children (N=2197): 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 (1069, 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)**

(a)OR, (adjusted) odds ratio; (a)RRR, (adjusted) 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.

antibiotic prescriptions. A majority of parents (n=1728, 54.2%) reported keeping 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%).

4.1. Strengths and Limitations

This study was based on a large survey conducted in geographical areas representing different stages of economic development in China. This is the first study to comprehensively examine parental treatment decisions regarding antibiotic use in children in both rural and urban settings across China. The cross-sectional design of the study prevented causal relationships from being drawn; however, it enabled causal hypotheses to be generated 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 higher than reported in this study, considering repeated infections throughout a year and non-prescription use at home [19]. This study showed that 18% of children with URTIs had already received antibiotics, without prescription, before the parent sought formal care.

4.2. Interpretation of study findings

Evidence from this study will inform interventions designed to reduce unnecessary antibiotic use for paediatric URTIs in China and other low-/middle-income countries that share similar challenges, including rising antibiotic consumption [20] and unsupervised (e.g., use of leftover antibiotics) or inappropriate (e.g., for viral infections or prevention) use of antibiotics [21,22]. This study highlighted the continuing need to tackle non-clinical drivers of inappropriate prescribing behaviours (e.g., patients' or caregivers' profile and behaviours), which should be addressed along with other factors such as poor diagnostic capacity and financial incentives [23,24], particularly in primary care and rural settings [25].

More than half 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 estimated 45% outpatient paediatric antibiotic use in the country. About 8% of Chinese parents in this study admitted to having asked doctors for antibiotics for paediatric URTIs, which is similar to that reported in some European countries [26]. The results of this study also highlighted parental preference for intravenous infusion for children. This phenomenon is a product of the financial incentives of Chinese hospitals, as well as the expectations of consumers for rapid recovery, and is fuelled by widespread acceptance of needle use in Chinese society [27] through the concept of acupuncture, an ancient traditional Chinese treatment. Since 2012, many Chinese hospitals have tried to reduce outpatient infusion treatments [28], yet regulations to address this have not been adopted by most lower level hospitals and have excluded paediatric patients. Furthermore, over-prescription in rural China may be due to the lack of diagnostic knowledge among providers [29]; therefore, improving their professional capacity is necessary. In addition, the influence of doctor-patient encounters on antibiotic prescriptions might be more complex than verbal communication. The data from the current study identified a surprisingly similar set of risk factors influencing antibiotic prescription outcomes for paediatric URTIs between parents who explicitly demanded antibiotics and those who did not. If Chinese doctors' prescribing behaviours for paediatric URTIs are mainly driven by poor diagnostic capacity or financial incentives, as suggested by previous literature [23,24], no association would be expected 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 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 [26,33]. These data highlight an urgent need to enhance clinician training focusing on 1) clinical guidelines and appropriate prescribing for paediatric URTIs, and 2) doctor-patient communication skills 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.

Furthermore, compared with the estimated antibiotic use in university students [15], 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 drive the overall high antibiotic consumption in China. In the current study, healthcare was sought for approximately 70% of children with common cold symptoms in the past month, which is about twice that in the UK (34-40%) [34]. The possibility of receiving an antibacterial prescription for such symptoms was around 33% in the UK [35,36], compared with 55% in the current study survey. An average Chinese child is estimated to consume more than three times the amount of antibiotics as their peers in the UK or other European countries [26,35,37,38]. The gap is even wider for Chinese children in infancy and early childhood because they have higher usage of medical care than older children. This estimate is alarming considering it does not account for non-prescription antibiotic use in Chinese children. The current study data indicate about 18.6% of children with a common cold within the month before the survey were self-medicated with non-prescription antibiotics by parents. In addition, a previous study [39] reported about 20% of children were given antibiotics for prophylaxis in the previous year. Therefore, non-prescription use of antibiotics for paediatric URTIs among Chinese children is estimated to be at least 4-6 times higher than in some European countries [26,37,38,40], although 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 [41]. Context-tailored patient/caregiver education interventions are needed on appropriate home care for paediatric URTIs and prudent antibiotic use. 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 of which were identified as effective channels for health information.

In some low- and middle-income countries, particularly in rural areas where there are challenges in healthcare delivery such as inadequate access, limited medical personnel, and lack of drug regulations, keeping medications (including antibiotics) at home for self-medication is a common practice [30-32]. The current study showed that in China, antibiotic misuse in children was mainly associated with parents' *access to antibiotics,* within or outside a clinical setting. Household antibiotic storage mainly arose from leftover antibiotics from previous prescriptions (60.6%) and over-the-counter purchases (37.5%). Cephalosporins, amoxicillins, and azithromycins were the most commonly used antibiotics to treat paediatric URTIs, both with and without prescription (data not shown). These are broad-spectrum antibiotics effective against a wide range of bacteria, thereby killing more normal microorganisms in the body than narrow-spectrum antibiotics, and should only be used under professional supervision in patients who are sick on presentation. Furthermore, participants from all regions reported to have obtained antibiotics from retail pharmacies. Antibiotic prescriptions are currently fulfilled and dispensed by packs, often more than the prescribed doses, leading to leftover antibiotics for future, unsupervised, self-medication at home. Therefore, in addition to improving responsible prescribing practice, interventions should address the loopholes in current Chinese antibiotic dispensing, including (1) strengthening the enforcement of the Chinese government's AMR policies [42] that ban over-the-counter purchases and cap antibiotic prescriptions (e.g., at 20% for county hospitals), and (2) enabling responsible antibiotics dispensing according to prescribed doses.

4.3. Policy implications

Findings from this study indicate that multifaceted, context-appropriate interventions are vital to untangle the perpetual problem of self-medication, over-prescription and ill-informed demands for antibiotics. Enhancing 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 other low- and middle-income countries will likely not be effective unless it is rigorously adapted to local context. Interventions enhancing parental *self-efficacy* of healthcare decision-making, particularly 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 the media to effectively cue parents to a proper response. Enforcing regulations on 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.

5. Conclusions

The current study data highlight an urgent need for multi-faceted, context-appropriate interventions to untangle the perpetual problem of self-medication, over-prescription and ill-informed demands for antibiotics. 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 the healthcare system in China. The findings in this study emphasise the need to prioritise interventions that enhance clinical training, neutralise the pressure from patients for antibiotics, educate on appropriate home care, discourage antibiotic self-medication and improve antibiotic dispensing.

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Declarations

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Ethical Approval: 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).

Contributors' Statement

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 subsequent 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 subsequent revisions of the manuscript.

All authors approved the final draft of this manuscript.

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