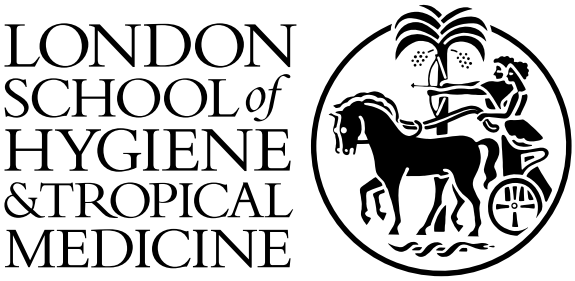


Modelling the effectiveness of quarantine and testing strategies during the COVID-19 pandemic

Billy J Quilty

Thesis submitted in accordance with the
requirements for the degree of
Doctor of Philosophy of the University of London

July 2023

Department of Infectious Disease Epidemiology
Faculty of Epidemiology and Population Health
London School of Hygiene and Tropical Medicine

Funded by the National Institute for Health Research,
the Bill & Melinda Gates Foundation, and the World Health Organization

Declaration of authorship

I, Billy Quilty, 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.

Signed:

Date: 12th July 2023

Abstract

The COVID-19 pandemic prompted governments to enact stringent non-pharmaceutical interventions to control transmission and limit mortality. Core to this was the detection and isolation of individuals either infected with, or potentially exposed to, SARS-CoV-2. In this thesis, I describe the application of individual-based mathematical modelling to determine the effectiveness of such measures in their ability to control transmission, while evaluating their costs to individuals and wider society, as the pandemic progressed.

Modelling of thermal screening at airports early in the pandemic revealed that approximately half of infected arrivals would go undetected, and go on to potentially spark outbreaks. I used mobile phone data to calculate the effectiveness of the cordon sanitaire around Hubei province in reducing spread to other provinces in China. As 14 days of quarantine became the norm, I estimated that this period could be reduced by half if arrivals were tested by PCR. When LFTs became available, I determined that daily testing could allow for the avoidance of quarantine entirely, provided repeatedly negative tests, despite their lower comparative sensitivity versus PCR. Finally, I assessed the hypothesis that lateral flow testing, through the detection of the most infectious individuals with the highest viral loads, could reduce the occurrence of superspreading, using a model incorporating real-world contact rates from the Comix contact survey. I identified uptake and adherence as key unknowns which may limit the effectiveness of such measures.

Model structure and parameterisation were influenced by the evolving state of knowledge of the transmission dynamics of SARS-CoV-2 (e.g. viral load kinetics), the technology available (such as rapid lateral flow testing), and epidemic conditions (e.g. prevalence) over the course of the pandemic. Overall, my work demonstrates the value of information gained from testing to allow for targeted pandemic control measures, reducing the individual and societal costs of quarantine and isolation.

Acknowledgements

Firstly I would like to thank my supervisors, Dr. Sam Clifford, Prof. Stefan Flasche, and Dr. Stéphane Hué, for their guidance, support, and mentorship throughout this PhD. Their combined expertise and insights have been invaluable in shaping my research and development as a scientist during such a pivotal time for those working in infectious disease epidemiology. I would like to thank Sam for his constant presence and support as a mentor and collaborator and for being available even late at night and on weekends despite starting a young family. I thank Stefan for supporting and guiding my career development, ensuring I would always have the funding required to keep working, and for his flexibility in allowing me to contribute towards the Covid response as well as continue my research in pneumococcal epidemiology. I'd also like to thank Stéphane for his patience during the course of this PhD, far removed from its initial proposal, and for encouraging me to take the opportunity to pursue a research passion - I hope to get around to doing some phylogenetics someday.

I would like to express my gratitude to my advisor, Prof. John Edmunds, for his insight into how I could direct my research to address the most pressing pandemic policy questions. I would also like to thank him for putting me forward and encouraging me to present my research at high-level meetings such as SAGE, which was a highlight of my career so far.

I'd also like to thank the National Institute for Health Research, the Bill & Melinda Gates Foundation, and World Health Organisation for funding this work, and for their flexibility.

I would also like to extend my gratitude to my colleagues at LSHTM and in CMMID. I have learned so much from all of you over the past few years and it was truly inspiring to see the COVID-19 Working Group come together and achieve so much.

Finally, I would like to thank my family for their love and encouragement and for being my biggest fans and publicists. Thanks for putting up with me for five months of lockdown; it was a stressful and uncertain time in the world but I'm grateful that we were able to be together. Thanks also to my friends, who I hope know by now that I don't work in the lab. I would like to extend my heartfelt thanks to all of you for being there.

Acronyms and abbreviations

CEPI Coalition for Epidemic Preparedness Innovations

COVID-19 Coronavirus Disease - 2019

Ct Cycle threshold

DCT Daily Contact Testing

DNA Deoxyribonucleic Acid

ECDC European Centre for Disease Control

GDP Gross Domestic Product

HCID High Consequence Infectious Disease

HIV Human Immunodeficiency Virus

k Overdispersion parameter of a negative binomial distribution

LFT Lateral Flow Test

MCMC Markov Chain Monte Carlo

MERS Middle Eastern Respiratory Syndrome

NHS National Health Service

NPI Non-pharmaceutical Intervention

NPV Negative Predictive Value

PCR Polymerase Chain Reaction

PHE Public Health England

PPV Positive Predictive Value

R Reproduction number

RAT Rapid Antigen Test

RCT Randomised Controlled Trial

RDT Rapid Diagnostic Test

RNA Ribonucleic Acid

RT-PCR Reverse Transcriptase Polymerase Chain Reaction

SAR Secondary Attack Rate

SARS Severe Acute Respiratory Syndrome

SARS-CoV-2 Severe Acute Respiratory Syndrome - Coronavirus - 2

VOC Variant Of Concern

WHO World Health Organization

Contents

List of Figures

List of Tables

1. Introduction

1.1 Motivation for PhD

The emergence of SARS-CoV-2 and subsequent pandemic of COVID-19 (Coronavirus Disease 2019) required rapid generation of evidence on the likely effectiveness of interventions or control measures including travel restrictions, quarantine, and testing, designed to contain or mitigate transmission.

However, during a rapidly evolving epidemic it is not always possible to carry out experimental trials to determine effectiveness due to the time required to gather enough data to precisely judge their effect. In these circumstances, mathematical modelling may be used in the absence of (or as a supplement to) trials to inform policy decisions in real-time.

Accurately modelling the dynamics of transmission in the context of travel restrictions, quarantine, and testing involves requires high-quality, fine-scale data on the natural history of infection, such as viral load kinetics, which can be sparse during the initial phase of an outbreak. As an epidemic progresses and more data becomes available, model assumptions may be updated to better represent the disease dynamics, including accounting for heterogeneity between individuals.

As well as the availability of data changing during a pandemic, the development of technology including rapid testing requires the development of updated models to determine impact. Furthermore, societal contexts may influence model development, such as the need to consider the feasibility, acceptability and impact of interventions on individuals' livelihoods and on the economy.

For this thesis I set out to describe the development and assessment through mathematical modelling of intervention strategies that aimed to reduce transmission of SARS-CoV-2 while also aiming to limit their potential burden. This research was carried out in 2020-2023 as the COVID-19 pandemic progressed with the aim of informing pandemic policy in the UK and elsewhere.

1.2 Background

In late 2019, an outbreak of pneumonia of unknown aetiology occurred in Wuhan, China's tenth-largest city. The outbreak, initially linked to one of the city's food markets, caused a severe acute respiratory disease characterised by fever, cough and pneumonia in those affected. On 31 December the WHO (World Health Organization) was notified [1], and on 9 January a novel coronavirus (initially termed 2019-nCoV, later SARS-CoV-2) similar to SARS-CoV was preliminarily identified as the causative agent of the disease [1], later named COVID-19 (Coronavirus Disease - 2019). The virus was found to be easily transmissible through respiratory droplets and in some cases through the air [2]. The reproduction number (R, the average number of secondary infections generated by one infected individual) was initially estimated to be between 2-3 [3, 4] with transmission occurring primarily through "superspreading", with 10% of individuals responsible for 80% of transmission [5]. Early estimates indicated an overall infection fatality ratio of around 1.3% [6], with a strong gradient of increasing risk of death with increasing age [7]. In addition, a study in France estimated that approximately 3% of individuals infected would be hospitalised, with a similar age gradient to that of mortality [8].

After the initial outbreak in Wuhan, SARS-CoV-2 was exported to other parts of China and internationally, leading to the WHO declaring a global pandemic on 11 March 2020 [9]. Many countries experienced large waves of infection, prompting governments to employ strict non-pharmaceutical interventions (NPIs) such as border closures and lockdowns to reduce transmission, protect health systems, and limit loss of life [10]. Measures were relaxed and tightened in response to rising and falling incidence throughout 2020 and 2021. In late 2020, vaccines including the AstraZeneca ChAdOx1, Pfizer BNT162b2 and Moderna mRNA-1273 were developed and found to be safe and highly efficacious against symptomatic disease and death [11, 12, 13], leading to countries approving their use and implementing population-wide vaccination campaigns beginning in early 2021 [14]. Late 2020 also saw the emergence of the first Variant Of Concern (VOC) with B.1.1.7 (later designated Alpha) in the UK, which was found to be more transmissible [15] and severe [16]. Subsequent waves were then largely driven by the emergence and spread of more transmissible variants including Delta and Omicron, the latter associated with an increase in the rate of reinfection [17]. As of December

2022, 6.7 million deaths due to COVID-19 have been reported, though estimates based on excess mortality are around three times higher [18, 19]. As well as the direct impacts due to disease, the pandemic has had a significant impact on the global economy, with the largest stock market crash since 1987 [20], 400 million jobs lost globally between April and June 2020 [21], and real GDP in the European Union falling by 6.7% in 2020 [22].

1.2.1 Fundamentals of infectious disease epidemiology: endemicity, outbreaks, epidemics, and pandemics

Infectious diseases, i.e. diseases caused by pathogen agents such as viruses or bacteria which can be transmitted from person-to-person, cause significant morbidity and mortality worldwide [23]. Infectious disease can exist at various levels in a community; those that are continually present at a relatively steady state in a community are said to be endemic [24]. Such dynamics result from an interplay between infection and immunity, with the continual infection of susceptible individuals (e.g. new births), followed by waning of immunity or evolution of immune system-evading variants allowing for individuals to become susceptible once more, followed by subsequent reinfection, results in a relative equilibrium on the population-level, with R averaging 1 (though this may vary seasonally) [25]. Different infections may be endemic in some regions and not others; for example, malaria is endemic in many tropics and subtropics countries (most notably tropical Africa) due to the conditions of high temperatures and rainfall being favourable for the *Anopheles* mosquito, host to the malaria parasite *Plasmodium* [26], though absent in regions with cooler climates; diseases may also be endemic in some countries and not others due to public health intervention. One example of this is rubella, a viral infection that causes birth defects if contracted by pregnant women. Vaccination efforts have successfully eliminated rubella in many countries, and most notably all countries in the Americas [27]. However, rubella remains endemic in some regions, particularly in parts of Africa, Southeast Asia, and the Western Pacific where vaccination is less accessible [28].

When cases of infectious disease rise above an expected level (either above the typical endemic level or from zero cases) this constitutes an epidemic (though the term outbreak may be used when cases are small and confined to a small geographic area) [24]. Epidemics may arise as a result of a pathogen being introduced to a community which lacks prior immunity,

or a community in which immunity has substantially waned, or due to the emergence of a novel or genetically distinct pathogen from those which currently circulate [29]. This may be geographically localised, or more widespread; epidemics which become established across a number of international borders or globally are referred to as pandemics [29, 30].

In the absence of intervention, epidemics and pandemics progress through a number of stages. Once an epidemic has initiated, the number of infections grows rapidly during what is known as the growth or acceleration phase [31] where R is >1 as the pathogen infects susceptible individuals. The growth phase continues until the proportion of the population no longer considered susceptible exceeds the herd immunity threshold (assuming a homogeneously mixed population [32]), at which point R falls below 1 and the epidemic begins to decline. During the decline phase, the rate of new infections gradually slows as the susceptible population decreases; this period is marked by a deceleration in growth and a transition to endemicity. During the endemic phase, the number of new infections becomes stable at a level predictable based on epidemiological parameters such as the reproductive number, individual susceptibility, degree of herd immunity, pathogen evolution, and the scale and effectiveness of interventions [25]. Any triggers that shift the pathogen-environment-host equilibrium can potentially cause a transition from endemicity back to an epidemic state, initiating another cycle of exponential increase in disease incidence.

Pandemics follow a similar pattern to epidemics but occur on a much larger geographical scale, often affecting multiple continents or worldwide [30]. The growth and decline phases are observed at different times in different geographical areas due to variation in the timing of pathogen introduction, local population susceptibility, and public health responses. This often leads to 'waves' of infection observed at a global scale [33].

Public health strategies targeting control at different phases of the epidemic curve, such as containment, mitigation, and suppression strategies, need to be tailored based on the proportions of the susceptible, infected and recovered individuals, and the characteristic epidemiological parameters unique to the pathogen causing the outbreak, epidemic, or pandemic. The majority of the research conducted in this thesis focuses on the assessment of a subset of non-pharmaceutical interventions (NPIs) during the earlier phase of the COVID-19 pandemic

when the majority of the population was susceptible to infection.

1.2.2 Non-pharmaceutical interventions for outbreaks of high consequence infectious diseases

During the early stages of the COVID-19 pandemic, key epidemiological information required to inform control strategies such as the natural history, severity of infection, and the dynamics of transmission, were unknown or highly uncertain; nor was there any evidence for the effectiveness of pharmaceutical interventions, therapeutic or preventative. Consequently, control in the initial stages of the pandemic was limited to the implementation of NPIs [34].

NPIs aim to control the spread of infectious disease without the use of pharmaceuticals such as vaccines or antivirals (Table 1.1). These typically comprise public health strategies aimed at interrupting transmission through changes in behaviour, development of infrastructure, or implementation of specific technologies. The exact form an NPI may take will vary depending on the route of transmission of the pathogen in question. Outbreaks of cholera, which is transmitted via the ingestion of water or food contaminated with faeces, may be controlled through the provision of clean drinking water, proper sewerage systems, and handwashing [35]. Sexually transmitted infections such as HIV may be prevented through the use of condoms [36] and regular testing [37]. For outbreaks of high-consequence infectious disease (HCIDs) which are known to be highly infectious (such as respiratory pathogens) and/or severe (such as Ebola), or for which the transmission route is unknown (such as for novel pathogens), interventions may be employed which seek to prevent contact between infected and susceptible persons entirely through NPIs such as travel restrictions, testing, quarantine, and isolation.

For outbreaks of HCIDs it is typical to initially pursue a policy of containment, which seeks to rapidly bring an end to an outbreak through 1. limiting geographical spread to the initially affected area through restrictions on travel and 2. reducing transmission within the affected area through more targeted measures such as the detection and isolation of cases and quarantine of exposed contacts (contact tracing) or less targeted measures such as school closures [38].

NPI	Strengths	Limitations
Lockdown	Highly effective in reducing transmission in the short term, minimises pressure on health services	Significant economic impact, mental health concerns, exacerbates inequality
Masks	Moderately effective at blocking droplet transmission, low cost, reusable	Variations in efficacy depending on type and fit, compliance and comfort issues, improper use can lead to false sense of security
Air Filtration	Reduces airborne transmission, substantial evidence of efficacy in healthcare settings	Cost of installation and maintenance, limited effectiveness based on room size and air changes per hour
Social Distancing	Reduces droplet transmission, applicable in various settings	Limitations in crowded settings, impacts societal interaction, difficult to maintain over long periods
Hand Sanitising	Easy to implement, low cost, reduces transmission through contaminated surfaces	Ineffective against airborne pathogens, over-reliance may neglect other measures, can lead to skin irritation or dryness
Protection Screens	Can prevent direct droplet transmission in face-to-face interactions e.g. shops	Limited to certain environments, does not prevent all forms of transmission, may limit fresh air circulation
UV lights	Demonstrated to kill or inactivate microorganisms, offers additional layer of disinfection	High upfront cost, potential health risks with prolonged exposure, effectiveness depends on intensity and exposure duration
Travel Restrictions	Slows spread across borders, allows more time for healthcare preparation	Economic impact particularly on tourism and flight industries, likely little impact once domestic epidemics underway
Quarantines	Highly effective in containing identified cases, controls speed of spread, allows for healthcare system to cope	Social and psychological impacts, needs effective monitoring and support systems, raises ethical and legal issues
Testing	Enables early identification and isolation of cases, facilitates contact tracing, helps in gauging prevalence	Variations in access and turnaround times, cost considerations, concerns about false positives or negatives, logistical challenges

Table 1.1: Overview of Non-Pharmaceutical Interventions (NPIs)

Travel restrictions

Past outbreaks have shown the potential for international air travel to rapidly disseminate an initially localised epidemic around the world. For example, during the 2009 H1N1 influenza pandemic, over 40 countries had declared outbreaks within two months of the first cases reported in Mexico [39] due to the high volume of outward travel (Figure 1.1). In an attempt to slow or prevent spread, countries implemented travel restrictions of varying stringency, ranging from airport screening for febrile individuals to outright travel bans [40]. The evidence on the effectiveness of such measures was mixed, translating to often contradictory public health recommendations. In 2007, prior to the 2009 H1N1 pandemic, travel restrictions in the initial stages of an influenza pandemic were recommended in a WHO report [38], though this advice was reversed in 2009 at the outset of the pandemic [41]. A 2014 systematic review concluded that even extensive travel restrictions "may delay the dissemination of pandemic influenza, but cannot prevent it" [42], citing the "extent and timeliness of restrictions, size of the epidemic, strain transmissibility, the heterogeneity of travel patterns, the geographical source, and urban density of international travel hubs" as key factors affecting the effect size of travel restrictions. Modelling studies estimated that even 99% effective travel restrictions may only delay the peak of an influenza pandemic on the order of 2-7 weeks depending on the volume of travel from an outbreak epicentre [43, 44]. However, epidemics of other high-consequence pathogens such as Ebola in 2014 (West Africa) and 2019 (Democratic Republic of Congo) were largely able to be contained without substantial intercontinental spread; this is likely due to the relatively low volume of outbound international air travel from affected regions, a long generation time (around 17 days [45]), and a reproduction number being between 1 and 2 [46], reducing the probability of an outbreak occurring elsewhere [47].

Testing

In addition to attempting to limit geographical spread, public health authorities may employ measures in the affected community such as testing and contact tracing in order to control transmission. Testing serves a variety of purposes during an outbreak, such as to diagnose an individual with a disease and enable specific clinical treatment; to track the size and extent of an outbreak in a population; to monitor genomic epidemiology for variants; and to prevent

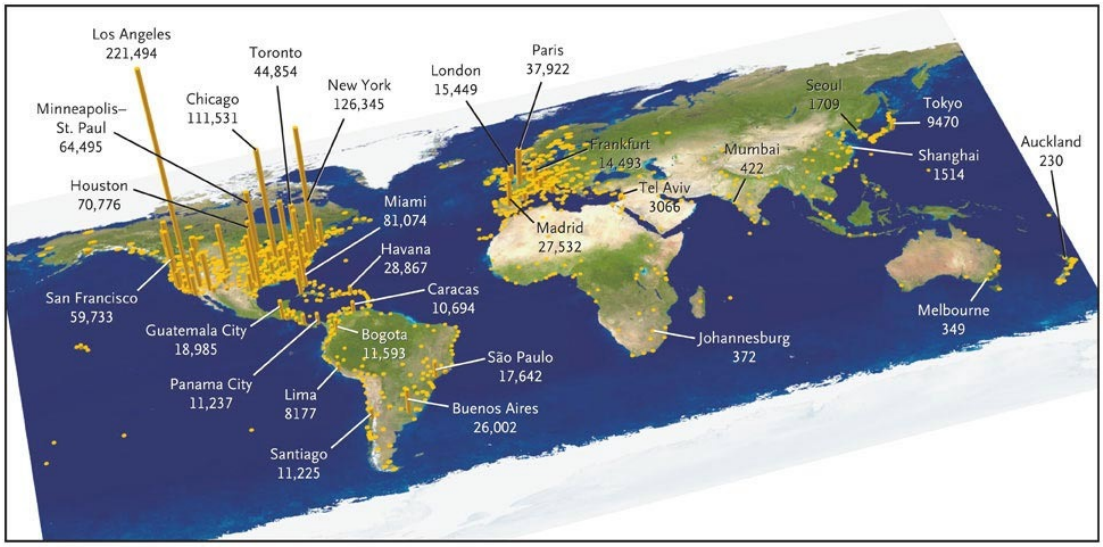


Figure 1.1: "Destination Cities and Corresponding Volumes of International Passengers Arriving from Mexico between March 1 and April 30, 2008." Reproduced with permission from Khan *et al.* 2009 [48], Copyright Massachusetts Medical Society.

onwards transmission through the isolation of identified cases from other susceptible individuals. Thus, the differing aims of testing mean the use of one type of test or testing strategy may be well-suited for one purpose, though suffer in another [49].

In the first instance, testing is usually prompted by the presentation of symptoms of disease which cause individuals to seek care. Upon initial clinical assessment, a medical professional will examine the patient and collect information on the symptom presentation. Some pathogens cause diseases with a specific, readily apparent set of symptoms which may be diagnosed with relatively high confidence visually; for example, Lyme disease, caused by the bacterium *Borrelia*, may manifest as a bullseye-shaped rash around the site of a tick bite [50]; genital warts caused by human papillomavirus have a clear presentation and are also often visually diagnosed by a dermatologist [51]. However other symptoms of infectious disease, such as a headache or cough, are non-specific, and could be caused by a variety of pathogens (or non-pathogenic diseases). In these cases, differential diagnosis [52] is required to narrow down the list of possible causative agents. This may involve the collection of additional information such as patient history, which may identify specific risk factors associated with certain diseases, e.g, who they have been in contact with (including sexual contact); where have they recently visited (e.g. a restaurant associated with a foodborne outbreak); or travelled to

(certain countries where an outbreak may be occurring, or where a certain disease may be endemic).

Based on the information collected, the clinician may request biological samples to be taken for further analysis with the aim of identifying the causative agent. For respiratory infections, this may involve swabbing of the upper airway; most typically, the nasopharynx (NP), which is colonised by a number of pathogenic and non-pathogenic bacteria and viruses. After sampling, the pathogen must be isolated and typed. Prior to the advent of molecular microbiology, phenotypic typing was the standard [53], with samples grown in a culture medium known to be amenable to growth of the suspected pathogen, then visually inspected (macro and/or microscopically) or subjected to additional testing (e.g., Gram staining, serotyping). Such methods involve a degree of subjectivity, are labour and time-intensive, and require that the organism is able to grow in a culture medium.

In the last few decades, molecular or genomic typing has largely replaced the need for phenotypic typing due to a reduction in cost and increased sensitivity and specificity. Molecular typing involves the extraction and subsequent amplification of genetic material (DNA or RNA) through a process such as reverse-transcription polymerase chain reaction (RT-PCR), with the resultant gene fragments compared against known samples to find closely related fragments.

In PCR, specific pathogen genes within a sample are targeted through the use of primers, which are a pair of short sequences of RNA or single-stranded DNA which bound a specific region of the genome. These regions may include genes known to be present in the genomes of entire domains, but vary slightly by, e.g., species (such as the 16S ribosomal RNA gene in bacteria), or genes present only within one specific species (such as the S, N, and ORF1 genes of SARS-CoV-2 [54, 55]). These DNA segments are then amplified (copied many millions of times) by cycles of heating and cooling which mediates the synthesis of new DNA copies through denaturation, primer annealing, and extension. An extension of RT-PCR, real-time PCR, or qPCR (quantitative PCR) includes the addition of fluorescent dyes which are amplified during the process and measured after each cycle to determine the concentration of target DNA [56]. The more DNA present in the sample, the greater the fluorescence, and the fewer cycles required to breach a threshold known as the cycle threshold (Ct). Typically PCR

will be run for 40 cycles before stopping, with samples that do not breach the cycle threshold considered to be negative for that gene fragment. As such, PCR is semi-quantitative, with lower Ct values inversely correlated with more genetic material in the sample [57]. Once amplified, the sample may then be sequenced to reveal the entire genetic sequence, allowing for the determination of the relatedness of different samples and the identification of genetic variants.

PCR first requires the identification of the pathogen and its specific gene targets as soon as possible in the course of an outbreak so as to enable subsequent PCR testing. For SARS-CoV-2 the first sequence - derived from a sample taken from a 41-year old man hospitalised in Wuhan Central Hospital on 26 December 2019 - was posted on Genbank [58] and described in a post on the open source site virological.org on the 11th of January 2020 [59] (later Nature [60]). This rapid sharing of information enabled the creation of PCR assays to test for SARS-CoV-2 genetic material in samples from suspected cases in China and overseas [61].

PCR was used extensively throughout the COVID-19 pandemic to detect SARS-CoV-2 infection due to high sensitivity (proportion of true positives that receive a positive test), as well as rule out other infections due to high specificity (proportion of true negatives that receive a negative test) (Figure 1.2, Table 1.2) [62]. However, PCR testing requires extensive resources to conduct, logistical infrastructure to transport samples, and lab capacity (personnel, reagents, etc.) to carry out the process itself. As such, PCR may not be appropriate or affordable in some resource-limited settings. In addition, if the process is not sufficiently optimised, it may take several days following sampling to return a result [63], which may be detrimental to the control of fast-spreading pathogens.

Alternatively, rapid diagnostic tests (RDTs) are a type of diagnostic test that can produce results in a short period of time, usually within minutes to an hour. RDTs have been used for many years to diagnose a variety of infectious diseases, including HIV [37], malaria [64], and tuberculosis [65], as well as in other applications such as testing for pregnancy. Before the COVID-19 pandemic, RDTs were widely used in resource-limited settings as they do not require specialised equipment or trained personnel. RDTs can be particularly useful where a rapid diagnosis is important in order to prompt subsequent action quickly, e.g. for initiating

Concept	Definition
Sensitivity	The proportion of actual positive cases that the test correctly identifies as positive.
Specificity	The proportion of actual negative cases that the test correctly identifies as negative.
Positive Predictive Value (PPV)	The probability that a person with a positive test result is truly positive.
Negative Predictive Value (NPV)	The probability that a person with a negative test result is truly negative.
False Positives	These represent cases that the test incorrectly identifies as positive when they are actually negative.
False Negatives	These are cases that the test incorrectly identifies as negative when they are actually positive.

Table 1.2: Introduction to Key Concepts in Diagnostic Testing

treatment and limiting onwards transmission.

RDTs vary in the specific method used to detect an infection; one type of test used extensively during the COVID-19 pandemic is that of a lateral flow antigen test (Ag-LFT, or simply LFT; also frequently called rapid antigen tests (RATs)) which detects specific immunogenic viral proteins (antigens, typically the nucleocapsid protein in the case of SARS-CoV-2). A swab sample is taken from the nose and/or throat, mixed in a liquid buffer solution which breaks up viral fragments, which is then deposited into a sample well on a device. The liquid then flows along a paper strip coated with antibodies conjugated to a visible label (e.g. gold, carbon, or latex nanoparticles). Any antigen present in the sample will then bind to these labelled antibodies and eventually flow to the test line, which is also coated with antibodies specific to the viral antigen, where the labelled antibody-antigen complex binds and becomes fixed to the strip. Any free labelled antibodies flow to the control line, which is coated with antibodies which bind and fix the free labelled antibodies. A positive test is indicated by the appearance of two lines (both test and control) which appears through the accumulation of the labelling marker, whereas a negative test will appear as a single line for the control [66].

Most LFTs for SARS-CoV-2 return a result in between 15-30 minutes, which can enable rapid action following the result. However, they may be less sensitive when compared against PCR as the gold standard, as they lack the amplification step which allows for the detection of very small quantities of viral genetic material. As such, the use of such tests was criticised by some parts of the public health community due to concern over the rate of false positives (as well

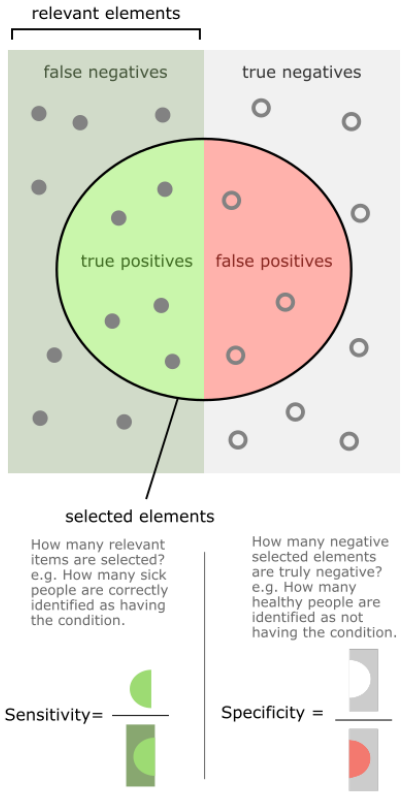


Figure 1.2: Diagram demonstrating the concepts of sensitivity and specificity. The section of the circle with solid dots represents individuals who have a certain condition, while the section with hollow dots represents those who do not have it. The circle in the diagram represents all individuals who have tested positive for the condition. Image by FeanDoe, modified from Walber's Precision and Recall. Available at https://commons.wikimedia.org/wiki/File:Precisionrecall.svg. Licensed under the Creative Commons Attribution-ShareAlike 4.0 International License. https://creativecommons.org/licenses/by-sa/4.0/legalcode

as false negatives) [67]. However, a key additional factor to consider is that of how sensitivity changes over the course of infection with changes in viral load and infectiousness (Figure 1.3). PCR may detect low levels of viral RNA long after the infectious period (as defined by the period in which culturable virus is shed), in some cases for weeks or months [68]. For LFTs the detection curve more closely correlates with that of culture; later in the pandemic, paired sample studies [69], daily longitudinal sampling studies [70] and challenge studies [71] found LFTs to be positive for 93-97% of culturable samples. Hence, while PCR may be more sensitive to viral RNA, it may be considered less specific if the aim of testing is to detect cases and isolate cases when they are most infectious to prevent onward transmission. Furthermore, the ability to repeatedly and frequently test with LFTs given their cost and ease of use increases the overall sensitivity of the testing regimen and may lead to earlier detection

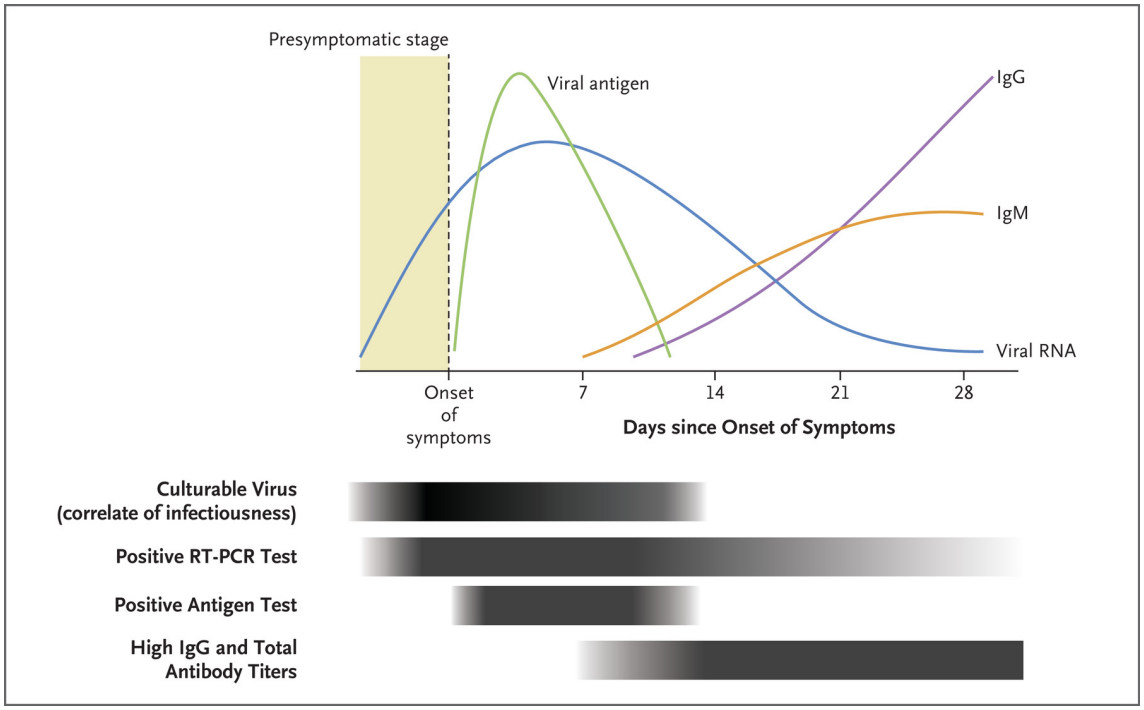


Figure 1.3: The ability of different tests to detect SARS-CoV-2 infection varies over the course of infection, here shown relative to the onset of symptoms, reproduced from Drain 2022 [66].

than a one-off PCR test [72, 73, 74] (Figure 1.4).

Distinct goals of testing, such as clinical testing for diagnosing disease and initiating treatment versus testing to inhibit onward transmission, are analogous to the divergent aims of medicine and public health – the former focusing on the direct benefit for the individual, and the latter on the indirect benefit to the population [75]. Consequently, the appraisal of tests for each purpose requires the assessment of different sets of variables. From a clinical perspective, diagnostic testing hinges on high sensitivity and specificity. High sensitivity is crucial to avoid missing crucial infections that require immediate medical intervention. High specificity, on the other hand, ensures that the medical resources are not wasted on false positives, including unnecessary treatments and patient anxiety. However, when viewed as a public health tool during a pandemic, the evaluation parameters for testing expand beyond sensitivity and specificity [76]. Considerations include the turnaround time for test results (which should ideally align with the infectious period of the disease), the extent and acceptance of testing in the population, and the frequency of testing. Different tests may vary in their capacity to meet these requirements, making some tests more useful for certain applications than others. As such, it is not just about having a test, but about having the right test for the right purpose,

evaluated on appropriate parameters.

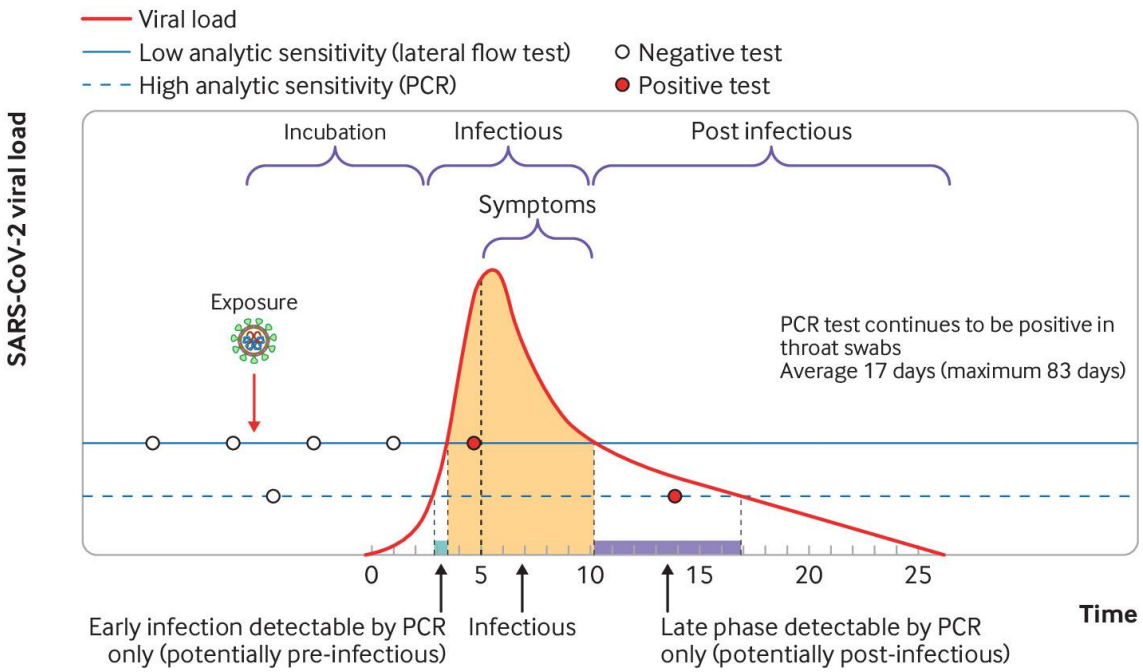


Figure 1.4: Testing for SARS-CoV-2 with PCR and LFTs. PCR has high analytical sensitivity but may detect viral RNA for an extended period and is infeasible to use at high frequency. LFTs have lower analytical sensitivity but may be more specific to the infectious period, and can be used frequently. Reproduced with permission from "Put to the test: use of rapid testing technologies for covid-19" by Crozier *et al.*, 372:n208, 2021, with permission from BMJ Publishing Group Ltd. [74].

In addition to PCR and rapid antigen testing, antibody tests may be conducted to find evidence of prior infection or vaccination. Such tests have been used to estimate the prevalence of immunity to SARS-CoV-2 on the population level in studies such as REACT-2 in the UK [77].

Symptomatic vs. asymptomatic testing

COVID-19 manifests as a respiratory illness varying in severity and symptom profile between individuals [78]. The majority experience a relatively mild illness, though some experience severe symptoms which result in hospitalisation and in some cases, death. The most common symptoms experienced were fever, cough, fatigue, and a loss or change in sense of taste or smell. During the pandemic, individuals experiencing such symptoms were advised to limit contact with others and seek out a test in most countries [79]. In the UK, this would prompt contact tracing through NHS Test & Trace, which was rapidly devised as a centralised contact tracing system [80].

Some countries introduced asymptomatic testing in addition to testing following symptom onset. This was primarily motivated by the reported proportion of asymptomatic cases and the extent of pre- and asymptomatic transmission [81, 82, 83, 84, 85]. Asymptomatic testing was introduced in multiple forms, though typically used LFTs due to their low cost, ease of use, and rapidity. Mass population-wide testing, which aimed to rapidly control SARS-CoV-2 transmission through the detection and rapid isolation of anyone who tested positive, was proposed by Larremore *et al.* [73] and was employed in high-profile campaigns such as the two rounds of whole-population testing in Slovakia (leading to an estimated 70% decrease in prevalence) [86] and the Liverpool mass testing trial in the UK [87] (estimated to have reduced hospitalisations in Liverpool by 43% [88]). Additionally, daily asymptomatic testing was employed for contacts in lieu of quarantine (daily contact testing; DCT) following modelling such as that described in this thesis (Chapter 3.1) and subsequent randomised controlled trials including a cluster RCT in schools [89] and an RCT in the general population [90].

An additional factor to consider when conducting asymptomatic testing is that the chance of an individual being truly infected with SARS-CoV-2 differs dramatically in the two scenarios. It can be reasonably assumed that there is a lower probability that an asymptomatic member of the public is truly infected with SARS-CoV-2 compared to an individual presenting with the core SARS-CoV-2 symptoms of a cough, fever, and loss of taste/smell, or someone who has recently been in contact with someone with a suspected or confirmed SARS-CoV-2 infection. As such, when combined with the false positive rate of the test, this affects the positive predictive value (PPV, the probability that someone who has a positive test truly has the disease) of testing. This may be mitigated through the use of a highly specific (low false positive rate) test, or an additional confirmatory testing for tests returned positive (though this may result in a loss of sensitivity) [91]. In addition, the current prevalence of infection in the community (i.e., the pre-test probability) will influence the PPV, with PPV increasing during times of high prevalence and decreasing during times of low prevalence.

Contact tracing

While identification of cases through testing is a key intervention, it will do little to control transmission unless further steps are taken, namely to prompt isolation of the case and trig-

ger contact tracing. Contact tracing aims to reduce transmission through the quarantine of exposed contacts of identified cases before they go on to infect others themselves. Contact tracing has been used extensively in the control of HIV [92] and during recent Ebola outbreaks such as in Liberia [93]. A 2021 review found its effectiveness to depend on - similarly to travel restrictions - transmissibility and timeliness, as well as factors such as the number of contacts traced, compliance, and the logistical challenges associated with tracing in large, rapidly growing outbreaks [94]. The speed of tracing relative to the timing of infectiousness has been identified as a key factor in its success [95, 96]. Contact tracing also depends on significant human resources, requiring a large team of tracers to interview cases, determine a contact diary, reach out to those contacts, and ensure they isolate, all before those contacts infect others. Furthermore, as an epidemic grows and more people test positive, the number of contacts grows non-linearly, all of whom must be contacted and asked to quarantine themselves [49], a task that may become prohibitively large given a large enough epidemic. Digital contact tracing, in which mobile app-based tracking systems are used to determine and rapidly inform contacts of their interaction with infected individuals, was proposed and used in some countries including the UK as a supplement to, or replacement for, human contact tracers during the COVID-19 pandemic [97, 98].

Extending the concepts of sensitivity and specificity to the assessment of NPIs

Evaluating the effectiveness of NPIs can benefit from the use of concepts traditionally used in diagnostic evaluations: sensitivity and specificity. Interventions like lockdowns, school and workplace closures, and quarantines might be seen as having a high sensitivity for capturing infected individuals and thus preventing transmission. However, within this framework, these measures have low specificity, as they also capture many individuals who are not infected. This is analogous to the negative impacts of false positives in diagnostics - people who face unnecessary costs or burden of the intervention despite not being infected. Some interventions might aim at improving this specificity; for example, testing individuals who have been asked to quarantine either as part of travel restrictions or in contact tracing may increase the specificity of quarantine by identifying truly infected individuals for isolation while allowing those not infected to leave quarantine. Adopting sensitivity and specificity as criteria may allow for a more comprehensive analysis of the costs associated with different measures relative to

the reductions in transmission observed.

1.2.3 Pathogen characteristics influencing transmission and control

Prior to the emergence of SARS-CoV-2, much of the evidence base for the effectiveness of NPIs against high consequence infectious diseases was for pandemic influenza [99, 100, 101], SARS [102], and Ebola [103]. The effectiveness of particular NPIs on control is likely to vary based on the characteristics of the pathogen, which will influence its transmission dynamics. As a respiratory pathogen, it could be assumed that NPIs that were effective against SARS or influenza would likely also be effective against SARS-CoV-2.

Key to the control of pathogens such as SARS and Ebola is the identification of cases through syndromic surveillance [104], as, for example, for SARS severe, specific symptoms developed in the majority of cases approximately 4 days after exposure [105], which allowed for the straightforward detection and isolation of cases and their contacts. Another key factor is the time interval between an index case becoming infected and subsequently infecting others, typically referred to as the generation time, which can be used to infer how infectious an individual may be over the course of infection. While the timing of the development of symptoms and infectiousness are usually assumed to be roughly correlated based on the assumption that symptoms indicate a high viral load and coughing/sneezing may facilitate transmission [106], there is a period of time where transmission may occur before the onset of symptoms. Fraser *et al.* estimated that the proportion of SARS transmission that occurs prior to the onset of symptoms, or from fully asymptomatic individuals, was <11% [105]. In contrast, an individual infected with HIV may be without symptoms and infectious for weeks to months before the development of symptoms (Fraser *et al.* estimated that >80% of HIV transmission occurs prior to the development of symptoms). Hence, the ability to control outbreaks of a novel pathogen through contact tracing of symptomatic cases will depend on this fraction, in addition to transmissibility (R_0) [105]. However, if case identification can occur prior to onset, i.e., through screening or testing, then this may be counteracted, depending on the point of infection where an individual becomes detectable. The importance of the incubation period, generation time, and the proportion of transmission that occurs before or in the absence of symptoms will also determine the success of travel interventions based on screening or testing.

A key study to elucidate these parameters early is the study of infector-infectee (or case-contact, or transmission) pairs that can be collected during the course of contact tracing. In this study, infected individuals are identified and interviewed, recording information such as their date of symptom onset and their contact history. These contacts are also then identified and followed up over time; if they become infected, their symptom onset timing is also recorded. This allows for the estimation of several key parameters:

- the incubation period (time between (presumed) exposure and symptom onset);
- the serial interval (the time between symptom onset in the index case (infector) and the secondary case (infectee) becoming symptomatic);
- an approximation of the generation time (time between infection in the index case and secondary case), for which the mean is often assumed to be approximately equal to the mean of the serial interval, assuming the infector and infected have the same incubation period distribution [107];
- the reproduction number (the expected number of secondary infections produced by one index case);
- and the secondary attack rate (the proportion of exposed contacts that become infected).

Recording the values of each of these parameters for multiple infector-infectee pairs allows for the estimation of the empirical density distribution of each, and subsequently an estimate of the population probability density distribution through making an assumption about the functional form (e.g. whether the parameter is strictly positive, or right-skewed) and using some method of fitting to data (e.g via maximum likelihood or Markov Chain Monte Carlo (MCMC)). Knowledge of the distribution rather than a single value such as the mean allows for the accounting of uncertainty and variability inherent in the data in subsequent modelling.

Incubation period: The duration of the incubation period - particularly its upper bound - has been key to control in the early stages of outbreaks of diseases such as Ebola as it determines the duration that contacts of cases should be monitored for [108]. Individuals infected with

Ebola are known to be infectious only once they become symptomatic, with little evidence of asymptomatic infection during the acute phase [84] (though delayed sexual transmission had been observed [109]). Hence it is a viable control strategy to monitor contacts of cases for symptoms for 21 days (the upper bound of the incubation period) and then release. For SARS-CoV-2 this upper bound (the 95% quantile) was identified early on as being approximately 14 days [110].

Serial interval and generation time: The serial interval is often used as a proxy for the generation time as it is more easily observed (especially early in an outbreak), though the serial interval may take negative values if symptom onset in the infectee precedes that of the infector, whereas the generation time can only be positive. The generation time can then be used in control by considering that to prevent 50% of transmission, infected individuals should be detected and isolated before the median generation time (as this is the point at which half of their contacts would have been infected). It then also follows that isolating individuals earlier subsequently prevents a greater proportion of their potential for transmission by truncating the generation time. The generation time can also be decomposed into two constituent parts: the latent (pre-infectious) period, and the infectious period [111].

Proportion of transmission occurring in the absence of symptoms: The relative duration of the incubation period and serial interval have significant relevance to control by giving an indication of the proportion of transmission that may occur before the onset of symptoms. If a substantial proportion of the serial interval distribution precedes that of the incubation period distribution then it can be inferred that transmission often occurs in the absence of symptoms [81]. In addition, the proportion of infected individuals who do not experience symptoms at all (or symptoms not included in the case definition [112]) may contribute to this fraction. This has been identified as a key factor in the control of outbreaks using syndromic surveillance, including SARS and Ebola [105].

Reproduction number: The reproduction number (R) is a central concept in infectious disease dynamics, representing the expected number of secondary infections that a single infected individual produces, with the basic reproduction number (R_0) being the expected number of secondary infections that a single infected individual produces in a susceptible popula-

tion [113]. If R is greater than 1, the disease is expected to grow exponentially. Conversely, if R0 is less than 1, the epidemic will decline. Estimation of R and R0 is crucial during the initial phase of an epidemic in order to forecast likely trajectories of the epidemic, the likely final size (the total proportion of the population likely to be infected over the course of the epidemic) [114], the likely herd immunity threshold (given by $1\text{-}1/R_0$), assuming a homogeneously mixed population [32]) and for designing and implementing effective control measures such as contact tracing, as it will determine the required reduction in transmission required to reduce R below 1 and achieve control [115].

Secondary attack rate: The secondary attack rate can be a useful metric to determine transmissibility and can be stratified within certain settings or groups, for example, amongst households, or amongst contacts at a social gathering. Estimates of the secondary attack rate for SARS-CoV-2 vary substantially based on the setting and variant [116, 117], though were typically lower for out-of-household contacts than for household contacts (e.g. estimated at 5.6% vs. 10.2% for the Alpha variant in 2021 [118]). Taking the complement of the secondary attack rate implies that 90%+ of contacts do not become infected (even greater for out-of-household contacts) implying the non-specificity of a policy based on quarantining all contacts regardless of infection status and the potential value of testing.

Infector-infectee pair studies and the parameters estimated may be biased by several factors [119]. The question of "who-infected-whom?" can be difficult to answer in the absence of sequencing data to reconstruct a transmission tree [120] (which may also be difficult in the case of slow-evolving pathogens such as bacteria - though this may be compensated for by the larger size of bacterial genomes) and may rely on somewhat circumstantial evidence, such as the index having known contact with a case in the days preceding contact with the secondary case, or that the pair reside in the same household. Nevertheless, in a high-prevalence epidemic, there is the distinct possibility that an infectee was actually infected by someone other than the presumed infector, or for there to be missing generations of infection. Contact tracing studies that estimate generation time via the serial interval by identifying individuals with specific symptoms will miss asymptomatic infections, which may have a different infectiousness profile to symptomatics (e.g., they won't isolate upon symptom onset (more infectious relative to symptomatics) or have lower viral loads (less infectious relative to symptomatics)). Studies

conducted during a growing epidemic will also be biased towards shorter serial intervals as more individuals are infected within a shorter span of time, with local competition for susceptible individuals occurring [121]. Interventions may also shorten the serial interval if individuals are detected and isolated earlier, truncating their infection profile [122].

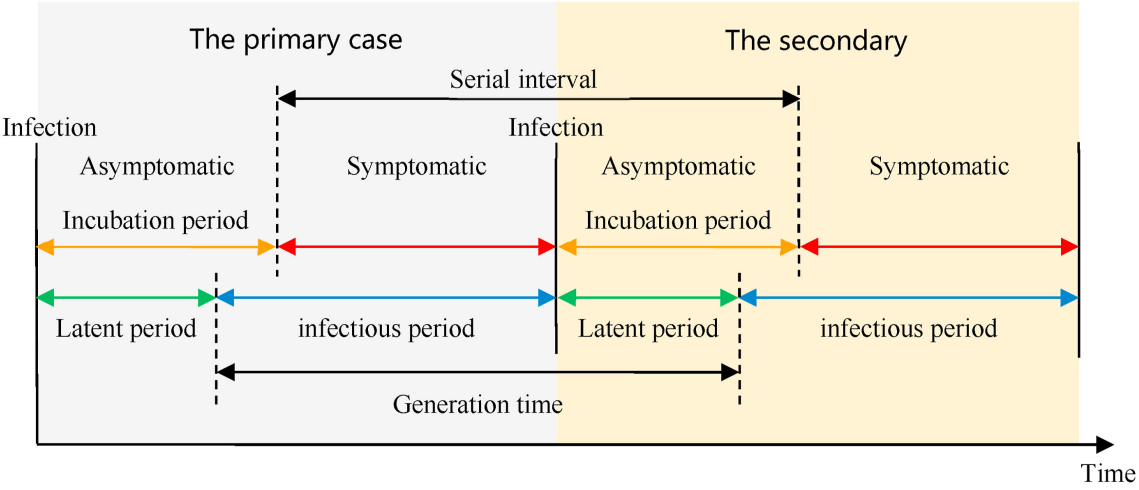


Figure 1.5: Key delay distributions, reproduced from Xiang *et al.* 2021 [123].

1.2.4 Human factors influencing transmission and control

In addition to the intrinsic characteristics of the pathogen, behavioural, societal, and environmental factors will influence the rate and extent of spread and the likelihood of control. These factors are also likely to vary substantially between individuals and across different demographics (heterogeneity).

As SARS-CoV-2 and other respiratory infections primarily transmit directly from person to person, the rate at which an individual makes contact with others has been identified as a key determinant of the rate of spread [124]. Social contact surveys such as POLYMOD [124] found contact rates to vary substantially by age, with individuals being more likely to mix with individuals in their own age group than others ("assortative" mixing), as well as clear patterns of mixing between generations (parent-child and vice versa). Social contacts also vary by setting (home, school, work, etc.) in their frequency, duration and intensity, with home contacts being more frequent, for longer, and closer than out-of-household contacts. The distribution of the number of contacts was also shown to be highly skewed, with some individuals making many more contacts than others. As well as the number of contacts, the underlying structure of a

contact network can be influential in transmission [125]. For example, social networks may be heterogeneous and clustered, with individuals making many contacts within a particular group more often than they do outside of that group; as an epidemic progresses through a particularly susceptible demographic subgroup, the depletion of susceptibility within that group may lead to a peak and decline lower than that expected if there was no heterogeneity in the contact network of the entire population. A clear example of this is in the global outbreak of Mpox in 2022, which predominantly spread though through the men who have sex with men (MSM) community with limited spread into other demographic groups, which could be reasonably explained by the heavy-tailed and clustered nature of the sexual partnership network in this community [126]. Contacts may also be heterogeneous over time, with school holidays [127] and public holidays such as Christmas resulting in a short-term change in contacts as well as in disassortative mixing as individuals make contact with others that they do not regularly interact on a day to day basis (e.g. grandparents and young children). Such changes in contacts have been implicated as a factor driving the seasonal nature of respiratory pathogen epidemiology such as measles [128]. Other such examples of changing contact rates influencing transmission include the suppression of RSV during COVID-19 mitigation measures [129] and outbreaks of "fresher's flu" (influenza-like illness in university students) reportedly disproportionately affecting 1st year undergraduates attending university for the first time [130].

Economic factors may also impact transmission and control. People living in poverty may be more likely to live in overcrowded or unsanitary conditions, increasing the risk of infection [131, 132, 133] and making true isolation within the household difficult or impossible. Those living on low incomes may be less likely to be able to fully isolate or quarantine compared to those on higher incomes as they may be forced to continue to attend work in order to make a living; thus support payments for those asked to quarantine have been identified as a key intervention to improve adherence [134].

The specifics and quality of how public health authorities and governments implement NPIs can have a significant impact on their effectiveness. As previously described, NPIs such as contact tracing require significant investment in infrastructure and human resources in order to function effectively; there are many ways in which new infections may continue to occur, stemming from not detecting a certain fraction of infections (dependent on testing coverage),

to tracing an insufficient proportion of contacts [115], to not ensuring contacts isolate promptly [96]. Each step of the process provides an opportunity for transmission to occur should the implementation fail to meet certain standards. Implementing each step requires significant investment, which may be prohibitive for certain countries.

The previously described measures such as contact tracing or travel restrictions, in requiring individuals to restrict their freedom of movement, infringe upon personal liberties usually taken for granted. The acceptability, participation and adherence of society to such measures are likely to have a significant impact on their effectiveness. Prior to the SARS-CoV-2 pandemic, there were concerns about what interventions may be required to manage a pandemic, and what the public could reasonably be asked to do. Following the 2009 H1N1 Influenza pandemic, Teasdale and Yardley led focus groups in the UK to explore public perceptions of health recommendations, finding participants to be "sceptical about the feasibility and appropriateness of government recommendations for managing the H1N1 pandemic", with "concerns regarding the perceived effectiveness and costs of recommendations to stay home if unwell and get vaccinated" [135]. They and others recommended that these concerns be assuaged through strong communication of the reasons for carrying out the intervention, as well as support for those asked to make personal sacrifices [134]. This perception of attitudes in the UK may be contrasted with that of East Asian countries, which had been most affected by the SARS pandemic. A discrete choice study in Singapore found that people were more likely to support stronger interventions that encroached upon civil liberties if it was clear that such measures would reduce the adverse health impacts of the outbreak [136]. Similarly in South Korea (which had an outbreak of MERS in 2015 with 186 cases and 36 deaths), individuals were willing to disclose detailed accounts of their movements if it was to be used for the public good [137]. Going into the SARS-CoV-2 pandemic there were considerable differences in the breadth of interventions deemed feasible and acceptable by governments in different countries, though most countries eventually followed China's approach of lockdowns to control transmission [10].

Such approaches, while likely to reduce transmission [138, 95], put a significant burden on individuals and society [139]. As such, there is an imperative to investigate alternative strategies and new technologies should they become available.

1.2.5 Modelling approaches

Estimating the impact of non-pharmaceutical interventions during a pandemic of a novel pathogen is difficult. As discussed in Section 1.2.3, interventions used previously in an outbreak of disease caused by one pathogen may be ineffective if used against another as a result of differences in the dynamics of infection and transmission. Interventions may also have to be implemented at short notice where conducting a controlled trial may lead to unacceptable delay. Mathematical modelling allows for the estimation of the impact of crucial public-health measures by distilling a complex real-world system into its most relevant components. Approaches vary in how they represent a population and epidemic dynamics; Lipsitch *et al.* modelled interventions against the 2003 SARS pandemic using a population-level deterministic compartmental model of the SEIR (susceptible, exposed, infected, recovered) form, modified to include additional compartments to accommodate quarantine and isolation [102] (with a stochastic analysis also included); other studies such as Ferguson *et al.* modelled pandemic influenza with an individual-level, spatially-explicit, household-structured, stochastic model, modelling the movements, demographics, and behaviour of millions of people, with interventions modelled as reductions in contact rates between individuals [43].

Population-based models may be used to predict the overall spread of an epidemic at a macroscale, and allow for the capture of emergent properties of an epidemic that occur on the population-level, such as the depletion of susceptibles which in turn leads to a decline in incidence. However, they are less useful in determining the influence of individual-level factors on transmission. For example, how infection progresses on an individual-level (particularly viral load kinetics over the course of infection) determines the ability of a test to detect an infected individual and subsequently prevent transmission through isolation [140, 141]. Such properties may also vary substantially between individuals based on other factors such as age, or vaccination status (heterogeneity), as well as be highly uncertain in situations with a sparsity of data. Individual-level simulations allow for agents in the model to have their own unique progression of disease and infectiousness by drawing from parameter distributions, with the outcome of interventions such as syndromic screening depending on that individual's current stage of infection at the point of implementation. This may also be extended to simulate the within-host dynamics of viral replication, which ultimately determine the pathogen's natural

history and transmission dynamics [142]. However, simulating individuals at high temporal resolution in this way is computationally intensive, and as such the modelling of small communities or a small number of generations of infection is more feasible than the populations of entire countries. Thus, a limitation of this approach is that the dynamics of an epidemic on the population-level are typically unable to be reproduced without significant computational capability [143]. However such factors - for example, susceptible depletion - may not have a substantial impact on modelled outcomes early in a pandemic when few individuals have been infected and hence may be omitted from model formulation for parsimony.

By incorporating individual-level heterogeneity and uncertainty in the modelling process, we can better represent heterogeneity and uncertainty in our estimated outcomes. Being explicit about the extent to which we have confidence in a model outcome allows for nuance in policy and decision-making, and may facilitate the allocation of resources to better understand a particular phenomenon identified as uncertain in the model e.g. through conducting observational or intervention studies.

1.3 Aim

The aim of this thesis is to determine the effectiveness of policies and strategies including travel restrictions, quarantine, and testing to both reduce transmission and limit the burden of restrictions during the COVID-19 pandemic.

1.4 Objectives

The objectives of the research presented in this PhD thesis were to:

1. Assess the impact of travel restrictions to limit geographical spread of SARS-CoV-2, including:
    (a) Evaluating the impact of thermal screening at airports;
    (b) Determining the effectiveness of *cordon sanitaires* to contain SARS-CoV-2 to a geographic area;

(c) Assessing the value of PCR testing to supplement or shorten quarantine for travellers;

(d) Estimating the risk of importation globally, and assessing the value of rapid antigen testing compared to PCR testing for travellers;

2. Determine the effectiveness of interventions to limit community spread, including:

(a) Estimating the effectiveness of PCR and rapid antigen testing to supplement or replace quarantine in contact tracing;

(b) Evaluating how heterogeneity in viral loads and contact rates contribute to heterogeneity in infection, and how this may be leveraged for transmission control with testing.

The objectives are addressed and presented as research papers in either their published form (Chapters 2.1, 2.2, 2.3, and 3.1) or as a pre-print (Chapters 2.4 and 3.2). This research was conducted as the pandemic progressed, with the objectives chosen based on consultation with advisory groups including the Scientific Pandemic Influenza Group on Modelling, Operational sub-group (SPI-M-O) of the Scientific Advisory Group for Emergencies (SAGE) in the UK [144] and non-governmental bodies including the World Health Organization (WHO) and European Centre for Disease Control (ECDC) to identify where there were gaps in current understanding, and in order to inform decision-making.

1.5 References

[1] *Archived: WHO Timeline - COVID-19*. https://www.who.int/news/item/27-04-2020-who-timeline—covid-19. (Visited on 12/29/2020).

[2] T. Greenhalgh, J. L. Jimenez, K. A. Prather, Z. Tufekci, D. Fisman, and R. Schooley. "Ten Scientific Reasons in Support of Airborne Transmission of SARS-CoV-2". In: *The Lancet* 397.10285 (May 2021), pp. 1603–1605. ISSN: 0140-6736, 1474-547X. DOI: 10.1016/S0140-6736(21)00869-2. (Visited on 01/18/2023).

[3] A. J. Kucharski et al. "Early Dynamics of Transmission and Control of COVID-19: A Mathematical Modelling Study". In: *The Lancet Infectious Diseases* 20.5 (May 2020), pp. 553–558. ISSN: 1473-3099. DOI: 10.1016/S1473-3099(20)30144-4. (Visited on 12/15/2022).

[4] J. Riou and C. L. Althaus. "Pattern of Early Human-to-Human Transmission of Wuhan 2019 Novel Coronavirus (2019-nCoV), December 2019 to January 2020". In: *Eurosurveillance* 25.4 (Jan. 2020), p. 2000058. ISSN: 1025-496X. DOI: 10.2807/1560-7917.ES.2020.25.4.2000058. (Visited on 12/15/2022).

[5] A. Endo, Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group, S. Abbott, A. J. Kucharski, and S. Funk. "Estimating the Overdispersion in COVID-19 Transmission Using Outbreak Sizes Outside China". In: *Wellcome Open Research* 5 (Apr. 2020), p. 67. ISSN: 2398-502X. DOI: 10.12688/wellcomeopenres.15842.1. (Visited on 04/19/2020).

[6] T. W. Russell et al. "Estimating the Infection and Case Fatality Ratio for Coronavirus Disease (COVID-19) Using Age-Adjusted Data from the Outbreak on the Diamond Princess Cruise Ship, February 2020". In: *Eurosurveillance* 25.12 (Mar. 2020), p. 2000256. ISSN: 1560-7917. DOI: 10.2807/1560-7917.ES.2020.25.12.2000256. (Visited on 12/15/2022).

[7] "Variation in the COVID-19 Infection–Fatality Ratio by Age, Time, and Geography during the Pre-Vaccine Era: A Systematic Analysis". In: *The Lancet* 399.10334 (Apr. 2022), pp. 1469–1488. ISSN: 0140-6736, 1474-547X. DOI: 10.1016/S0140-6736(21)02867-1. (Visited on 12/15/2022).

[8] H. Salje et al. “Estimating the Burden of SARS-CoV-2 in France”. In: *Science (New York, N.Y.)* 369.6500 (July 2020), pp. 208–211. ISSN: 1095-9203. DOI: 10.1126/science.abc3517.

[9] D. Cucinotta and M. Vanelli. “WHO Declares COVID-19 a Pandemic”. In: *Acta Bio Medica Atenei Parmensis* 91.1 (Mar. 2020), pp. 157–160. ISSN: 25316745, 03924203. DOI: 10.23750/abm.v91i1.9397. (Visited on 12/15/2022).

[10] *COVID-19 Government Response Tracker*. https://www.bsg.ox.ac.uk/research/covid-19-government-response-tracker. (Visited on 12/15/2022).

[11] M. Voysey et al. “Single-Dose Administration and the Influence of the Timing of the Booster Dose on Immunogenicity and Efficacy of ChAdOx1 nCoV-19 (AZD1222) Vaccine: A Pooled Analysis of Four Randomised Trials”. In: *The Lancet* 397.10277 (Mar. 2021), pp. 881–891. ISSN: 0140-6736. DOI: 10.1016/S0140-6736(21)00432-3. (Visited on 12/15/2022).

[12] F. P. Polack et al. “Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine”. In: *New England Journal of Medicine* 383.27 (Dec. 2020), pp. 2603–2615. ISSN: 0028-4793. DOI: 10.1056/NEJMoa2034577. (Visited on 12/15/2022).

[13] L. R. Baden et al. “Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine”. In: *New England Journal of Medicine* 384.5 (Feb. 2021), pp. 403–416. ISSN: 0028-4793. DOI: 10.1056/NEJMoa2035389. (Visited on 12/15/2022).

[14] *Coronavirus Vaccine Rollout*. https://www.instituteforgovernment.org.uk/explainers/coronavirus-vaccine-rollout. Jan. 2021. (Visited on 12/15/2022).

[15] N. G. Davies et al. “Estimated Transmissibility and Impact of SARS-CoV-2 Lineage B.1.1.7 in England”. In: *Science* (Mar. 2021). ISSN: 1095-9203. DOI: 10.1126/science.abg3055.

[16] N. G. Davies, C. I. Jarvis, W. J. Edmunds, N. P. Jewell, K. Diaz-Ordaz, and R. H. Keogh. “Increased Mortality in Community-Tested Cases of SARS-CoV-2 Lineage B.1.1.7”. In: *Nature* (Mar. 2021), pp. 1–5. ISSN: 1476-4687. DOI: 10.1038/s41586-021-03426-1. (Visited on 03/15/2021).

[17] J. R. C. Pulliam, C. van Schalkwyk, N. Govender, A. von Gottberg, C. Cohen,

M. J. Groome, J. Dushoff, K. Mlisana, and H. Moultrie. “Increased Risk of SARS-CoV-2 Reinfection Associated with Emergence of Omicron in South Africa”. In: *Science (New York, N.Y.)* 376.6593 (May 2022), eabn4947. ISSN: 1095-9203. DOI: 10.1126/science.abn4947.

[18] *The Pandemic’s True Death Toll*. https://www.economist.com/graphic-detail/coronavirus-excess-deaths-estimates. (Visited on 12/14/2022).

[19] W. Msemburi, A. Karlinsky, V. Knutson, S. Aleshin-Guendel, S. Chatterji, and J. Wakefield. “The WHO Estimates of Excess Mortality Associated with the COVID-19 Pandemic”. In: *Nature* (Dec. 2022), pp. 1–8. ISSN: 1476-4687. DOI: 10.1038/s41586-022-05522-2. (Visited on 12/15/2022).

[20] *Coronavirus: How the Pandemic Has Changed the World Economy - BBC News*. https://www.bbc.co.uk/news/business-51706225. (Visited on 12/15/2022).

[21] V. McKeever. *The Coronavirus Is Expected to Have Cost 400 Million Jobs in the Second Quarter, UN Labor Agency Estimates*. https://www.cnbc.com/2020/06/30/coronavirus-expected-to-cost-400-million-jobs-in-the-second-quarter.html. (Visited on 12/15/2022).

[22] *The EU Economy after COVID-19: Implications for Economic Governance*. https://cepr.org/voxeu/columns/eu-economy-after-covid-19-implications-economic-governance. (Visited on 12/15/2022).

[23] T. Vos et al. “Global Burden of 369 Diseases and Injuries in 204 Countries and Territories, 1990–2019: A Systematic Analysis for the Global Burden of Disease Study 2019”. In: *The Lancet* 396.10258 (Oct. 2020), pp. 1204–1222. ISSN: 0140-6736, 1474-547X. DOI: 10.1016/S0140-6736(20)30925-9. (Visited on 07/10/2023).

[24] CDC. *Principles of Epidemiology | Lesson 1 - Section 11*. https://www.cdc.gov/csels/dsepd/ss1978/lesson1/section11.html. Dec. 2021. (Visited on 07/07/2023).

[25] F. Brauer, C. Castillo-Chavez, and Z. Feng. “Endemic Disease Models”. In: *Mathematical Models in Epidemiology* 69 (June 2019), pp. 63–116. DOI: 10.1007/978-1-4939-9828-9_3. (Visited on 07/10/2023).

[26] B. Autino, A. Noris, R. Russo, and F. Castelli. “Epidemiology of Malaria in Endemic

Areas". In: *Mediterranean Journal of Hematology and Infectious Diseases* 4.1 (Oct. 2012), e2012060. ISSN: 2035-3006. DOI: 10.4084/MJHID.2012.060. (Visited on 07/07/2023).

[27] D. G. M. Jr. "Rubella Has Been Eliminated From the Americas, Health Officials Say". In: *The New York Times* (Apr. 2015). ISSN: 0362-4331. (Visited on 07/10/2023).

[28] S. Reef. "Rubella Mass Campaigns". In: *Mass Vaccination: Global Aspects — Progress and Obstacles*. Ed. by S. A. Plotkin. Current Topics in Microbiology and Immunology. Berlin, Heidelberg: Springer, 2006, pp. 221–229. ISBN: 978-3-540-36583-9. DOI: 10.1007/3-540-36583-4_12. (Visited on 07/10/2023).

[29] M. Porta. "A Dictionary of Epidemiology". In: *A Dictionary of Epidemiology*. Oxford University Press, July 2016. ISBN: 978-0-19-997672-0. (Visited on 07/08/2023).

[30] N. Madhav, B. Oppenheim, M. Gallivan, P. Mulembakani, E. Rubin, and N. Wolfe. "Pandemics: Risks, Impacts, and Mitigation". In: *Disease Control Priorities: Improving Health and Reducing Poverty*. Ed. by D. T. Jamison, H. Gelband, S. Horton, P. Jha, R. Laxminarayan, C. N. Mock, and R. Nugent. 3rd. Washington (DC): The International Bank for Reconstruction and Development / The World Bank, 2017. ISBN: 978-1-4648-0527-1 978-1-4648-0528-8. (Visited on 07/08/2023).

[31] *Pandemic Intervals Framework (PIF) | Pandemic Influenza (Flu) | CDC*. https://www.cdc.gov/flu/pandemic-resources/national-strategy/intervals-framework.html. Mar. 2022. (Visited on 07/10/2023).

[32] P. Fine, K. Eames, and D. L. Heymann. ""Herd Immunity": A Rough Guide". In: *Clinical Infectious Diseases* 52.7 (Apr. 2011), pp. 911–916. ISSN: 1058-4838, 1537-6591. DOI: 10.1093/cid/cir007. (Visited on 07/10/2023).

[33] G. Cacciapaglia, C. Cot, and F. Sannino. "Multiwave Pandemic Dynamics Explained: How to Tame the next Wave of Infectious Diseases". In: *Scientific Reports* 11.1 (Mar. 2021), p. 6638. ISSN: 2045-2322. DOI: 10.1038/s41598-021-85875-2. (Visited on 07/10/2023).

[34] Y. Liu et al. "The Impact of Non-Pharmaceutical Interventions on SARS-CoV-2 Transmission across 130 Countries and Territories". In: *BMC Medicine* 19.1 (Feb. 2021), p. 40. ISSN: 1741-7015. DOI: 10.1186/s12916-020-01872-8. (Visited on 03/09/2021).

[35] *Cholera*. https://www.who.int/news-room/fact-sheets/detail/cholera. (Visited on 12/13/2022).

[36] S. D. Pinkerton and P. R. Abramson. “Effectiveness of Condoms in Preventing HIV Transmission”. In: *Social Science & Medicine (1982)* 44.9 (May 1997), pp. 1303–1312. ISSN: 0277-9536. DOI: 10.1016/s0277-9536(96)00258-4.

[37] K. Pottie, O. Medu, V. Welch, G. P. Dahal, M. Tyndall, T. Rader, and G. Wells. “Effect of Rapid HIV Testing on HIV Incidence and Services in Populations at High Risk for HIV Exposure: An Equity-Focused Systematic Review”. In: *BMJ open* 4.12 (Dec. 2014), e006859. ISSN: 2044-6055. DOI: 10.1136/bmjopen-2014-006859.

[38] World Health Organization. *WHO | WHO Interim Protocol: Rapid Operations to Contain the Initial Emergence of Pandemic Influenza*. Tech. rep. World Health Organization, Oct. 2007. (Visited on 03/15/2021).

[39] “Timeline: Swine Flu”. In: *Nature* (Apr. 2009). ISSN: 1476-4687. DOI: 10.1038/news.2009.416. (Visited on 01/09/2023).

[40] P. Bajardi, C. Poletto, J. J. Ramasco, M. Tizzoni, V. Colizza, and A. Vespignani. “Human Mobility Networks, Travel Restrictions, and the Global Spread of 2009 H1N1 Pandemic”. In: *PLoS ONE* 6.1 (Jan. 2011), e16591. ISSN: 1932-6203. DOI: 10.1371/journal.pone.0016591. (Visited on 01/10/2023).

[41] “WHO Not Recommending Swine Flu Travel Restrictions”. In: *Reuters* (Apr. 2009). (Visited on 01/10/2023).

[42] A. L. P. Mateus, H. E. Otete, C. R. Beck, G. P. Dolan, and J. S. Nguyen-Van-Tam. “Effectiveness of Travel Restrictions in the Rapid Containment of Human Influenza: A Systematic Review”. In: *Bulletin of the World Health Organization* 92.12 (Dec. 2014), pp. 868–880D. ISSN: 1564-0604. DOI: 10.2471/BLT.14.135590.

[43] N. M. Ferguson, D. A. T. Cummings, C. Fraser, J. C. Cajka, P. C. Cooley, and D. S. Burke. “Strategies for Mitigating an Influenza Pandemic”. In: *Nature* 442.7101 (July 2006), pp. 448–452. ISSN: 1476-4687. DOI: 10.1038/nature04795.

[44] B. S. Cooper, R. J. Pitman, W. J. Edmunds, and N. J. Gay. “Delaying the International Spread of Pandemic Influenza”. In: *PLOS Medicine* 3.6 (May 2006), e212. ISSN: 1549-1676. DOI: 10.1371/journal.pmed.0030212. (Visited on 02/05/2023).

[45] G. Chowell and H. Nishiura. “Transmission Dynamics and Control of Ebola Virus

Disease (EVD): A Review". In: *BMC Medicine* 12 (Oct. 2014), p. 196. ISSN: 1741-7015. DOI: 10.1186/s12916-014-0196-0. (Visited on 02/05/2023).

[46] C. L. Althaus. "Estimating the Reproduction Number of Ebola Virus (EBOV) During the 2014 Outbreak in West Africa". In: *PLoS Currents* 6 (Sept. 2014). ISSN: 2157-3999. DOI: 10.1371/currents.outbreaks.91afb5e0f279e7f29e7056095255b288. (Visited on 03/17/2021).

[47] M. Hartfield and S. Alizon. "Introducing the Outbreak Threshold in Epidemiology". In: *PLoS Pathogens* 9.6 (June 2013). Ed. by G. F. Rall, e1003277. ISSN: 1553-7374. DOI: 10.1371/journal.ppat.1003277. (Visited on 02/19/2020).

[48] K. Khan et al. "Spread of a Novel Influenza A (H1N1) Virus via Global Airline Transportation". In: *New England Journal of Medicine* 361.2 (July 2009), pp. 212–214. ISSN: 0028-4793. DOI: 10.1056/NEJMc0904559. (Visited on 02/05/2023).

[49] T. R. Mercer and M. Salit. "Testing at Scale during the COVID-19 Pandemic". In: *Nature Reviews Genetics* 22.7 (July 2021), pp. 415–426. ISSN: 1471-0064. DOI: 10.1038/s41576-021-00360-w. (Visited on 01/10/2023).

[50] R. L. Bratton, J. W. Whiteside, M. J. Hovan, R. L. Engle, and F. D. Edwards. "Diagnosis and Treatment of Lyme Disease". In: *Mayo Clinic Proceedings* 83.5 (May 2008), pp. 566–571. ISSN: 1942-5546. DOI: 10.4065/83.5.566.

[51] D. J. Wiley, J. Douglas, K. Beutner, T. Cox, K. Fife, A.-B. Moscicki, and L. Fukumoto. "External Genital Warts: Diagnosis, Treatment, and Prevention". In: *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 35.Suppl 2 (Oct. 2002), S210–224. ISSN: 1537-6591. DOI: 10.1086/342109.

[52] C. E. Cook and S. Décary. "Higher Order Thinking about Differential Diagnosis". In: *Brazilian Journal of Physical Therapy* 24.1 (2020), pp. 1–7. ISSN: 1413-3555. DOI: 10.1016/j.bjpt.2019.01.010. (Visited on 01/09/2023).

[53] Y.-W. Tang, N. M. Ellis, M. K. Hopkins, D. H. Smith, D. E. Dodge, and D. H. Persing. "Comparison of Phenotypic and Genotypic Techniques for Identification of Unusual Aerobic Pathogenic Gram-Negative Bacilli". In: *Journal of Clinical Microbiology* 36.12 (Dec. 1998), pp. 3674–3679. ISSN: 0095-1137. (Visited on 08/11/2022).

[54] D. K. W. Chu et al. "Molecular Diagnosis of a Novel Coronavirus (2019-nCoV)

Causing an Outbreak of Pneumonia". In: *Clinical Chemistry* 66.4 (Apr. 2020), pp. 549–555. ISSN: 1530-8561. DOI: 10.1093/clinchem/hvaa029.

[55] J. F.-W. Chan et al. "A Familial Cluster of Pneumonia Associated with the 2019 Novel Coronavirus Indicating Person-to-Person Transmission: A Study of a Family Cluster". In: *Lancet (London, England)* 395.10223 (Feb. 2020), pp. 514–523. ISSN: 1474-547X. DOI: 10.1016/S0140-6736(20)30154-9.

[56] P. Kralik and M. Ricchi. "A Basic Guide to Real Time PCR in Microbial Diagnostics: Definitions, Parameters, and Everything". In: *Frontiers in Microbiology* 8 (2017). ISSN: 1664-302X. (Visited on 08/15/2022).

[57] Public Health England. *Understanding Cycle Threshold (Ct) in SARS-CoV-2 RT-PCR*. Tech. rep. (Visited on 12/17/2020).

[58] *Severe Acute Respiratory Syndrome Coronavirus 2 Isolate Wuhan-Hu-1, Complete Genome*. Mar. 2020. (Visited on 12/20/2022).

[59] *Novel 2019 Coronavirus Genome - SARS-CoV-2 Coronavirus*. https://virological.org/t/novel-2019-coronavirus-genome/319. Jan. 2020. (Visited on 12/19/2022).

[60] F. Wu et al. "A New Coronavirus Associated with Human Respiratory Disease in China". In: *Nature* 579.7798 (Mar. 2020), pp. 265–269. ISSN: 1476-4687. DOI: 10.1038/s41586-020-2008-3. (Visited on 12/19/2022).

[61] V. M. Corman et al. "Detection of 2019 Novel Coronavirus (2019-nCoV) by Real-Time RT-PCR". In: *Eurosurveillance* 25.3 (Jan. 2020), p. 2000045. ISSN: 1025-496X. DOI: 10.2807/1560-7917.ES.2020.25.3.2000045. (Visited on 10/06/2022).

[62] B. Böger, M. M. Fachi, R. O. Vilhena, A. F. Cobre, F. S. Tonin, and R. Pontarolo. "Systematic Review with Meta-Analysis of the Accuracy of Diagnostic Tests for COVID-19". In: *American Journal of Infection Control* 49.1 (Jan. 2021), pp. 21–29. ISSN: 0196-6553. DOI: 10.1016/j.ajic.2020.07.011. (Visited on 12/20/2022).

[63] UK Government. *Weekly NHS Test and Trace Bulletin, England: 20 August to 26 August 2020*. Tech. rep. Department of Health & Social Care, Mar. 2020.

[64] D. Bell and R. W. Peeling. "Evaluation of Rapid Diagnostic Tests: Malaria". In: *Nature Reviews Microbiology* 4.9 (Sept. 2006), S34–S38. ISSN: 1740-1534. DOI: 10.1038/nrmicro1524. (Visited on 12/19/2022).

[65] N. Engel, E. A. Ochodo, P. W. Karanja, B.-M. Schmidt, R. Janssen, K. R. Steingart, and S. Oliver. “Rapid Molecular Tests for Tuberculosis and Tuberculosis Drug Resistance: A Qualitative Evidence Synthesis of Recipient and Provider Views”. In: *Cochrane Database of Systematic Reviews* 2022.4 (2022). ISSN: 1465-1858. DOI: 10.1002/14651858.cd014877.pub2. (Visited on 02/08/2023).

[66] P. K. Drain. “Rapid Diagnostic Testing for SARS-CoV-2”. In: *The New England Journal of Medicine* (Jan. 2022), NEJMcp2117115. ISSN: 0028-4793. DOI: 10.1056/NEJMcp2117115. (Visited on 12/20/2022).

[67] I. Torjesen. “Covid-19: How the UK Is Using Lateral Flow Tests in the Pandemic”. In: *BMJ* 372 (Feb. 2021), n287. ISSN: 1756-1833. DOI: 10.1136/bmj.n287. (Visited on 01/13/2023).

[68] M. Cevik, M. Tate, O. Lloyd, A. E. Maraolo, J. Schafers, and A. Ho. “SARS-CoV-2, SARS-CoV, and MERS-CoV Viral Load Dynamics, Duration of Viral Shedding, and Infectiousness: A Systematic Review and Meta-Analysis”. In: *The Lancet Microbe* (Nov. 2020), S2666524720301725. ISSN: 26665247. DOI: 10.1016/S2666-5247(20)30172-5. (Visited on 12/02/2020).

[69] S. Pickering et al. “Comparative Performance of SARS-CoV-2 Lateral Flow Antigen Tests and Association with Detection of Infectious Virus in Clinical Specimens: A Single-Centre Laboratory Evaluation Study”. In: *The Lancet Microbe* 2.9 (Sept. 2021), e461–e471. ISSN: 2666-5247. DOI: 10.1016/S2666-5247(21)00143-9. (Visited on 03/03/2022).

[70] R. Ke et al. *Daily Sampling of Early SARS-CoV-2 Infection Reveals Substantial Heterogeneity in Infectiousness*. Preprint. Infectious Diseases (except HIV/AIDS), July 2021. DOI: 10.1101/2021.07.12.21260208. (Visited on 12/23/2021).

[71] B. Killingley et al. *Safety, Tolerability and Viral Kinetics during SARS-CoV-2 Human Challenge*. Mar. 2022. DOI: 10.21203/rs.3.rs-1121993/v1. (Visited on 03/03/2022).

[72] B. J. Quilty, S. Clifford, J. Hellewell, T. W. Russell, A. J. Kucharski, CMMID COVID-19 Working Group, S. Flasche, and W. J. Edmunds. “Quarantine and Testing Strategies in Contact Tracing for SARS-CoV-2: A Modelling Study”. In: *Lancet Public Health* (Jan. 2021). DOI: 10.1016/S2468-2667(20)30308-X. (Visited on 02/20/2021).

[73] D. B. Larremore, B. Wilder, E. Lester, S. Shehata, J. M. Burke, J. A. Hay, M. Tambe, M. J. Mina, and R. Parker. “Test Sensitivity Is Secondary to Frequency and Turnaround Time for COVID-19 Screening”. In: *Science Advances* 7.1 (Jan. 2021), eabd5393. ISSN: 2375-2548. DOI: 10.1126/sciadv.abd5393.

[74] A. Crozier, S. Rajan, I. Buchan, and M. McKee. “Put to the Test: Use of Rapid Testing Technologies for Covid-19”. In: *BMJ* 372 (Feb. 2021), n208. ISSN: 1756-1833. DOI: 10.1136/bmj.n208. (Visited on 09/26/2022).

[75] H. V. Fineberg. “Public Health and Medicine: Where the Twain Shall Meet”. In: *American Journal of Preventive Medicine* 41.4 (Oct. 2011), S149–S151. ISSN: 0749-3797, 1873-2607. DOI: 10.1016/j.amepre.2011.07.013. (Visited on 07/09/2023).

[76] M. J. Mina and K. G. Andersen. “COVID-19 Testing: One Size Does Not Fit All”. In: *Science* 371 (Jan. 2021), pp. 126–127. ISSN: 0036-8075. DOI: 10.1126/science.abe9187. (Visited on 07/09/2023).

[77] H. Ward et al. “SARS-CoV-2 Antibody Prevalence in England Following the First Peak of the Pandemic”. In: *Nature Communications* 12.1 (Feb. 2021), p. 905. ISSN: 2041-1723. DOI: 10.1038/s41467-021-21237-w. (Visited on 12/20/2022).

[78] M. C. Grant, L. Geoghegan, M. Arbyn, Z. Mohammed, L. McGuinness, E. L. Clarke, and R. G. Wade. “The Prevalence of Symptoms in 24,410 Adults Infected by the Novel Coronavirus (SARS-CoV-2; COVID-19): A Systematic Review and Meta-Analysis of 148 Studies from 9 Countries”. In: *PLOS ONE* 15.6 (June 2020), e0234765. ISSN: 1932-6203. DOI: 10.1371/journal.pone.0234765. (Visited on 12/30/2020).

[79] *Coronavirus (COVID-19): What Is Self-Isolation and Why Is It Important? - UK Health Security Agency*. https://ukhsa.blog.gov.uk/2020/02/20/what-is-self-isolation-and-why-is-it-important/. (Visited on 12/20/2022).

[80] *NHS Test and Trace: The Journey so Far - The Health Foundation*. https://www.health.org.uk/publications/long-reads/nhs-test-and-trace-the-journey-so-far. (Visited on 09/26/2022).

[81] Y. Liu, S. Funk, and S. Flasche. *The Contribution of Pre-Symptomatic Infection to the*

Transmission Dynamics of COVID-2019. Apr. 2020. DOI: 10.12688/wellcomeopenres.15788.1. (Visited on 11/17/2022).

[82] D. C. Buitrago-Garcia, D. Egli-Gany, M. J. Counotte, S. Hossmann, H. Imeri, A. M. Ipekci, G. Salanti, and N. Low. *Asymptomatic SARS-CoV-2 Infections: A Living Systematic Review and Meta-Analysis*. Preprint. Epidemiology, Apr. 2020. DOI: 10.1101/2020.04.25.20079103. (Visited on 08/05/2020).

[83] R. Zhou, F. Li, F. Chen, H. Liu, J. Zheng, C. Lei, and X. Wu. "Viral Dynamics in Asymptomatic Patients with COVID-19". In: *International Journal of Infectious Diseases* 96 (July 2020), pp. 288–290. ISSN: 1201-9712. DOI: 10.1016/j.ijid.2020.05.030. (Visited on 01/05/2021).

[84] P. Mbala, M. Baguelin, I. Ngay, A. Rosello, P. Mulembakani, N. Demiris, W. J. Edmunds, and J.-J. Muyembe. "Evaluating the Frequency of Asymptomatic Ebola Virus Infection". In: *Philosophical Transactions of the Royal Society B: Biological Sciences* 372.1721 (May 2017), p. 20160303. ISSN: 0962-8436. DOI: 10.1098/rstb.2016.0303. (Visited on 10/11/2022).

[85] O. Byambasuren, M. Cardona, K. Bell, J. Clark, M.-L. McLaws, and P. Glasziou. *Estimating the Extent of Asymptomatic COVID-19 and Its Potential for Community Transmission: Systematic Review and Meta-Analysis*. Preprint. Infectious Diseases (except HIV/AIDS), May 2020. DOI: 10.1101/2020.05.10.20097543. (Visited on 08/14/2020).

[86] M. Pavelka et al. "The Impact of Population-Wide Rapid Antigen Testing on SARS-CoV-2 Prevalence in Slovakia". In: *Science* 372.6542 (May 2021), pp. 635–641. DOI: 10.1126/science.abf9648. (Visited on 01/12/2023).

[87] M. García-Fiñana, D. M. Hughes, C. P. Cheyne, G. Burnside, M. Stockbridge, T. A. Fowler, V. L. Fowler, M. H. Wilcox, M. G. Semple, and I. Buchan. "Performance of the Innova SARS-CoV-2 Antigen Rapid Lateral Flow Test in the Liverpool Asymptomatic Testing Pilot: Population Based Cohort Study". In: *BMJ* 374 (July 2021), n1637. ISSN: 1756-1833. DOI: 10.1136/bmj.n1637. (Visited on 03/03/2022).

[88] X. Zhang, B. Barr, M. Green, D. Hughes, M. Ashton, D. Charalampopoulos, M. García-Fiñana, and I. Buchan. "Impact of Community Asymptomatic Rapid Antigen Testing on Covid-19 Related Hospital Admissions: Synthetic Control Study".

In: *BMJ* 379 (Nov. 2022), e071374. ISSN: 1756-1833. DOI: 10.1136/bmj-2022-071374. (Visited on 01/12/2023).

[89] B. C. Young et al. “Daily Testing for Contacts of Individuals with SARS-CoV-2 Infection and Attendance and SARS-CoV-2 Transmission in English Secondary Schools and Colleges: An Open-Label, Cluster-Randomised Trial”. In: *The Lancet* 398.10307 (Oct. 2021), pp. 1217–1229. ISSN: 01406736. DOI: 10.1016/S0140-6736(21)01908-5. (Visited on 03/03/2022).

[90] N. K. Love et al. “Daily Use of Lateral Flow Devices by Contacts of Confirmed COVID-19 Cases to Enable Exemption from Isolation Compared with Standard Self-Isolation to Reduce Onward Transmission of SARS-CoV-2 in England: A Randomised, Controlled, Non-Inferiority Trial”. In: *The Lancet Respiratory Medicine* 10.11 (Nov. 2022), pp. 1074–1085. ISSN: 2213-2600. DOI: 10.1016/S2213-2600(22)00267-3. (Visited on 01/12/2023).

[91] *Confirmatory Testing with a Second Lateral Flow Test May Mitigate False Positives at Low Levels of SARS-CoV-2 Prevalence in English Schools*. https://cmmid.github.io/topics/covid19/lft_confirm_testing_schools.html. Mar. 2021. (Visited on 04/16/2021).

[92] K. Ramstedt, G. Hallhagen, B. I. Lundin, C. Håkansson, G. Johannisson, G. B. Löwhagen, G. Norkrans, and J. Giesecke. “Contact Tracing for Human Immunodeficiency Virus (HIV) Infection”. In: *Sexually Transmitted Diseases* 17.1 (1990), pp. 37–41. ISSN: 0148-5717.

[93] K. C. Swanson, C. Altare, C. S. Wesseh, T. Nyenswah, T. Ahmed, N. Eyal, E. L. Hamblion, J. Lessler, D. H. Peters, and M. Altmann. “Contact Tracing Performance during the Ebola Epidemic in Liberia, 2014-2015”. In: *PLOS Neglected Tropical Diseases* 12.9 (Sept. 2018), e0006762. ISSN: 1935-2735. DOI: 10.1371/journal.pntd.0006762. (Visited on 12/20/2022).

[94] K. J. T. Craig, R. Rizvi, V. C. Willis, W. J. Kassler, and G. P. Jackson. “Effectiveness of Contact Tracing for Viral Disease Mitigation and Suppression: Evidence-Based Review”. In: *JMIR Public Health and Surveillance* 7.10 (Oct. 2021), e32468. DOI: 10.2196/32468. (Visited on 01/10/2023).

[95] A. J. Kucharski et al. “Effectiveness of Isolation, Testing, Contact Tracing, and

Physical Distancing on Reducing Transmission of SARS-CoV-2 in Different Settings: A Mathematical Modelling Study". In: *The Lancet Infectious Diseases* (June 2020), S1473309920304576. ISSN: 14733099. DOI: 10.1016/S1473-3099(20)30457-6. (Visited on 08/05/2020).

[96] M. E. Kretzschmar, G. Rozhnova, M. C. J. Bootsma, M. van Boven, J. H. H. M. van de Wijgert, and M. J. M. Bonten. "Impact of Delays on Effectiveness of Contact Tracing Strategies for COVID-19: A Modelling Study". In: *The Lancet Public Health* (July 2020), S2468266720301572. ISSN: 24682667. DOI: 10.1016/S2468-2667(20)30157-2. (Visited on 08/05/2020).

[97] L. Ferretti, C. Wymant, M. Kendall, L. Zhao, A. Nurtay, L. Abeler-Dörner, M. Parker, D. Bonsall, and C. Fraser. "Quantifying SARS-CoV-2 Transmission Suggests Epidemic Control with Digital Contact Tracing". In: *Science (New York, N.y.)* 368.6491 (May 2020), eabb6936. ISSN: 0036-8075. DOI: 10.1126/science.abb6936. (Visited on 01/17/2023).

[98] C. Wymant et al. "The Epidemiological Impact of the NHS COVID-19 App". In: *Nature* 594.7863 (June 2021), pp. 408–412. ISSN: 1476-4687. DOI: 10.1038/s41586-021-03606-z.

[99] J. E. Aledort, N. Lurie, J. Wasserman, and S. A. Bozzette. "Non-Pharmaceutical Public Health Interventions for Pandemic Influenza: An Evaluation of the Evidence Base". In: *BMC public health* 7 (Aug. 2007), p. 208. ISSN: 1471-2458. DOI: 10.1186/1471-2458-7-208.

[100] S. M. S. Smith, S. Sonego, G. R. Wallen, G. Waterer, A. C. Cheng, and P. Thompson. "Use of Non-Pharmaceutical Interventions to Reduce the Transmission of Influenza in Adults: A Systematic Review". In: *Respirology (Carlton, Vic.)* 20.6 (Aug. 2015), pp. 896–903. ISSN: 1440-1843. DOI: 10.1111/resp.12541.

[101] World Health Organization Writing Group, D. Bell, A. Nicoll, K. Fukuda, P. Horby, A. Monto, F. Hayden, C. Wylks, L. Sanders, and J. Van Tam. "Non-Pharmaceutical Interventions for Pandemic Influenza, International Measures". In: *Emerging Infectious Diseases* 12.1 (Jan. 2006), pp. 81–87. ISSN: 1080-6040. DOI: 10.3201/eid1201.051370.

[102] M. Lipsitch et al. "Transmission Dynamics and Control of Severe Acute Respiratory

Syndrome". In: *Science* 300.5627 (June 2003), pp. 1966–1970. ISSN: 0036-8075, 1095-9203. DOI: 10.1126/science.1086616. (Visited on 03/15/2021).

[103] A. Dénes and A. B. Gumel. "Modeling the Impact of Quarantine during an Outbreak of Ebola Virus Disease". In: *Infectious Disease Modelling* 4 (Feb. 2019), pp. 12–27. ISSN: 2468-2152. DOI: 10.1016/j.idm.2019.01.003. (Visited on 12/15/2022).

[104] A. Wilder-Smith, C. J. Chiew, and V. J. Lee. "Can We Contain the COVID-19 Outbreak with the Same Measures as for SARS?" In: *The Lancet Infectious Diseases* 20.5 (May 2020), e102–e107. ISSN: 1473-3099, 1474-4457. DOI: 10.1016/S1473-3099(20)30129-8. (Visited on 03/15/2021).

[105] C. Fraser, S. Riley, R. M. Anderson, and N. M. Ferguson. "Factors That Make an Infectious Disease Outbreak Controllable". In: *Proceedings of the National Academy of Sciences* 101.16 (Apr. 2004), pp. 6146–6151. ISSN: 0027-8424, 1091-6490. DOI: 10.1073/pnas.0307506101. (Visited on 03/09/2021).

[106] R. Dhand and J. Li. "Coughs and Sneezes: Their Role in Transmission of Respiratory Viral Infections, Including SARS-CoV-2". In: *American Journal of Respiratory and Critical Care Medicine* 202.5 (Sept. 2020), pp. 651–659. ISSN: 1073-449X. DOI: 10.1164/rccm.202004-1263PP. (Visited on 07/12/2023).

[107] D. Chen et al. "Inferring Time-Varying Generation Time, Serial Interval, and Incubation Period Distributions for COVID-19". In: *Nature Communications* 13.1 (Dec. 2022), p. 7727. ISSN: 2041-1723. DOI: 10.1038/s41467-022-35496-8. (Visited on 07/12/2023).

[108] M. Eichner, S. F. Dowell, and N. Firese. "Incubation Period of Ebola Hemorrhagic Virus Subtype Zaire". In: *Osong Public Health and Research Perspectives* 2.1 (June 2011), pp. 3–7. ISSN: 2210-9099. DOI: 10.1016/j.phrp.2011.04.001. (Visited on 10/11/2022).

[109] A. Christie et al. "Possible Sexual Transmission of Ebola Virus — Liberia, 2015". In: *Morbidity and Mortality Weekly Report* 64.17 (May 2015), pp. 479–481. ISSN: 0149-2195. (Visited on 02/07/2023).

[110] Q. Bi et al. "Epidemiology and Transmission of COVID-19 in 391 Cases and 1286 of Their Close Contacts in Shenzhen, China: A Retrospective Cohort Study". In: *The Lancet Infectious Diseases* 20.8 (Aug. 2020), pp. 911–919. ISSN: 1473-3099,

1474-4457. DOI: 10.1016/S1473-3099(20)30287-5. (Visited on 02/05/2023).

[111] Roy M. Anderson and Robert M. May. *Infectious Diseases of Humans: Dynamics and Control*. (Visited on 10/11/2022).

[112] A. Crozier, J. Dunning, S. Rajan, M. G. Semple, and I. E. Buchan. "Could Expanding the Covid-19 Case Definition Improve the UK's Pandemic Response?" In: *BMJ* (June 2021), n1625. ISSN: 1756-1833. DOI: 10.1136/bmj.n1625. (Visited on 07/10/2023).

[113] P. L. Delamater, E. J. Street, T. F. Leslie, Y. T. Yang, and K. H. Jacobsen. "Complexity of the Basic Reproduction Number (R0)". In: *Emerging Infectious Diseases* 25.1 (Jan. 2019), p. 1. DOI: 10.3201/eid2501.171901. (Visited on 07/11/2023).

[114] V. Andreasen. "The Final Size of an Epidemic and Its Relation to the Basic Reproduction Number". In: *Bulletin of Mathematical Biology* 73.10 (Oct. 2011), pp. 2305–2321. ISSN: 1522-9602. DOI: 10.1007/s11538-010-9623-3. (Visited on 07/11/2023).

[115] J. Hellewell et al. "Feasibility of Controlling COVID-19 Outbreaks by Isolation of Cases and Contacts". In: *The Lancet Global Health* 8.4 (Apr. 2020), e488–e496. ISSN: 2214109X. DOI: 10.1016/S2214-109X(20)30074-7. (Visited on 03/13/2021).

[116] Z. J. Madewell, Y. Yang, I. M. Longini Jr, M. E. Halloran, and N. E. Dean. "Household Secondary Attack Rates of SARS-CoV-2 by Variant and Vaccination Status: An Updated Systematic Review and Meta-analysis". In: *JAMA Network Open* 5.4 (Apr. 2022), e229317. ISSN: 2574-3805. DOI: 10.1001/jamanetworkopen.2022.9317. (Visited on 01/21/2023).

[117] Y. Liu, R. M. Eggo, and A. J. Kucharski. "Secondary Attack Rate and Superspreading Events for SARS-CoV-2". In: *The Lancet* 395.10227 (Mar. 2020), e47. ISSN: 0140-6736, 1474-547X. DOI: 10.1016/S0140-6736(20)30462-1. (Visited on 01/21/2023).

[118] UK Health Security Agency. *SARS-CoV-2 Variants of Concern and Variants under Investigation*. Tech. rep.

[119] T. Britton and G. Scalia Tomba. "Estimation in Emerging Epidemics: Biases and Remedies". In: *Journal of The Royal Society Interface* 16.150 (Jan. 2019), p. 20180670. DOI: 10.1098/rsif.2018.0670. (Visited on 10/10/2022).

[120] *Epidemic Reconstruction in a Phylogenetics Framework: Transmission Trees as*

Partitions of the Node Set | PLOS Computational Biology. https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1004613. (Visited on 10/11/2022).

[121] E. Kenah, M. Lipsitch, and J. M. Robins. "Generation Interval Contraction and Epidemic Data Analysis". In: *Mathematical Biosciences* 213.1 (May 2008), pp. 71–79. ISSN: 0025-5564. DOI: 10.1016/j.mbs.2008.02.007. (Visited on 06/19/2023).

[122] S. T. Ali, L. Wang, E. H. Y. Lau, X.-K. Xu, Z. Du, Y. Wu, G. M. Leung, and B. J. Cowling. "Serial Interval of SARS-CoV-2 Was Shortened over Time by Nonpharmaceutical Interventions". In: *Science* 369.6507 (Aug. 2020), pp. 1106–1109. DOI: 10.1126/science.abc9004. (Visited on 10/11/2022).

[123] Y. Xiang, Y. Jia, L. Chen, L. Guo, B. Shu, and E. Long. "COVID-19 Epidemic Prediction and the Impact of Public Health Interventions: A Review of COVID-19 Epidemic Models". In: *Infectious Disease Modelling* 6 (Jan. 2021), pp. 324–342. ISSN: 2468-0427. DOI: 10.1016/j.idm.2021.01.001. (Visited on 02/05/2023).

[124] J. Mossong et al. "Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases". In: *PLOS Medicine* 5.3 (Mar. 2008), e74. ISSN: 1549-1676. DOI: 10.1371/journal.pmed.0050074. (Visited on 12/28/2022).

[125] I. Z. Kiss, D. M. Green, and R. R. Kao. "Disease Contact Tracing in Random and Clustered Networks". In: *Proceedings of the Royal Society B: Biological Sciences* 272.1570 (July 2005), pp. 1407–1414. ISSN: 0962-8452, 1471-2954. DOI: 10.1098/rspb.2005.3092. (Visited on 12/28/2022).

[126] A. Endo, H. Murayama, S. Abbott, R. Ratnayake, C. A. B. Pearson, W. J. Edmunds, E. Fearon, and S. Funk. "Heavy-Tailed Sexual Contact Networks and Monkeypox Epidemiology in the Global Outbreak, 2022". In: *Science* 378.6615 (Oct. 2022), pp. 90–94. DOI: 10.1126/science.add4507. (Visited on 12/28/2022).

[127] S. Cauchemez, A.-J. Valleron, P.-Y. Boëlle, A. Flahault, and N. M. Ferguson. "Estimating the Impact of School Closure on Influenza Transmission from Sentinel Data". In: *Nature* 452.7188 (Apr. 2008), pp. 750–754. ISSN: 1476-4687. DOI: 10.1038/nature06732. (Visited on 12/29/2022).

[128] P. E. Fine and J. A. Clarkson. "Measles in England and Wales–I: An Analysis of Factors Underlying Seasonal Patterns". In: *International Journal of Epidemiology*

11.1 (Mar. 1982), pp. 5–14. ISSN: 0300-5771. DOI: 10.1093/ije/11.1.5.

[129] M. Koltai, F. Krauer, D. Hodgson, E. van Leeuwen, M. Treskova-Schwarzbach, M. Jit, and S. Flasche. “Determinants of RSV Epidemiology Following Suppression through Pandemic Contact Restrictions”. In: *Epidemics* 40 (Sept. 2022), p. 100614. ISSN: 1755-4365. DOI: 10.1016/j.epidem.2022.100614. (Visited on 06/19/2023).

[130] K. T. D. Eames, M. L. Tang, E. M. Hill, M. J. Tildesley, J. M. Read, M. J. Keeling, and J. R. Gog. “Coughs, Colds and “Freshers’ Flu” Survey in the University of Cambridge, 2007–2008”. In: *Epidemics* 42 (Mar. 2023), p. 100659. ISSN: 1755-4365. DOI: 10.1016/j.epidem.2022.100659. (Visited on 06/19/2023).

[131] A. Federgruen and S. Naha. “Crowding Effects Dominate Demographic Attributes in COVID-19 Cases”. In: *International Journal of Infectious Diseases* 102 (Jan. 2021), pp. 509–516. ISSN: 1201-9712. DOI: 10.1016/j.ijid.2020.10.063. (Visited on 12/29/2022).

[132] W. A. de Glanville, L. F. Thomas, E. A. J. Cook, B. M. d. C. Bronsvoort, N. C. Wamae, S. Kariuki, and E. M. Fèvre. “Household Socio-Economic Position and Individual Infectious Disease Risk in Rural Kenya”. In: *Scientific Reports* 9 (Feb. 2019), p. 2972. ISSN: 2045-2322. DOI: 10.1038/s41598-019-39375-z. (Visited on 12/29/2022).

[133] World Health Organization. *WHO Housing and Heath Guidelines*. World Health Organization, 2018. (Visited on 12/29/2022).

[134] R. K. Webster, S. K. Brooks, L. E. Smith, L. Woodland, S. Wessely, and G. J. Rubin. “How to Improve Adherence with Quarantine: Rapid Review of the Evidence”. In: *Public Health* 182 (May 2020), pp. 163–169. ISSN: 0033-3506. DOI: 10.1016/j.puhe.2020.03.007. (Visited on 03/16/2021).

[135] E. Teasdale and L. Yardley. “Understanding Responses to Government Health Recommendations: Public Perceptions of Government Advice for Managing the H1N1 (Swine Flu) Influenza Pandemic”. In: *Patient Education and Counseling* 85.3 (Dec. 2011), pp. 413–418. ISSN: 1873-5134. DOI: 10.1016/j.pec.2010.12.026.

[136] *Public Preferences for Interventions to Prevent Emerging Infectious Disease Threats: A Discrete Choice Experiment | BMJ Open*. https://bmjopen.bmj.com/content/8/2/e017355.abstract. (Visited on 03/16/2021).

[137] M. Zastrow. “South Korea Is Reporting Intimate Details of COVID-19 Cases: Has It

Helped?" In: *Nature* (Mar. 2020). DOI: 10.1038/d41586-020-00740-y. (Visited on 03/16/2021).

[138] K. Prem et al. "The Effect of Control Strategies to Reduce Social Mixing on Outcomes of the COVID-19 Epidemic in Wuhan, China: A Modelling Study". In: *The Lancet Public Health* 5.5 (May 2020), e261–e270. ISSN: 2468-2667. DOI: 10.1016/S2468-2667(20)30073-6. (Visited on 01/17/2023).

[139] G. Fink, F. Tediosi, and S. Felder. "Burden of Covid-19 Restrictions: National, Regional and Global Estimates". In: *eClinicalMedicine* 45 (Mar. 2022). ISSN: 2589-5370. DOI: 10.1016/j.eclinm.2022.101305. (Visited on 01/17/2023).

[140] S. M. Kissler et al. "Viral Dynamics of Acute SARS-CoV-2 Infection and Applications to Diagnostic and Public Health Strategies". In: *PLOS Biology* 19.7 (July 2021), e3001333. ISSN: 1545-7885. DOI: 10.1371/journal.pbio.3001333. (Visited on 11/25/2021).

[141] R. Ke et al. "Daily Longitudinal Sampling of SARS-CoV-2 Infection Reveals Substantial Heterogeneity in Infectiousness". In: *Nature Microbiology* 7.5 (May 2022), pp. 640–652. ISSN: 2058-5276. DOI: 10.1038/s41564-022-01105-z. (Visited on 12/20/2022).

[142] A. Goyal, D. B. Reeves, E. F. Cardozo-Ojeda, J. T. Schiffer, and B. T. Mayer. "Viral Load and Contact Heterogeneity Predict SARS-CoV-2 Transmission and Super-Spreading Events". In: *eLife* 10 (Feb. 2021). Ed. by A. M. Walczak, L. Childs, and J. Forde, e63537. ISSN: 2050-084X. DOI: 10.7554/eLife.63537. (Visited on 11/25/2021).

[143] M. J. Keeling and L. Danon. "Mathematical Modelling of Infectious Diseases". In: *British Medical Bulletin* 92.1 (Dec. 2009), pp. 33–42. ISSN: 0007-1420, 1471-8391. DOI: 10.1093/bmb/ldp038. (Visited on 01/21/2023).

[144] SPI-MO. *Consensus Statement 28th July 2021*. Tech. rep. UK Government, July 21. (Visited on 11/25/2022).

2. Travel restrictions

2.1 Effectiveness of airport screening at detecting travellers infected with novel coronavirus (2019-nCoV)

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	1703195	**Title**	Mr
First Name(s)	Billy		
Surname/Family Name	Quilty		
Thesis Title	Modelling the effectiveness of quarantine and testing strategies during the COVID-19 pandemic		
Primary Supervisor	Stefan Flasche		

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?	Eurosurveillance		
When was the work published?	6 February 2020		
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?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*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?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

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)	I co-led in the conceptualisation of this work and contributed substantially to the discussions on how to formulate the model. I then used R to program the initial individual-based model based on sampling from reported delay distributions, and from this programmed the first iteration of the interactive R Shiny app, which was then refined with contribution from co-authors. I then produced the results and figures for the paper, and co-led the writing of the first draft of the manuscript.

SECTION E

Student Signature	Billy Quilty
Date	07/02/2023

Supervisor Signature	Stefan Flasche
Date	07/02/2023

Rapid communication

Effectiveness of airport screening at detecting travellers infected with novel coronavirus (2019-nCoV)

Billy J Quilty[1] , Sam Clifford[1] , CMMID nCoV working group[2] , Stefan Flasche[1,3] , Rosalind M Eggo[1,3]
1. Centre for the Mathematical Modelling of Infectious Diseases, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom
2. The members of the Centre for the Mathematical Modelling of Infectious Diseases (CMMID) nCoV working group are listed at the end of the article
3. These authors contributed equally to this work

Correspondence: Billy J Quilty (Billy.Quilty@lshtm.ac.uk)

Citation style for this article:
Quilty Billy J , Clifford Sam , CMMID nCoV working group , Flasche Stefan , Eggo Rosalind M . Effectiveness of airport screening at detecting travellers infected with novel coronavirus (2019-nCoV). Euro Surveill. 2020;25(5):pii=2000080. https://doi.org/10.2807/1560-7917.ES.2020.25.5.2000080

Article submitted on 30 Jan 2020 / accepted on 06 Feb 2020 / published on 06 Feb 2020

We evaluated effectiveness of thermal passenger screening for 2019-nCoV infection at airport exit and entry to inform public health decision-making. In our baseline scenario, we estimated that 46% (95% confidence interval: 36 to 58) of infected travellers would not be detected, depending on incubation period, sensitivity of exit and entry screening, and proportion of asymptomatic cases. Airport screening is unlikely to detect a sufficient proportion of 2019-nCoV infected travellers to avoid entry of infected travellers.

As at 4 February 2020, 20,471 confirmed cases of novel coronavirus (2019-nCoV) have been reported from China with 425 deaths confirmed so far [1]. There were cases in at least 23 other countries, identified because of symptoms and recent travel history to Hubei province, China. This strongly suggests that the reported cases constitute only a small fraction of the actual number of infected individuals in China [2]. While the most affected region, Hubei province, has ceased air travel and closed major public transport routes [3] the number of exported cases are still expected to increase [4].

Despite limited evidence for its effectiveness, airport screening has been previously implemented during the 2003 SARS epidemic and 2009 influenza A(H1N1) pandemic to limit the probability of infected cases entering other countries or regions [5-7]. Here we use the available evidence on the incubation time, hospitalisation time and proportion of asymptomatic infections of 2019-nCoV to evaluate the effectiveness of exit and entry screening for detecting travellers entering Europe with 2019-nCoV infection. We also present an online tool so that results can be updated as new information becomes available.

Simulation of travellers at each stage of infection with 2019-nCoV

We simulated 100 2019-nCoV infected travellers planning to board a flight who would pose a risk for seeding transmission in a new region. The duration of travel was considered as the flight time plus a small amount of additional travel time (ca 1 hour) for airport procedures. We assumed that infected individuals will develop symptoms, including fever, at the end of their incubation period (mean 5.2 days (Table)) [8] and progress to more severe symptoms after a few days, resulting in hospitalisation and isolation. We also took into account that individuals may have asymptomatic (subclinical) infection that would not be detected by thermal scanning or cause them to seek medical care, although these individuals may be infectious, and that infected travellers may exhibit severe symptoms during their travel and be hospitalised upon arrival without undergoing entry screening. We then estimated the proportion of infected travellers who would be detected by exit and entry screening, develop severe symptoms during travel, or go undetected, under varying assumptions of: (i) the duration of travel; (ii) the sensitivity of exit and entry screening; (iii) the proportion of asymptomatic infections; (iv) the incubation period and (v) the time from symptom onset to hospitalisation (Table).

We assume that the time of starting travel is randomly and uniformly distributed between the time of infection and twice the expected time to severe disease, ensuring that simulated travellers are travelling during their incubation period. However, we only consider those travellers who depart before their symptoms progress to being so severe that they would require hospital care [8]. We simulate travellers with individual incubation period, time from onset to severe disease, flight start times and detection success at exit and entry screening according to the screening sensitivities (Figure 1). An individual will be detected at exit screening if their

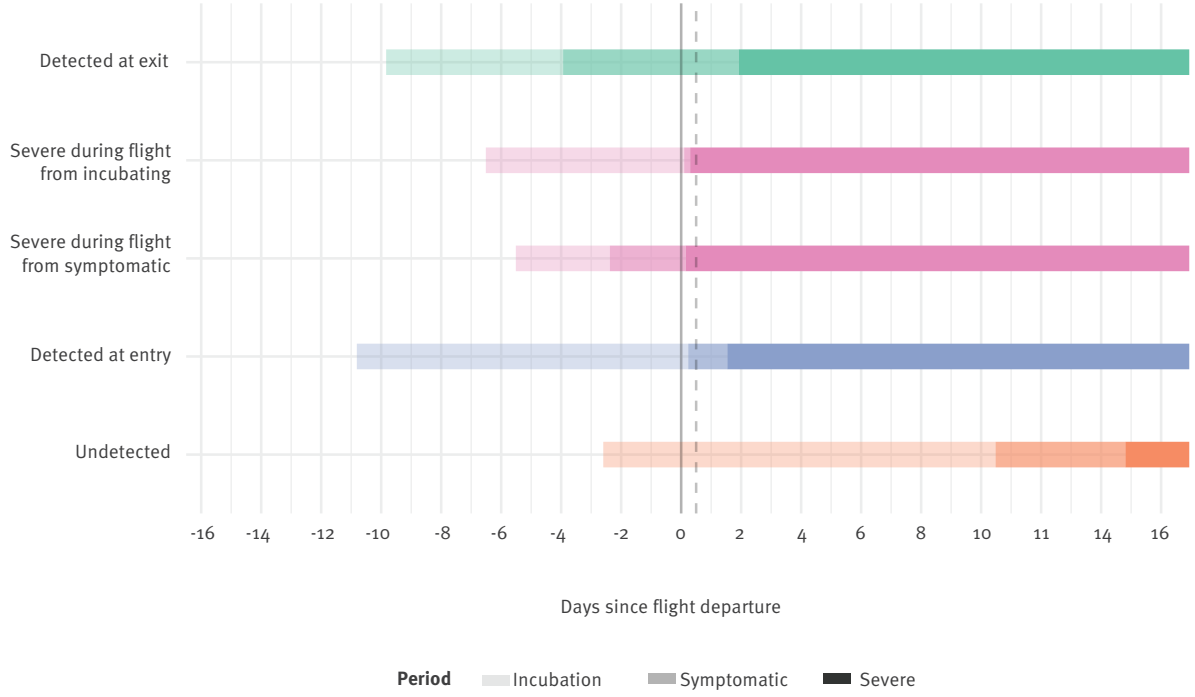
Table

Parameter values and assumptions for the baseline scenario estimating effectiveness of exit and entry screening at airports for detecting passengers infected with novel coronavirus (2019-nCoV)

Parameter	Value (baseline scenario)	Source
Duration of travel	12 hours	Beijing – London [18]
Sensitivity of exit screening	86%	Sensitivity of infrared thermal image scanners [19]
Sensitivity of entry screening	86%	Sensitivity of infrared thermal image scanners [19]
Proportion of asymptomatic infections undetectable by typical screening procedures	17%	1 of 6 reported asymptomatic in a 2019-nCoV family cluster [11]
Incubation period	Mean 5.2 days, variance 4.1 days	Reported Gamma distributed mean, variance estimated from uncertainty interval of mean [8]
Time from symptom onset to hospitalisation	Mean 9.1 days, variance 14.7 days	Reported Gamma distributed mean, variance estimated from uncertainty interval of mean [8]

Figure 1

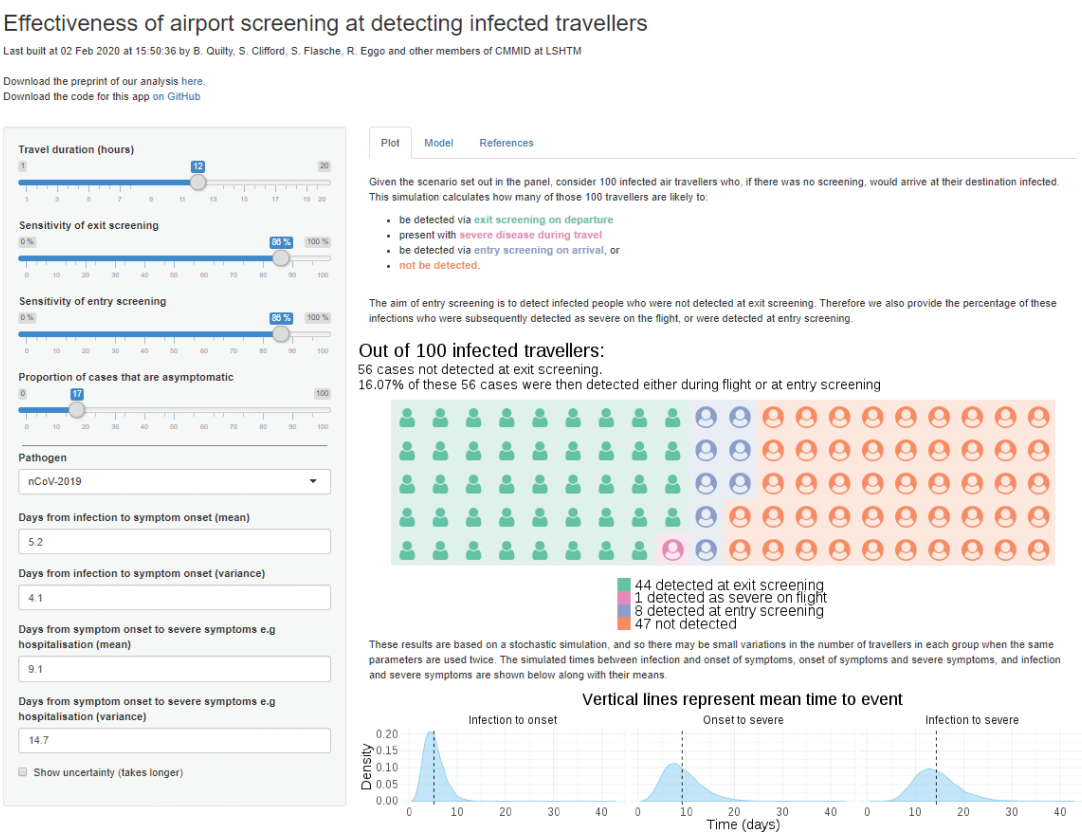
Simulated infection histories of travellers infected with novel coronavirus (2019-nCoV)



The incubation period begins on infection and travellers then progress to being symptomatic and having severe symptoms. Travellers may fly at any point within the incubation or symptomatic phases; any would-be travellers who show (severe) symptoms and are hospitalised before exit. Vertical lines represent the exit screening at start of travel (solid) and entry screening at end of travel (dashed) 12 hours later.

FIGURE 2

Screenshot of Shiny app[a] displaying the number of travellers infected with novel coronavirus (2019-nCoV) detected at airport exit and entry screening with baseline assumptions[b], 95% bootstrap confidence intervals, time distributions for incubation period and time to severe disease*



[a] Source [9].

[b] Baseline assumptions according to the Table.

Results are from stochastic simulation, and so there may be small variations in the number of travellers in each group when the same parameters are used twice. Sliders are provided to modify the duration of travel, the sensitivity of both exit and entry screening, the proportion symptomatic, and the natural history parameters for the infection.

infection is symptomatic i.e. has detectable fever, their departure time exceeds their incubation period, and their stochastic exit screening success indicates detection. An individual will be detected at entry screening if their infection is symptomatic, their incubation period ends after their departure but before their arrival, they have not been detected at exit screening, and their entry screening result is positive despite imperfect sensitivity. Entry screening detections are further divided into detection due to severe symptoms and detection of mild symptoms via equipment such as thermal scanners. We used 10,000 bootstrap samples to calculate 95% confidence intervals (CI).

The model code is available via GitHub [9] and the results can be further explored in a Shiny app [10] at https://cmmid-lshtm.shinyapps.io/traveller_screening/ (Figure 2).

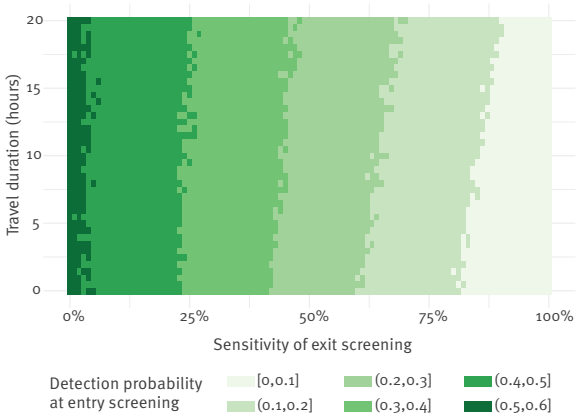
Effect of screening on detection

For the baseline scenario we estimated that 44 (95% CI: 33–56) of 100 infected travellers would be detected by exit screening, no case (95% CI: 0–3) would develop severe symptoms during travel, nine (95% CI: 2–16) additional cases would be detected by entry screening, and the remaining 46 (95% CI: 36–58) would not be detected.

The effectiveness of entry screening is largely dependent on the effectiveness of the exit screening in place. Under baseline assumptions, entry screening could detect 53 (95% CI: 35–72) instead of nine infected travellers if no exit screening was in place. However, the probability of developing symptoms during the flight increases with flight time and hence exit screening is more effective for longer flights (Figure 3).

Figure 3

Probability of detecting travellers infected with novel coronavirus (2019-nCoV) at airport entry screening by travel duration and sensitivity of exit screening



Each cell is a mean of 10,000 model simulations. Other parameters (incubation period, symptom onset to hospitalisation period, and proportion of asymptomatic infections) were fixed at baseline assumptions (Table). Intervals are probabilities of detection, binned at increments of 10% (0–10%, 10–20%, etc.).

Syndromic screening designed to prevent infected and potentially infectious cases entering a country undetected is highly vulnerable to the proportion of asymptomatic infections and long incubation periods. If our baseline scenario is modified to have 0% asymptomatic 2019-nCoV infections and 100% sensitivity of entry screening, the incubation period will need to be around 10-fold shorter than the period from symptom onset to severe disease (e.g. hospitalisation) in order to detect more than 90% of infected travellers that would not otherwise report illness at either exit or entry screening.

Discussion and conclusions

As a response to the ongoing outbreak of the 2019-nCoV originating in Wuhan, exit screening has been implemented for international flights leaving China's major airports. Thermal scanning, which can identify passengers with fever (high external body temperature), allows for passengers exhibiting symptoms of 2019-nCoV infection to be tested before they board a plane. Similarly, entry screening for flights originating in the most affected regions may be under consideration at airports in regions in and outside China. We estimate that the key goal of syndromic screening at airports - to prevent infected travellers from entering countries or regions with little or no ongoing transmission - is only achievable if the rate of asymptomatic infections that are transmissible is negligible, screening sensitivity is almost perfect, and the incubation period is short. Based on early data from Li et al. [8], 2019-nCoV appears to have a shorter incubation period than severe acute respiratory syndrome (SARS), and a higher rate of asymptomatic infections [11]. Under generally conservative assumptions on sensitivity, we find that 46 of 100 infected travellers will enter undetected.

Entry screening is an intuitive barrier for the prevention of infected people entering a country or region. However, evidence on its effectiveness remains limited and given its lack of specificity, it generates a high overhead of screened travellers uninfected with the targeted pathogen [5]. For example, when entry screening was implemented in Australia in response to the 2003 SARS outbreak, 1.84 million people were screened, 794 were quarantined, and no cases were confirmed [12]. While some cases of 2019-nCoV infection have been identified through airport screening in the current outbreak, our estimates indicate that likely more infected travellers have not been detected by screening.

It is important to note that our estimates are based on a number of key assumptions that cannot yet be informed directly by evidence from the ongoing 2019-nCoV outbreak. The current outbreak has spread rapidly and early evidence suggests that the average disease severity is lower than that of SARS. This may also suggest a substantial proportion of asymptomatic cases. A recent analysis of a family transmission cluster is based on a small sample size but one in six infections was asymptomatic [11]; this is a major impediment for the effectiveness of syndromic screening. However, if asymptomatic cases were not infectious they would not pose a risk for seeding infection chains on arrival. To allow easy adaptation of our results as new insight becomes available in the coming weeks, we developed a free interactive online tool, available at https://cmmid-lshtm.shinyapps.io/traveller_screening/.

While the most up-to-date data on the incubation period or the time until recovery from 2019-nCoV infection have been used in this analysis, these figures are likely to change over time as more data become available. Unless the incubation period is only a small fraction of the duration of infection in relation to that of symptomatic disease, and fever in particular, syndromic screening is likely to detect an insufficient fraction of infected cases to prevent local infections. In addition, the sensitivity of airport screening for the detection of 2019-nCoV has not been evaluated. However, we chose conservative estimates and show that with reduced sensitivity, the effectiveness of syndromic screening would further decline.

In many international airports, information is provided to travellers from affected regions recommending action if they develop symptoms on or after arrival [13-16]. Some countries, for example Japan, also require incoming passengers to complete forms detailing their past and future travel in order to aid tracing [17]. Due to the duration of the incubation period of 2019-nCoV infection, we find that exit or entry screening at airports for initial symptoms, via thermal scanners or similar, is unlikely to prevent passage of infected travellers into

new countries or regions where they may seed local transmission.

*Erratum

Figure 2 was replaced on 7 February 2020.

Members of the Centre for the Mathematical Modelling of Infectious Diseases (CMMID) nCoV working group

Yang Liu, Charlie Diamond, W John Edmunds, Sebastian Funk, Amy Gimma, James D Munday, Hamish Gibbs, Nikos I Bosse, Sam Abbott, Timothy W Russell, Petra Klepac, Mark Jit, Joel Hellewell.

Acknowledgements

SF and SC are supported by a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (Grant number 208812/Z/17/Z).

RME acknowledges an HDR UK Innovation Fellowship (Grant number MR/S003975/1).

BJQ was funded by the National Institute for Health Research (NIHR) (16/137/109) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NIHR or the UK Department of Health and Social Care.

CMMID nCoV working group funding statements:

Yang Liu (Gates (INV-003174), NIHR (16/137/109)), Charlie Diamond (NIHR (16/137/109)), Sebastian Funk (Wellcome Trust (210758/Z/18/Z)), Amy Gimma (Global Challenges Research Fund (GCRF) for the project "RECAP" managed through RCUK and ESRC (ES/P010873/1)), James D Munday (Wellcome Trust (210758/Z/18/Z)), Hamish Gibbs (NIHR (ITCRZ 03010)), Sam Abbott (Wellcome Trust (210758/Z/18/Z)), Timothy W Russell (Wellcome Trust (206250/Z/17/Z)), Petra Klepac (Gates (INV-003174)), Mark Jit (Gates (INV-003174), NIHR (16/137/109)), Joel Hellewell (Wellcome Trust (210758/Z/18/Z)).

Conflict of interest

None declared.

Authors' contributions

Conceptualisation: BJQ, SF, SC, RME; model formulation: SC, BJQ, SF; analysis: BJQ, SC; writing: RME, SF, SC, BJQ; app testing: RME and the Centre for the Mathematical Modelling of Infectious Diseases (CMMID) nCoV working group. The members of the CMMID nCoV working group contributed equally in processing, data cleaning, interpreting findings, testing the interactive tool, reviewing the manuscript and approving the work for publication. The order was assigned randomly.

References

1. World Health Organization (WHO). Novel Coronavirus (2019-nCoV) Situation Report-15. Geneva: WHO; 4 Jan 2020. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200204-sitrep-15-ncov.pdf?sfvrsn=88fe8ad6_2
2. Imperial College London. News / Wuhan Coronavirus. MRC Centre for Global Infectious Disease Analysis: News / Wuhan Coronavirus. London: Imperial College London. [Accessed 27 Jan 2020]. Available from: http://www.imperial.ac.uk/medicine/departments/school-public-health/infectious-disease-epidemiology/mrc-global-infectious-disease-analysis/news--wuhan-coronavirus/
3. Reuters. Wuhan lockdown 'unprededented', shows commitment to contain virus: WHO representative in China. [Accessed 4 Feb 2020]. Available from: https://www.reuters.com/article/us-china-health-who-idUSKBN1ZM1G9
4. Kucharski AJ, Russell TW, Diamond C. CMMID nCoV working group, Funk S, Eggo RM. Early dynamics of transmission and control of 2019-nCoV: a mathematical modelling study (pre-print). Medrxiv. 2020. http://dx.doi.org/ https://doi.org/10.1101/2020.01.31.20019901
5. Gostic KM, Kucharski AJ, Lloyd-Smith JO. Effectiveness of traveller screening for emerging pathogens is shaped by epidemiology and natural history of infection. eLife. 2015;4:e05564. https://doi.org/10.7554/eLife.05564 PMID: 25695520
6. Mabey D, Flasche S, Edmunds WJ. Airport screening for Ebola. BMJ. 2014;349(oct14 17):g6202. PMID: 25316030
7. Pitman RJ, Cooper BS, Trotter CL, Gay NJ, Edmunds WJ. Entry screening for severe acute respiratory syndrome (SARS) or influenza: policy evaluation. BMJ. 2005;331(7527):1242-3. https://doi.org/10.1136/bmj.38573.696100.3A PMID: 16176938
8. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020;NEJMoa2001316. PMID: 31995857
9. GitHub. Traveller Screening GitHub Repository. San Francisco: GitHub. [Accessed 5 Feb 2020]. Available from: https://github.com/bquilty25/airport_screening
10. Chang W, Cheng J, Allaire JJ, Xie Y, McPherson J. shiny: Web Application Framework for R. R package version 1.4.0. 2019. [Accessed 27 Jan 2020]. Available from: https://CRAN.R-project.org/package=shiny
11. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;0(0):S0140-6736(20)30154-9. PMID: 31986261
12. Samaan G, Patel M, Spencer J, Roberts L. Border screening for SARS in Australia: what has been learnt? Med J Aust. 2004;180(5):220-3. https://doi.org/10.5694/j.1326-5377.2004.tb05889.x PMID: 14984341
13. European Centre for Disease Prevention and Control (ECDC). Advice for travellers: outbreak of a novel coronavirus 2019-nCoV. Stockholm: ECDC. 30 Jan 2020. Available from: https://www.ecdc.europa.eu/en/publications-data/advice-travellers-outbreak-novel-coronavirus-2019-ncov
14. San Francisco International Airport. Passengers arriving from Wuhan, China are being screened for the novel coronavirus. San Francisco: San Francisco International Airport. [Accessed 27 Jan 2020]. Available from: https://www.flysfo.com/passengers-arriving-wuhan-china-are-being-screened-novel-coronavirus
15. Department of Health. Coronavirus: latest information and advice. London: GOV.UK. [Accessed 27 Jan 2020]. Available from: https://www.gov.uk/guidance/wuhan-novel-coronavirus-information-for-the-public#advice-for-travellers-from-wuhan
16. DiGiovanni C, Conley J, Chiu D, Zaborski J. Factors influencing compliance with quarantine in Toronto during the 2003 SARS outbreak. Biosecur Bioterror. 2004;2(4):265-72. https://doi.org/10.1089/bsp.2004.2.265 PMID: 15650436
17. The Japan Times. Countries around world gear up response to new coronavirus. 2020. [Accessed 5 Feb 2020]. Available from: https://www.japantimes.co.jp/news/2020/01/22/asia-pacific/science-health-asia-pacific/countries-around-world-gear-response-new-coronavirus/
18. British Airways. Timetables. British Airways. [Accessed 27 Jan 2020]. Available from: https://www.britishairways.com/travel/schedules/public/en_gb
19. Priest PC, Duncan AR, Jennings LC, Baker MG. Thermal image scanning for influenza border screening: results of an airport screening study. PLoS One. 2011;6(1):e14490. https://doi.org/10.1371/journal.pone.0014490 PMID: 21245928

2.2 The effect of travel restrictions on the geographical spread of COVID-19 between large cities in China: a modelling study

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	1703195	**Title**	Mr
First Name(s)	Billy		
Surname/Family Name	Quilty		
Thesis Title	Modelling the effectiveness of quarantine and testing strategies during the COVID-19 pandemic		
Primary Supervisor	Stefan Flasche		

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?	BMC Medicine		
When was the work published?	19 August 2020		
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?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*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?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

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)	I co-led in the conceptualisation of this work. I then led in the formulation, programming, and analysis of the branching process outbreak model in R, which integrated the travel data aspect which was primarly conducted by my coauthors with my input. I then co-led in producing the results and figures of the work and the writing of the first draft of the manuscript.

SECTION E

Student Signature	Billy Quilty
Date	07/02/2023

Supervisor Signature	Stefan Flasche
Date	07/02/2023

Quilty *et al. BMC Medicine* (2020) 18:259
https://doi.org/10.1186/s12916-020-01712-9

BMC Medicine

RESEARCH ARTICLE Open Access

The effect of travel restrictions on the geographical spread of COVID-19 between large cities in China: a modelling study

Billy J. Quilty*†, Charlie Diamond*†, Yang Liu, Hamish Gibbs, Timothy W. Russell, Christopher I. Jarvis, Kiesha Prem, Carl A. B. Pearson, Samuel Clifford, Stefan Flasche, CMMID COVID-19 working group, Petra Klepac††, Rosalind M. Eggo†† and Mark Jit††

Abstract

Background: To contain the spread of COVID-19, a *cordon sanitaire* was put in place in Wuhan prior to the Lunar New Year, on 23 January 2020. We assess the efficacy of the *cordon sanitaire* to delay the introduction and onset of local transmission of COVID-19 in other major cities in mainland China.

Methods: We estimated the number of infected travellers from Wuhan to other major cities in mainland China from November 2019 to February 2020 using previously estimated COVID-19 prevalence in Wuhan and publicly available mobility data. We focused on Beijing, Chongqing, Hangzhou, and Shenzhen as four representative major cities to identify the potential independent contribution of the *cordon sanitaire* and holiday travel. To do this, we simulated outbreaks generated by infected arrivals in these destination cities using stochastic branching processes. We also modelled the effect of the *cordon sanitaire* in combination with reduced transmissibility scenarios to simulate the effect of local non-pharmaceutical interventions.

Results: We find that in the four cities, given the potentially high prevalence of COVID-19 in Wuhan between December 2019 and early January 2020, local transmission may have been seeded as early as 1–8 January 2020. By the time the *cordon sanitaire* was imposed, infections were likely in the thousands. The *cordon sanitaire* alone did not substantially affect the epidemic progression in these cities, although it may have had some effect in smaller cities. Reduced transmissibility resulted in a notable decrease in the incidence of infection in the four studied cities.

Conclusions: Our results indicate that sustained transmission was likely occurring several weeks prior to the implementation of the *cordon sanitaire* in four major cities of mainland China and that the observed decrease in incidence was likely attributable to other non-pharmaceutical, transmission-reducing interventions.

Keywords: Travel restrictions, COVID-19, Wuhan, China, Modelling, Outbreaks, Delay, SARS-CoV-2, Mobility, *Cordon sanitaire*

* Correspondence: billy.quilty@lshtm.ac.uk; charlie.diamond@lshtm.ac.uk
†Billy J. Quilty and Charlie Diamond are joint first authors contributed equally to this work.
††Petra Klepac, Rosalind M. Eggo and Mark Jit are joint last authors contributed equally to this work.
Centre for Mathematical Modelling of Infectious Diseases, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, WC1E 7HT, London, UK

Background

Since late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has spread to over 114 countries and was declared a pandemic on 11 March 2020 [1]. Some countries have enacted *cordon sanitaire*-type travel restrictions, either to prevent the export of infections from an initial disease epicentre (such as Wuhan in January 2020 [2] or Northern Italy in March 2020 [3]) to other countries and regions or to prevent the import of infections from high-risk countries or regions (such as the USA's ban on travel from Europe [4]). *Cordon sanitaires* aim to curb the number of infected travellers entering a region with a high proportion of susceptible individuals, where they may seed additional chains of transmission. However, historically, they at best delay, rather than prevent outbreaks elsewhere [5]. Hence, the efficacy of *cordon sanitaires* in averting or delaying outbreaks in other locations is an open question.

Chinese authorities imposed a *cordon sanitaire* on the city of Wuhan on 23 January 2020 [2] and extended the travel restrictions to the whole of Hubei province by 26 January 2020 [6]. The restrictions were imposed 1 day prior to the Lunar New Year (LNY) holidays and during *Chunyun*, the 40-day holiday travel period that marks the largest annual human migration event in the world [7]. At the same time, other public health interventions, such as physical distancing, were also enacted across China [8].

This study aims to assess the impacts of the *cordon sanitaire* around Wuhan, the epicentre of the COVID-19 pandemic, on reducing incidence and delaying outbreaks in other well-connected large population centres in mainland China. We used publicly available mobility data based on location-based service (LBS) provided by Baidu Huiyan, to construct four mobility scenarios. Combined with daily estimated prevalence of COVID-19 in Wuhan before 11 February 2020 by Kucharski et al. [9], we simulated the daily importations of infected travellers to Beijing, Chongqing, Hangzhou, and Shenzhen to assess the risk that they would cause sustained local transmission.

Methods

Estimating number of infected travellers

We obtained daily prefecture-level human mobility data, expressed by a relative index scale, for mainland China from Baidu Huiyan for both the 2019 and 2020 travel periods surrounding the LNY, known as *Chunyun*. The platform aggregates mobile phone travel data from an estimated 189 million daily active users, processing > 120 billion daily positioning requests mainly through WiFi and GPS [10].

We examined the proportions of the total outflow leaving Wuhan and entering all other prefectures in China (excluding Wuhan). We then selected Beijing, Chongqing, Hangzhou, and Shenzhen for further analysis as major population centres with substantial travel with Wuhan and a wide geographic spread. We assume that the early transmission dynamics of SARS-CoV-2 in cities of this size were similar to that in Wuhan.

To estimate the absolute number of daily travellers leaving Wuhan, we assumed that each unit of Baidu's migration index corresponds linearly to 50,000 travellers. This was chosen as the most credible value after synthesising evidence from several sources [8, 11–14] (see Additional file 1: Supplementary Appendix 1).

We calculated the total number of daily travellers leaving Wuhan and entering each city by taking the product of the scaling factor, the total daily outflow index from Wuhan, and the daily proportion of travellers from Wuhan entering the four cities. Daily estimated COVID-19 prevalence in Wuhan was retrieved from the exposed (incubating) and infectious compartments of a published SEIR model on the early dynamics of COVID-19 transmission in Wuhan [9]. We estimated the number of daily infected arrivals in a destination city as a Poisson process governed by the daily number of travellers and prevalence in Wuhan (Additional file 1: Supplementary Appendix 2). Each day, we simulated this arrival process 100 times to capture the uncertainty in the process; this represents 7100 samples for the 71 days for each city in each scenario. We assumed that individuals would travel regardless of their infection status, and Wuhan was the sole source of infected individuals and populations within destination cities mixed homogeneously.

We examined four travel scenarios (Table 1): Scenario 1 is based on the observed travel pattern in 2020 and represents the *Chunyun* period with *cordon sanitaire* introduced on 23 January. Scenario 2 represents a counterfactual travel pattern used to evaluate how the COVID-19 outbreak would spread if no *cordon sanitaire* was implemented. This was based upon the actual travel from Wuhan for the equivalent *Chunyun* period in 2019. In scenario 3, we synthesised a hypothetical travel pattern to represent a typical non-*Chunyun* period with *cordon sanitaire* introduced on 23 January, using outward travel flow on representative non-*Chunyun* days in 2019. Scenario 4 is a variation on scenario 3 in which no *cordon sanitaire* was implemented.

We extended the corresponding outflow time series to the early stages of the outbreak (22 November 2019), by assuming the outflow from Wuhan to equal to the average daily outflow on representative non-*Chunyun* days, whilst accounting for weekday effects. The pairwise travel flow proportions between Wuhan and each other

Table 1 Scenarios describing different possible travel patterns out of Wuhan used in simulations

Scenario	Time of the year	Source year	*Cordon sanitaire* imposed	Observed/hypothetical
1	*Chunyun*	2020	Yes	Observed
2	*Chunyun*	2019	No	Observed
3	Non-*Chunyun*	2019 and 2020	Yes	Hypothetical
4	Non-*Chunyun*	2019	No	Hypothetical

prefecture-level city was only available between 1 January and 1 March, 2020, so an approximation of the general flow magnitude was used for dates outside of the observed range (22 November–31 December) and in simulated aspects of our scenarios, i.e. *Chunyun* affected travel days in non-*Chunyun* scenarios. A more detailed description of how each scenario was formulated is in Additional file 1: Supplementary Appendix 3.

Branching process transmission model

As cases in China during the early epidemic were likely underreported [15], we used a stochastic branching process model to simulate outbreaks in each of the four cities. Consistent with the prevalence estimates from Wuhan [9], we began simulating travel from Wuhan on 22 November 2019 and calculated incidence up to 1 February 2020. For each simulated infected arrival in each city on a given day, an independent branching process is generated, with:

- A negative binomial offspring distribution with a time-varying mean effective reproduction number (R_e) with baseline 2.2 [16] and overdispersion (k, variability in the number of secondary cases resulting from an infected case) of 0.1 [17]
- A log-normal serial interval (SI) with mean of 4.7 days and standard deviation of 2.9 [18]

We assume that in the initial phases of the epidemic (prior to the *cordon sanitaire*), the effective daily reproduction number (R_e) was 2.2 [16, 19]. The date at which the probability of sustained transmission exceeded a threshold of 95% (i.e. an outbreak occurring) given R_e of 2.2 and $k = 0.1$ was used to evaluate the effect of travel restrictions (details in Additional file 1: Supplementary Appendix 4) [20]. A sensitivity analysis for k using the lower and upper bounds from Endo et al. [17] (0.04, 0.2) and H1N1-like (2.0) [21] overdispersion in R_e is shown in Fig. 4. We also perform a sensitivity analysis on the serial interval, using a gamma-distributed SI of mean 7.5 days and standard deviation of 3.4 days [19] (Additional file 1: Figure S3 and S5) [18, 22]. To simulate the effect of local non-pharmaceutical intervention measures (NPIs) such as physical distancing and workplace and school closures in addition to travel restrictions [23], we compare $R_e = 2.2$ in the absence of interventions (no change, unmitigated local outbreak), to 1.1 (50% reduction, slowing epidemic, $R_e > 1$), or 0.55 (75% reduction, suppressing epidemic, $R_e < 1$). We assume additional interventions took effect on the same date as the introduction of the *cordon sanitaire*, 23 January 2020.

Implementation

All analyses were carried out using R version 3.6.2. The branching process model was implemented using the package *projections* version 0.4.1 [24].

Results

Effect of the *cordon sanitaire* on mobility

A gradual increase in the outflow from Wuhan in the weeks prior to the LNY was observed in both 2020 and 2019, exemplifying the *Chunyun* period (Fig. 1). Comparing the 23 days prior to the introduction of the *cordon sanitaire* in scenarios 1 and 2, we estimate daily outflow was 21.7% (95% CI 9.78–33.6%) higher in 2020 than the equivalent period in 2019. A surge in volume in the 3 days preceding the *cordon sanitaire* can be seen in scenario 1 (2020), where an estimated 1.69 million left Wuhan, in line with other estimates [8]. A similar outflow immediately before the LNY observed in scenario 2 (2019) suggests the surge cannot necessarily be attributed to upcoming travel restrictions. This is further reflected by the 22.5% between-year increase during this 3-day window not being substantially greater than the average daily outflow increase.

The *cordon sanitaire* had a stark effect on reducing the total outflow from Wuhan. Comparing the mean daily outflow in the 23 days preceding restrictions with the 23 days after, volume fell by 92.7%, from 345,000 (95% CI 299,000–390,000) average daily travellers to 25,300 (95% CI 8590–42,000). In comparison, volume fell by 30.2% during the equivalent period in 2019 from 290,000 (95% CI 252,000–328,000) to 203,000 (95% CI 177,000–228,000). After restrictions were imposed, travel volume declined to a low plateau over 5 days, during which approximately 330,000 people left. On the lowest day (3 February), we estimate 10,500 people left Wuhan, which likely represents only essential journeys.

In our hypothetical scenarios, we simulated the outbound flow with the additional travel volume due to *Chunyun* removed. By comparing scenarios 2 and 4 during *Chunyun* (10 January–18 February, 2020) we

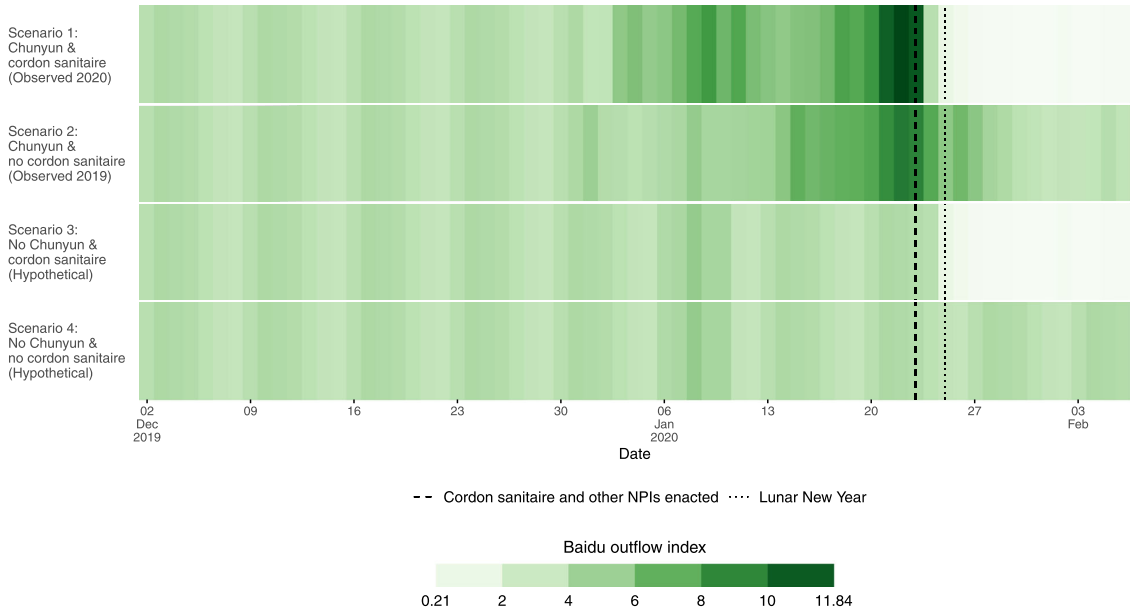


Fig. 1 Total domestic travel outflow from Wuhan under 4 travel pattern scenarios

estimate that 60,000 (95% CI 32,000–88,100) extra travellers left Wuhan every day because of *Chunyun*.

We found that in all but one prefecture with over 7 million inhabitants, the *cordon sanitaire* on 23 January did not substantially change the time at which sustained transmission was likely to occur (Additional file 1: Figure S1 A-F), but the picture was more mixed in smaller cities. Of the four representative major cities selected for further analysis, during their pre-restriction travel phase in scenario 1 (1 January–23 January, 2020): Beijing experienced a high volume of travel with approximately 1510 (95% CI 1200–1820) mean daily travellers from Wuhan; Chongqing had the highest at 1650 (95% CI 1320–1970); Hangzhou received relatively fewer with 451 (95% CI 362–541); and Shenzhen had a medium travel volume from Wuhan with 820 (95% CI 664–976) mean daily travellers.

Effect of the *cordon sanitaire* on importations of infected persons to other major Chinese cities

We estimate infected individuals began arriving on a daily basis in other major population centres in mid-December in scenario 1 (observed *Chunyun* travel profile and *cordon sanitaire imposed*) (Fig. 2). The estimated median number of infected arrivals on a given day peaked prior to the travel restrictions at 37 (95% uncertainty interval (UI) 26–47) in Beijing, 95 (95% UI 77–115) in Chongqing, 13 (95% UI 6–19) in Hangzhou, and 33 (95% UI 23–44) in Shenzhen. Travel restrictions reduced the number of infected arrivals to below 1 in all four cities within 2 days (Fig. 2a). In scenario 2 (*Chunyun* travel profile without *cordon sanitaire*), the number of daily infected arrivals decreases slightly after the *Chunyun* travel period (Fig. 2a). In cities with populations below 7 million, infected individuals began arriving later, so the *cordon sanitaire* may have acted to delay or prevent the arrival of infected individuals (Additional file 1: Figure S1 A-F).

In scenario 3 (non-*Chunyun* with travel restrictions), the estimated number of daily infected arrivals is marginally lower than scenario 1, peaking at 35 (95% UI 25–46) in Beijing, 39 (95% UI 28–50) in Chongqing, 11 (95% UI 5–17) in Hangzhou, and 25 (95% UI 15–34) in Shenzhen.

Effect of the *cordon sanitaire* on outbreaks in other major Chinese cities

Due to the volume of outbound travel from Wuhan in scenario 1, we estimate that sustained local transmission was likely to have already occurred in the four cities in early January, several weeks prior to the introduction of the *cordon sanitaire* (Table 2). On the date travel restrictions from Wuhan were imposed, local infections were likely to be in the thousands in the four cities (Table 2). Outbreaks started later and were smaller on the date of the shutdown in Hangzhou and Shenzhen compared to Beijing and Chongqing, which reflects the relative volume of travel from Wuhan.

No substantial difference was observed in the daily incidence in the scenarios with and without travel

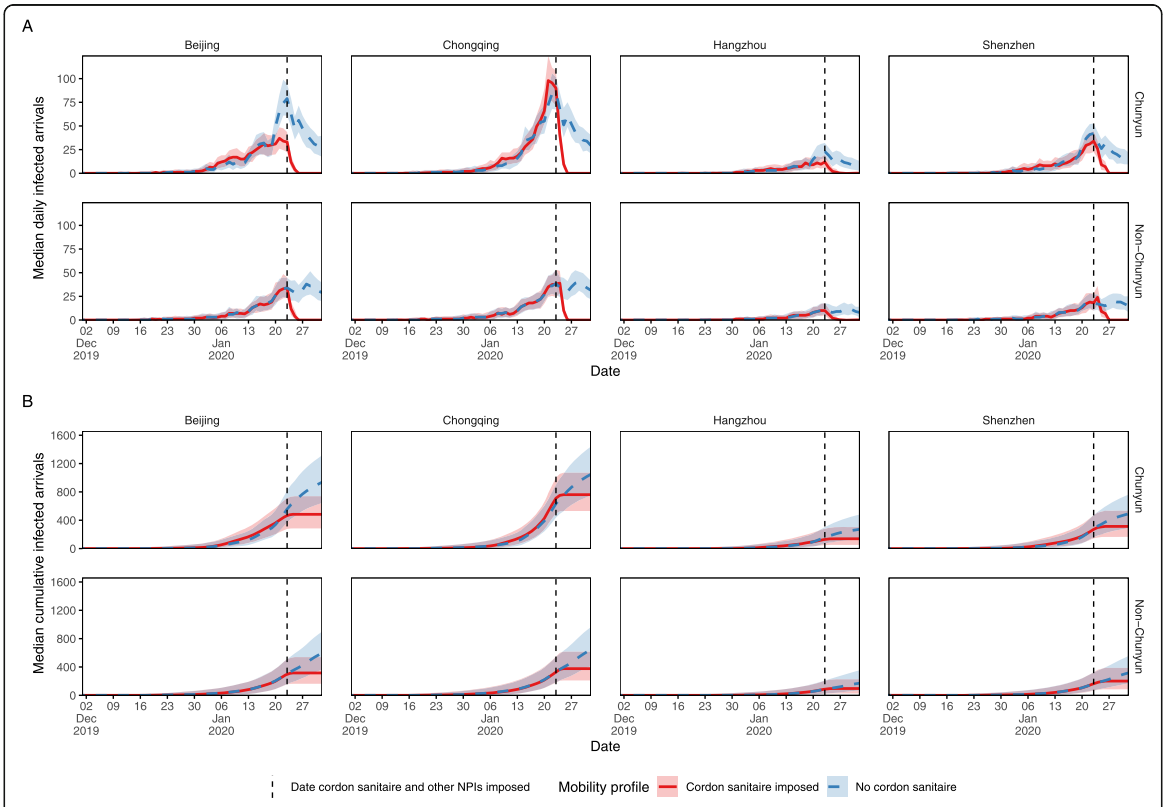


Fig. 2 a Estimated median number of daily infected arrivals and **b** estimated cumulative number of infected arrivals from Wuhan for the four chosen cities (Beijing, Chongqing, Hangzhou, and Shenzhen, left to right) for *Chunyun* vs. non-*Chunyun* and *cordon sanitaire* imposed vs. no *cordon sanitaire*. The shaded area indicates the 95% uncertainty interval. The vertical dashed line indicates the date the *cordon sanitaire* was imposed

restrictions in the four cities after the *cordon sanitaire* was imposed on 23 January; there were enough infected people to sustain local transmission in the absence of imported infections (Fig. 3 and Additional file 1: Figure S4). After the implementation of the *cordon sanitaire* on 23 January, the trajectory of the epidemic is determined primarily by reductions in R_e to simulate local transmission-reducing interventions. In an unmitigated outbreak where R_e remains at 2.2, incidence continues to increase exponentially in both scenarios; with R_e reduced to 1.1, incidence steadies; and with R_e reduced to 0.55, incidence decreased towards zero. The incidence after 23 January did not differ in scenarios with or without the implementation of the *cordon sanitaire*, and no additional effect was observed due to the *cordon sanitaire* after reducing R_e.

No substantial differences were observed in the estimated cumulative number of infections by 1 February with and without *cordon sanitaire* in any of the four cities, after accounting for uncertainty resulting from the importation process and variability in the number of

Table 2 Estimated number of local infections in each of the four cities of interest in the baseline scenario on 23 January 2020, the date the *cordon sanitaire* was imposed

Prefecture-level city	Cumulative number of infected arrivals by 23 January (median, 95% confidence interval)	Cumulative number of locally transmitted infections by 23 January (median, 95% uncertainty interval)
Beijing	465 (286–710)	4007 (1410–25,467)
Chongqing	713 (489–1007)	3936 (1321–29,678)
Hangzhou	127 (45–277)	1004 (229–12,030)
Shenzhen	271 (147–457)	1859 (399–14,261)

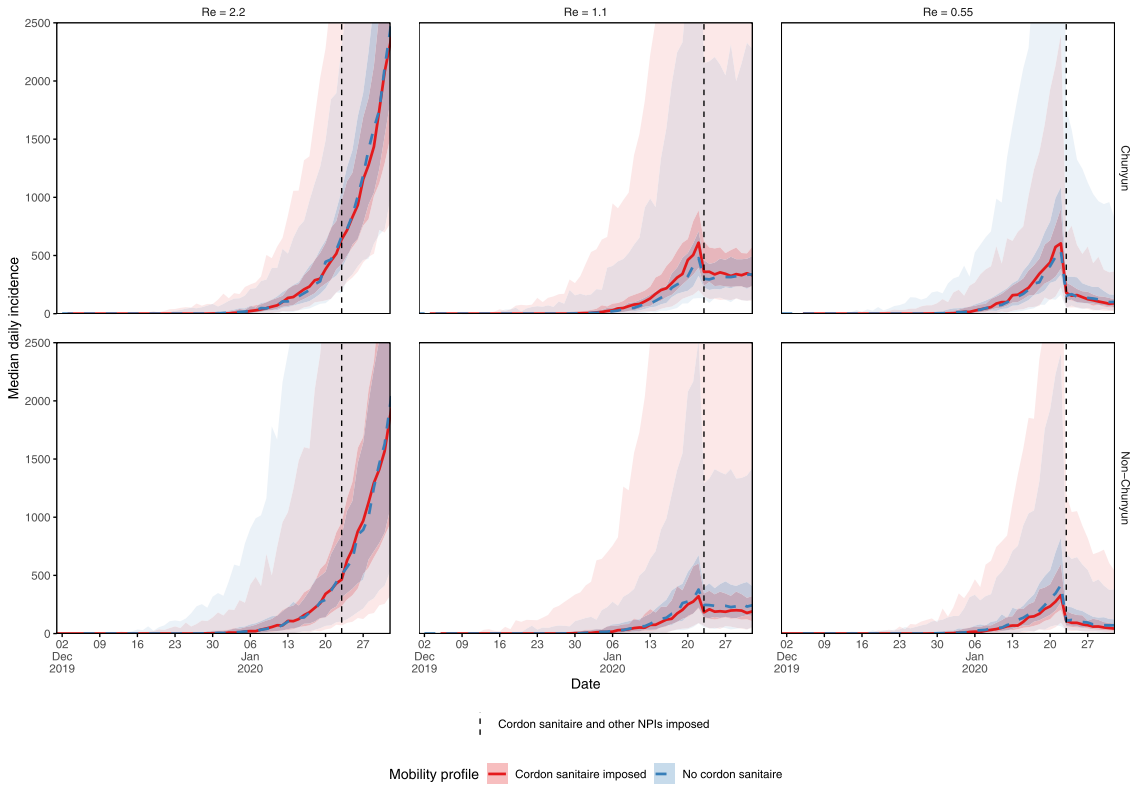


Fig. 3 Median daily incidence of COVID-19 (shaded areas indicate 50% and 95% confidence intervals) in Beijing, for *Chunyun* vs. non-*Chunyun* and *cordon sanitaire* imposed (red, solid) vs. no *cordon sanitaire* (blue, dashed) and for varying values of the effective reproduction number R_e, where $R_e = 2.2$ (no change, unmitigated local outbreak), reduced from 2.2 by 50% to 1.1 (mitigation of outbreak, $R_e > 1$), and 75% to 0.55 (suppression of outbreak, $R_e < 1$)

secondary cases resulting from an infected case (overdispersion) (Fig. 3).

Decreasing the overdispersion parameter k from the baseline 0.1 to 0.04 [17] results in a delay to the likely date of an outbreak (Fig. 4); despite this, an outbreak was highly probable in all four cities prior to the date of the *cordon sanitaire*. Increasing k to 0.2 [17], 0.54 [16], and 2.0 (influenza-like) [21] further advanced the likely date of an outbreak.

Discussion

By utilising publicly available mobility data to model the spread of the outbreak from Wuhan to other large population centres in China, we find that infected travellers from Wuhan likely led to local transmission in other major Chinese cities weeks before the *cordon sanitaire*. Cities with more travellers from Wuhan likely experienced higher incidence sooner. Modelling the trajectory of the outbreaks up to 1 February, in scenarios with and without the effect of the *cordon sanitaire*, we find no substantial differences in the cumulative number of infections generated.

By comparing *Chunyun* and non-*Chunyun* travel scenarios, no substantial difference was observed in terms of the cumulative number of infections generated by 1 February. This is likely due to the consistently high volume of travel these cities receive from Wuhan year round, resulting in enough infected travellers arriving to seed chains of transmission even during a period of regular travel volume. This however may differ in smaller cities which receive highly seasonal influxes of travellers from Wuhan relating to *Chunyun*.

The increase in mobility in 2020 compared to 2019 prior to LNY could be explained by a variety of factors, including year-to-year variations and potential factors related to COVID-19, such as the rumours of a rapidly growing outbreak and impending travel restrictions. In Northern Italy, a leaked COVID-19 plan might have driven thousands to flee south [25].

Our simulated number of arrivals of COVID-19 infections for Shenzhen by late January is broadly consistent with results shown in an observational study in Guangdong Province [26] (see Additional file 1: Supplementary

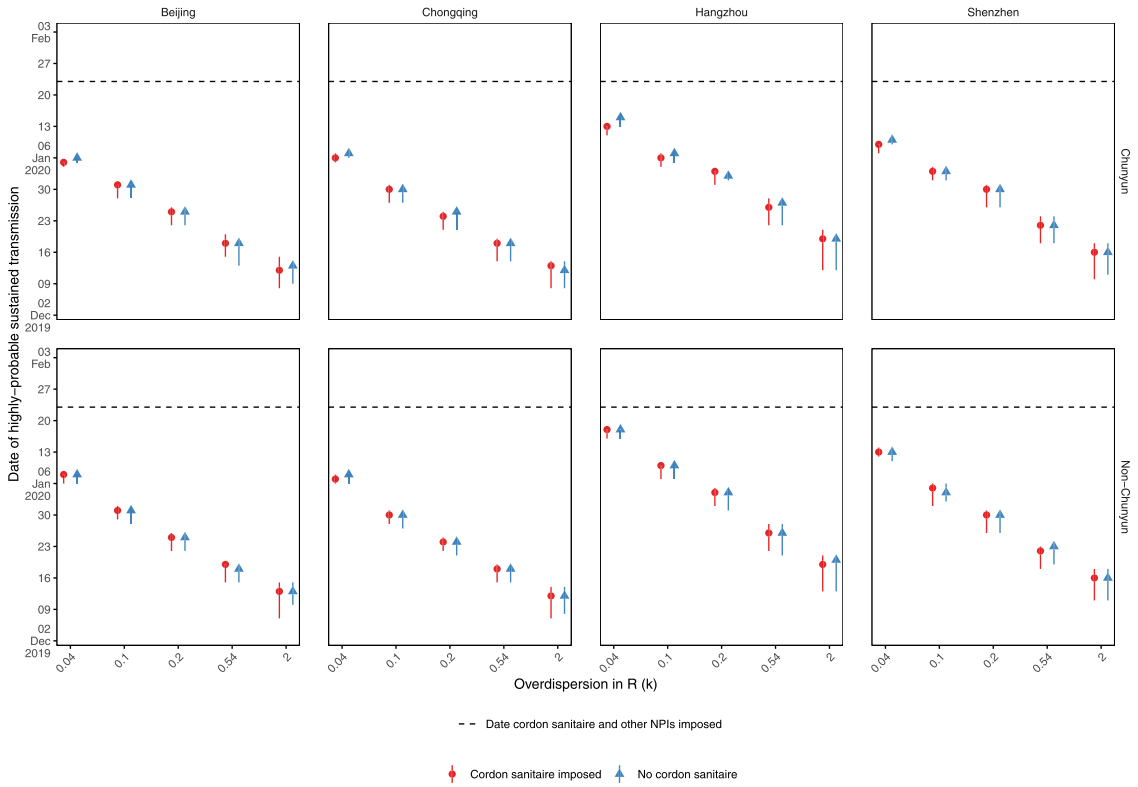


Fig. 4 Estimated date on which the probability of an outbreak exceeds 95% in the 4 cities of interest, for *Chunyun* vs. non-*Chunyun* and *cordon sanitaire* imposed vs. no *cordon sanitaire* and for varying values of the overdispersion parameter *k* [15, 21, 22]. Median (and 95% CI) estimated cumulative number of infections on 1 March in the four cities of interest, *Chunyun* vs. non-*Chunyun*, *cordon sanitaire* imposed vs. no *cordon sanitaire*, and for varying values of R_e, where $R = 2.2$ (no change, unmitigated local outbreak), reduced from 2.2 by 50% to 1.1 (mitigation of outbreak, $R > 1$), and 75% to 0.55 (suppression of outbreak, $R < 1$)

Appendix 5, Figure S6 and Figure S7) [27–29]. However, the simulated number of locally transmitted cases around the same time is considerably higher than that observed. This disparity could be explained by testing programmes oversampling individuals with a recent travel history from highly affected areas, inflating the proportion of cases that were imported from outside Guangdong and missing cases which obtained the virus locally [30]. Furthermore, in scenarios when R_e was set to 0.55 after 23 January (Fig. 3 and Additional file 1: Figure S4), we also see case numbers decline at a similar rate and timeframe to the epidemic observed in Guangdong [23], suggesting stringent local NPIs played a key role in suppressing the outbreak.

In the formulation of the travel scenarios, we assumed that the Baidu Huiyan mobility index values were relative and linear and corresponded to 50,000 travellers per unit. This was based on widely quoted estimates of people leaving Wuhan and the inter-city capacity of the travel network [8, 11–14, 31, 32] (Additional file 1: Supplementary Appendix 1). However, the index may represent a different number of travellers, or the scale may even be non-linear and the result of a more complex function, but without other evidence we assume linearity, as have other studies [8, 13]. If we chose a higher scaling factor, similar to ones used in other studies [12, 13], it is likely that infected travellers would have arrived even earlier and in greater numbers to the four destination cities. Additionally, by reconstructing travel outflows for both dates outside of the observed range (22 November–31 December) and simulated aspects of our scenarios, i.e. *Chunyun* affected travel days in non-*Chunyun* scenarios, the actual travel pattern may not have been accurately represented. Further assumptions were also made surrounding the pairwise travel flows, as observed data was only available for 2020, and the travel flows between Wuhan and each other prefecture-level city may have differed in 2019. We only considered Wuhan to be the sole source of infected individuals, and we only accounted for travellers making single-leg journeys to their destination. As such, we may

underestimate the number of infected persons arriving by not considering the number of travellers which may have stopped in an intermediate location, become infected, and then arrived at the destination to seed local transmission, or indeed infected travellers arriving from outside of Wuhan. Hence, most of our assumptions likely underestimated the number of travellers from Wuhan, and our conclusions would likely be the same even if the true number was higher. However, we also assumed that individuals would travel regardless of their infection status, which may overestimate the number of infections in destination cities.

In our model, we assume all chains of transmission are independent and populations in each city mix homogeneously. These assumptions are likely only valid in the early stages of an epidemic; however, as we only model the initial introduction of cases and their contact networks, the effect of changing these assumptions is unlikely to alter our conclusions. Moreover, the overdispersion parameter k likely captures the spread of R_e and acts to counter the assumed homogeneous population mixing. Reducing the overdispersion parameter k from 0.1 (~ 10% of individuals responsible for 80% of transmission [17]) to 0.04 (~ 5% of individuals responsible for 80% of transmission) resulted in a delay to the date of an outbreak, yet not past the date of the *cordon sanitaire*.

As recent studies have shown [8, 9, 33], strict physical distancing measures soon decreased the effective reproduction number to 1 or less in Wuhan and other cities in China. By incorporating this decrease into our model, we find that *cordon sanitaire* alone, implemented after outbreaks were likely to be established in other cities, was likely ineffective in stopping or slowing outbreaks of COVID-19 in other major population centres. To have a greater impact, the *cordon sanitaire* would need to be implemented earlier, as investigated in [34, 16], and be accompanied by other NPIs, such as general physical distancing and school and work closures [8, 23]. Similarly, it is unlikely that *cordon sanitaires* in other countries with well-established, geographically dispersed outbreaks will substantially delay COVID-19 spread. An open question is whether travel restrictions may be more efficacious to prevent or delay reintroductions after the lifting of other NPIs.

Whilst earlier restrictions on travel from Wuhan may have had a larger impact, in countries with a high-degree of inter-city travel, it may be difficult to implement such highly disruptive travel restrictions at an early stage of the epidemic, before local transmission has occurred in other cities. We find that local transmission in the four cities we studied (here defined as the probability of sustained transmission exceeding a 95% threshold) was most likely established between 1 January and 8 January; it was only on 8 January that the aetiology of the "mystery pneumonia" (which was not yet confirmed to spread from person-to-person [35]) was determined as a novel coronavirus, and the first death occurred [36]. It is difficult to see how the *cordon sanitaire* could have been justified any earlier, as almost every aspect of COVID-19 virology and epidemiology was unknown. Hence, it is likely that the sustained decline in COVID-19 incidence in other cities of China several months into the outbreak is primarily due to other public health measures to reduce the disease transmissibility, i.e. to reduce the reproduction number to 1 or below [9, 23, 33]. The *cordon sanitaire* may have been more efficacious in delaying outbreaks internationally, as the relative number of travellers is orders of magnitude lower [8, 37]; the same may also apply to lower-traffic destinations from Wuhan within China, such as small cities geographically distant from Wuhan, as observed in Tian et al. [8]. We found a mixed picture in these cities, where the *cordon sanitaire* may have been more efficacious at delaying or preventing outbreaks (Additional file 1: Figure S1 A-F). However, COVID-19 transmission dynamics may differ in comparison to large cities, and as such, we chose to focus on the effect of travel restrictions in large cities with large volumes of travel from Wuhan, where data on R and k from the early outbreak in Wuhan are likely generalisable. Furthermore, these destinations with low traffic from Wuhan are more likely to be seeded by outbreaks in other, comparatively closer, large cities first. Hence, our assumption of a single outbreak source would have been much less realistic.

Our estimated dates of introduction in other cities are earlier than those observed [1] and reported in other studies [38]. This is due in part to correction for underreporting, both by using the estimated daily prevalence in Wuhan from Kucharski et al. [9], which is significantly higher than the confirmed number of cases [20], and by not relying on reported cases in other provinces. The effect of underreporting is likely more pronounced early in the outbreak prior to a well-defined case definition or widespread testing [15]. Hence, reconstructing the early outbreak through a simulation approach was more appropriate in this setting.

We concur with Tian et al. 2020 [8] that prohibiting travel alone did not act to reduce the number of COVID-19 infections in four major cities outside of Wuhan or Hubei and that other local control measures were likely instrumental in reducing incidence. Likewise, Kraemer et al. [38] conclude that whilst a decrease in the growth rate was observed in large cities after the *cordon sanitaire* was imposed, this is difficult to disentangle from local control measures.

Conclusion

In conclusion, the introduction of *cordon sanitaire*-type travel restrictions around a COVID-19 epidemic centre

after community transmission is already occurring in other well-connected population centres on its own likely has little effect on altering their epidemic trajectories. Stringent NPIs in cities are more likely to have a bigger impact in reducing incidence and pressure on healthcare systems. Further research should examine the role of travel restrictions during the partial lifting of NPIs across China and elsewhere.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12916-020-01712-9.

Additional file 1 : Supplementary Appendix 1–5. Table S1 - Various scaling factors calculated from different sources. **Table S2** - Parameters used to estimate the total number of travellers leaving Wuhan and entering other prefecture-level cities for each scenario. **Table S3.** Bivariate regression results where y = number of imported cases into Guangdong (by date of symptom onset) and x = imported cases into Guangdong (by date of arrival), for an increasing amount of day lags. **Figure S1.** Date at which the mean probability of sustained transmission breaches 95% in each prefecture, by region (A-F). **Figure S2.** Location of Wuhan and the four cities of interest in mainland China. **Figure S3.** Delay distributions for the serial interval of COVID-19 infection from literature. **Figure S4.** Median daily incidence of COVID-19 in the four cities of interest. **Figure S5.** Median daily incidence of COVID-19 in the four cities of interest with alternative serial interval of mean 7.5 days (SD: 3.4). **Figure S6.** Estimated daily infected arrivals in Guangdong Province. **Figure S7.** Observed imported cases by date of symptom onset vs. predicted imported cases by date of arrival with a lag of 4 days.

Abbreviations

k: Overdispersion parameter; LBS: Location-based service; LNY: Lunar New Year; NPIs: Non-pharmaceutical interventions; R_e: Effective reproduction number; SI: Serial interval; UI: Uncertainty interval

Authors' contributions

BJQ, CD, YL, KP, PK, RME, and MJ conceived the study. BJQ and CD designed and programmed the model and made the figures. YL, HG, TWR, and CIJ provided the data. YL, HG, TWR, CIJ, KP, CABP, SC, SF, PK, REM, and MJ consulted on the analyses. BJQ, CD, YL, and MJ wrote the manuscript. The CMMID COVID-19 working group members contributed to processing, cleaning, and interpretation of data; interpreted the study findings; contributed to the manuscript; and approved the work for publication. All authors interpreted the findings, contributed to writing the manuscript, and approved the final version for publication.

Funding

BJQ, CD, YL, and MJ were funded by the National Institute for Health Research (NIHR; 16/137/109). YL, PK, KP, and MJ were funded by the Bill & Melinda Gates Foundation (INV-003174). MJ was funded by European Commission grant EpiPose (101003688). HG was funded by the Department of Health and Social Care (ITCRZ 03010). TWR was funded by the Wellcome Trust (206250/Z/17/Z). CIJ was funded by the Global Challenges Research Fund (ES/P010873/1). CABP was funded by the NTD Modelling Consortium by the Bill and Melinda Gates Foundation (OPP1184344). SF and SC were funded by the Sir Henry Dale Fellowship (208812/Z/17/Z). RME was funded by Health Data Research UK (MR/S003975/1). This research was partly funded by the NIHR (16/137/109) using aid from the UK Government to support global health research. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the UK Department of Health and Social Care.

We would like to acknowledge the other members of the London School of Hygiene & Tropical Medicine CMMID COVID-19 modelling group, who contributed to this work. Their funding sources are as follows: Jon C Emery and Rein M G J Houben (European Research Council Starting Grant, Action Number #757699); Megan Auzenbergs and Kathleen O'Reilly (Bill and Melinda Gates Foundation, OPP1191821); Nicholas Davies (NIHR HPRU-2012-10096); Emily S Nightingale (Bill and Melinda Gates Foundation, OPP1183986); Kevin van Zandvoort (Elrha's Research for Health in Humanitarian Crises [R2HC] Programme, UK Government [Department for International Development], Wellcome Trust, and NIHR); Thibaut Jombart (Research Public Health Rapid Support Team, NIHR Health Protection Research Unit Modelling Methodology); Arminder K Deol; W John Edmunds; Joel Hellewell, Sam Abbott, James D Munday, Nikos I Bosse and Sebastian Funk (Wellcome Trust 210758/Z/18/Z); Fiona Sun (NIHR; 16/137/109); Akira Endo (The Nakajima Foundation; The Alan Turing Institute); Alicia Rosello (NIHR: PR-OD-1017-20002); Amy Gimma (Global Challenges Research Fund ES/P010873/1); Simon R Procter (Bill and Melinda Gates Foundation, OPP1180644); Graham Medley (NTD Modelling Consortium by the Bill and Melinda Gates Foundation (OPP1184344); Adam J Kucharski (Wellcome Trust, 206250/Z/17/Z), and Gwen Knight (UK Medical Research Council, MR/P014658/1).

Availability of data and materials

The mobility data was sourced from Baidu Haiyan migration dashboard at https://qianxi.baidu.com/.

The code for this analysis is available on GitHub at https://github.com/bquilty25/wuhan_travel_restrictions.

Ethics approval and consent to participate

Neither patients nor the public were involved with the design, conduct, reporting, or dissemination plans of our research. As this work is a simulation study, there are no participants to which we can disseminate the results of this research.

Consent for publication

Not applicable.

Competing interests

MJ is a Board Member for the Journal. AE received a research grant from Taisho Pharmaceutical Co., Ltd. We declare no other competing interests.

Received: 24 April 2020 Accepted: 16 July 2020
Published online: 19 August 2020

References

1. World Health Organisation. Novel coronavirus (2019-nCoV) situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed 30 Mar 2020.
2. Virus-hit Chinese city shuts public transport. BBC News. 2020. https://www.bbc.com/news/world-asia-china-51215348. Accessed 1 Apr 2020.
3. Il governo firma il decreto coronavirus: l'Italia divisa in 3 zone (Translated: The government signs the coronavirus decree: Italy divided into 3 areas). la Repubblica. 2020. https://www.repubblica.it/politica/2020/03/01/news/coronavirus_misure_governo-249980561/. Accessed 1 Apr 2020.
4. Zurcher A. Trump's virus travel ban on Europe comes into force. BBC News 2020. https://www.bbc.com/news/world-us-canada-51883728. Accessed 1 Apr 2020.
5. Mateus AL, Otete HE, Beck CR, Dolan GP, Nguyen-Van-Tam JS. Effectiveness of travel restrictions in the rapid containment of human influenza: a systematic review. WHO. 2014. https://www.who.int/bulletin/volumes/92/12/14-135590/en/. Accessed 29 Jun 2020.
6. 襄阳火车站关闭, 湖北省最后一个地级市"封城"_媒体_澎湃新闻-The Paper. https://www.thepaper.cn/newsDetail_forward_5671283. Accessed 1 Apr 2020.
7. Wang X, Liu C, Mao W, Hu Z, Gu L. Tracing the largest seasonal migration on Earth. arXiv. 2014. http://arxiv.org/abs/1411.0983. Accessed 20 Mar 2020.
8. Tian H, Liu Y, Li Y, Wu C-H, Chen B, Kraemer MUG, et al. An investigation of transmission control measures during the first 50 days of the COVID-19 epidemic in China. Science. 2020. https://doi.org/10.1126/science.abb6105.
9. Kucharski AJ, Russell TW, Diamond C, Liu Y, Edmunds J, Funk S, et al. Early dynamics of transmission and control of COVID-19: a mathematical modelling study. Lancet Infect Dis 2020;0. doi:https://doi.org/10.1016/S1473-3099(20)30144-4.
10. Baidu. 首页-百度地图慧眼 (Translated: Baidu map). https://huiyan.baidu.com/. Accessed 1 Apr 2020.
11. Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. The novel coronavirus, 2019-nCoV, is highly contagious and more infectious than

initially estimated. medRxiv. 2020. doi:https://doi.org/10.1101/2020.02.07.20021154.
12. Cao Z, Zhang Q, Lu X, Pfeiffer D, Wang L, Song H, et al. Incorporating Human Movement Data to Improve Epidemiological Estimates for 2019-nCoV. medRxiv. 2020. https://doi.org/10.1101/2020.02.07.20021071.
13. Zhou C. Evaluating new evidence in the early dynamics of the novel coronavirus COVID-19 outbreak in Wuhan, China with real time domestic traffic and potential asymptomatic transmissions. medRxiv. 2020. https://doi.org/10.1101/2020.02.15.20023440.
14. 春运前十天, 武汉铁公空发送400余万人次, 公共交通运送8000余万人次_首页武汉_新闻中心_长江网 (Translated: Ten days before the Spring Festival, Wuhan Railway Express sent more than 4 million passengers, and public transportation delivered more than 80 million passengers.). http://news.cjn.cn/sywh/202001/t3539167.htm. Accessed 23 Mar 2020.
15. Using a delay-adjusted case fatality ratio to estimate under-reporting. CMMID Repository. 2020. https://cmmid.github.io/topics/covid19/severity/global_cfr_estimates.html. Accessed 25 Mar 2020.
16. Riou J, Althaus CL. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. Eurosurveillance. 2020;25:2000058.
17. Endo A, Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group, Abbott S, Kucharski AJ, Funk S. Estimating the overdispersion in COVID-19 transmission using outbreak sizes outside China. Wellcome Open Res. 2020;5:67.
18. Nishiura H, Linton NM, Akhmetzhanov AR. Serial interval of novel coronavirus (COVID-19) infections. Int J Infect Dis. 2020;93:284–6.
19. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N Engl J Med. 2020;382:1199–207.
20. Hartfield M, Alizon S. Introducing the outbreak threshold in epidemiology. PLoS Pathog. 2013;9:e1003277.
21. Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading and the effect of individual variation on disease emergence. Nature. 2005;438:355–9.
22. Jombart T, Cori A, Kamvar ZN, Schumacher D. epitrix: Small helpers and tricks for epidemics analysis. 2019. https://CRAN.R-project.org/package=epitrix. Accessed 29 May 2020.
23. Prem K, Liu Y, Russell TW, Kucharski AJ, Eggo RM, Davies N, et al. The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study. Lancet Public Health 2020;0. doi:https://doi.org/10.1016/S2468-2667(20)30073-6.
24. Project Future Case Incidence. http://www.repidemicsconsortium.org/projections/. Accessed 11 Mar 2020.
25. Leaked coronavirus plan to quarantine 16m sparks chaos in Italy. The Guardian. 2020. https://www.theguardian.com/world/2020/mar/08/leaked-coronavirus-plan-to-quarantine-16m-sparks-chaos-in-italy. Accessed 27 Mar 2020.
26. Lu J, du Plessis L, Liu Z, Hill V, Kang M, Lin H, et al. Genomic epidemiology of SARS-CoV-2 in Guangdong Province, China. Cell. 2020;181:997–1003.e9.
27. Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20–28 January 2020. Eurosurveillance. 2020;25. https://doi.org/10.2807/1560-7917.ES.2020.25.5.2000062.
28. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581:465–9.
29. Chau NVV, Thanh Lam V, Thanh Dung N, Yen LM, Minh NNQ, Hung LM, et al. The natural history and transmission potential of asymptomatic SARS-CoV-2 infection. Clin Infect Dis. https://doi.org/10.1093/cid/ciaa711.
30. China CDC. 新型冠状病毒肺炎流行病学调查指南 (Translated: Guidelines for the epidemiological investigation of new coronavirus pneumonia). http://www.chinacdc.cn/jkzt/crb/zl/szkb_11803/jszl_11815/202003/W020200309540843000869.pdf. Accessed 27 Mar 2020.
31. 北京三大火车站迎节前客流最高峰 预计62万人次乘火车离京-新华网 (Translated: Beijing's three major railway stations have the highest peak passenger flow before the festival, and 620,000 people are expected to leave Beijing by train). http://www.xinhuanet.com/fortune/2019-02/02/c_1124077797.htm. Accessed 14 Apr 2020.
32. 春运期间首都机场预计进出港旅客1151万人次--财经-- (Translated: During the Spring Festival transport, Capital Airport is expected to have 11.51 million passengers in and out of Hong Kong). http://finance.people.com.cn/n1/2019/0121/c1004-30581248.html. Accessed 14 Apr 2020.
33. Zhang J, Litvinova M, Liang Y, Wang Y, Wang W, Zhao S, et al. Age profile of susceptibility, mixing, and social distancing shape the dynamics of the novel coronavirus disease 2019 outbreak in China; 2020. https://doi.org/10.1101/2020.03.19.20039107.
34. Lai S, Ruktanonchai NW, Zhou L, Prosper O, Luo W, Floyd JR, et al. Effect of non-pharmaceutical interventions for containing the COVID-19 outbreak in China. medRxiv. 2020. doi:https://doi.org/10.1101/2020.03.03.20029843.
35. Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;395:514–523.
36. Qin A, Hernández JC. China reports first death from new virus. The New York Times. 2020. https://www.nytimes.com/2020/01/10/world/asia/china-virus-wuhan-death.html. Accessed 26 Mar 2020.
37. Chinazzi M, Davis JT, Ajelli M, Gioannini C, Litvinova M, Merler S, et al. The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak. Science. 2020. https://doi.org/10.1126/science.aba9757.
38. Kraemer MUG, Yang C-H, Gutierrez B, Wu C-H, Klein B, Pigott DM, et al. The effect of human mobility and control measures on the COVID-19 epidemic in China. Science. 2020. https://doi.org/10.1126/science.abb4218.

Publisher's Note

Supplementary Appendix

1. Estimating the scaling factor

To estimate the absolute number of daily travellers leaving Wuhan from Baidu's migration index, we needed a suitable scaling factor to convert the index score to the absolute number of travellers. In lieu of other evidence, we assumed this relationship to be linear cohering with other studies [8, 13]. We synthesised estimates from a number of sources (Table S1) in order to select the most viable result. In each case the scaling factor was calculated using the following equation:

$$S = \frac{\sum_{t_{\min}}^{t_{\max}} \psi_t}{\sum_{t_{\min}}^{t_{\max}} \sigma_t}$$

Where the sum of the daily estimated number of travellers ψ_t leaving Wuhan for the dates t_{min} to t_{max}, divided by the sum of the daily outflow index from Wuhan σ_t, for the same date range, equals the scaling factor S.

Table S1 - Various scaling factors calculated from different sources.

Reference	**Date range (t_{min} to t_{max})**	**Sum of traveller numbers leaving Wuhan (ψ_t)**	**Sum of Baidu travel index leaving Wuhan (σ_t)**	**Estimated scaling factor (S)**
Tian (2020) [8]	Jan 11 - Jan 25	4,325,563*	105.69	40,926.89
Sanche (2020) [11]	Jan 10 - Jan 23	5,000,000	107.12	46,676.62
News report (2020) [14]	Jan 10 - Jan 20	4,098,600	73.40	55,839.24

Cao (2020) [12]	Jan 16 - Jan 22	7,014,199*	58.45	120,003.40
Zhou (2020) [13]	Unknown	Unknown	Unknown	138,412.00

* Based on data extracted from figures, subject to slight error.

Combining evidence from the first three sources in Table S1, we chose a scaling factor of 50,000. This assumes each unit of Baidu's migration index corresponds to 50,000 outbound travellers. This produced the most reasonable outbound travel volume estimates, using scaling factors of 120,003.40 and 138,412, found in Cao (2020) and Zhou (2020) respectively, yielded unrealistically large travel magnitudes. These scaling factors would suggest that on Beijing's single busiest day of *Chunyun* (23 Jan, 2020), in excess of 2.8 million people left the city. This is substantially larger than Beijing's maximum daily outbound travel capacity by air and rail, which is estimated to be 920,000 daily passengers [31, 32]. This estimate does not consider passengers traveling by road, however this form of transportation accounts for a relatively small proportion of the total inter-prefecture travel.

2. Estimating number of infected travellers

The number of travellers arriving in each city from Wuhan is summarised as:

$$\omega_{it} = S \times \sigma_t \times \kappa_{it}$$

Where S is the scaling factor, σ_t is the total daily outflow index from Wuhan, κ_{it} is the daily proportion of outflow entering each city i, and ω_{it} is the daily number of total arrivals from Wuhan in city i.

The number of daily infected arrivals to a given prefecture i is simulated by making 100 draws from a Poisson process:

$$\lambda_{it} \sim \text{Pois}\left(\omega_{it} \times \rho_{it}\right)$$

Where ω_{it} is the daily estimated travel from Wuhan to prefecture *i* on day *t,* ρ_{it} is the daily prevalence in Wuhan, and λ_{it} is the number of infected individuals arriving per day.

3. Travel flow scenario formulation

The observed travel outflow from Wuhan in 2019 and 2020 were matched by the date of the Lunar New Year in 2020 so as to align the *Chunyun* travel patterns. Each scenario is driven by differences in the parameters used to estimate the total daily number of travellers arriving from Wuhan in a given prefecture-level city. In all scenarios the scaling factor was assumed to be constant at 50,000. Differences between scenarios are summarised in the table and equations below:

Table S2 - Parameters used to estimate the total number of travellers leaving Wuhan and entering other prefecture-level cities for each scenario.

Scenario and description	**Daily outflow from Wuhan (σ_t)**	**Daily proportion of travellers leaving Wuhan and entering each prefecture-level city (κ_{it})**
Scenario 1 - *Chunyun* & *cordon sanitaire*	22 Nov - 31 Dec: $\overline{\sigma_t}$ * 1 Jan - 1 Mar: $\boldsymbol{\sigma_t}$ (Observed 2020)	22 Nov - 31 Dec: $\overline{\kappa_i}$† 1 Jan - 1 Mar: $\boldsymbol{\kappa_{it}}$ (Observed 2020)
Scenario 2 - *Chunyun* & no *cordon sanitaire*	22 Nov - 31 Dec: $\overline{\sigma_t}$ *	22 Nov - 31 Dec: $\overline{\kappa_i}$†

	1 Jan - 1 Mar: $\boldsymbol{\sigma_t}$ (Observed 2019^)	1 Jan - 19 Jan: $\boldsymbol{\kappa_{it}}$ (Observed 2020) 20 Jan - 1 Mar: $\overline{\kappa_i}$†
Scenario 3 - No *Chunyun* & *cordon sanitaire*	22 Nov - 5 Jan: $\overline{\sigma_t}$ * 6 Jan - 10 Jan: $\boldsymbol{\sigma_t}$ (Observed 2019^) 11 Jan - 23 Jan: $\overline{\sigma_t}$ * 24 Jan - 1 Mar: $\boldsymbol{\sigma_t}$ (Observed 2020)	22 Nov - 23 Jan: $\overline{\kappa_i}$† 24 Jan - 1 Mar: $\boldsymbol{\kappa_{it}}$ (Observed 2020)
Scenario 4 - No *Chunyun* & no *cordon sanitaire*	22 Nov - 5 Jan: $\overline{\sigma_t}$ * 6 Jan - 10 Jan: $\boldsymbol{\sigma_t}$ (Observed 2019^) 11 Jan - 7 Feb: $\overline{\sigma_t}$ * Feb 8 - 1 Mar: $\boldsymbol{\sigma_t}$ (Observed 2019^)	22 Nov - 1 Mar: $\overline{\kappa_i}$†

^ Equivalent *Chunyun* dates aligned to the 2020 calendar.

* See equation 1.

† See equation 2.

Equation 1:

$$\overline{\sigma_t} = \frac{\sum_{17\text{Jan}}^{21\text{Jan}} \sigma_t + \sum_{19\text{Feb}}^{12\text{Mar}} \sigma_t}{n}$$

The above equation estimates the mean daily outflow index from Wuhan in 2019 for the following dates; 17 Jan - 21 Jan and 19 Feb - 12 Mar. These dates are understood to be days of regular travel volume, and as such can be used to construct an estimate of an average travel flow for a representative non-*Chunyun* period.

Equation 2:

$$\overline{\kappa_i} = \frac{\sum_{t_{\min}}^{t_{\max}} (\sigma_t \times \kappa_{it})}{\sum_{t_{\min}}^{t_{\max}} \sigma_t}$$

Equation 2 approximates the general daily proportion of travellers leaving Wuhan and entering a given city *i*. For the length of the study period (t_{min} to t_{max}), we take the sum of the estimated travel flow leaving Wuhan and entering city *i* ($\sigma_t \times \kappa_{it}$) and divide it by the sum of the total outflow from Wuhan σ_t over the same period. This was a key assumption as the pairwise travel flows between Wuhan and each other prefecture-level city was only available between 1 Jan - 1 Mar, 2020. Therefore this approximation of general flow magnitude was used for both out of date ranges (22 Nov - 31 Dec) and simulated aspects of our scenarios i.e. *Chunyun* affected travel days in non-*Chunyun* scenarios.

4. Probability of sustained transmission (outbreak threshold)

The probability of sustained transmission was calculated using methods detailed in the Supplement of Hartfield and Alizon 2013 [20], which we will briefly summarise here.

Given a secondary case distribution with mean *R* and dispersion parameter *k*, the individual probability of a outbreak *q* can be numerically solved by:

$$\left[1+\frac{R}{k}q\right]^{-k}=1-q$$

The number of individuals required (*i*) such that the probability at least one of them causes an outbreak is then:

$$i=\frac{\ln(1-c)}{\ln(1-q)}$$

Where *c* (the outbreak threshold) was chosen as 0.95.

The impact of travel restrictions was assessed by comparing the daily probability of an outbreak occurring $\mathcal{O}$ for 2020 (restrictions imposed) and 2019 ("business-as-usual").

5. Comparison with Observational Study in Guangdong

Whilst the modelling presented in this study can be a useful tool to help understand the dynamics and spread of COVID-19 between large cities in China, it is important to contextualise the results against those observed and reported in other studies. To do this, we compared our predicted number of daily imported cases (by date of arrival) against the number of daily reported imported cases (by date of symptom onset) reported by Lu et al. (2020) in Guangdong from late December 2019 to early February 2020 (Figure S6). The two time-series show striking similarities by both rising and falling at broadly comparable rates, albeit with different magnitudes, and a delay of approximately 4 days. After adjusting for a 4 day lag, when statistically compared in a bivariate linear regression, results yield an adjusted R^2 value of 0.67 signifying that our estimated number

of imported cases, by date of arrival has a reasonably strong ability to explain variance in the reported case numbers by date of symptom onset (Figure S7). This relationship can be summarised by the following formula:

*Observed imported cases = 7.83883 + (predicted arrival cases lag_4 * 0.58174)*

This can be interpreted as approximately 58.2% of the total predicted arrivals plus 7.84 cases, are able to explain 67% of the variation in the observed reported case numbers, by date of symptom onset. We further examined different values of lag to see if this would improve the models fit. Full results of this can be seen in Table S3. In terms of maximising the adjusted R^2 value, a lag of four days appears optimum. A lag of zero days produces a substantially worse fit, suggesting as expected that there is a delay before an infected arrival gets reported. Although this explains a large proportion of the variation in the observed cases numbers by symptom onset, a substantial part remains unknown and is potentially attributable to several key differences in the definition of our predicted case numbers and the observed reported values.

Table S3 - Bivariate regression results where y = number of imported cases into Guangdong (by date of symptom onset) and x = imported cases into Guangdong (by date of arrival), for an increasing amount of day lags.

Independent variable (x)	**Intercept**	**Effect size**	**Adjusted R^2**
Imported cases by date of arrival	14.2174	0.3438	0.20
Imported cases by date of arrival, lag 1 day	12.06987	0.41871	0.32
Imported cases by date of arrival, lag 2 day	10.05409	0.49544	0.47

Imported cases by date of arrival, lag 3 day	8.61880	0.55539	0.60
Imported cases by date of arrival, lag 4 day	7.83993	0.58174	0.67
Imported cases by date of arrival, lag 5 day	8.76404	0.56087	0.63
Imported cases by date of arrival, lag 6 day	10.67585	0.50511	0.52

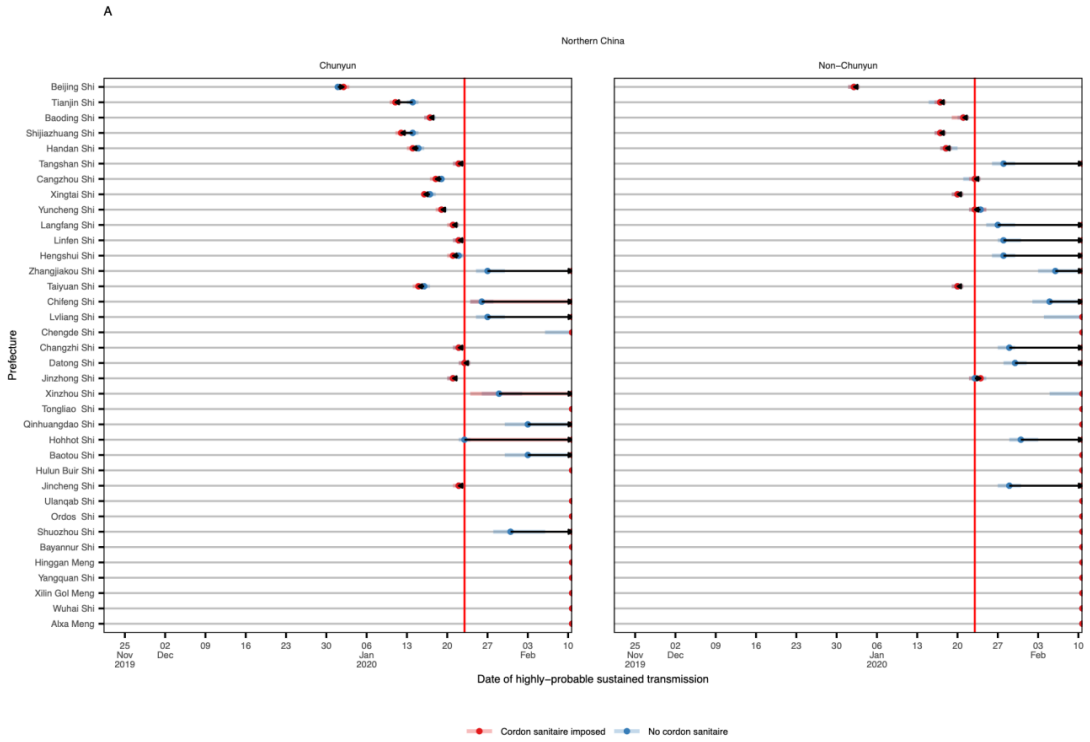
Firstly, the case data presented in Lu et al. (2020) is defined as somebody “with travel history from Hubei or other epidemic regions and did not have close contact with local positive cases in the 14 days preceding illness onset”. At the beginning of this pandemic, we can assume most domestically imported cases in Guangdong are from Hubei and not other provinces. However, in our study we explicitly only model cases arriving from Wuhan, one of 17 prefecture-level units in the Hubei province. Wuhan is the only location with prevalence estimates during that time, and travel was completely stopped on Jan 23rd. Travellers from other prefectures in Hubei were able to travel out until Jan 26-27th, based on our knowledge of local movement restriction policies. Thus, travellers in our study (compared to those in Lu et al. (2020)) not only came from different locations, but also travelled at different times. Since the proportion of reported cases imported from Wuhan were not presented in Lu et al. (2020), comparisons between the observed reported importations and our predicted importations would potentially not capture the whole story.

Secondly, our outcome is generated in terms of the date of arrival into a given city. In order to convert this date to a symptom onset date (which is only available for symptomatic individuals) and make it more comparable to Lu et al. 2020, we need to consider the following:

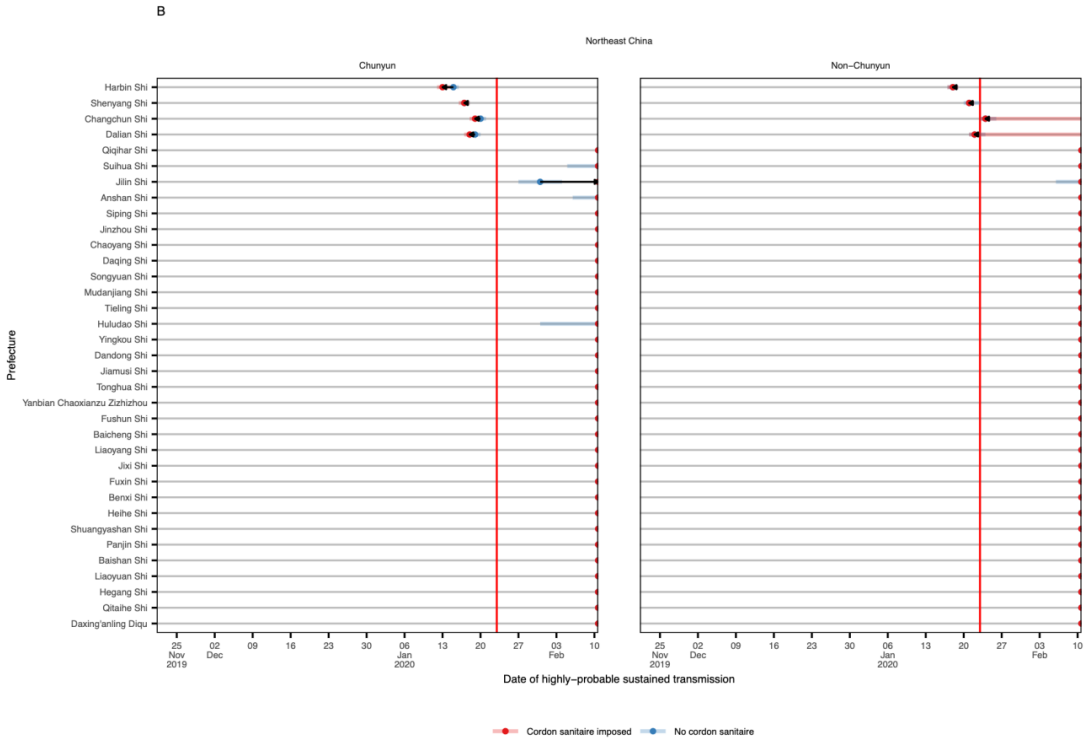
1. Each individuals' incubation period (time from infection to symptoms onset), estimated to have 95% range of 2.1 to 11.1 days, with a median of 6.4 [27]. For simplicity, we will use the median (t1)
2. Each individuals' recovery time (time from symptoms onset to loss of infectious period). This may last to around 10 days, with a median 7-8 days [28]. For simplicity, we will use 8 days (t2).
3. Cases are confirmed based on being PCR positive, and not based on their infectiousness. Cases could be PCR positive for up to three weeks after the time of infection [28]. For simplicity, we will use 14 days (t3).
4. At the beginning of the outbreak, syndromic surveillance was not fully utilised, so symptomatic individuals may still have travelled. This means, for a symptomatic individual arriving on a given date d, the onset date could be anywhere from d-t2 or d-t3 to d+t1. This is roughly a 2-3 week range (t1+t2 or t1+t3). The entire time horizon we focus on is roughly 6 weeks. So the uncertainty is quite substantial, even when we only consider the point estimates in 1-3.
5. Probability of detection, which varies by travel time [29]. For instance, travellers that arrive in Guangdong more than a week after symptom onset are less likely to be detected than those arriving in Guangdong 1 day after symptom onset although, at the time, they are equally likely to travel.

Based on these factors, we believe that the direct comparison between imported infected travellers by their arrival date, and imported cases by their symptom onset date should be interpreted with extreme caution, even after accounting for lag. A more accurate comparison could be done using a mechanistic model explicitly accounting for the relevant disease parameters presented above (and their associated uncertainties), and with more accurate locations of traveller origin.

6. Supplementary figures and tables

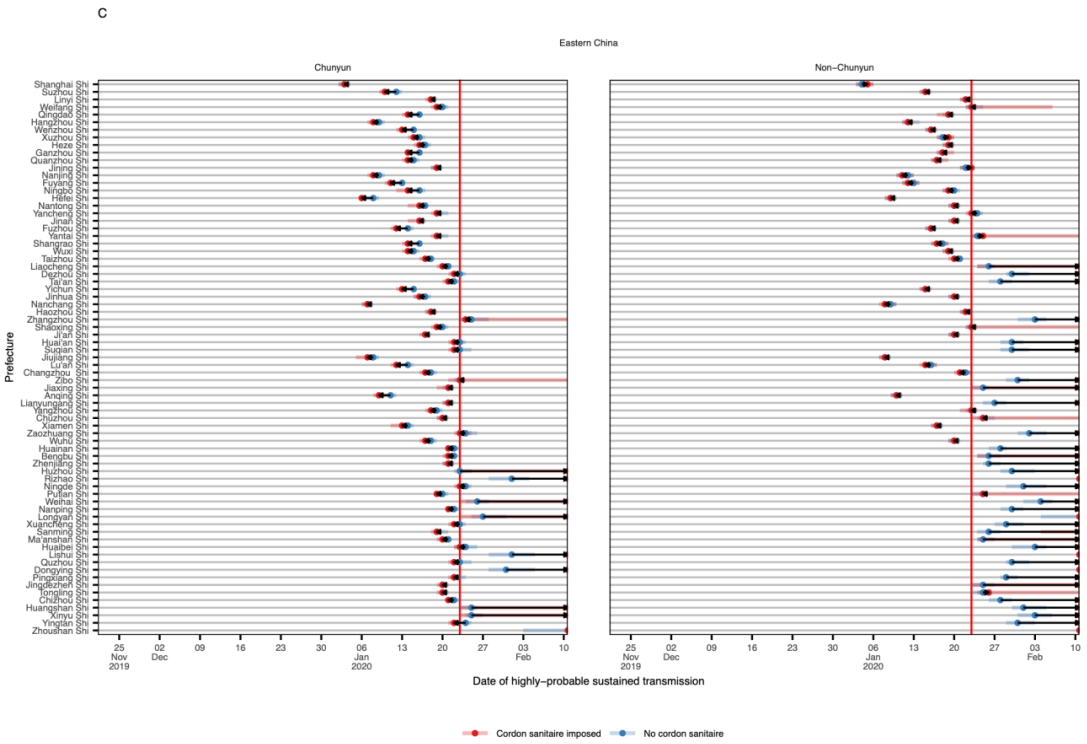


10


B
Northeast China
Chunyun
Non−Chunyun
Prefecture
Harbin Shi
Shenyang Shi
Changchun Shi
Dalian Shi
Qiqihar Shi
Suihua Shi
Jilin Shi
Anshan Shi
Siping Shi
Jinzhou Shi
Chaoyang Shi
Daqing Shi
Songyuan Shi
Mudanjiang Shi
Tieling Shi
Huludao Shi
Yingkou Shi
Dandong Shi
Jiamusi Shi
Tonghua Shi
Yanbian Chaoxianzu Zizhizhou
Fushun Shi
Baicheng Shi
Liaoyang Shi
Jixi Shi
Fuxin Shi
Benxi Shi
Heihe Shi
Shuangyashan Shi
Panjin Shi
Baishan Shi
Liaoyuan Shi
Hegang Shi
Qitaihe Shi
Daxing'anling Diqu
25 Nov 2019
02 Dec
09
16
23
30
06 Jan 2020
13
20
27
03 Feb
10
Date of highly−probable sustained transmission
Cordon sanitaire imposed
No cordon sanitaire

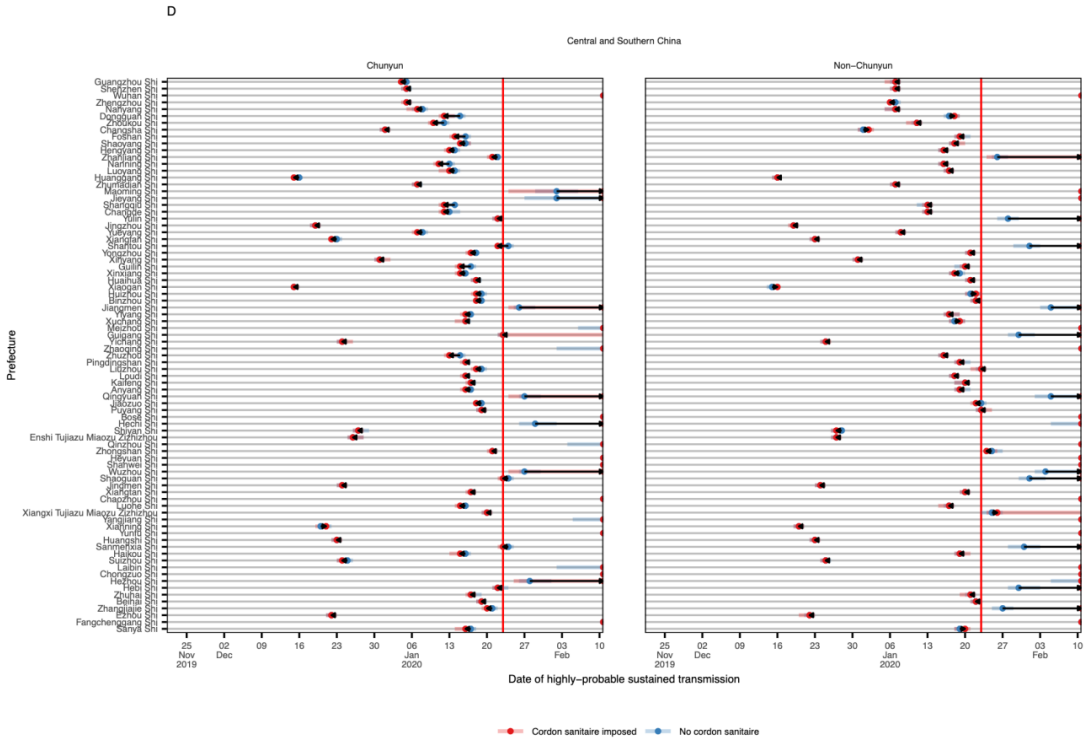
164

11

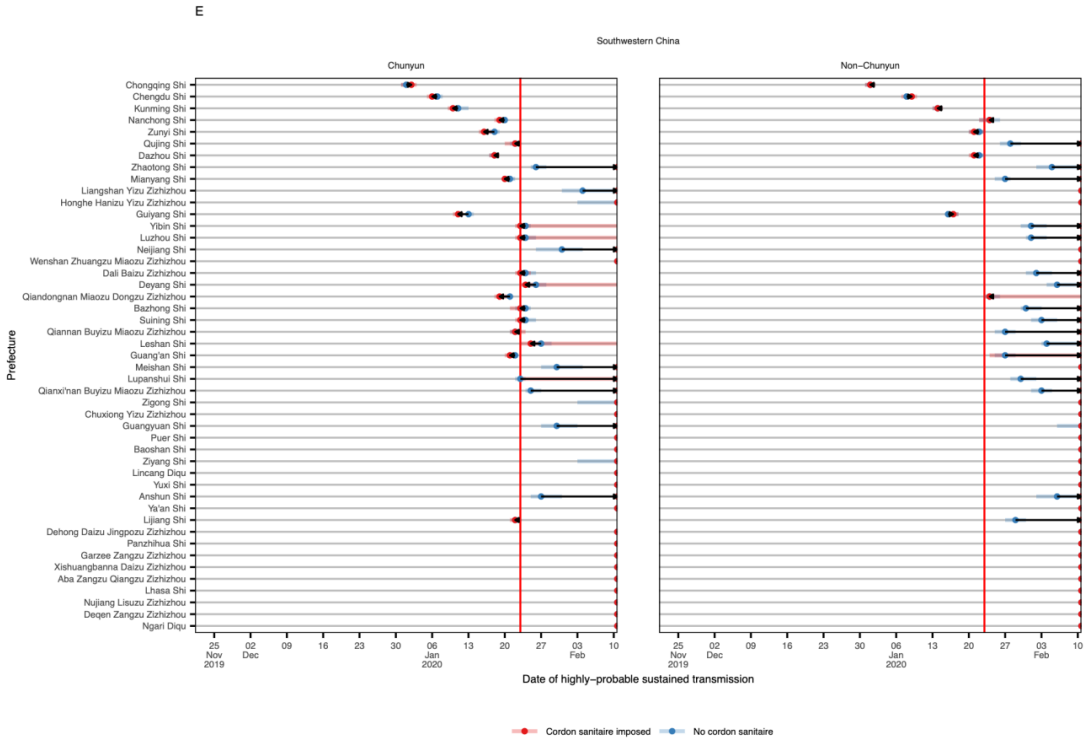

C
Eastern China
Chunyun
Non−Chunyun
Prefecture
25 Nov 2019
02 Dec
09
16
23
30
06 Jan 2020
13
20
27
03 Feb
10
Date of highly−probable sustained transmission
Cordon sanitaire imposed
No cordon sanitaire

165

12


D
Central and Southern China
Chunyun
Non−Chunyun
Prefecture
Guangzhou Shi
Shenzhen Shi
Wuhan Shi
Zhengzhou Shi
Nanyang Shi
Dongguan Shi
Zhoukou Shi
Changsha Shi
Foshan Shi
Shaoyang Shi
Hengyang Shi
Zhanjiang Shi
Nanning Shi
Huangshi Shi
Zhoushan Shi
Maoming Shi
Jiangmen Shi
Shangqiu Shi
Changde Shi
Jilin Shi
Jingzhou Shi
Yueyang Shi
Xiangfan Shi
Shantou Shi
Yongzhou Shi
Xinyang Shi
Guilin Shi
Xinxiang Shi
Huaihua Shi
Xiaogan Shi
Huizhou Shi
Binzhou Shi
Jiangmen Shi
Yiyang Shi
Xuchang Shi
Meizhou Shi
Guigang Shi
Yichang Shi
Zhaoqing Shi
Zhuzhou Shi
Pingdingshan Shi
Luzhou Shi
Loudi Shi
Kaifeng Shi
Anyang Shi
Qingyuan Shi
Jiaozuo Shi
Puyang Shi
Bose Shi
Chechi Shi
Shiyan Shi
Enshi Tujiazu Miaozu Zizhizhou Shi
Qinzhou Shi
Zhongshan Shi
Heyuan Shi
Weifang Shi
Wuzhou Shi
Shaoguan Shi
Xiaogan Shi
Chaozhou Shi
Luohe Shi
Xiangxi Tujiazu Miaozu Zizhizhou Shi
Yangjiang Shi
Xuchang Shi
Yunfu Shi
Huangshi Shi
Sanmenxia Shi
Haikou Shi
Suizhou Shi
Laibin Shi
Chongzuo Shi
Heyuan Shi
Hebi Shi
Zhuhai Shi
Beihai Shi
Zhangjiajie Shi
Pzhou Shi
Fangchenggang Shi
Sanya Shi
25 Nov 2019
02 Dec
09
16
23
30
06 Jan 2020
13
20
27
03 Feb
10
Date of highly−probable sustained transmission
Cordon sanitaire imposed
No cordon sanitaire

166


E
Southwestern China
Chunyun
Non−Chunyun
Chongqing Shi
Chengdu Shi
Kunming Shi
Nanchong Shi
Zunyi Shi
Qujing Shi
Dazhou Shi
Zhaotong Shi
Mianyang Shi
Liangshan Yizu Zizhizhou
Honghe Hanizu Yizu Zizhizhou
Guiyang Shi
Yibin Shi
Luzhou Shi
Neijiang Shi
Wenshan Zhuangzu Miaozu Zizhizhou
Dali Baizu Zizhizhou
Deyang Shi
Qiandongnan Miaozu Dongzu Zizhizhou
Bazhong Shi
Suining Shi
Qiannan Buyizu Miaozu Zizhizhou
Leshan Shi
Guang'an Shi
Meishan Shi
Lupanshui Shi
Qianxi'nan Buyizu Miaozu Zizhizhou
Zigong Shi
Chuxiong Yizu Zizhizhou
Guangyuan Shi
Puer Shi
Baoshan Shi
Ziyang Shi
Lincang Diqu
Yuxi Shi
Anshun Shi
Ya'an Shi
Lijiang Shi
Dehong Daizu Jingpozu Zizhizhou
Panzhihua Shi
Garzee Zangzu Zizhizhou
Xishuangbanna Daizu Zizhizhou
Aba Zangzu Qiangzu Zizhizhou
Lhasa Shi
Nujiang Lisuzu Zizhizhou
Deqen Zangzu Zizhizhou
Ngari Diqu
Prefecture
25 Nov 2019
02 Dec
09
16
23
30
06 Jan 2020
13
20
27
03 Feb
10
Date of highly−probable sustained transmission
Cordon sanitaire imposed
No cordon sanitaire

167

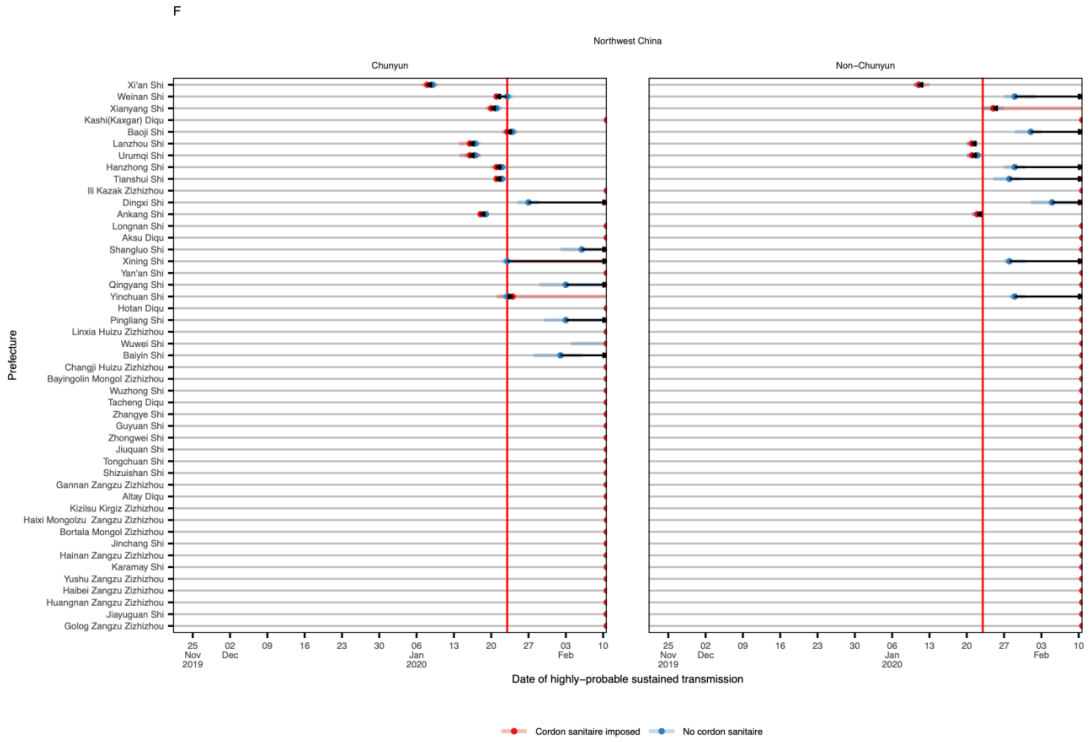


Figure S1 - Date at which the mean probability of sustained transmission breaches 95% [20] for cordon sanitaire imposed (red) vs no cordon sanitaire (blue) for Chunyun (left panel) and Non-Chunyun (right panel) travel patterns for each prefecture given travel patterns from Wuhan. Red vertical line indicates the date the cordon sanitaire was imposed. Black lines with arrows indicate time difference between scenarios; arrows pointing right indicate delay, arrows pointing left indicate advance. Points on the right limit of the graph indicate that no outbreak has occurred by that date. Outbreak probability calculated with R0=2.2 and k=0.1. Prefectures sorted by population. Prefectures grouped into six regions of China based on the first digit of the administrative unit code. A = Northern China, B = Northeast China, C = Eastern China, D = Central and Southern China, E = Southwestern China, F = Northwest China.

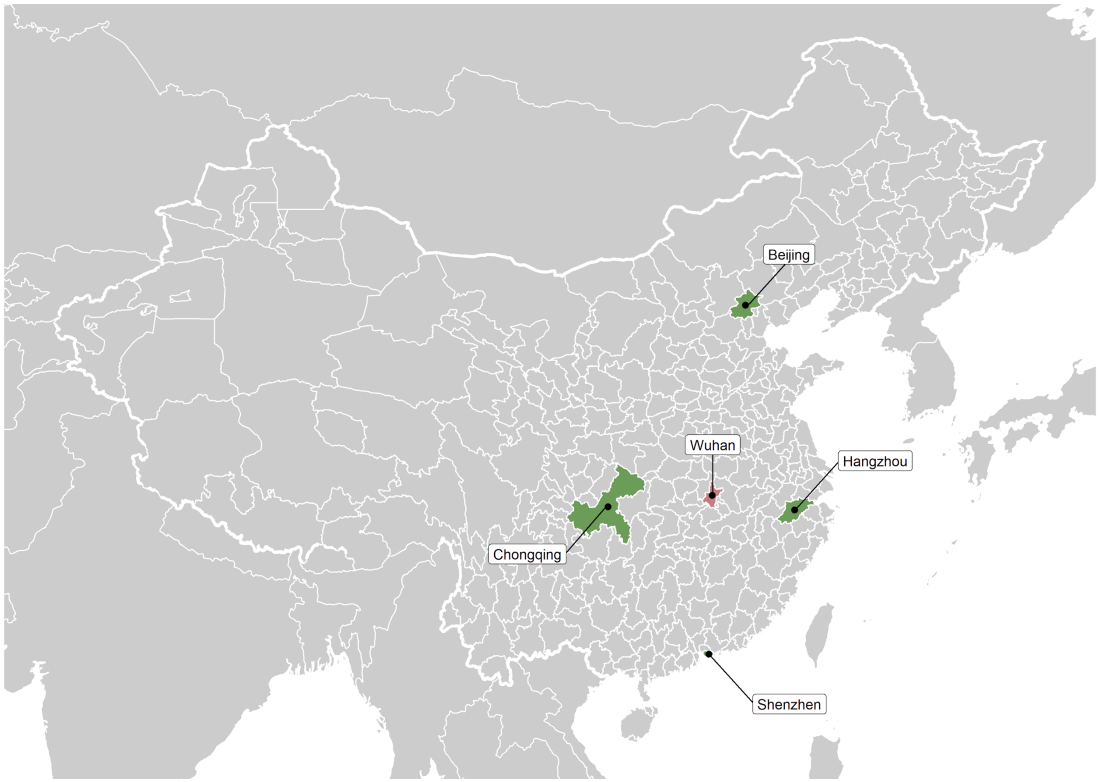
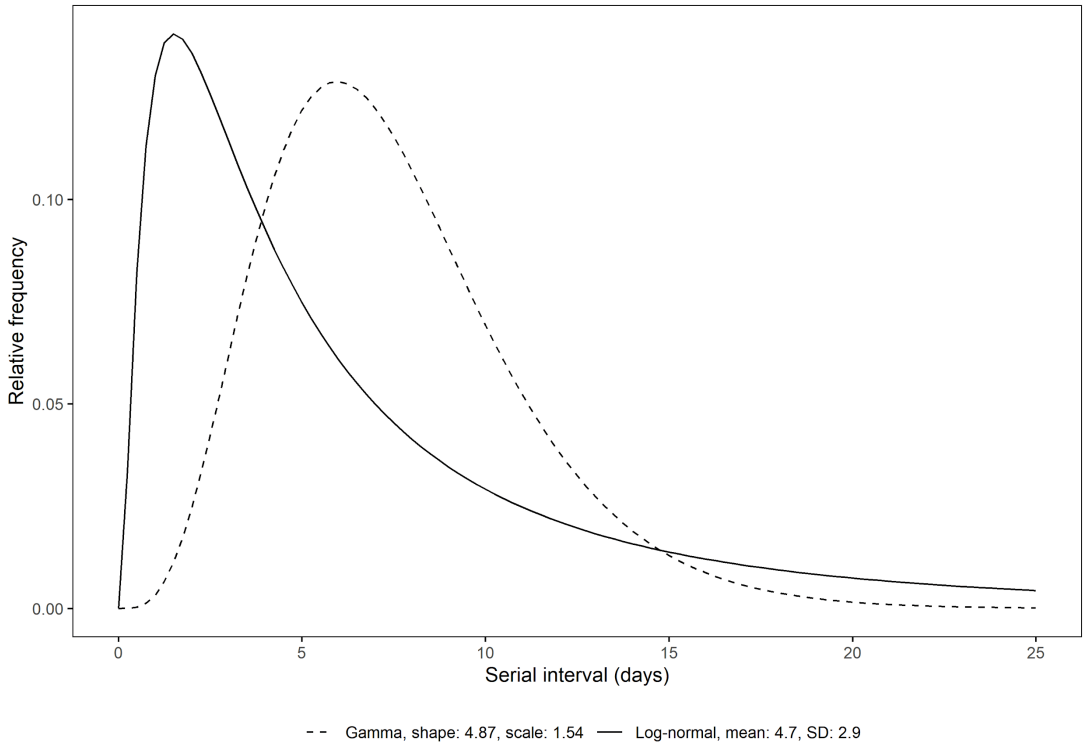


Figure S2 - Location of Wuhan (centre, pink) and the four cities of interest (green) in mainland China.



182

183 *Figure S3 - Delay distributions for the serial interval of COVID-19 infection from literature. Log-normal with mean 4.7*
184 *days and standard deviation of 2.9 days [18] and a Gamma with mean 7.5 days and standard deviation of 3.4 days [19]*
185 *(converted to shape = 4.87 and scale = 1.54 using epitrix R package [22]).*

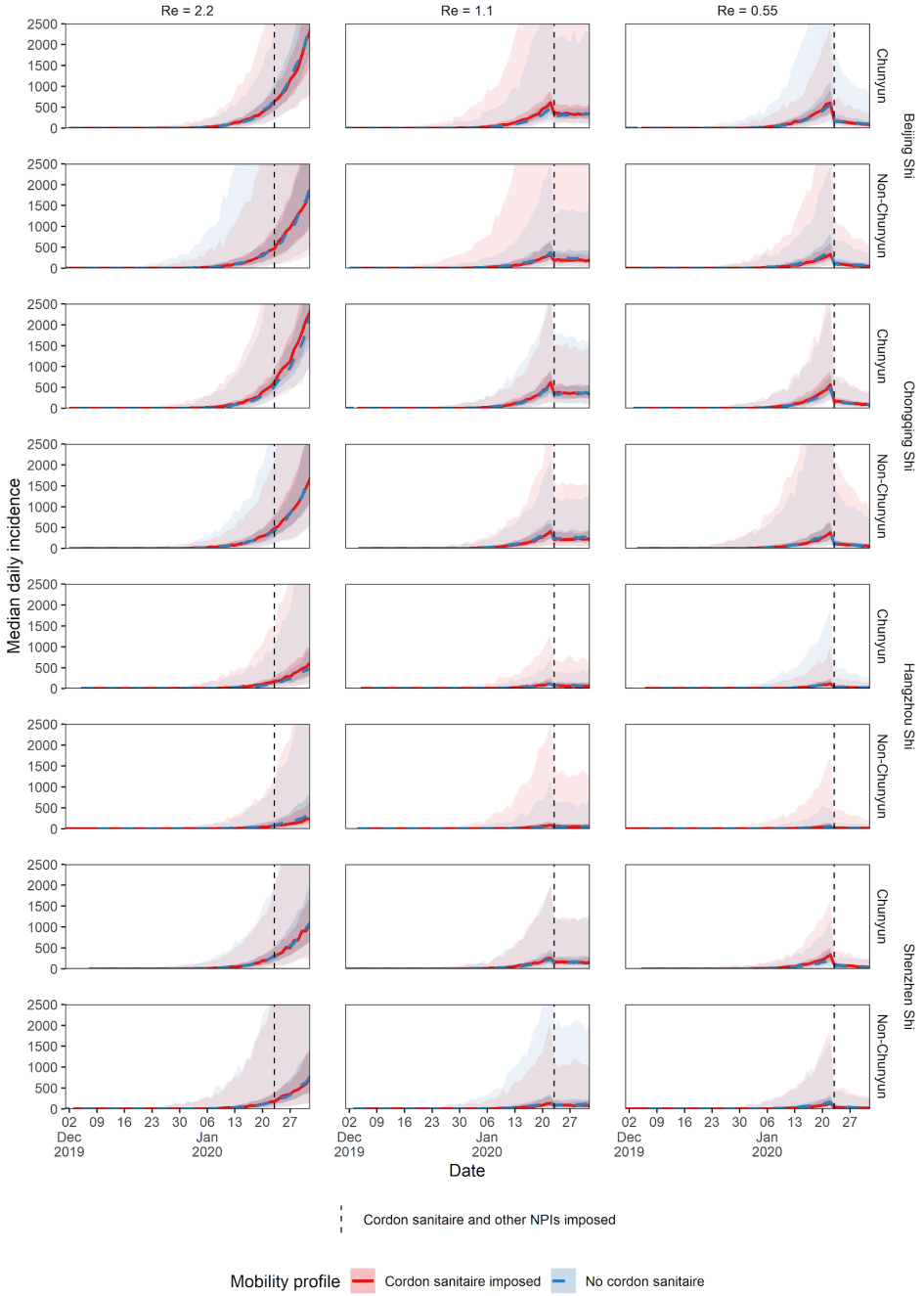
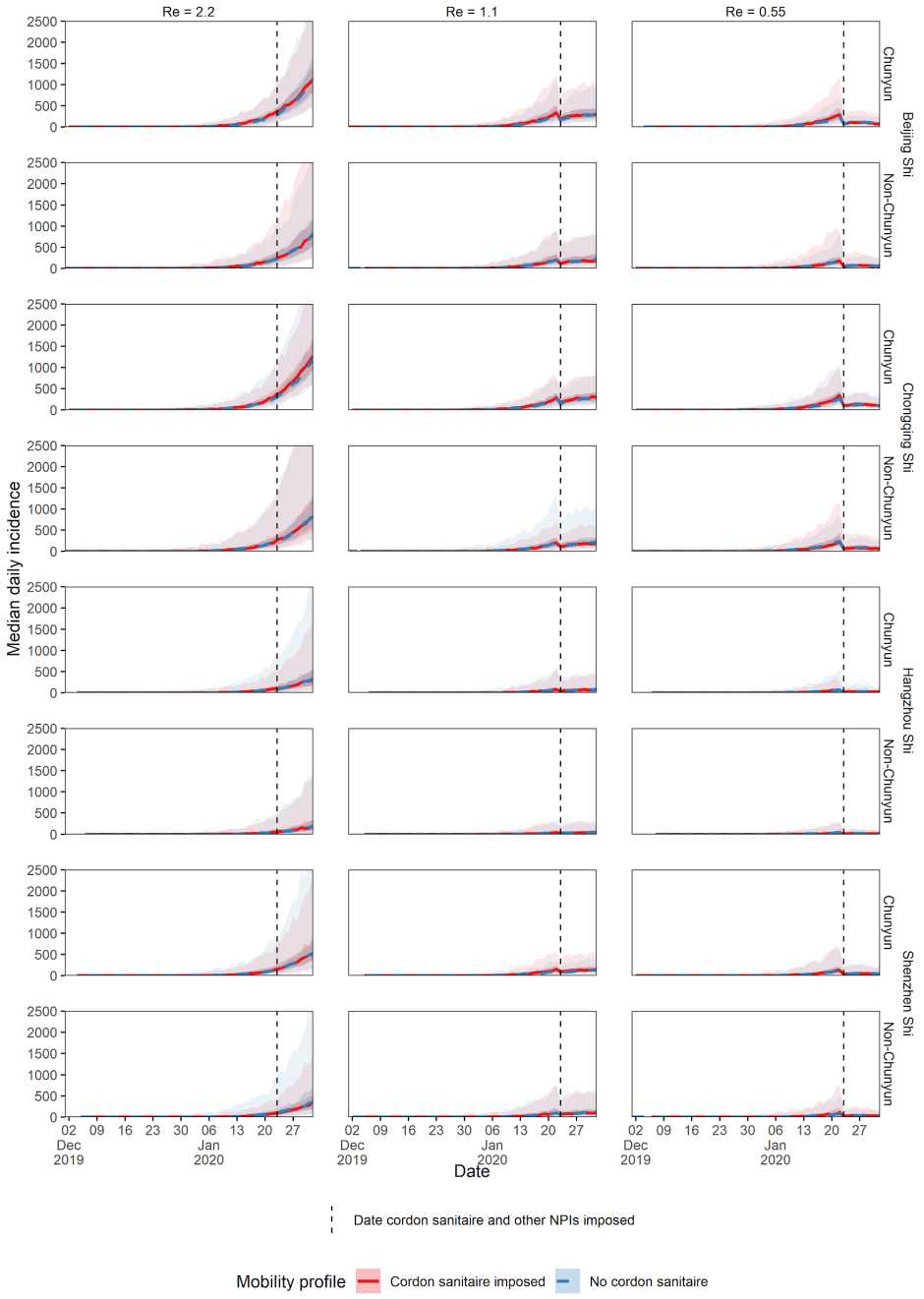


Figure S4 - Median daily incidence of COVID-19 (log-scale, shaded areas indicate 50% and 95% confidence intervals) in the four cities of interest, for Chunyun vs. Non-Chunyun, cordon sanitaire imposed (red, solid) vs. no cordon sanitaire (blue, dashed), and for varying values of the effective reproduction number R_e, where $R_e = 2.2$ (no change, unmitigated

local outbreak), reduced from 2.2 by 50% to 1.1 (mitigation of outbreak, R_e>1), and 75% to 0.55 (suppression of outbreak, R_e<1).



19

Figure S5 - Alternative serial interval of mean 7.5 days (SD: 3.4). Median daily incidence of COVID-19 (shaded areas indicate 50% and 95% confidence intervals) in the four cities of interest, for Chunyun vs. Non-Chunyun, cordon sanitaire imposed (red, solid) vs. no cordon sanitaire (blue, dashed), and for varying values of the effective reproduction number Re, where Re = 2.2 (no change, unmitigated local outbreak), reduced from 2.2 by 50% to 1.1 (mitigation of outbreak, Re>1), and 75% to 0.55 (suppression of outbreak, Re<1).

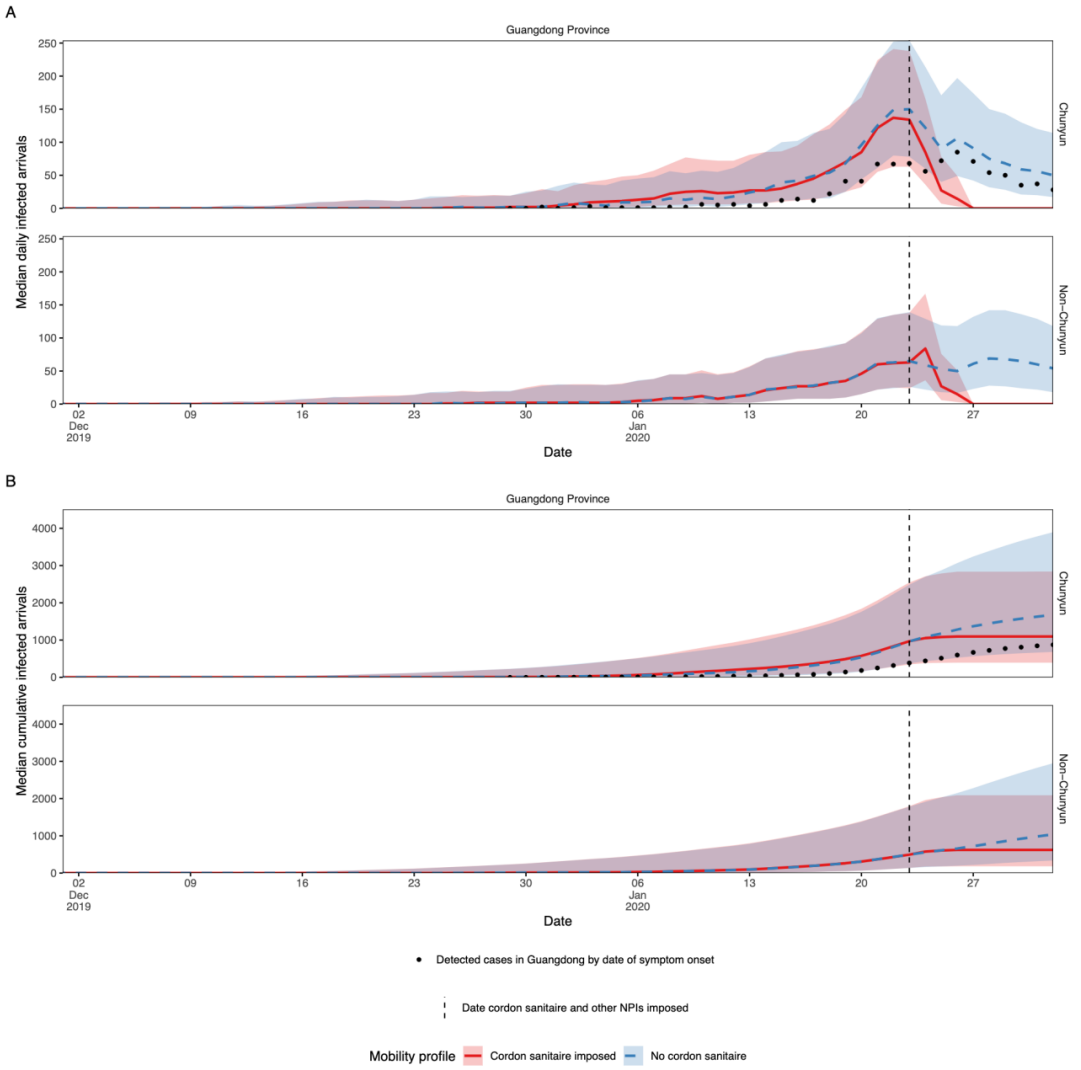


Figure S6 - Simulated infected arrivals to Guangdong province from Wuhan (median and 95% UI). A. Estimated median number of daily infected arrivals and B. Estimated cumulative number of infected arrivals from Wuhan for Chunyun vs.

Non-Chunyun, and cordon sanitaire imposed (red, solid) vs no cordon sanitaire (blue, dashed). Shaded area indicates the 95% uncertainty interval. Vertical dashed line indicates the date the cordon sanitaire was imposed. In Scenario 1, infected arrivals appear to follow a similar rising and falling trend as the reported imported cases in Lu et al. (2020), albeit with a lag of several days [26] (black dotted line).

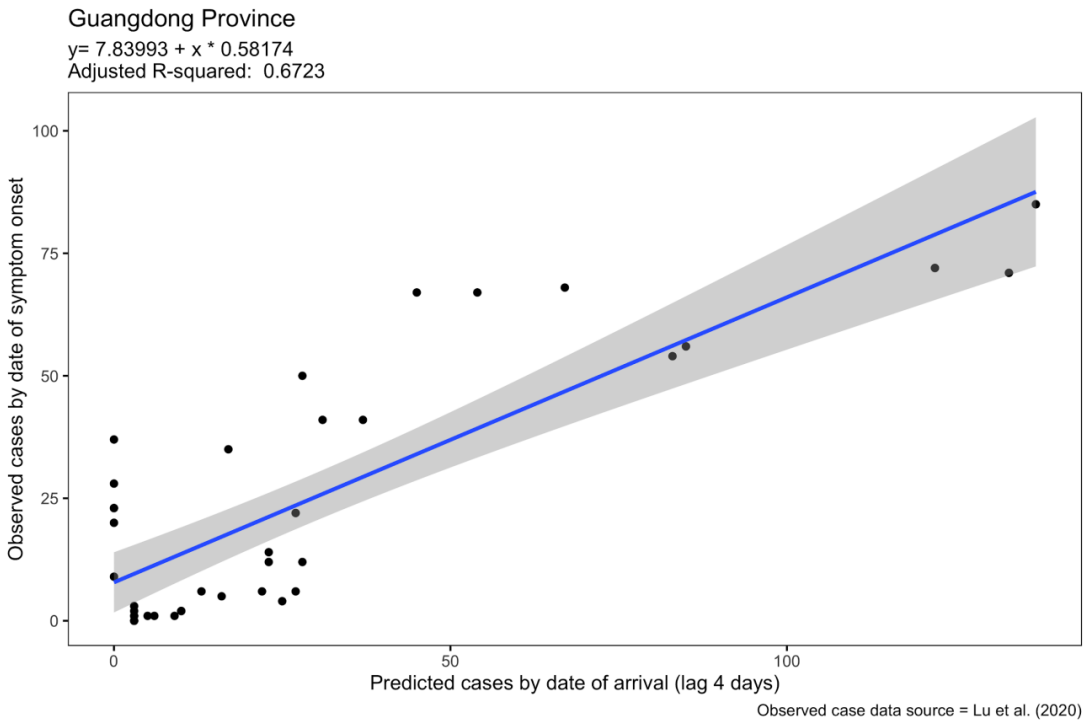


Figure S7 - Observed imported cases by date of symptom onset vs. predicted imported cases by date of arrival with a lag of 4 days.

2.3 Strategies to reduce the risk of SARS-CoV-2 importation from international travellers: modelling estimations for the United Kingdom, July 2020

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	1703195	**Title**	Mr
First Name(s)	Billy		
Surname/Family Name	Quilty		
Thesis Title	Modelling the effectiveness of quarantine and testing strategies during the COVID-19 pandemic		
Primary Supervisor	Stefan Flasche		

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?	Eurosurveillance		
When was the work published?	21 September 2021		
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?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*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?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

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)	I co-led in the conceptualisation of this work. I then co-led in the formulation, programming, and analysis of the screening model, integrating the prevalence model produced by co-authors, as well as in producing the results and figures. I then co-led in the writing of the first draft of the manuscript.

SECTION E

Student Signature	Billy Quilty
Date	07/02/2023

Supervisor Signature	Stefan Flasche
Date	07/02/2023

RESEARCH

Strategies to reduce the risk of SARS-CoV-2 importation from international travellers: modelling estimations for the United Kingdom, July 2020

Samuel Clifford[1,*], Billy J Quilty[1,*], Timothy W Russell[1], Yang Liu[1], Yung-Wai D Chan[1], Carl A B Pearson[1], Rosalind M Eggo[1], Akira Endo[1,2], CMMID COVID-19 Working Group[2], Stefan Flasche[1,], W John Edmunds[1,**]**

1. Centre for Mathematical Modelling of Infectious Diseases, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom
2. The members of the group are listed under Investigators

* These authors contributed equally and share first authorship

** These authors contributed equally and share last authorship

Correspondence: Samuel Clifford (sam.clifford@lshtm.ac.uku), Billy Quilty (billy.quilty@lshtm.ac.uk)

Investigators: The investigators are listed at the end of the article.

Citation style for this article:
Clifford Samuel, Quilty Billy J, Russell Timothy W, Liu Yang, Chan Yung-Wai D, Pearson Carl A B, Eggo Rosalind M, Endo Akira, CMMID COVID-19 Working Group, Flasche Stefan, Edmunds W John. Strategies to reduce the risk of SARS-CoV-2 importation from international travellers: modelling estimations for the United Kingdom, July 2020. Euro Surveill. 2021;26(39):pii=2001440. https://doi.org/10.2807/1560-7917.ES.2021.26.39.2001440

Article submitted on 25 Jul 2020 / accepted on 16 Feb 2021 / published on 30 Sep 2021

Background: To mitigate SARS-CoV-2 transmission risks from international air travellers, many countries implemented a combination of up to 14 days of self-quarantine upon arrival plus PCR testing in the early stages of the COVID-19 pandemic in 2020. **Aim:** To assess the effectiveness of quarantine and testing of international travellers to reduce risk of onward SARS-CoV-2 transmission into a destination country in the pre-COVID-19 vaccination era. **Methods:** We used a simulation model of air travellers arriving in the United Kingdom from the European Union or the United States, incorporating timing of infection stages while varying quarantine duration and timing and number of PCR tests. **Results:** Quarantine upon arrival with a PCR test on day 7 plus a 1-day delay for results can reduce the number of infectious arriving travellers released into the community by a median 94% (95% uncertainty interval (UI): 89–98) compared with a no quarantine/no test scenario. This reduction is similar to that achieved by a 14-day quarantine period (median › 99%; 95% UI: 98–100). Even shorter quarantine periods can prevent a substantial amount of transmission; all strategies in which travellers spend at least 5 days (mean incubation period) in quarantine and have at least one negative test before release are highly effective (median reduction 89%; 95% UI: 83–95)). **Conclusion:** The effect of different screening strategies impacts asymptomatic and symptomatic individuals differently. The choice of an optimal quarantine and testing strategy for unvaccinated air travellers may vary based on the number of possible imported infections relative to domestic incidence.

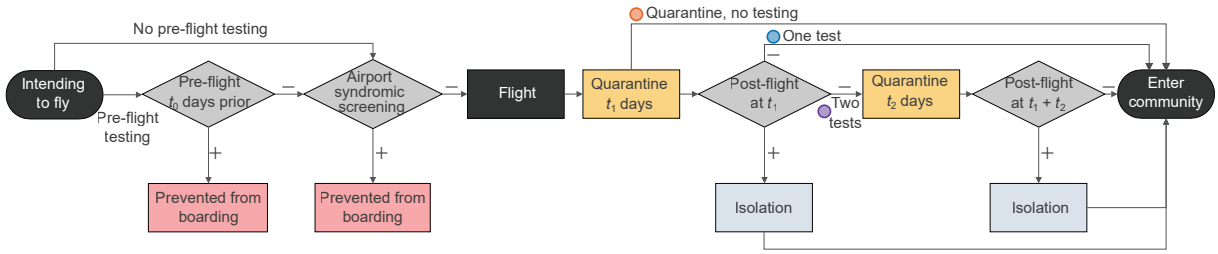
Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease (COVID-19), emerged in Wuhan, China in late 2019 and was rapidly disseminated globally through international air travel in the first half of 2020 [1]. In addition to non-pharmaceutical interventions (NPIs) to reduce domestic transmission, many countries implemented restrictions on incoming international travel such as mandatory quarantine, testing and travel bans, with the aim of preventing or reducing further importation and onward transmission [2].

During this early period of the COVID-19 pandemic prior to the roll-out of vaccines in late 2020, a number of countries in Europe and the Asia Pacific region implemented a mandatory quarantine upon arrival, which typically had a duration of 14 days [2,3]. It is expected that, by day 14, at least 95% of all infected individuals who will become symptomatic have done so [4]. However, the median incubation period for SARS-CoV-2 is ca 5 days (95% confidence interval: 4.1 to 7.0) [4] and, assuming that travellers are equally likely to travel at any point in this period, a 5-day quarantine on arrival should suffice to allow more than 50% of the infected travellers to become symptomatic and be managed accordingly. Quarantine, either at home or at managed facilities [5], may lead to negative psychological effects stemming from social isolation [6,7] and financial stress [8]. Hence, there is considerable interest in reducing the period of quarantine, assuming it is safe to do so.

Figure 1

Possible traveller trajectories for the considered SARS-CoV-2 screening scenarios pre- and post-flight



SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

Testing for SARS-CoV-2 infection (grey diamonds) may be conducted pre-flight and/or post-flight and may occur alongside quarantine periods (yellow boxes). Travellers who are found to be infected pre-flight are prevented from boarding (pink boxes); travellers found to be infected during quarantine are diverted to isolation (light blue boxes). Travellers enter the community after the required number of negative tests (regardless of infection status) or after finishing their allocated duration of quarantine or isolation. Coloured circles indicate the number of tests along that trajectory.

In addition to quarantine, several countries introduced a requirement for travellers to undergo testing for SARS-CoV-2 infection with RT-PCR (hereafter PCR). Such testing is commonly performed by taking nasopharyngeal or throat swabs of individuals and analysing the resulting sample for the presence of SARS-CoV-2 RNA [9]. PCR screening may be conducted before the flight and/or after arrival to allow detection of infected travellers. In some countries, testing is also used to reduce or eliminate quarantine for travellers without a confirmed infection. For example, in the summer of 2020, Japan allowed business travellers from designated low-risk countries to bypass the 14-day quarantine period given a negative PCR test result upon arrival [10].

Here we investigated the effectiveness of several strategies available in the pre-vaccination era of the SARS-CoV-2 pandemic to reduce the number of arriving infectious travellers as well as the potential for transmission in the community. We assessed the impact of varying the duration of quarantine and the timing and number of PCR tests, as well as the prevalence in and travel volume from the European Union (EU) and the United States (US) to the United Kingdom (UK) as of July 2020, while also accounting for the natural history of SARS-CoV-2 infection.

Methods

Travel screening trajectories

The possible SARS-CoV-2 screening outcomes for air travellers are as follows: (i) prevented from travelling following detection of SARS-CoV-2 infection either through syndromic screening at the airport or a positive pre-flight PCR test, (ii) released after the mandatory isolation period following detection of SARS-CoV-2 infection either by a positive PCR test upon entry or a follow-up positive PCR test after a negative result upon entry, (iii) released after a second negative test during the quarantine period, and (iv) in the absence of post-entry testing, travellers will be released after the mandatory quarantine period (which, in the model, may have a duration of 0 days) (Figure 1).

Estimating the number of infected travellers

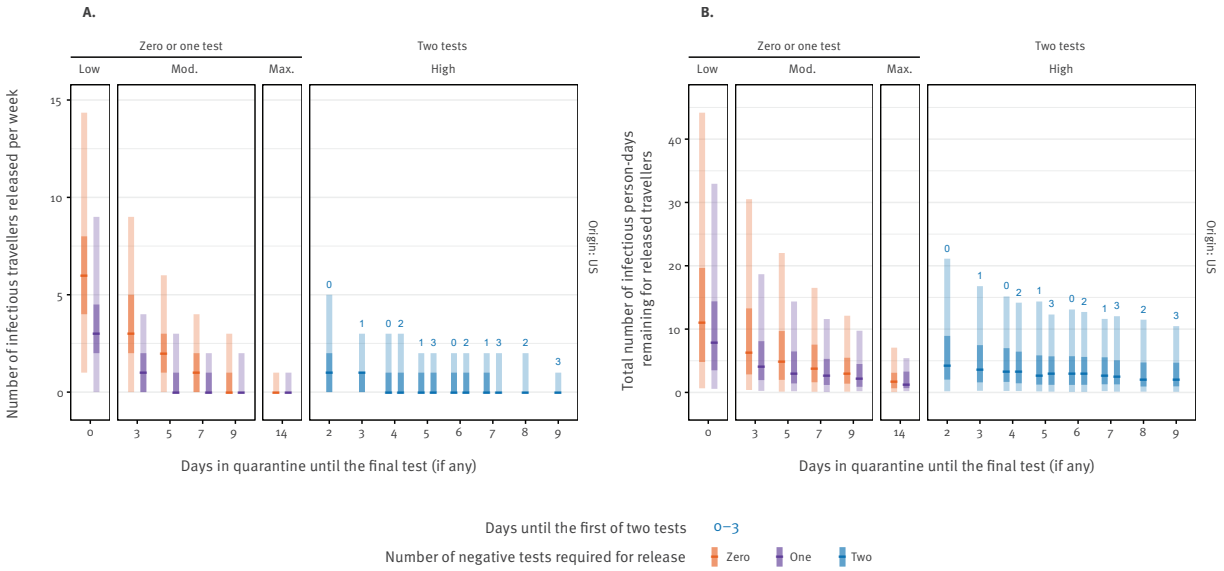
We simulated the number of infected air travellers intending to fly to a destination country in a given week based on the monthly volume of flights between the origin and destination, and considering the prevalence of COVID-19 in the origin country (Supplementary Table S1). We used the UK as a case study for the destination country. We assumed that the inbound and outbound travel is balanced on average. To estimate the number of people travelling into the UK, we halved the total number of monthly traveller movements.

The time of each intending traveller's flight was sampled uniformly between the time of exposure to SARS-CoV-2 and time of recovery. We modelled international travellers coming either from the US or the EU, using publicly available Civil Aviation Authority data for April and May 2020 [11,12]. Estimates of current COVID-19 infection prevalence were derived from reported cases and death time series data while adjusting for reporting delays and under-reporting based on case-fatality ratio estimates [13,14]. EU-wide prevalence was calculated as a population-weighted mean of available country-level estimates of the non-UK EU countries (except Malta, for which a prevalence estimate was not available).

For each simulation, we sampled the number of weekly intending travellers, the proportion of those who were infected, and the proportion of infected travellers who were symptomatic and asymptomatic [15] (details are provided in Supplementary Table S1).

FIGURE 2

Expected number of infectious and pre-infectious individuals entering the United Kingdom from the United States (A) and total infectious person-days remaining after release (B) based on estimated travel volumes and quarantine duration with no pre-flight testing, United Kingdom, July 2020



Test results are assumed to be delayed by 1 day and individuals leave quarantine 1 day after their final test. Central dash: median; light bar: 95% uncertainty interval; dark bar: 50% uncertainty interval.

Risk mitigation strategies

We considered several risk mitigation strategies. Travellers are subjected to a quarantine which lasts either (i) 0 days (low stringency); (ii) 3, 5, 7 or 9 days (moderate stringency); or (iii) 14 days (high/maximum stringency) (Supplementary Table S2). In the low and moderate stringency levels, travellers may also be tested on the final day of their quarantine and wait an additional day for their results [16]; in the low stringency setting, this effectively enforces a 1-day quarantine. For the high stringency scenario, travellers are assumed to undergo two stages of PCR testing; if they receive two negative tests during their post-arrival quarantine period, they are cleared to leave quarantine early (i.e. the day after their final test to account for test delays). Travellers who become symptomatic during their quarantine period must meet all of the following conditions for release: (i) they must no longer display symptoms, (ii) it must be at least 7 days since the onset of symptoms, and (iii) they must have been in quarantine for at least 14 days [3].

Model assumptions

We assumed that syndromic screening is performed before departure, which may consist of thermal scanning and/or monitoring of symptoms such as cough and fever [17]. Given the awareness of the pandemic and guidance issued on travelling while ill, we assumed in all scenarios that 70% of currently-symptomatic travellers do not fly (as modelled by Gostic et al. [18,19]).

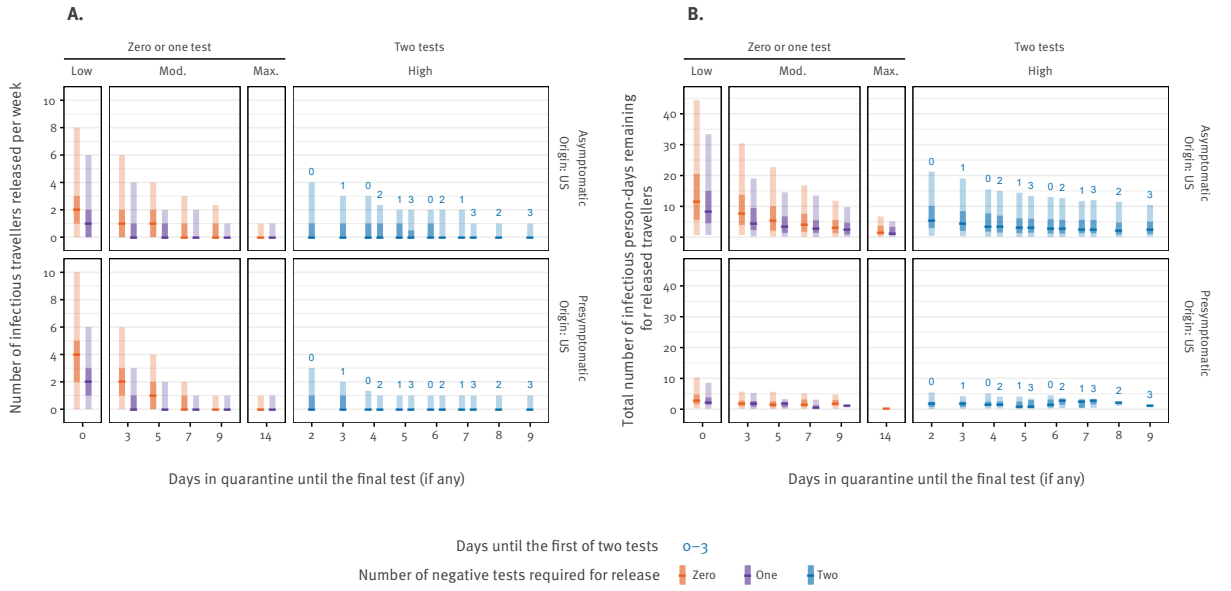
Pre-flight PCR testing was required by some countries and airlines. In July 2020, the International Air Transport Association recommended testing within 24 h of departure [20] but some countries required testing within 7 days of the flight [21]. Considering this wide range of pre-travel test recommendations, we chose to include a 4-day pre-flight test as a midpoint.

Case definitions and detection of infected travellers

We defined a symptomatic infection as an individual whose symptoms e.g. fever, cough, loss of sense of taste or smell, would be detectable by the individual, airport staff, quarantine staff, or a healthcare worker and typically lead to self-isolation, consistent with that defined by the UK's National Health Service [22]. We defined an asymptomatic infection as one where the individual never develops symptoms throughout the duration of their infection, according to Buitrago-Garcia et al. [15]. We assumed that the sensitivity of PCR testing for a nasopharyngeal or throat swab varies over the course of infection, peaking around onset of symptoms [23], and that test specificity is 100% [24]. We assumed that the probability of detecting an asymptomatic infection through PCR testing is 0.62 times that of a symptomatic infection, as reported by Chau et al. [25] for nasopharyngeal or throat swab samples collected from quarantining travellers (Supplementary Table S3). We derived the proportion of asymptomatic travellers by quantile, matching the 95% prediction interval (0.03–0.55) of Buitrago-Garcia et al. as a beta

Figure 3

Expected number of infectious and pre-infectious individuals entering the United Kingdom from the United States (A) and total infectious person-days remaining after release (B) based on estimated travel volumes and quarantine duration with no pre-flight testing, stratified by asymptomatic or pre-symptomatic infection, United Kingdom, July 2020



Max: maximum; Mod: moderate; US: United States.

Test results are assumed to be delayed by 1 day and individuals leave quarantine 1 day after their final test. Central dash: median; light bar: 95% uncertainty interval; dark bar: 50% uncertainty interval.

distribution, giving a median of 0.21 (i.e. 21% of travellers being asymptomatic on average across model simulations) [15].

The duration of the incubation period (time from exposure to onset of symptoms, and assumed here to also represent the timing of peak probability of detection in both symptomatic and asymptomatic individuals) was taken from Lauer et al. [26] (Supplementary Table S3). The duration of the latent period (time from exposure to the onset of infectiousness) [27], was derived from Ashcroft et al. (corrected version of He et al.), and was also assumed to be equal for symptomatic and asymptomatic individuals [28,29]. The duration of the infectious period of symptomatic cases was derived from Wolfel et al. [30], while that of asymptomatic cases was derived from Byrne et al. [31], with asymptomatic cases being infectious for a shorter period than symptomatic cases (median: 5.2 vs 7.1 days) (Supplementary Table S3).

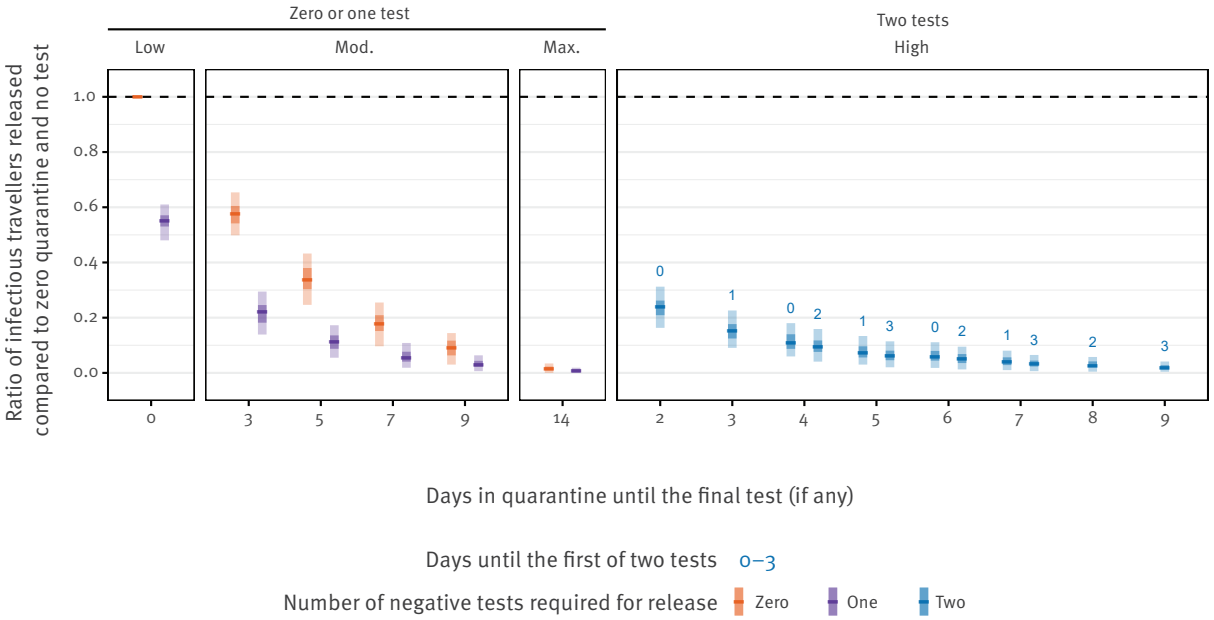
Given the natural history of infection parameters, we estimated the number of infected travellers entering the community in each scenario who would have the potential to cause onward transmission, i.e. those still in their infectious or pre-infectious period. In addition, we calculated the number of infectious days spent in the community for each infected traveller following their release. These values were then summed for all individuals to give the total person-days of infectiousness spent in the community for each scenario. We report these values for the estimated weekly travellers based on travel volumes and per 10,000 infected travellers, with 1,000 bootstrap replications each to generate medians and 95% and 50% uncertainty intervals (UI). We calculated rate ratios (RR) in each screening scenario for the number of infectious individuals released and infectious days remaining compared to the low scenario (syndromic screening, no quarantine, and no PCR testing) and maximum scenario (14-day quarantine, no testing) were calculated with 10,000 travellers per simulation to avoid small number biases and were bootstrapped 1,000 times to generate medians and 95% and 50% UI. All analysis was conducted in R version 4.0.2 [32] and the code is available https://github.com/cmmid/pcr_entry_screening_eurosurv.

Results

Based on the prevalence of COVID-19 in the respective countries on 20 July 2020, we estimated that the expected proportion of travellers who entered the UK while infectious was substantially higher for flights originating in the US than for those originating in the EU (Supplementary Figure S3). However, as the prevalence

FIGURE 4

Risk reduction per infected traveller compared to a baseline of syndromic screening and no quarantine and no testing on arrival, United Kingdom, July 2020



Max: maximum; Mod: moderate.

Baseline scenario is indicated by the left-most value (Low, 0 days quarantine, no testing). We assumed that test results are delayed by 1 day and individuals leave quarantine 1 day after their final test. Central dash: median; light bar: 95% uncertainty interval; dark bar: 50% uncertainty interval. Product of 1,000 infected arriving travellers and 1,000 simulations per scenario.

of COVID-19 in the US was ca 14 times that in the EU in July 2020 and travel volumes were ca 8 times lower than those from the EU, we expect approximately half the number of infectious travellers arriving from the EU than from the US (Supplementary Table S1). Here we focus on the estimates for travel from the US and provide results for travel from the EU for comparison in the Supplement (Figure S1 and S2).

Effectiveness of quarantine and testing

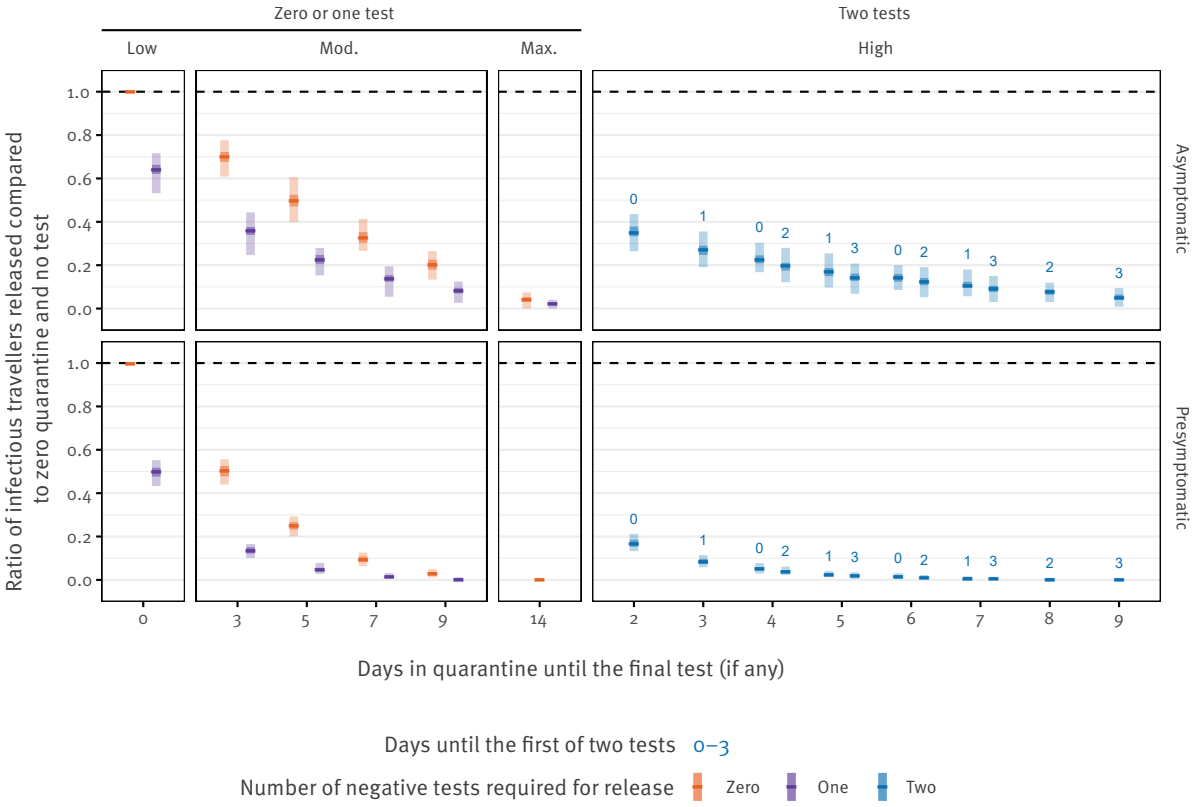
As a baseline for comparison, we used the lowest stringency scenario considered i.e. 70% of currently symptomatic travellers are prevented from boarding, but no quarantine or testing is conducted. In this scenario, a median of six infectious travellers (95% UI: 1–14.2) would enter the community from the US per week (Figure 2A). By introducing a mandatory quarantine period of 7 days, this can be reduced to one infectious traveller (95% UI: 0–4), preventing ca 80% of infectious travellers from entering the community (RR: 0.17; 95% UI: 0.10–0.26). A mandatory quarantine period of 14 days resulted in zero to one infectious entry per week, almost fully preventing importation (RR: 0.02; 95% UI: 0.00–0.03).

Longer quarantine periods increase the fraction of pre-symptomatic infected travellers who would have their onset of symptoms during the quarantine and hence self-isolate until symptoms subside (Figure 2A, Figure 3A). Accordingly, we estimated a more pronounced impact of interventions targeting travellers on the number of infectious person-days from travellers, particularly for those who would eventually become symptomatic (Figure 2B, Figure 3B). The uncertainty in the number of remaining infectious person-days is driven by variability in the detection of asymptomatic infections, as they will never be detected by pre-flight syndromic screening, are less likely to be detected by PCR and will never develop symptoms that trigger mandatory isolation.

Conducting a single test for all travellers at the end of the described quarantine periods further reduced the median number of infectious entering travellers from the US, with an RR of 0.55 (95% UI: 0.48–0.61) for a test on arrival, with release on day 1; an RR of 0.11 (95% UI: 0.05–0.17) for a test on day 5, release on day 6; an RR of 0.06 (95% UI: 0.02–0.11) for a test on day 7, release on day 8; an RR of 0.03 (95% UI: 0.00–0.06) for a test on day 9 with release on day 10; and an RR of 0.01 (95% UI: 0.00–0.02) for a test on day 14, release

Figure 5

Risk reduction per infected traveller compared to a baseline of syndromic screening and no quarantine and no testing on arrival, stratified by asymptomatic or pre-symptomatic infection, United Kingdom, July 2020



Max: maximum; Mod: moderate.

Baseline scenario is indicated by the left-most value (Low, 0 days quarantine, no testing). We assumed that test results are delayed by 1 day and individuals leave quarantine 1 day after their final test. Central dash: median; light bar: 95% uncertainty interval; dark bar: 50% uncertainty interval. Product of 1,000 infected arriving travellers and 1,000 simulations per scenario.

on day 15, when compared with the lowest stringency scenario (Figure 4). Requiring a second round of testing had marginal impact, although a quarantine period of 9 days with two tests and early exit may be able to largely replicate the impact of a 14-day quarantine period (RR: 0.02; 95% UI: 0.00–0.04).

Rate ratios by symptom status

We stratified the above RR by whether the infection is asymptomatic or pre-symptomatic. We observed that the strategies are more effective against those with pre-symptomatic than asymptomatic infections (Figure 5). The introduction of a test on arrival (Figure 5, low, 1 day) reduces the number of asymptomatic entering travellers by 36% (95% UI: 28–47) and pre-symptomatic by 50% (95% UI: 45–56), beyond that which is captured by syndromic screening alone (Figure 5, low, 0 days). At maximum stringency, a 14-day quarantine period is able to reduce the number of symptomatic entering travellers by more than 99% (95% UI: 99–100) and asymptomatic entering travellers by 96% (95% UI: 93–100).

For single test strategies, a 9-day quarantine with no test reduces the symptomatic entering travellers by 97% (95% UI: 95–99) but asymptomatic entering travellers are only reduced by 80% (95% UI: 4–87), reflecting the difficulty of relying on symptom onset during quarantine. By introducing a PCR test on day 9 and release on day 10, the number of symptomatic entering travellers is reduced by more than 99% (95% UI: 9–100) and asymptomatic entering travellers by 92% (95% UI: 88–97). This difference in detectability of symptomatic and asymptomatic entering travellers, coupled with simulations involving their small absolute numbers, is responsible for driving the wide uncertainty observed in the number of infectious arriving travellers from the US entering the community (Figure 2).

Effect of reducing the duration of quarantine

To determine if a 14-day quarantine can be replaced by a shorter quarantine with testing, we made RR comparisons to a 14-day quarantine with no test. We see that shorter quarantine periods of 9 days with either one or two rounds of testing may have a similar effect to that of the 14-day quarantine period (RR: 2.0; 95% UI: 1.00–infinity for a test on day 9 with release on day 10; RR: 1.24; 95% UI: 0.53–infinity for a test on day 3 and day 9) (Supplementary Figure S6).

Pre-flight testing

The impact of pre-flight testing on the number of infectious travellers entering the community was greatest if implemented the day before departure (within 24 h) in scenarios with no post-flight testing, with an RR of 0.69 (95% UI: 0.64–0.73) compared with no testing either before departure or after arrival (Supplementary Figure S4). As quarantine increases in duration, the additional effect of pre-flight testing diminishes.

Discussion

Here we analysed the effect of different combinations of PCR testing and quarantine times on the number of infectious individuals entering a country, beyond the effect of syndromic screening at the site of departure in the pre-COVID-19 vaccination era. We found that a quarantine period of at least 5 days, combined with a single PCR test on the final day, resulted in a reduction of 89% in the number of infectious individuals entering the community. A 7-day quarantine with a test on the final day can reduce infectious entering travellers by an average of 95%, with a small marginal benefit for additional rounds of testing. In addition, pre-flight testing appears ineffective unless conducted within 24 h of departure; the marginal effect of these tests disappears with increased quarantine duration and post-arrival testing.

We also found that the 14-day quarantine period is highly effective, reducing the number of infectious entering travellers by 99%, on average. Because the 14-day quarantine strategy almost completely eliminates infectious entering travellers, the number of infected entering travellers for other strategies (i.e. 7 or 9 days of quarantine with testing) may represent a two- to fivefold increase in RR. However, the absolute risk of entry is small in these scenarios and so the increase in RR should be interpreted in light of this. The risk stemming from the arrival of infectious travellers will need to be assessed in the context of local infection incidence. For example, six to 11 infectious travellers arriving per week from the EU or US in July 2020 into a community with thousands of live infections (such as that in the UK on 12 June 2020, with a prevalence estimated at 45 infections per 10,000 inhabitants; 95% UI: 24–92) will likely have little impact on control efforts. In contrast, if local infection prevalence is lower (as in the UK on 20 July 2020 with an estimated nine infections per 10,000 inhabitants; 95% UI: 4–18) a higher number of incoming infectious travellers may pose a large risk for seeding outbreaks in the community [33]. Likewise, countries that have pursued policies to eliminate COVID-19 within their borders such as New Zealand may consider any risk of reintroduction as unacceptable [2,34] and therefore continue to pursue policies which minimise the risk as much as practically possible.

We presented the risk from incoming infected travellers as the number of infectious travellers entering the community. To account for the differential residual duration of their infectiousness with the different strategies, we also presented the number of infectious person-days in the community from travellers. While the latter measure indicates an increased effectiveness of longer quarantine, this approach may still underestimate the true effect since the measure only considers that travellers are still infectious, and not how likely transmission is given the viral load. Of note, it is likely that infectiousness is correlated with viral load and declines over the course of infection [35,36]. Hence, with a peak infectivity around the onset of symptoms at ca 5 days, a minimum quarantine period of 7 days is likely to result in the release of fewer infectious travellers, and those who are released at 7 days have less potential for transmission with or without the use of a test.

We assumed that inbound travel volumes were 50% of total traveller movements, as reported by the Civil Aviation Authority, which may not reflect asymmetric patterns of travel. The total number of traveller movements between the UK and both the US and the EU in April and May 2020 were ca 1% of that reported in 2019, indicating that the combination of travel restrictions and suspended airline flights led to a sharp decrease in the number of potentially infected travellers. If travel volumes return to pre-pandemic levels, the likely number of infectious arriving travellers will increase unless prevalence is severely reduced internationally or a greater proportion of the international population is either vaccinated or naturally infected and recovered. In our analysis, we considered a constant air passenger volume and did not consider that shortening of quarantine may lead to an increase in the number of travellers. To address this, we have provided estimates in terms of the number of infectious entering travellers per 10,000 arriving travellers for the given international prevalence.

The work presented here is based on estimates of prevalence, under-ascertainment and travel volumes as of July 2020, as well as the contemporaneous understanding of incubation period, infectiousness and ability to detect an infection by PCR. Multiple studies have found that infectivity peaks around onset of symptoms [28,35,36] and that asymptomatic infections follow similar peak timings but that the detectability by PCR is shorter in duration [37] and lesser in magnitude [25]. We assumed that 70% of travellers with currently symptomatic infections (e.g. with a cough or fever)

would be detected or self-report and hence not travel. The remaining 30% are therefore the infectious travellers, who are either symptomatic but undetected, pre-symptomatic or fully asymptomatic. The longer the duration of quarantine, the greater the chance that pre-symptomatic individuals will develop symptoms and self-isolate, further reducing the number of infectious entering travellers. Hence, the primary purpose of quarantine and PCR testing is to reduce possible transmission from asymptomatic travellers who are only detectable by PCR. We also assumed that if individuals subsequently become symptomatic after quarantine, they follow national guidelines to immediately re-enter quarantine and seek an additional test as part of the local test and trace strategy; we assumed that traveller sensitisation is high at this point in the pandemic [38,39]. We do not make any assumptions about the potential for self-isolating infectious travellers to infect their household upon arrival or the resulting onwards transmission. We assumed full adherence to self-isolation, although a first negative test and a long duration of quarantine may reduce adherence to quarantine rules [6,8]. Hence, by assuming perfect adherence, we may overestimate the added benefit of long periods of quarantine in terms of the person-days of infectiousness in the community.

Conclusions

As the pandemic progresses, public health authorities must carefully balance the need for traveller-targeted interventions that reduce the likelihood of seeding local COVID-19 outbreaks with their social, psychological, financial, and economic costs. While the acceptable number of infected travellers entering the community will depend on the local context of SARS-CoV-2 transmission, we found that for travellers arriving from low prevalence destinations, the absolute risk of infectious entering travellers is likely to be low. Hence, testing and/or quarantine-based strategies may not reduce such risk further, particularly when many infectious arriving travellers are asymptomatic. However, as we have highlighted here, testing is likely the only way to detect asymptomatic infections, and may also detect pre-symptomatic, infectious travellers, leading to earlier isolation. For arriving travellers from countries with ongoing community transmission, quarantine on arrival will limit the risk for onward transmission into the local community in the absence of a safe and effective vaccine against COVID-19. While a 14-day quarantine will likely prevent most transmission from travellers, an 8-day quarantine (with testing on day 7) can capture almost as many infectious individuals in approximately half the time. Testing passengers is resource-intensive but presents a way to either further reduce risks or allow a shorter quarantine at the same level of risk, particularly for travellers arriving from countries with widespread SARS-CoV-2 transmission. Thus, our results contribute to an evidence-based discussion on the benefits and risks of alternative policies on border security regarding SARS-CoV-2 introduction via international air travel.

Investigators

Centre for Mathematical Modelling of Infectious Diseases (CMMID) COVID-19 Working Group: Katharine Sherratt, Stéphane Hué, Matthew Quaife, Nikos I Bosse, Graham Medley, Megan Auzenbergs, Adam J Kucharski, Nicholas G Davies, Oliver Brady, Sophie R Meakin, Rein M G J Houben, Katherine E Atkins, Kiesha Prem, C Julian Villabona-Arenas, Hamish P Gibbs, Thibaut Jombart, Charlie Diamond, Petra Klepac, Arminder K Deol, Rachel Lowe, James W Rudge, Mark Jit, Sebastian Funk, Gwenan M. Knight, Simon R. Procter, David Simons, Quentin J Leclerc, James D Munday, Amy Gimma, Georgia R Gore-Langton, Christopher I Jarvis, Jon C Emery, Anna M Foss, Kathleen O'Reilly, Joel Hellewell, Emily S Nightingale, Kevin van Zandvoort, Damien C Tully, Sam Abbott, Kaja Abbas, Fiona Yueqian Sun, Alicia Rosello

Acknowledgements

Funding: The following funding sources are acknowledged as providing funding for the named authors. This research was partly funded by the Bill & Melinda Gates Foundation (INV-003174: YL; NTD Modelling Consortium OPP1184344: CABP). DFID/Wellcome Trust (Epidemic Preparedness Coronavirus research programme 221303/Z/20/Z: CABP). This project has received funding from the European Union's Horizon 2020 research and innovation programme - project EpiPose (101003688: WJE, YL). HDR UK (MR/S003975/1: RME). This research was partly funded by the National Institute for Health Research (NIHR) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care (16/136/46: BJQ; 16/137/109: BJQ, YL; PR-OD-1017-20002: WJE). UK MRC (MC_PC_19065 - Covid 19: Understanding the dynamics and drivers of the COVID-19 epidemic using real-time outbreak analytics: RME, SC, WJE, YL). Wellcome Trust (206250/Z/17/Z: TWR; 208812/Z/17/Z: SC, SFlasche). The Alan Turing Institute and The Nakajima Foundation (AE). No funding (YWDC).

The following funding sources are acknowledged as providing funding for the working group authors. BBSRC LIDP (BB/M009513/1: DS). This research was partly funded by the Bill & Melinda Gates Foundation (INV-001754: MQ; INV-003174: KP, MJ; NTD Modelling Consortium OPP1184344: GM; OPP1180644: SRP; OPP1183986: ESN; OPP1191821: KO'R, MA). BMGF (OPP1157270: KA). DFID/Wellcome Trust (Epidemic Preparedness Coronavirus research programme 221303/Z/20/Z: KvZ). DTRA (HDTRA1-18-1-0051: JWR). Elrha R2HC/UK DFID/Wellcome Trust/This research was partly funded by the National Institute for Health Research (NIHR) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care (KvZ). ERC Starting Grant (#757688: CJVA, KEA; #757699: JCE, MQ, RMGJH). This project has received funding from the European Union's Horizon 2020 research and innovation programme - project EpiPose (101003688: KP, MJ, PK). This research was partly funded by the Global Challenges Research Fund (GCRF) project 'RECAP' managed through RCUK and ESRC (ES/P010873/1: AG, CIJ, TJ). NIHR (16/137/109: CD, FYS, MJ; Health Protection Research Unit for Immunisation NIHR200929: NGD; Health Protection Research Unit for Modelling Methodology HPRU-2012-10096: TJ; NIHR200929: MJ; PR-OD-1017-20002: AR). Royal Society (Dorothy Hodgkin Fellowship: RL; RP\EA\180004: PK). UK DHSC/UK Aid/NIHR (ITCRZ 03010: HPG). UK MRC (LID DTP MR/N013638/1: GRGL, QJL; MC_PC_19065 - Covid 19: Understanding the dynamics and drivers of the COVID-19 epidemic using real-time outbreak analytics: AG, NGD, TJ; MR/P014658/1: GMK). Authors of this research receive funding from UK Public Health Rapid

Support Team funded by the United Kingdom Department of Health and Social Care (TJ). Wellcome Trust (206250/Z/17/Z: AJK; 206471/Z/17/Z: OJB; 210758/Z/18/Z: JDM, JH, KS, NIB, SA, SFunk, SRM). No funding (AKD, AMF, DCT, SH).

Conflict of interest

Akira Endo received a research grant from Taisho Pharmaceutical Co. Ltd.

Authors' contributions

SC, BJQ, SF and WJE conceived the study and wrote the report. SC, BJQ, AE, SF and WJE designed the model. SC and BJQ led the development and analysis of the screening model and produced the results and figures. TWR led the development of and analysis of the prevalence model. TWR, YL, YWDC, CABP, AE, SF, RME and WJE consulted on the analyses. The CMMID COVID-19 Working Group members contributed by interpreting the study findings, contributing to the report, and approving the work for publication. All authors approved the final version for publication.

References

1. Chinazzi M, Davis JT, Ajelli M, Gioannini C, Litvinova M, Merler S, et al. The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak. Science. 2020;368(6489):395-400. https://doi.org/10.1126/science.aba9757 PMID: 32144116
2. Han E, Tan MMJ, Turk E, Sridhar D, Leung GM, Shibuya K, et al. Lessons learnt from easing COVID-19 restrictions: an analysis of countries and regions in Asia Pacific and Europe. Lancet. 2020;396(10261):1525-34. https://doi.org/10.1016/S0140-6736(20)32007-9 PMID: 32979936
3. Department of Health and Social Care and Department for Transport. Coronavirus (COVID-19): how to self-isolate when you travel to the UK. London: United Kingdom Government. [Accessed: 20 Jul 2020]. Available from: https://www.gov.uk/government/publications/coronavirus-covid-19-how-to-self-isolate-when-you-travel-to-the-uk/coronavirus-covid-19-how-to-self-isolate-when-you-travel-to-the-uk
4. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382(13):1199-207. https://doi.org/10.1056/NEJMoa2001316 PMID: 31995857
5. World Health Organisation (WHO). Operational considerations for case management of COVID-19 in health facility and community. Report No.: WHO/2019-nCoV/HCF_operations/2020.1. Geneva: WHO; 2020. Available from: https://www.who.int/publications/i/item/10665-331492
6. Brooks SK, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, et al. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. Lancet. 2020;395(10227):912-20. https://doi.org/10.1016/S0140-6736(20)30460-8 PMID: 32112714
7. Pfefferbaum B, North CS. Mental health and the covid-19 pandemic. N Engl J Med. 2020;383(6):510-2. https://doi.org/10.1056/NEJMp2008017 PMID: 32283003
8. Webster RK, Brooks SK, Smith LE, Woodland L, Wessely S, Rubin GJ. How to improve adherence with quarantine: rapid review of the evidence. Public Health. 2020;182:163-9. https://doi.org/10.1016/j.puhe.2020.03.007 PMID: 32334182
9. United States Food and Drug Administration (FDA). Quest SARS-CoV-2 rRT-PCR (Quest Diagnostics Infectious Disease, Inc.) - Manufacturer Instructions/Package Insert. Silver Spring: FDA. [Accessed: 16 Jul 2020]. Available from: https://www.fda.gov/media/136231/
10. Nikkei Staff Writers. Japan set to lift quarantines for business travelers in summer. Nikkei Asian Review. [Accessed: 6 Jul 2020]. Available from: https://asia.nikkei.com/Business/Travel-Leisure/Japan-set-to-lift-quarantines-for-business-travelers-in-summer
11. Civil Aviation Authority. Airport data. 2019 07 | London: Civil Aviation Authority. [Accessed: 20 Jul 2020]. Available from: https://www.caa.co.uk/Data-and-analysis/UK-aviation-market/Airports/Datasets/UK-Airport-data/Airport-data-2019-07
12. Civil Aviation Authority. Airport data. 2020 05. London: Civil Aviation Authority. [Accessed: 4 Jul 2020]. Available from: https://www.caa.co.uk/Data-and-analysis/UK-aviation-market/Airports/Datasets/UK-Airport-data/Airport-data-2020-05
13. Russell TW, Golding N, Hellewell J, Abbott S, Wright L, Pearson CAB, et al. Reconstructing the early global dynamics of under-ascertained COVID-19 cases and infections. BMC Med. 2020;18(1):332. https://doi.org/10.1186/s12916-020-01790-9 PMID: 33087179
14. Russell TW, Wu JT, Clifford S, Edmunds WJ, Kucharski AJ, Jit M, et al. Effect of internationally imported cases on internal spread of COVID-19: a mathematical modelling study. Lancet Public Health. 2021;6(1):e12-20. https://doi.org/10.1016/S2468-2667(20)30263-2 PMID: 33301722
15. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. PLoS Med. 2020;17(9):e1003346. https://doi.org/10.1371/journal.pmed.1003346 PMID: 32960881
16. United Kingdom Government. Coronavirus (COVID-19): getting tested. London: gov.uk. [Accessed: 12 Jun 2020]. Available from: https://www.gov.uk/guidance/coronavirus-covid-19-getting-tested
17. Quilty BJ, Clifford S, Flasche S, Eggo RM, CMMID nCoV working group. Effectiveness of airport screening at detecting travellers infected with novel coronavirus (2019-nCoV). Euro Surveill. 2020;25(5):2000080. https://doi.org/10.2807/1560-7917.ES.2020.25.5.2000080 PMID: 32046816
18. Gostic K, Gomez AC, Mummah RO, Kucharski AJ, Lloyd-Smith JO. Estimated effectiveness of symptom and risk screening to prevent the spread of COVID-19. eLife. 2020;9:e55570. https://doi.org/10.7554/eLife.55570 PMID: 32091395
19. Gostic K. Estimated effectiveness of symptom and risk screening to prevent the spread of COVID-19. San Francisco: Github. [Accessed: 16 Jul 2020]. Available from: https://kgostic.github.io/traveller_screening
20. International Air Transport Association (IATA). Criteria for COVID-19 testing in the air travel process. Geneva: IATA. [Accessed: 4 Jul 2020]. Available from: https://www.iata.org/en/pressroom/pr/2020-06-16-02/
21. Xinhua Global Service. [Beijing Railway Department: Implementing ticket purchase restrictions for high-risk groups and leaving Beijing with a negative certificate of nucleic acid test within 7 days]. Xinhuanet. [Accessed: 6 Jul 2020]. Chinese. Available from: http://www.xinhuanet.com/politics/2020-06/23/c_1126152337.htm
22. National Health Service (NHS). Main symptoms of coronavirus (COVID-19). London: NHS. [Accessed: 20 Jul 2020]. Available from: https://www.nhs.uk/conditions/coronavirus-covid-19/symptoms/main-symptoms
23. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polymerase chain reaction-based SARS-CoV-2 tests by time since exposure. Ann Intern Med. 2020;173(4):262-7. https://doi.org/10.7326/M20-1495 PMID: 32422057
24. Grassly N, Pons Salort M, Parker E, White P, Ainslie K, Baguelin M, et al. Report 16: Role of testing in COVID-19 control. London: Imperial College London; 2020. Available from: https://spiral.imperial.ac.uk:8443/handle/10044/1/78439
25. Van Vinh Chau N, Lam VT, Dung NT, Yen LM, Minh NNQ, Hung LM, et al. The natural history and transmission potential of asymptomatic SARS-CoV-2 infection. Clin Infect Dis. 2020;71(10):2679. https://doi.org/10.1093/cid/ciaa711 PMID: 32497212
26. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020;172(9):577-82. https://doi.org/10.7326/M20-0504 PMID: 32150748
27. Davies NG, Klepac P, Liu Y, Prem K, Jit M, CMMID COVID-19 working group, Eggo RM. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med. 2020;26(8):1205-11. https://doi.org/10.1038/s41591-020-0962-9 PMID: 32546824
28. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020;26(5):672-5. https://doi.org/10.1038/s41591-020-0869-5 PMID: 32296168
29. Ashcroft P, Huisman JS, Lehtinen S, Bouman JA, Althaus CL, Regoes RR, et al. COVID-19 infectivity profile correction. Swiss Med Wkly. 2020;150:w20336. PMID: 32757177
30. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020;581(7809):465-9. https://doi.org/10.1038/s41586-020-2196-x PMID: 32235945

31. Byrne AW, McEvoy D, Collins AB, Hunt K, Casey M, Barber A, et al. Inferred duration of infectious period of SARS-CoV-2: rapid scoping review and analysis of available evidence for asymptomatic and symptomatic COVID-19 cases. BMJ Open. 2020;10(8):e039856. https://doi.org/10.1136/bmjopen-2020-039856 PMID: 32759252
32. R Core Team. R: A Language and Environment for Statistical Computing. Vienna: R Foundation for Statistical Computing; 2020. Available from: https://www.R-project.org
33. Russell TW, Wu JT, Clifford S, Edmunds WJ, Kucharski AJ, Jit M, Centre for the Mathematical Modelling of Infectious Diseases COVID-19 working group. Effect of internationally imported cases on internal spread of COVID-19: a mathematical modelling study. Lancet Public Health. 2021;6(1):e12-20. https://doi.org/10.1016/S2468-2667(20)30263-2 PMID: 33301722
34. Baker MG, Kvalsvig A, Verrall AJ. New Zealand's COVID-19 elimination strategy. Med J Aust. 2020;213(5):198-200.e1. https://doi.org/10.5694/mja2.50735 PMID: 32789868
35. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. Lancet Microbe. 2021;2(1):e13-22. https://doi.org/10.1016/S2666-5247(20)30172-5 PMID: 33521734
36. Kissler SM, Fauver JR, Mack C, Olesen SW, Tai C, Shiue KY, et al. Viral dynamics of acute SARS-CoV-2 infection and applications to diagnostic and public health strategies. PLoS Biol. 2021;19(7):e3001333. https://doi.org/10.1371/journal.pbio.3001333 PMID: 34252080
37. Quilty BJ, Clifford S, Hellewell J, Russell TW, Kucharski AJ, Flasche S, et al. Quarantine and testing strategies in contact tracing for SARS-CoV-2: a modelling study. Lancet Public Health. 2021;6(3):e175-83. https://doi.org/10.1016/S2468-2667(20)30308-X PMID: 33484644
38. Hellewell J, Abbott S, Gimma A, Bosse NI, Jarvis CI, Russell TW, et al. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. Lancet Glob Health. 2020;8(4):e488-96. https://doi.org/10.1016/S2214-109X(20)30074-7 PMID: 32119825
39. Clifford S, Pearson CAB, Klepac P, Van Zandvoort K, Quilty BJ, Eggo RM, et al. Effectiveness of interventions targeting air travellers for delaying local outbreaks of SARS-CoV-2. J Travel Med. 2020;27(5):taaa068. https://doi.org/10.1093/jtm/taaa068 PMID: 32384159
40. Pya N, Wood SN. Shape constrained additive models. Stat Comput. 2015;25(3):543-59. https://doi.org/10.1007/s11222-013-9448-7
41. Devroye L. General Principles in Random Variate Generation. Non-Uniform Random Variate Generation. Springer: New York, NY; 1986. https://doi.org/10.1007/978-1-4613-8643-8_2

License, supplementary material and copyright

Strategies to reduce the risk of SARS-CoV-2 importation from international travellers, modelling estimations, July 2020 - Supplementary Appendix

This supplementary material is hosted by Eurosurveillance as supporting information alongside the article “Strategies to reduce the risk of SARS-CoV-2 importation from international travellers, modelling estimations, July 2020” on behalf of the authors, who remain responsible for the accuracy and appropriateness of the content. The same standards for ethics, copyright, attributions and permissions as for the article apply. Supplements are not edited by Eurosurveillance and the journal is not responsible for the maintenance of any links or email addresses provided therein.

Number of infected travellers

Civil Aviation Authority data for April and May 2020 indicates that traveller volume was approximately 99% lower compared to the same period in 2019 (Table S1). The traveller volumes in July 2020 are therefore assumed to be approximately 1% of those in July 2019.

Table S1: Traveller movements in June 2019 and year on year change for May 2020 compared to May 2019 between UK airports, and airports in the European Union (EU) and United States of America (USA). Source: Civil Aviation Authority Tables 10.1 and 12.1 for July 2019 [1], May 2019 [1] and May 2020 [2].

	EU	**USA**	**Source**
Total traveller volume July 2019	18,186,680	2,249,856	[1]
Year-on-year change for April and May 2020 compared to April and May 2019, %	-99%	-99%	[2] EU: Table S10.1 USA: Table S12.1
Calculated total traveller volume July 2020 using May year-on-year change, n	181,187	22,499	[1,2] EU: Table S10.1 USA: Table S12.1
Duration of typical flight (hours)	2	8	Assumed
Prevalence of SARS-CoV-2 on 20 July 2020	2.8 per 10,000	40.0 per 10,000	[3]
Number of infected individuals intending to travel in a given week. Median and 95% interval from 1000 simulations.	Symptomatic: 4 (1, 10) Asymptomatic: 1 (0, 5)	Symptomatic: 8 (2, 21) Asymptomatic: 2 (0, 10)	Proportion asymptomatic derived from [4]

We assume that the observed weekly travel volume, here, W, is those who have not been screened out or self-selected out based on onset of symptoms, i.e. the sum of the number of uninfected, asymptomatic, and those ever-symptomatic travellers not currently symptomatic The total number of intending travellers, W', is W, plus those who do not travel, δW. We

calculate W' as follows. First, sample $W \sim Bin(p = 7/30, \lceil n/2 \rceil)$. For α, the proportion of infections which are asymptomatic, π, the prevalence at the travel origin, ξ, the proportion of ever-symptomatic cases who are symptomatic at intended time of departure, and ρ, the proportion of currently symptomatic travellers prevented from boarding, δW is distributed according to a negative binomial distribution with size W and $p = 1 - \pi(1 - \alpha)\rho\xi$. $\xi$is estimated by sampling a large number of ever-symptomatic travellers, along with flight departure times and symptomatic periods and determining which proportion are symptomatic at time of intended departure.

The number of uninfected travellers, S, is then $S \sim Bin(1 - \pi, W + \delta W)$; the number of asymptomatic infected travellers is $I_a \sim Bin(\alpha, W + \delta W - S)$; the number of travellers symptomatic at time of departure is $I_s \sim Bin\left(\xi, W + \delta W - S - I_a\right)$and the number of ever-symptomatic travellers who are permitted to travel is therefore $W + \delta W - S - I_a - I_s$ and is composed of those who are not yet symptomatic, those who are post-symptomatic, and those who are symptomatic but not detected by syndromic screening.

Risk mitigation strategies

At maximum stringency, the 14 day quarantine period aims to ensure that even a traveller who was infected just before or during the flight would likely spend their whole infectious period in quarantine and thereby not infect others. The moderately stringent strategy, on the other hand, aims to ensure that travellers spend a sufficient amount of time in quarantine to allow for the development of symptoms and probability of a positive PCR test leading to isolation for those infected. These strategies would, however, risk that some asymptomatically infected travellers (that is, infected travellers who will never display symptoms) will enter the community before the end of their infectious period.

Table S2 - Strategies for risk mitigation. Where one of the described lines contains “or”, we consider all combinations contained within. For all levels of stringency we consider scenarios with the following pre-flight PCR policies: no pre-flight testing, pre-flight testing within 1 day of departure, within 4 days of departure, or within 1 week of departure.

Stringency of screening policy*	**Description of screening policy**
Low	01. No mandatory quarantine on arrival, and 02. Either no post-flight testing, *or* a single PCR test on arrival. 03. Release immediately after arrival (no test) or on receipt of negative result (test). *We consider a no-quarantine, no-testing scenario as the primary baseline for comparison.*
Moderate	01. Mandatory 3, 5 or 7 days quarantine on arrival, and 02. Either no post-flight testing *or* a single PCR test at end of mandatory quarantine 03. Release at end of mandatory quarantine period (no test) *or* on receipt of negative test at end of mandatory quarantine period.
High	01. Mandatory quarantine on arrival, and 02. A first PCR test 0, 1 or 2 days after arrival, and

	03. A second PCR test either 2, 4 or 6 days after the first 04. Release after two negative post-arrival results or 14 days after earliest positive post-arrival test.
Maximum	01. Mandatory 14 days quarantine on arrival 02. Either no post-flight testing *or* a single PCR test at end of mandatory quarantine 03. Release at end of mandatory quarantine period (no test) *or* on receipt of negative test at end of mandatory quarantine period.

* In all scenarios we assumed that syndromic screening is implemented at the departure airport, hence low stringency rather than no stringency.

Detection model

The time-varying PCR sensitivity is modelled as a function of the time since an individual's exposure (Figure 1, Kucirka et al. 2020 [5]) and derived by fitting a Generalised Additive Model (GAM) with a Binomial likelihood and penalised B-spline basis (P-spline) [6], to the data collected by Kucirka et al. (2020) [5]. We shift the observations, as they have, by an incubation period of 5 days [7], and augment by a pseudo-negative test on day 0 for each of the constituent data sets.

Table S3 - Values of parameters in simulation of travellers' infection histories and PCR testing. Gamma distributions are parameterised in terms of a mean and variance, $\Gamma(\mu, \sigma^2)$, and these are converted to shape and rate parameters via moment matching. Where quantiles are given but no distribution described, the parameter is derived from other distributions in the table and has no closed-form.

Model parameter	Description	Value	Source
Incubation period (days)	Time from exposure to onset of symptoms.	$\Gamma\left(\mu = 5.5,\ \sigma^2 = 6.5\right)$ Median: 5.1 days IQR: (3.6, 6.9) days 95%: (1.7, 11.5) days	Derived from quantile matching with Median: 5.1 days, 97.5%: 11.5 days [7]
Time to infectiousness (symptomatic cases)	Time after exposure (and before onset of symptoms) from which pre-symptomatic transmission can occur.	Median: 3.4 days IQR: (2.3, 4.9) days 95%: (0.9, 8.6) days	Derived from [8]
Infectious period (symptomatic cases, days)	Duration of period in which case is able to infect others	Median: 7.1 days IQR: (5.7, 8.5) days 95%: (2.5, 11.6) days	Derived from [9]
Symptomatic period (symptomatic cases, days)	Time after onset of symptoms until no longer symptomatic	$\Gamma(\mu = 9.1,\ \sigma^2 = 14.7)$ Median: 8.6 days IQR: (6.3, 11.3) days 95%: (3.2, 18.0) days	Derivation from [10] based on moment matching distributions in [11]

Fraction of currently symptomatic travellers, ξ	Proportion of ever-symptomatic infections symptomatic at intended departure time	0.44	Derived from simulation of travellers
Syndromic screening detection rate, ρ	Proportion of symptomatic individuals intending to travel who are either screened out at point of departure or self-select out of travelling	0.7	Derived from [12]
Infectious period (asymptomatic cases, days)	Duration of period in which case is able to infect others	$\Gamma\left(\mu = 6, \sigma^2 = 12\right)$ Median: 5.3 days IQR: (3.5, 7.8) days 95%: (1.2, 14.4) days	Assumption based on [13]
PCR sensitivity for symptomatic infections (Figure S1A)	Probability of testing PCR positive *t* days after infection, if infection is symptomatic	$P(t)$	Penalised B-spline fit to data in [5]
PCR specificity	Probability of a negative PCR test given no infection with SARS-CoV-2.	1	Assumption consistent with [14]
Asymptomatic fraction, α	Proportion of infections which are asymptomatic.	$Beta(1.9,\ 6.3)$ Median: 0.21 IQR: (0.12, 0.32) 95%: (0.03, 0.55)	Derived from quantile matching, 95%: (0.03, 0.55) [4]
PCR sensitivity for asymptomatic infections	Probability of testing PCR positive t days after infection, if infection is asymptomatic	$0.62 * P(t)$	Scaling factor derived from [15]

According to He et al. (2020) infectiousness of symptomatic cases begins up to 12.3 days (95%: (5.9, 17) days) prior to the onset of symptoms and peaks at onset of symptoms (0 days, 95%: -0.9, 0.9 days) [8,16]. We sampled this pre-symptomatic infectious period duration to derive the time from exposure to infectiousness by matching the quantiles of the distribution of time to onset of symptoms to the quantiles of the distribution of infectiousness lead times for each traveller, preserving order, ensuring that no time to infectiousness occurs before exposure. The duration of the infectious period for symptomatic cases was derived from the data of Wölfel et al. (2020) [9] by fitting a Binomial GAM with P-splines to determine the probability of no longer being infectious as a function of days since onset of symptoms. The time to non-infectiousness is sampled from the fitted GAM, which has range (0,1), by the inverse transform method [17].

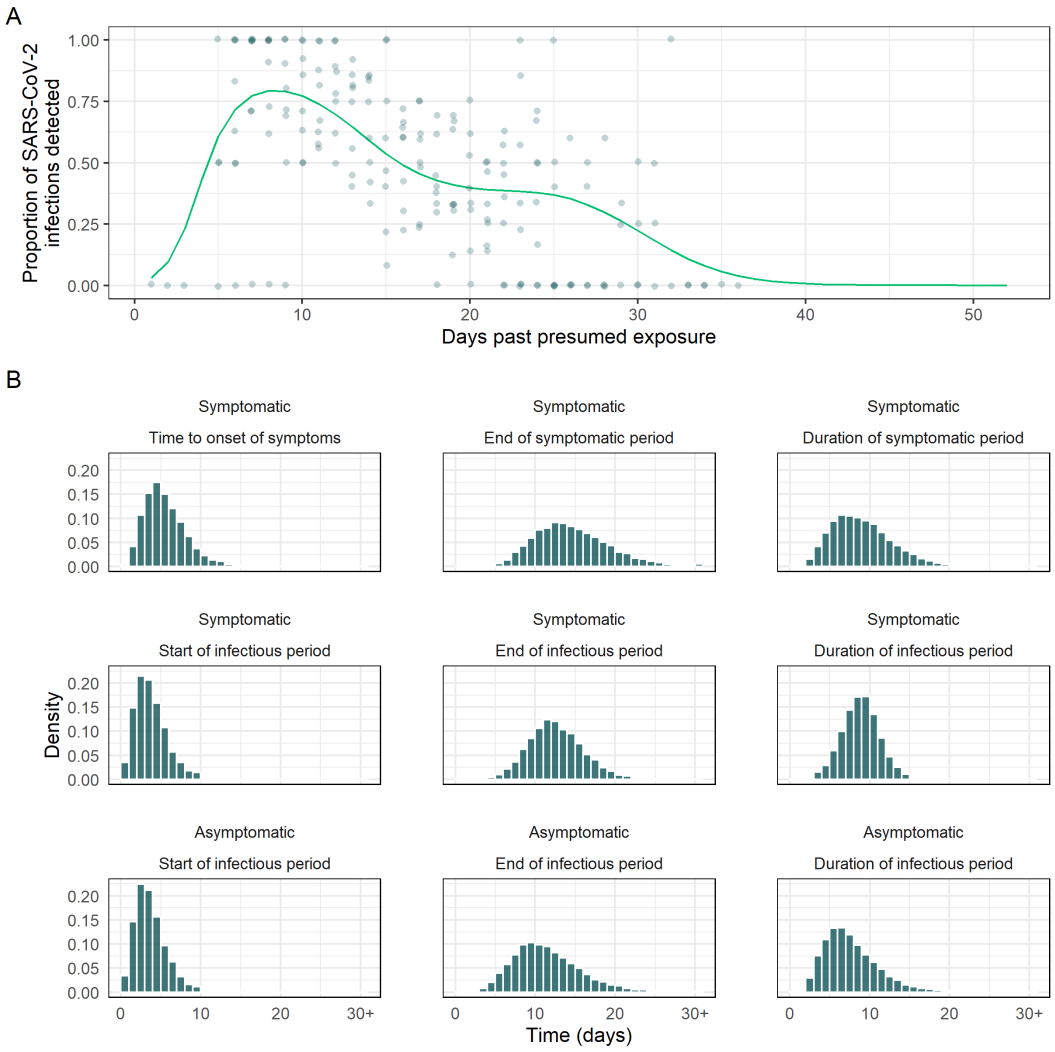


Figure S1 - A. Traveller PCR sensitivity curves, obtained by fitting a Binomial GAM to the data collated in Kucirka et al. (2020) [5] The mean fit is used as the time-varying sensitivity function, $P(t)$, and hence no uncertainty is shown in the figure. B. Distributions of times to clinically relevant events, namely time from exposure to start and end, and duration, of symptoms for symptomatic infections (dark green), and infectiousness for both symptomatic and asymptomatic (light green) infections. Times greater than 30 days are collapsed to a single “30+” bin.

Results

As a baseline for comparison, we use the lowest stringency scenario considered: 70% of currently symptomatic travellers are prevented from boarding, but no quarantine or testing is conducted. In this scenario, between 2 and 12 (EU), and 3 and 24 (USA) infectious travellers would enter the community (Figure S2A, low, no testing). By introducing a mandatory quarantine period of 7 days, this can be reduced to 0 to 3 infectious persons per week from the EU and 0 to 4 from the USA (Figure S2A, Mod.), preventing approximately 80% of

travellers from entering the community while being infectious (Rate Ratios, median and 95% UI: EU: 0.18 (0.00, 0.42), USA: 0.18 (0.10, 0.27)). A mandatory quarantine period of 14 days resulted in 0 to 1 infectious entries per week each from the EU and USA (Figure S2A, Max.), an almost completely effective reduction (RR: EU: 0.00 (0.00, 0.01), USA: 0.01 (0.00, 0.04)).

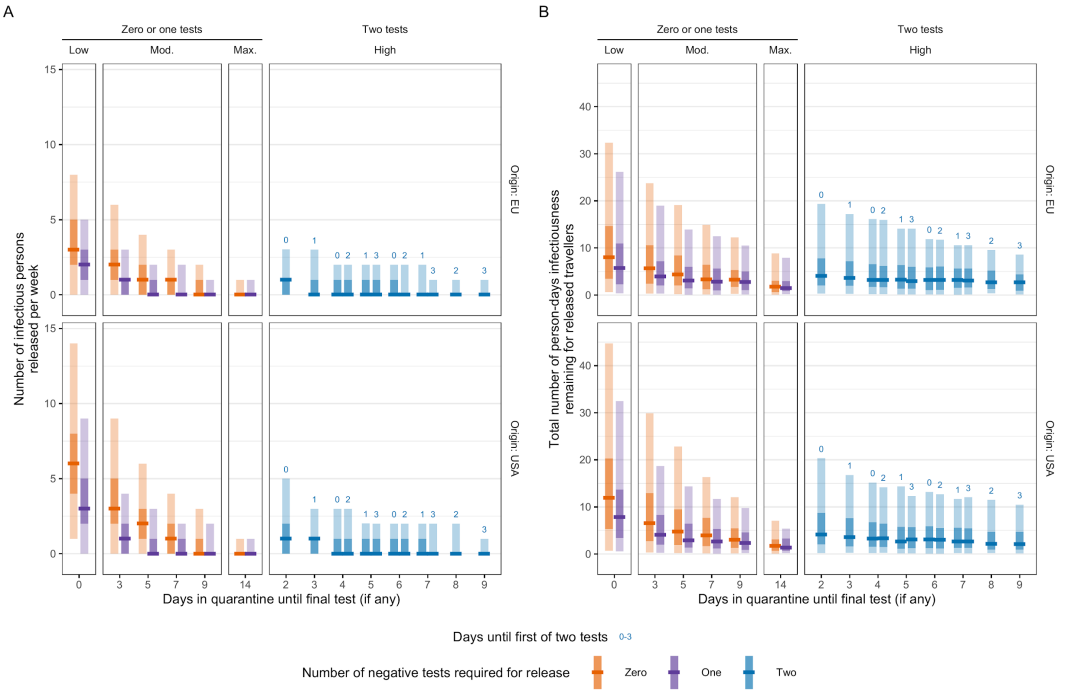


Figure S2: A. Expected number of infectious and pre-infectious persons free to enter the UK from the EU and USA based on observed travel volumes in each of the scenarios and how long they spend in quarantine before release, with no pre-flight testing. B. Total person-days of infectiousness remaining after release, based on observed travel volumes. We assume that test results are delayed by 1 day and hence persons leave quarantine 1 day after their final test. Central bar = median; light bar = 95% uncertainty interval; dark bar = 50% uncertainty interval.

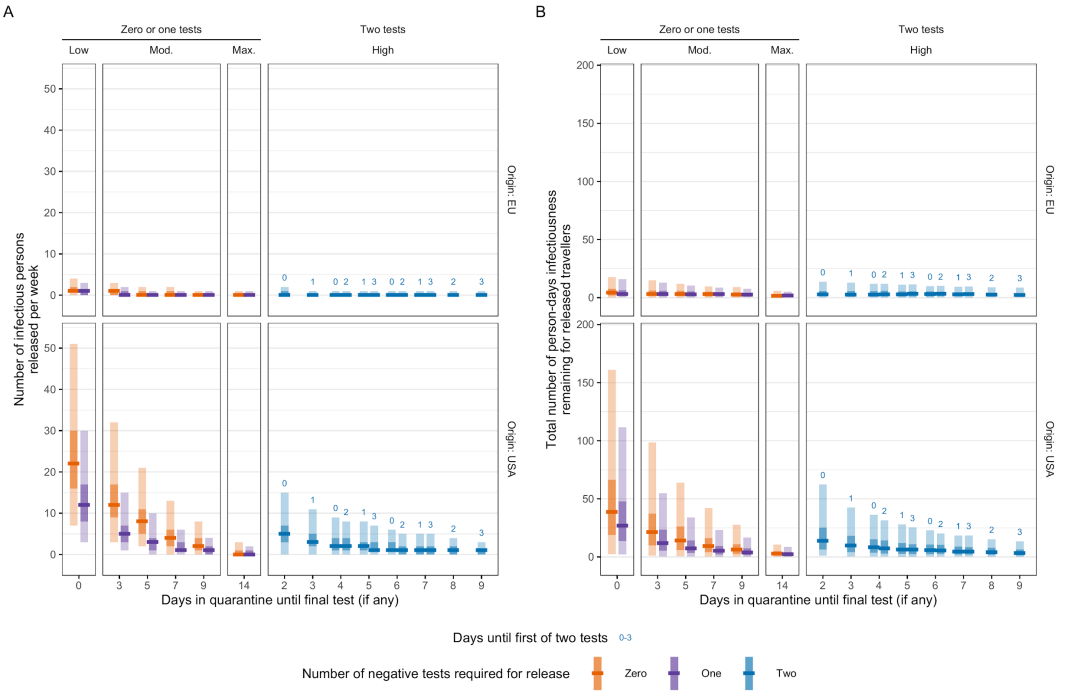


Figure S3 - As for Figure S1 but per 10,000 travellers rather than observed flight volumes.

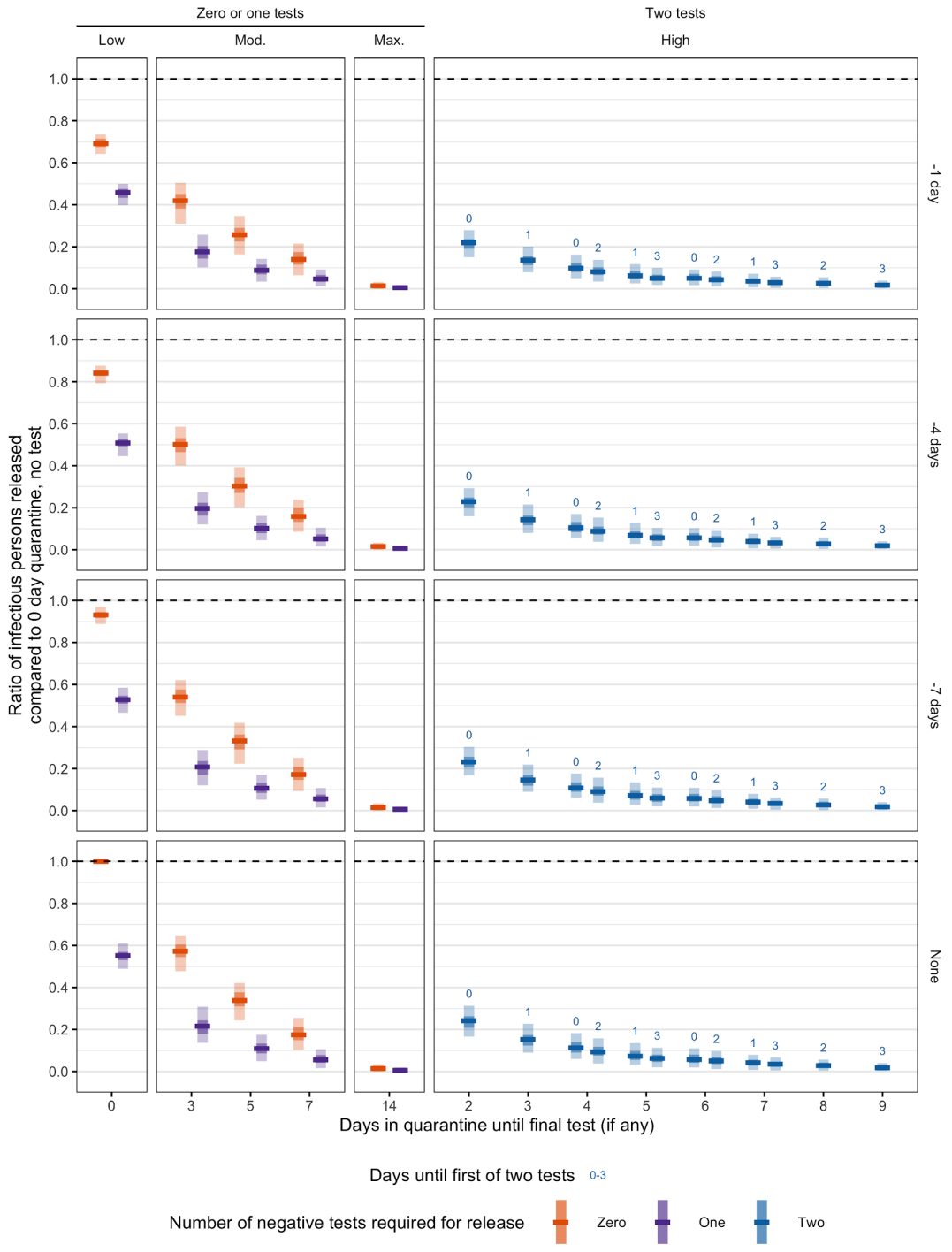


Figure S4 - Per-infected traveller reduction in risk given by each strategy in comparison to a baseline of a 0 day quarantine on arrival with no testing, considering either no pre-flight testing, or pre-flight testing 1, 4 or 7 days prior to departure. We assume that test results are delayed by 1 day and hence persons leave quarantine 1 day after their second test. Central bar = median; light bar = 95% uncertainty interval; dark bar = 50% uncertainty interval. Product of 1000 infected arrivals and 1000 simulations per scenario.Persons showing symptoms at departure were assumed to be prevented from travel, and post-infectious persons were assumed to not carry any

risk of seeding transmission. We assume that test results are delayed by 1 day and hence persons leave self-isolation 1 day after their final test. Central bar = median; light bar = 95% uncertainty interval; dark bar = 50% uncertainty interval.

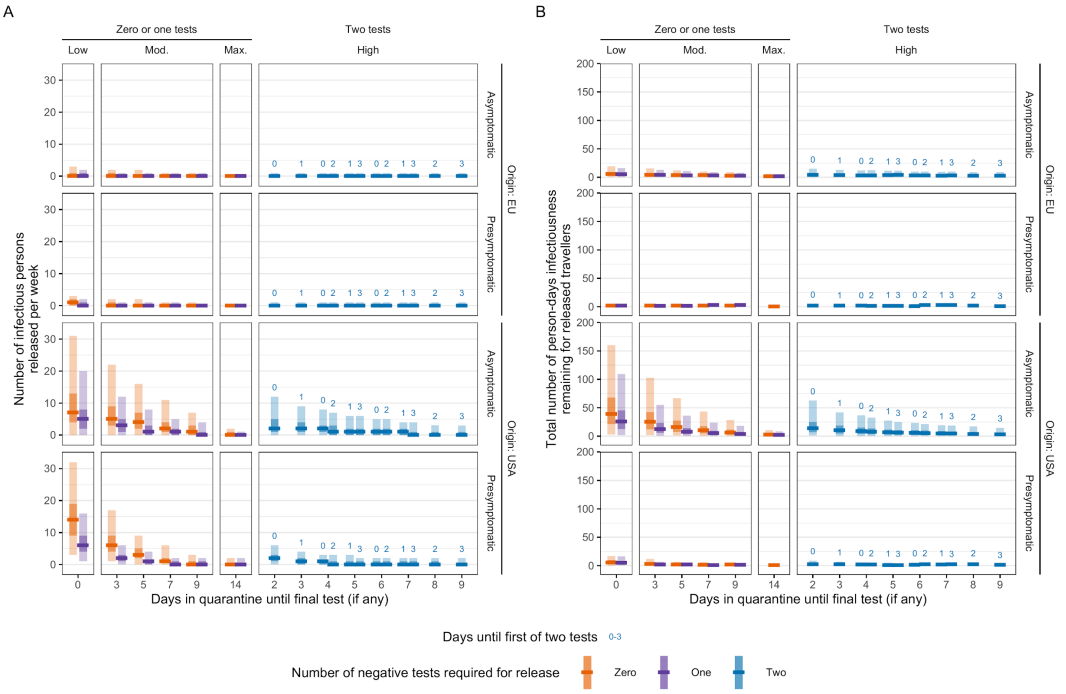


Figure S5 - As for Figure S3 but stratified on whether infection is asymptomatic or presymptomatic.

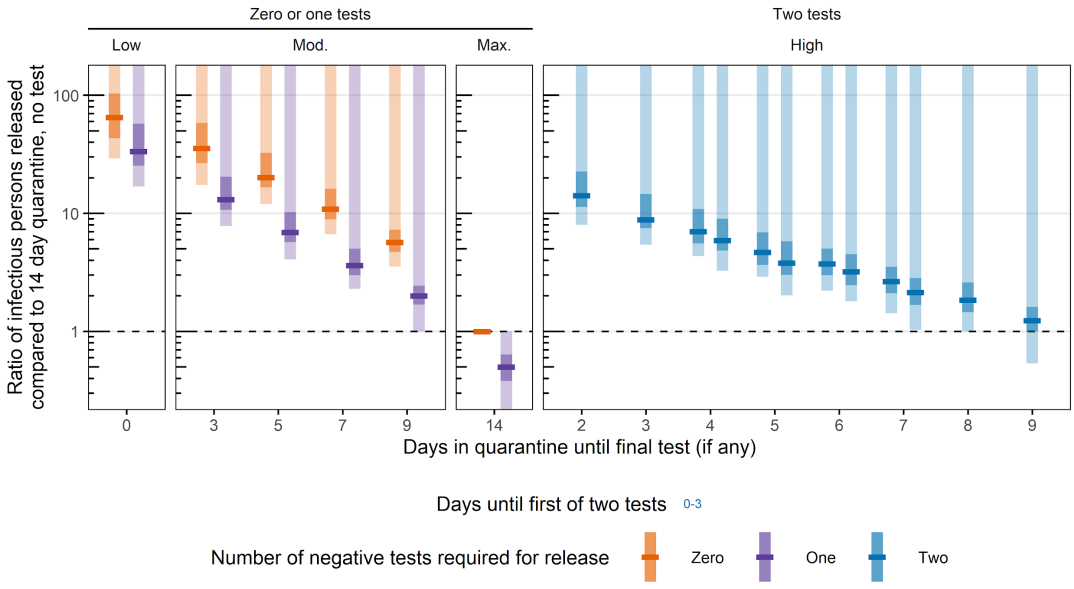


Figure S6 - Per-infected traveller reduction in risk given by each strategy in comparison to a baseline of a 14 day quarantine on arrival with no testing. We assume that test results are delayed by 1 day and hence persons leave quarantine 1 day after their final test. Central bar = median; light bar = 95% uncertainty interval; dark bar = 50% uncertainty interval. Product of 1000 infected arrivals and 1000 simulations per scenario.

[1] Airport data 2019 07 | UK Civil Aviation Authority n.d. https://www.caa.co.uk/Data-and-analysis/UK-aviation-market/Airports/Datasets/UK-Airport-data/Airport-data-2019-07/ (accessed July 20, 2020).
[2] Airport data 2020 05 | UK Civil Aviation Authority n.d. https://www.caa.co.uk/Data-and-analysis/UK-aviation-market/Airports/Datasets/UK-Airport-data/Airport-data-2020-05/ (accessed July 4, 2020).
[3] Russell TW, Joel Hellewell SA, Golding N, Gibbs H, Jarvi CI, Kevin van Zandvoort, et al. Using a delay-adjusted case fatality ratio to estimate under-reporting. 2020.
[4] Buitrago-Garcia DC, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. The role of asymptomatic SARS-CoV-2 infections: rapid living systematic review and meta-analysis. Epidemiology 2020. https://doi.org/10.1101/2020.04.25.20079103.
[5] Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction-Based SARS-CoV-2 Tests by Time Since Exposure. Ann Intern Med 2020. https://doi.org/10.7326/M20-1495.
[6] Pya N, Wood SN. Shape constrained additive models. Stat Comput 2015;25:543–59. https://doi.org/10.1007/s11222-013-9448-7.
[7] Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med 2020;172:577–82. https://doi.org/10.7326/M20-0504.
[8] He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med 2020;26:672–5. https://doi.org/10.1038/s41591-020-0869-5.
[9] Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature 2020;581:465–9. https://doi.org/10.1038/s41586-020-2196-x.
[10] Quilty BJ, Clifford S, Flasche S, Eggo RM, CMMID nCoV working group. Effectiveness of airport screening at detecting travellers infected with novel coronavirus (2019-nCoV). Euro Surveill 2020;25. https://doi.org/10.2807/1560-7917.ES.2020.25.5.2000080.
[11] Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med 2020;382:1199–207. https://doi.org/10.1056/NEJMoa2001316.
[12] Gostic K, Gomez AC, Mummah RO, Kucharski AJ, Lloyd-Smith JO. Estimated effectiveness of symptom and risk screening to prevent the spread of COVID-19. Elife 2020;9. https://doi.org/10.7554/eLife.55570.
[13] Byrne AW, McEvoy D, Collins A, Hunt K, Casey M, Barber A, et al. Inferred duration of infectious period of SARS-CoV-2: rapid scoping review and analysis of available evidence for asymptomatic and symptomatic COVID-19 cases. Epidemiology 2020. https://doi.org/10.1101/2020.04.25.20079889.
[14] Grassly N, Pons Salort M, Parker E, White P, Ainslie K, Baguelin M, et al. Report 16: Role of testing in COVID-19 control 2020. https://doi.org/10.25561/78439.
[15] Chau NVV, Thanh Lam V, Thanh Dung N, Yen LM, Minh NNQ, Hung LM, et al. The natural history and transmission potential of asymptomatic SARS-CoV-2 infection. Clin Infect Dis 2020. https://doi.org/10.1093/cid/ciaa711.
[16] Ashcroft P, Huisman JS, Lehtinen S, Bouman JA, Althaus CL, Regoes RR, et al. COVID-19 infectivity profile correction. arXiv [q-bioPE] 2020.
[17] Devroye L. General Principles in Random Variate Generation. Non-Uniform Random Variate Generation 1986:27–82. https://doi.org/10.1007/978-1-4613-8643-8_2.

2.4 Quarantine and testing strategies to reduce transmission risk from imported SARS-CoV-2 infections: a global modelling study

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	1703195	**Title**	Mr
First Name(s)	Billy		
Surname/Family Name	Quilty		
Thesis Title	Modelling the effectiveness of quarantine and testing strategies during the COVID-19 pandemic		
Primary Supervisor	Stefan Flasche		

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 Travel Medicine
Please list the paper's authors in the intended authorship order:	Billy J Quilty, Timothy W Russell, Samuel Clifford, Stefan Flasche, Suzanne Pickering, Stuart JD Neil, Rui Pedro Galão, W John Edmunds, CMMID COVID-19 Working Group
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)	I co-led in the conceptualisation of this work following the awarding of WHO funding. I led the formulation and development of the PCR and LFT testing model which was integrated with my coauthor's analysis of prevalence and travel volume. I then co-led the main analysis, production of figures and results, and writing of the draft manuscript.

SECTION E

Student Signature	Billy Quilty
Date	07/02/2023

Supervisor Signature	Stefan Flasche
Date	07/02/2023

Quarantine and testing strategies to reduce transmission from imported SARS-CoV-2 infections: a global modelling study

Billy J Quilty[1], Timothy W Russell[1], Samuel Clifford[1], Stefan Flasche[1], Suzanne Pickering[2], Stuart JD Neil[2], Rui Pedro Galão[2], W John Edmunds[1], CMMID COVID-19 Working Group[1]

[1]Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, LONDON WC1E 7HT, United Kingdom

[2]Department of Infectious Diseases, School of Immunology & Microbial Sciences, King's College London, LONDON SE1 9RT, United Kingdom

The following authors were part of the Centre for Mathematical Modelling of Infectious Disease COVID-19 Working Group. Each contributed in processing, cleaning and interpretation of data, interpreted findings, contributed to the manuscript, and approved the work for publication: Oliver Brady, James D Munday, Amy Gimma, Joel Hellewell, Katherine E. Atkins, Paul Mee, Sebastian Funk, Kathleen O'Reilly, Christopher I Jarvis, Yang Liu, Kaja Abbas, Frank G Sandmann, Gwenan M Knight, Rachel Lowe, Nikos I Bosse, C Julian Villabona-Arenas, Simon R Procter, Sophie R Meakin, Katharine Sherratt, Matthew Quaife, Rosanna C Barnard, Sam Abbott, Emilie Finch, Fiona Yueqian Sun, Lloyd A C Chapman, Nicholas G. Davies, Rosalind M Eggo, Yalda Jafari, Kiesha Prem, Stéphane Hué, Ciara V McCarthy, Akira Endo, Alicia Rosello, Hamish P Gibbs, Mark Jit, William Waites, Damien C Tully, Rachael Pung, Graham Medley, Adam J Kucharski, Kerry LM Wong, Carl A B Pearson, David Hodgson, Mihaly Koltai.

Abstract

Background

Many countries require incoming air travellers to quarantine on arrival and/or undergo testing to limit importation of SARS-CoV-2.

Methods

We developed mathematical models of SARS-CoV-2 viral load trajectories over the course of infection to assess the effectiveness of quarantine and testing strategies. We consider the utility of pre and post-flight Polymerase Chain Reaction (PCR) and lateral flow testing (LFT) to reduce transmission risk from infected arrivals and to reduce the duration of, or replace, quarantine. We also estimate the effect of each strategy to reduce transmission relative to domestic incidence, and limits of achievable reduction, for 99 countries where flight data and case numbers are estimated.

Results

We find that LFTs immediately pre-flight are more effective than PCR tests 3 days before departure in decreasing the number of departing infectious travellers. Pre-flight LFTs and post-flight quarantines, with tests to release, may prevent the majority of transmission from infectious arrivals while reducing the required duration of quarantine; a pre-flight LFT followed by 5 days in quarantine with a test to release would reduce the transmission potential of an infected traveller compared to symptomatic self-isolation alone by 85% (95% UI: 74%, 96%) for

PCR and 85% (95% UI: 70%, 96%) for LFT, even assuming imperfect adherence to quarantine (28% of individuals) and self-isolation following a positive test (86%). Under the same adherence assumptions, 5 days of daily LFT testing would reduce transmission potential by 91% (95% UI: 75%, 98%).

Conclusions

Strategies aimed at reducing transmission from imported cases should be considered with respect to: domestic incidence, transmission, and susceptibility; measures in place to support quarantining travellers; and incidence of new variants of concern in travellers' origin countries. Daily testing with LFTs for 5 days is comparable to 5 days of quarantine with a test on exit or 14 days with no test.

Introduction

SARS-CoV-2 emerged in late 2019 in Wuhan, China, and spread rapidly around the world through international travel. Many countries have since acted to reduce importation of infectious individuals with measures including border closures, partial travel restrictions, entry or exit screening, and quarantine of travellers (1). The effectiveness of such policies in detecting infectious travellers will be influenced by factors including the natural history of SARS-CoV-2 infection, the performance of tests used for screening, and the level of adherence with guidelines for both quarantine (i.e. the separation of individuals, independent of their case-status, from the wider community) and self-isolation (i.e. the separation of symptomatic or test-positive individuals from the wider community) (2). In addition, the absolute risk of transmission from imported infections to each country will be determined by the volume of travel from, and prevalence of infection in, other countries (3). The emergence of more transmissible and virulent variants of SARS-CoV-2 in late 2020 has brought a new impetus to assessing the effectiveness of travel restrictions. Here we combine previously published models for estimating prevalence and incidence, travel volume, infectivity, and effectiveness of testing and quarantine strategies to estimate the reduction in risk of importing new infections and compare the number of infectious arrivals to the size of the domestic epidemic in 99 countries. We also estimate the extent to which each strategy (quarantine of varying duration with/without test at exit; daily LFTs; and the use of pre-flight tests) may avert onward transmission in the destination country by considering the reduction in the expected reproduction number of arrivals compared to a scenario with no interventions specifically targeting travellers.

Method

Briefly, we estimate the proportion of infected travellers who would be detected by each of the considered quarantine and testing scenarios (and at which point in their journey, Figure 1) and calculate the relative reduction in the expected number or secondary cases generated by an infected traveller, *R*. We then estimate the total number of travellers arriving to each destination country and the prevalence of SARS-CoV-2 infection in each origin country in order to estimate the number of infected travellers who would arrive under a no-intervention scenario. As in

previous work (3), we then describe a relative risk rating of importation as being the ratio of daily infectious arrivals and domestic incidence in the destination country, and explore exportation of the variant of concern B.1.1.7 from the UK as a case study. The following subsections describe each component of the model in further detail.

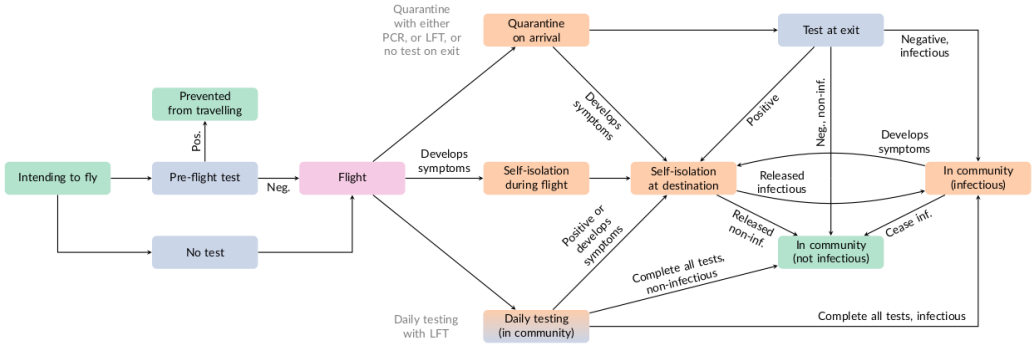


Figure 1: Schematic of quarantine and testing strategies, showing endpoints of travel process (green), flight (red), pre- and post-flight testing (blue), and quarantine and self-isolation points (orange). Individuals are assumed to only develop symptoms once. Individuals are subject to a strategy of either post-flight quarantine (upper arm) or daily testing (lower arm); under both types of strategy, a positive test or development of symptoms results in self-isolation and eventual release either while still infectious or while not infectious. Adapted from (4).

Viral load trajectories

For each infected individual, we simulate a viral load trajectory based on publicly available data of the longitudinal sampling of individuals by Polymerase Chain Reaction (PCR) (5,6) from which we derive individual-level infectiousness over the course of infection and the probability of testing positive at time of sampling (Figure 2). Key assumptions of viral load dynamics are that both symptomatic and asymptomatic infections' cycle threshold (Ct) values reach their lowest level (i.e., viral load peak), in accordance with the incubation period, 5.1 days (95% range: 2.3, 11.5 days) after the infecting exposure (7), at a mean Ct of 22.3 (SD: 4.2) (5). We assume that viral shedding continues until 17 days (SD: 0.94 days) after exposure for symptomatics (6) and that for asymptomatics this duration is reduced by 40% (5,6). We also assume that between 24% and 38% of individuals are asymptomatic throughout the course of infection (8), and, for each model run, sample the fraction of intending travellers who are infected from a Beta distribution whose 95% interval matches (24%, 38%). Assuming that the ability to culture virus from a given viral load is a reasonable proxy for, if contact was made, the ability to infect others (here defined as "infectiousness") (9) we fitted a logistic regression model to estimate infectiousness from the ability to culture virus for a given viral load (in Ct) using data from Pickering et al. (10) using R's *glm* function (Figure 2B), giving a value between 0 and 1. Given the previously simulated viral load trajectories, this model is then used to estimate an infectiousness curve over the course of infection (Figure 2C). To estimate the reduction in potential infectiousness, we calculate the area under the entirety of this infectiousness curve (AUC) over period of time that Ct values are lower

than 25, i.e, the approximate viral load at which the virus becomes culturable (Figure 2), to give an overall individual-level value for potential infectiousness (11), which can then be truncated on the left by the time of departure from the origin country to allow for the possibility of in-flight transmission, and on the right by quarantine or self-isolation upon symptom onset or a positive test result. The fraction of the AUC removed by truncation is considered to be proportional to a reduction in transmission potential (TP) under a given strategy.

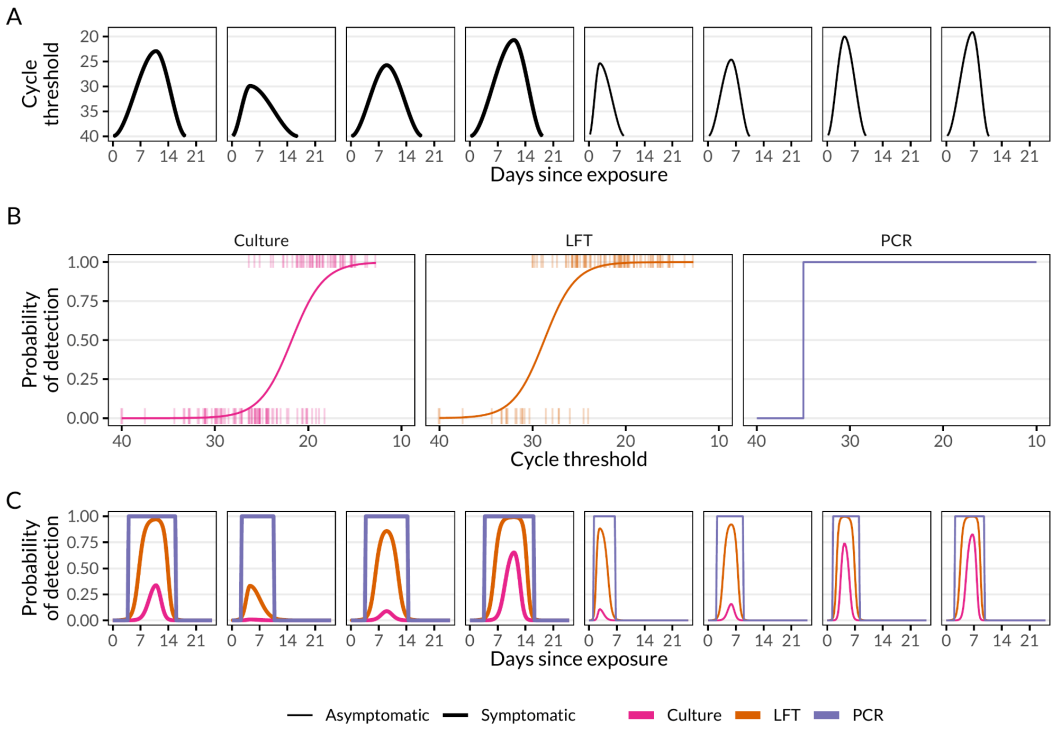


Figure 2: A) Eight randomly sampled viral load trajectories over the course of infection (symptomatic and asymptomatic), B) the functions to estimate probability of detection by culture (the assumed infectivity function), the Innova lateral-flow antigen test, and PCR, given a certain cycle threshold, and C) the produced detection curves over the course of infection.

Testing

We model the sensitivity of LFTs using the results of the Innova SARS-CoV-2 Antigen Rapid Qualitative Test as evaluated by Pickering et al. (10) namely whether a swab returned a positive result under LFT when infection was detected by PCR with an associated Ct value (Figure 2). We fitted a logistic regression model using *glm* in R to estimate the mean probability of detection for a given Ct value, i.e, the viral load at time of sampling, after regrouping “strongly positive”, “clearly positive”, and “weakly positive” as “positive” test results (Figure 2B). PCR tests are assumed to have a detection threshold at a Ct value of 35; below this threshold value, we assume PCR is 100% sensitive and that it is 0% sensitive for Ct values greater than 35 (Figure 2B). Sensitivity of LFTs varies with viral load, and therefore with time. At a Ct of 35 the probability of

detection is 0.02; at the mean simulated peak Ct of 22.3 the probability of detection is 0.98. The proportion adhering to self-isolation following a positive test, either by PCR or LFT, is assumed to be 86% (12).

Intervention strategies

Air travellers may be subjected to interventions that vary in stringency with the aim of both preventing infectious arrivals and reducing their potential for transmission in the destination country (Figure 1). Within our modelling framework, travellers may either not be tested (baseline) or be tested pre-flight by either PCR or LFT, where a negative test result is required to board the plane (with sensitivity analysis for varying delays from test to departure). Upon arrival (an assumed six hours after departure) travellers are subject to quarantine and/or testing (Figure 1). Travellers may enter a post-flight quarantine of 0 (baseline), 3, 5, 7, 10 or 14 days duration with, on the final day of quarantine, either no test, an LFT test, or a PCR test. A positive test at the end of quarantine leads to an additional 10 days of self-isolation. Based on published estimates from Norway, we assume that the proportion of individuals adhering to quarantine in the absence of symptoms is 28%, with individuals either fully adherent or non-adherent, although asymptotically there should be no difference between 28% of individuals adhering and all individuals adhering 28% (13). Alternatively, travellers may take LFT tests daily for 3, 5, 7 or 10 days without quarantine, only self-isolating upon the receipt of a positive test. We assume that individuals who develop symptoms (fever or high temperature, a cough that has lasted for at least several hours, shortness of breath, aches and pains (e.g. in back, neck, shoulders or joints), blocked nose, sore throat and feeling unusually tired) will self-isolate for 10 days (or not board the plane if symptomatic upon flight departure), with the proportion adhering to symptomatic self-isolation being 71% as reported by the ONS in the UK (14).

Detection process

Infected travellers may be detected either: prior to departure by either a pre-flight PCR test three days prior to departure or an LFT test immediately pre-flight; by a post-flight test (either daily LFT testing or at the end of quarantine); or by developing symptoms either during their flight or during or after the quarantine period (each of which triggers the need for isolation). All passengers detected pre-flight are considered to contribute no risk of further infection in the destination. Based on the viral load dynamics of those who do travel, we estimate whether individuals still pose a risk of community transmission in the destination country. Those who still pose a risk are either: asymptomatic, infectious but not detected by daily testing; those who do not adhere to quarantine guidance while infectious; those who remain infectious after their release from quarantine (either without a test or a false negative result); those who do not isolate on development of symptoms; or those who do not isolate after receiving a positive test result. For each quarantine and testing scenario we simulate 1000 infected travellers (bootstrapped 1000 times to estimate uncertainty) and estimate the proportion of travellers detected at each stage, whether they pose a risk of community transmission, and the expected reduction in transmission of each strategy. We also estimate the effectiveness of the best case for each strategy, i.e. the proportion adhering to quarantine, self-isolation after symptom onset,

and self-isolation after a positive test, are all 100%, rather than 28%, 71% and 86% respectively. Results are presented, both for the proportion of the would-be infectious or eventually infectious arrivals in each detection and infection group and the effectiveness of an intervention as a reduction in transmission potential (TP), as medians and uncertainty intervals (UIs) calculated as the quantiles of the sampled values within the simulations for each scenario.

Estimating the number of travellers

We estimate the number of infectious arrivals to a given country by the method of Russell et al. (3). By applying an estimate of case under-ascertainment rates based on reported deaths and infection fatality ratio, we estimate the prevalence of infection in each country. We assume that the prevalence in the general population is the same as the prevalence in travellers and so the total number of infectious arrivals per day for a given country is the sum of the estimated daily travel volume from each origin to that country, weighted by estimated prevalence. Estimates of travel volume are obtained from the publicly available OpenSky database, which provides daily data on the number of flights between airports (15). We estimate the number of arrivals per flight (at the current stage of the pandemic) with the mean number of travellers per flight, 142, the total number of passenger movements divided by the total number of passenger flight movements as of 20 March 2021 (16) and note that this implies similar aircraft are used on all international flights. Countries with no available flight data (n=71) were excluded from the model. The OpenSky database is estimated to cover 45% of the total number of flights globally, with methods and explicit coverage estimates detailed in Strohmeier et al. (17).

Variants of concern

As a case study to investigate the importation risk of SARS-CoV-2 Variants Of Concern (VOCs) relative to domestic incidence, we estimated the number of infectious cases exported from the United Kingdom infected with the B.1.1.7 Variant of Concern (35) to six other countries from October 2020 through to April 2021. Total domestic incidence (calculated using the underascertainment model described previously) in destination countries was used as the denominator as local B.1.1.7 incidence data were not available. The choice of B.1.1.7 was made due to data availability (both for the variant and flights) but the approach is variant agnostic. We show results for two countries selected at random from each of High Income Countries and Upper Middle Income Countries (according to World Bank classifications) as well as the United States of America and Singapore as countries with, respectively, high and low incidence.

All analyses were conducted in R version 4.0.5 (18).

Results

Outcome of quarantine and testing for infectious or eventually infectious arrivals

Pre-flight LFT and PCR testing detects 66% (95% UI: 48%, 86%) and 85% (95% UI: 73%, 96%) of infectious and eventually infectious travellers, respectively, indicating that pre-flight testing alone may play a substantial role in preventing the seeding of new outbreaks by preventing their arrival in the destination country (Figure 3).

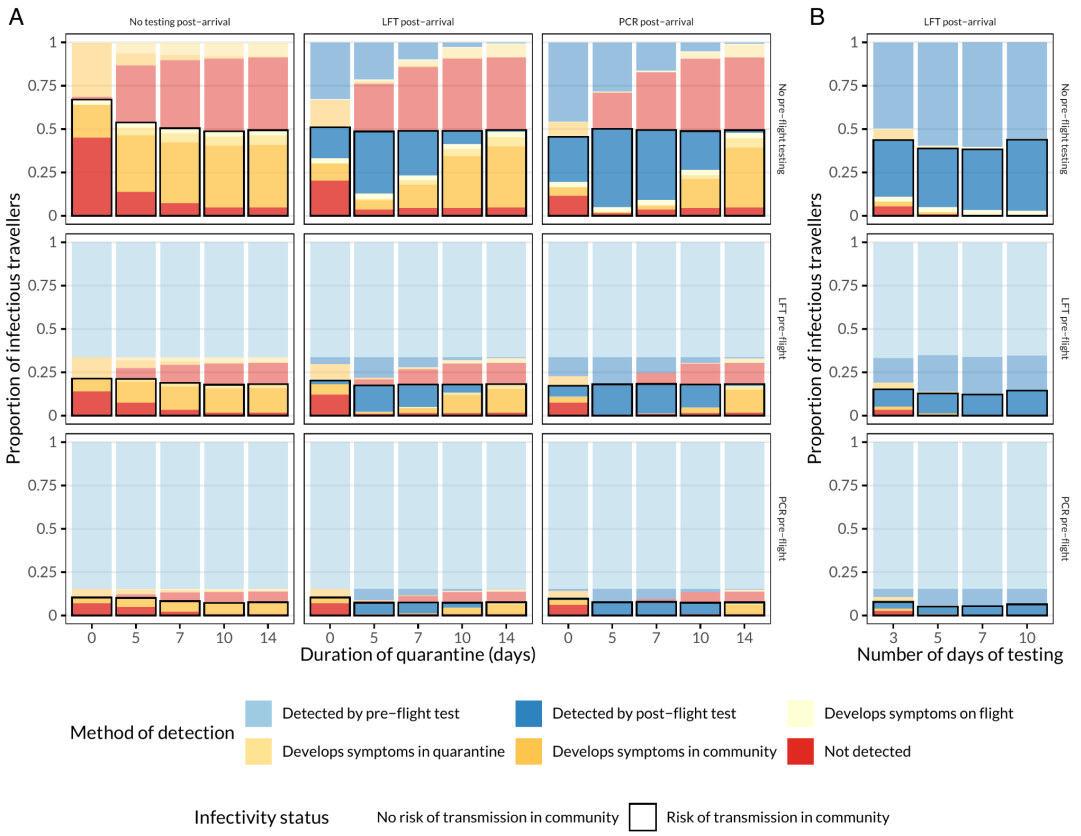


Figure 3: Mean proportion of intending travellers who would otherwise arrive infectious or become infectious detected at each stage of the quarantine and testing strategies (either: A) quarantine with no test, Lateral Flow test, or Polymerase Chain Reaction test or B) Daily Lateral Flow testing, and) assuming 28% adherence to quarantine guidance, 71% adherence to isolation guidance after the onset of symptoms and 86% adherence to isolation guidance after receipt of a positive test. Solid colours with black borders are those individuals who pose a risk of transmission in the community (i.e, still in the infectious period after leaving quarantine, self-isolation, or finishing the testing programme); semi-transparent colours pose no risk of transmission in the community.

In the baseline scenario of imperfect adherence (28% adherence to quarantine guidance, 71% adherence to isolation guidance after the onset of symptoms and 86% adherence to isolation guidance after receipt of a positive test), the most lenient travel restrictions (no quarantine and no pre-flight test) results in 67% (95% UI: 40%, 92%) of infectious or eventually infectious travellers entering the country undetected (Figure 3). This group is comprised of 7% (95% UI: 5%, 11%) of arrivals who develop symptoms in flight and do not self-isolate, 20% (95% UI: 7%, 38%) who develop symptoms on arrival and do not self-isolate, and 45% (95% UI: 20%, 66%) asymptomatic infections. With increasing duration of quarantine, those who become symptomatic will develop symptoms while in quarantine instead of in the community, and those who are released from quarantine are more likely to no longer be infectious. The addition of PCR or LFT testing at the conclusion of quarantine periods results in additional detection, allowing for their isolation and release when likely no longer infectious (Figure 3). After 5 days of quarantine with no pre-flight test, PCR testing at the end of quarantine results in 49% (95% UI: 31%, 70%) of infectious or eventually infectious individuals entering the community, using an an LFT test instead results in a similar proportion (51% (95% UI: 32%, 71%)). The marginal benefit of a post-quarantine test-to-release is reduced for longer quarantines, as individuals are more likely to develop symptoms before the test is conducted, or become less likely to test positive as viral shedding wanes.

Under daily testing scenarios, travellers are released into the community upon arrival and are tested every day with lateral flow tests. After 5 days of testing, the proportion of cases which go undetected by testing or by the development of symptoms is 7% (95% UI: 5%, 13%), decreasing to 0% after 10 days of testing. The reduction in the number of people self-isolating due to the onset of symptoms also decreases with a greater number of tests as a result of individuals receiving positive tests before symptom onset. However, imperfect adherence to self-isolation following a positive test or the onset of symptoms substantially decreases the programme's effectiveness, with 39% (95% UI: 18%, 55%) of infectious or eventually infectious arrivals posing a transmission risk in the community (Figure 3).

Sensitivity analysis (Figure S1) indicates that full adherence to quarantine and isolation guidelines substantially reduces the risk of individuals entering the community while infectious or incubating. The proportion of infectious arrivals decreases to 0% for a 14 day quarantine without a test and can be shortened with the same prevention of infectious arrivals achieved by the addition of a PCR test to release on Day 7 or an LFT on Day 10. A combination of pre-flight lateral flow or PCR tests (which may prevent 66% (95% UI: 48%, 86%) and 85% (95% UI: 73%, 96%) of infectious arrivals respectively) with a 7 or 5 day quarantine with full adherence with a PCR or lateral flow test to release, respectively, would also eliminate the risk of infectious arrivals (Figure S1).

Stratifying by whether the individual remains asymptomatic or first engages with the quarantine and testing symptoms while in a pre-symptomatic state indicates that longer quarantines ensure that asymptomatic infections exit quarantine no longer infectious (Figure S2). The effect of post-quarantine testing is to divert a substantial number of asymptomatic infections to self-isolation, where imperfect quarantine adherence results in increased transmission risk

(Figure 6). The effect of pre-flight tests is to more than halve the number of infectious arrivals who may cause onwards transmission. As post-flight testing becomes more sensitive to low viral loads (early in infection and asymptomatic cases) by moving from no test to LFT to PCR, a greater number of infectious travellers are diverted to self-isolation, peaking around day 5 for both LFT and PCR in both asymptomatic and ever-symptomatic infections. Earlier post-quarantine tests are likely to miss early stage infections and later tests allow symptoms to develop in ever-symptomatic cases. For daily testing, pre-flight testing picks up as many cases as for quarantine (as this is a measure in the country of departure). In the absence of pre-flight testing, 3 days of daily testing still allows some infectious asymptomatic cases to go undetected (15% (9%, 35%)), the risk of which drops to zero by 10 days of testing. As viral load increases prior to onset of symptoms, detectability of a pre-symptomatic infection with a daily LFT means the development of symptoms is rare and the individual may be diverted to self-isolation with an adherence level of 86%.

Transmission potential of arrivals

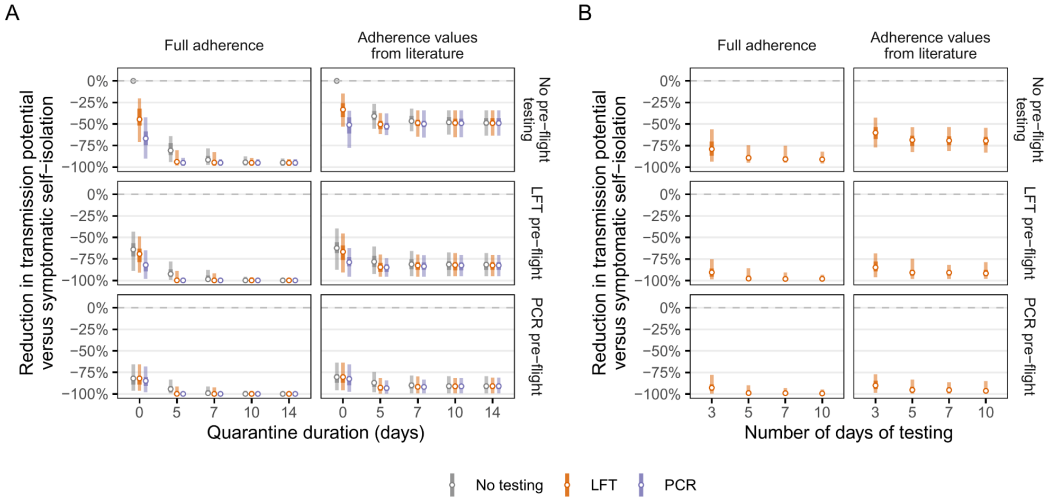


Figure 4: Change in transmission potential of infectious arrivals entering the community compared to symptomatic self-isolation only with full adherence (top row of plots) or adherence values from literature (28% of individuals adhering to quarantine and 86% adhering to post-positive test isolation, bottom row of plots), and with or without pre-flight tests. A) Quarantine of varying durations with or without testing with LFTs and PCR. B) Daily testing without quarantine with lateral flow tests, with self-isolation only upon a positive test result. Vertical lines represent 95% (outer) and 50% (inner) uncertainty intervals around medians (points). Note discrete x-axis values for quarantine duration and number of days of testing. Change in transmission potential without adjustment for symptomatic self-isolation shown in Figure S3.

We estimate that individuals isolating only upon the onset of symptoms after they arrive (assuming an imperfect adherence of 71%) would on its own reduce the transmission potential (TP) of arrivals by 45% (95% UI: 28%, 64%) (Figure S3). After adjusting for the assumption that symptomatic self-isolation is adhered to at this proportion in all scenarios, a pre-flight lateral

flow test would reduce transmission potential by an additional 62% (95% UI: 39%, 88%) (Figure 4) and a pre-flight PCR test would reduce transmission potential by an additional 80% (95% UI: 64%, 96%). Testing immediately after the flight with no quarantine (assuming no pre-flight testing) results in a smaller reduction in transmission potential to pre-flight testing (LFT: 33% (95% UI: 15%, 53%), PCR: 51% (95% UI: 35%, 77%) (Figure 4), due to assumed lower adherence to post-positive test self-isolation in the destination country compared to the complete elimination of transmission of a positive pre-flight test.

Requiring travellers to quarantine upon arrival averts additional transmission, as does requiring a test at the end of quarantine. A 14 day quarantine would reduce transmission potential by 49% (95% UI: 34%, 64%) compared to symptomatic self-isolation alone, with identical impact with or without a test (Figure 4). If more individuals are assumed to adhere to self-isolation following a positive test than they would to quarantine (in the absence of symptoms), shorter quarantines of 5 days with a test to release would reduce transmission potential to a similar or greater degree (LFT: 50% (95% UI: 37%, 62%), PCR: 53% (95% UI: 38%, 63%) than that of a 14 day quarantine (Figure 4).

Combining both a pre-flight test and a short quarantine (e.g 5 days) on arrival with a test to release would reduce the transmission potential of arrivals further (Figure 4). A pre-flight LFT and 5 days of quarantine with an LFT to release would reduce the transmission potential of would-be arrivals by 85% (95% UI: 70%, 96%); a pre-flight LFT with 5 days of quarantine with PCR to release would reduce transmission potential by 85% (95% UI: 74%, 96%); a pre-flight PCR with 5 days of quarantine with LFT to release would reduce transmission potential by 93% (95% UI: 81%, 100%); and a pre-flight PCR with 5 days of quarantine with PCR to release would reduce transmission potential by 93% (95% UI: 84%, 100%).

Alternatively, replacing the requirement to quarantine with daily rapid tests upon arrival may reduce transmission potential by 60% (95% UI: 43%, 77%) for 3 days of testing, 68% (95% UI: 54%, 82%) for 5 days of testing, 69% (95% UI: 53%, 81%) for 7 days of testing, and 69% (95% UI: 54%, 83%) for 10 days of testing, assuming adherence to self-isolation is 86%. Combining daily testing with pre-flight testing may further reduce transmission potential (pre-flight LFT plus 5 days of tests on arrival: 91% reduction (95% UI: 75%, 98%); pre-flight PCR plus 5 days of tests on arrival: 95% reduction (95% UI: 83%, 100%) (Figure 4)).

If, instead of the published values, adherence is assumed to be 100% for both quarantine and self-isolation (i.e, in a managed quarantine facility, with zero transmission during this period) then a 10 day quarantine without a test to release averts 94% (95% UI: 87%, 98%) of transmission, which rises to 95% (95% UI: 89%, 99%) with an LFT test to release and 95% (95% UI: 91%, 100%) with a PCR test to release. The remaining transmission potential may occur during the flight, and through undetected infections, and can be eliminated with either a pre-flight LFT or PCR test (Figure 4). No additional transmission is averted through a quarantine period longer than 14 days.

Delays between the taking of pre-flight tests and the time of flight departure may introduce additional transmission risk in the destination country as individuals may become exposed in the interim, leading to less sensitive but rapid tests averting more transmission if they can be conducted immediately prior to the flight (Figure S4). For example, a 3 day delay from PCR test to flight (as required by many countries) may reduce transmission potential by 41% (95% UI: 14%, 63%) whereas an immediate pre-flight LFT may reduce transmission potential by 64% (95% UI: 43%, 89%).

Number of infectious arrivals

The number of infectious arrivals to each country is a function of the prevalence in, and flight volumes from, all other countries and varies substantially across and within regions (Figure 5). Amongst the studied countries only Australia (AUS), China (CHN), Singapore (SGP), and Vietnam (VNM) are at very high risk (where, in the absence of any interventions aimed at restricting importation, infectious importations are more than 100% of domestic incidence), due to having extremely low incidence based on the available data.

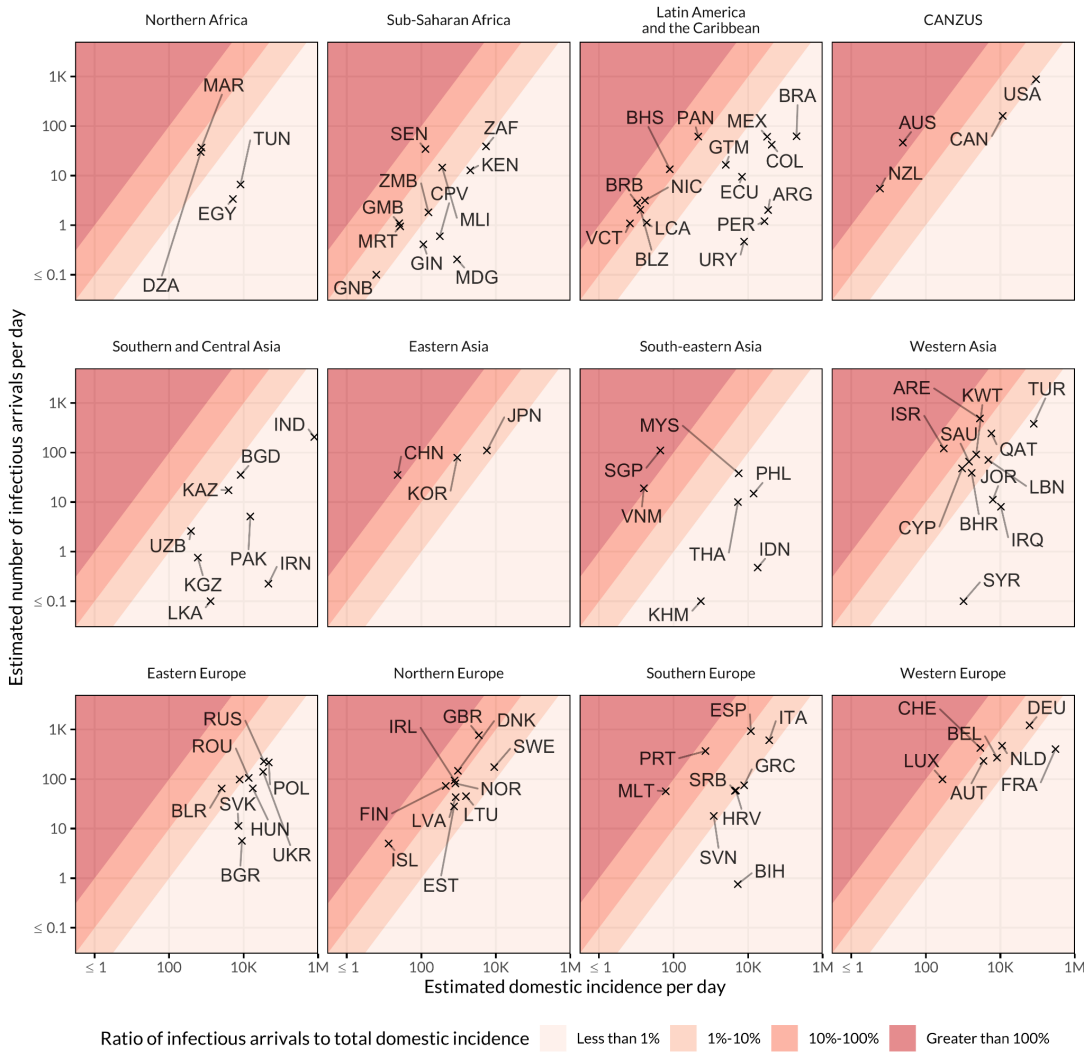


Figure 5: Estimated median relative risk rating of infectious imported cases as of April 2021. Relative risk ratings is represented as the ratio of infectious imported cases per day to domestic incidence in the destination country, as of 26 May 2021. Countries are grouped by UN region and subregion except for Northern America and Australia and New Zealand (CANZUS) and Southern Asia and Central Asia (Southern and Central Asia).

Given a current rate of importation of infections and domestic incidence, achieving a particular target relative risk rating (the ratio of infectious cases imported per day to daily domestic incidence) in a given country will require different effectiveness of interventions (Figure 5, Figure 6). For example, the introduction of daily tests for five days (with a pre-flight LFT) would reduce Luxembourg's risk rating from a median of 35% (95%: 16%, 179%) to a median risk rating of 6% (95%: 3%, 31%). In contrast, the introduction of this strategy in Singapore would reduce its risk rating only as low as 43% (95%: 7%, 153%) as its baseline risk rating is among the highest in the world (249%, 95%: 42%, 882%) due to a large number of arrivals and low domestic incidence. Conversely, the United States' high domestic incidence means the risk rating of importation with

no intervention strategy is 1% (95%: 0.6%, 3.2%) indicating that restrictions on travellers may not be an effective way to prevent onwards transmission, even if the introduction of daily testing would reduce the median risk rating from importation to 0.2%.

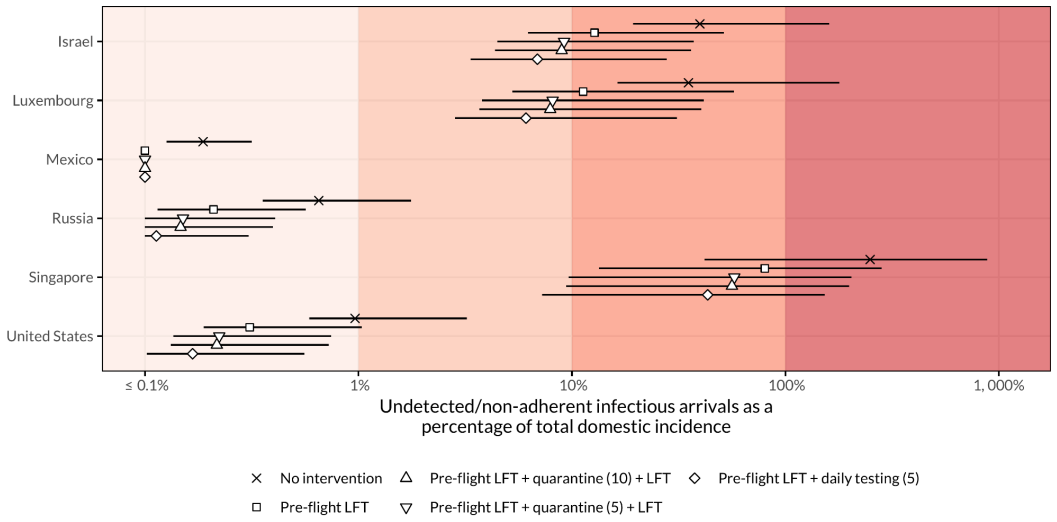


Figure 6: Effectiveness of four testing and/or quarantine strategies, compared to no intervention as of April 2021. Risk ratings are given as as the ratio of new infectious arrivals to domestic incidence, expressed as a percentage. Results are shown for six selected countries for the following strategies in increasing order of reduction of entries: no intervention; pre-flight LFT with no further quarantine or testing; pre-flight LFT followed by five days of quarantine with an LFT at exit; pre-flight LFT with ten days of quarantine and an LFT at exit; pre-flight LFT followed by daily LFT for five days. Points represent median risk ratings, with the horizontal line showing the 95% UI; where the median or endpoint of the UI is less than 0.1%, the value is shown as "≤0.1%". Plots for all included countries may be found in the Supplementary appendix (Figure S5).

Variants of concern

Importation of the B.1.1.7 variant (first identified in the United Kingdom) has varied over time with incidence of the variant in the UK and travel from the UK to other countries (Figure 7). Importation as a percentage of domestic incidence is therefore dependent on the epidemic at both ends of the travel route and the proportion of UK cases which are the variant of concern, and hence many different importation risk profiles, over time, may be observed (solid circles in Figure 7). We consider the implementation of the intervention we specify as a strategy for comparison, a pre-flight LFT, five days of quarantine and LFT at completion (assuming adherence with isolation and quarantine guidance from published literature). Assuming LFT and PCR do not exhibit variant-specific sensitivity, such an intervention would reduce the risk of importation of infected travellers by 88% (95% UI: 72%, 94%) (open circles in Figure 7) and the risk of importation of infectious travellers by 84% (64%, 95%). Here we present results for infected arrivals, whether infectious or not, for Israel, Luxembourg, Mexico, Russia, Singapore and the United States of America.

At one extreme, Singapore has a small domestic epidemic (on the order of tens of cases per day) during the time October 2020 to March 2021. Importation of non-B.1.1.7 peaks in November 2020, approximately 62 times that of the total domestic incidence (95% UI: 57-fold, 68-fold) and B.1.1.7 importation peaks a month later in December, at approximately 46 times the total domestic incidence (95% UI: 42-fold, 51-fold). In contrast, the United States has incidence of the order 10,000s-100,000s and importation from the UK of B.1.1.7 peaks at a risk rating of only 3% (95% UI: 2%, 3%) of total domestic incidence in December 2020 with non-B.1.1.7 declining steadily from a peak of 9% (95% UI: 5%, 12%) of domestic incidence in October 2020 to less than 0.1% (95% UI: 0%, <0.1%) by December 2020. Similar patterns to the USA are seen in Mexico and Russia, where incidence was in the tens of thousands and peaked in either December 2020 (Russia) or January 2021 (Mexico). Israel's risk rating for B.1.1.7 from the UK has been increasing since January 2021 as its estimated domestic epidemic peaked at that time (8218, 95%: 7933, 9071) and the B.1.1.7 makes up a larger proportion of exported cases from the UK and there is an increasing amount of air travel from the UK to Israel over this time.

A table providing the total domestic incidence and risk ratings of B.1.1.7 and non-B.1.1.7 importation for the countries in Figure 7 from October 2020 to March 2021 is provided in the Supplementary Appendix (Table S1).

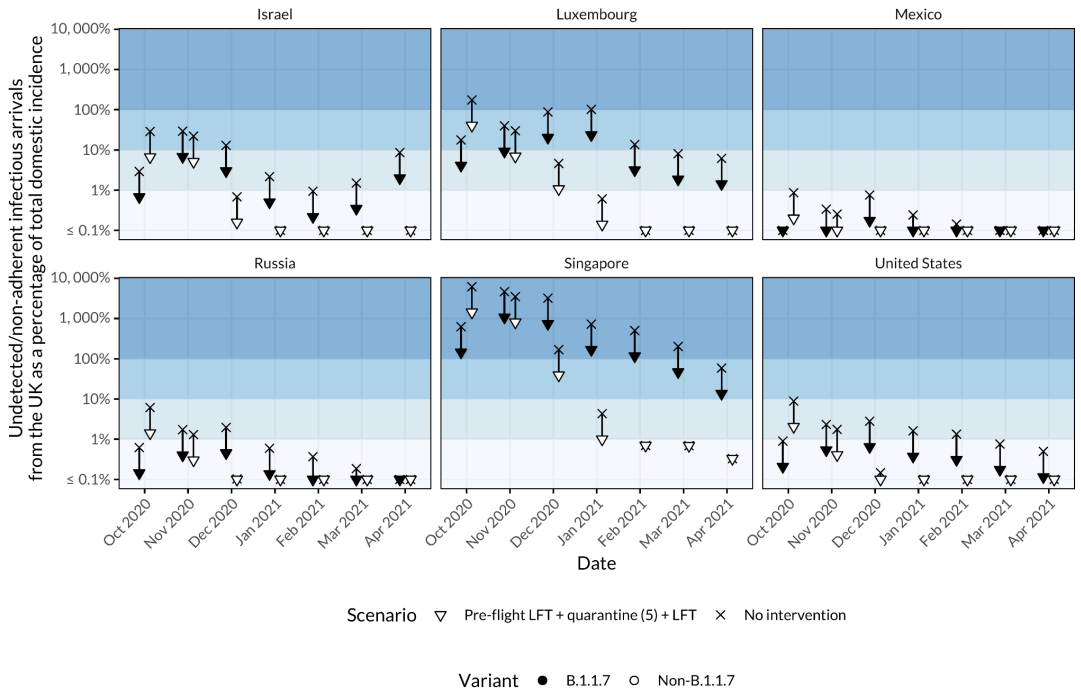


Figure 7: Median risk ratings of importation of the B.1.1.7 (diamonds) variant of concern and non-B.1.1.7 (circles) variants from the United Kingdom as a proportion of total domestic incidence. Filled points indicate baseline rates of importation, and open points represent the impact of the intervention scenario (pre-flight LFT, 5 day quarantine with LFT at exit). The y axis is cropped at 0.1% although some very low risk rating

months for some countries have both a baseline risk rating and reduced risk rating less than 0.1% (e.g. March 2021 in Mexico for both B.1.1.7 and non-B.1.1.7 with and without intervention).

Discussion

Here we estimate the risk of SARS-CoV-2 case importation to 99 countries, and evaluate possible strategies to reduce onward transmission from those imported cases through quarantine and/or testing. Interventions enacted at the origin such as pre-flight testing may prevent the majority of infectious arrivals (pre-flight LFT and PCR preventing 66% (95% UI: 48%, 86%) and 85% (95% UI: 73%, 96%) respectively). We find that a requirement of strict isolation upon symptom onset will avert a substantial volume of post-flight transmission (reduction in transmission potential: 45% (95% UI: 28%, 64%)). Furthermore, testing with LFTs or PCR after 5 days of quarantine (with release if negative) may match or exceed the effectiveness of the 14-day quarantine period in reducing transmission potential. Alternatively, daily LFTs upon arrival may avert a substantial amount of transmission while allowing for the avoidance of quarantine if negative. We find combined strategies involving both pre- and post-flight testing such as a pre-flight LFT combined with daily LFT tests for 5 days on arrival may prevent most infectious individuals from flying and avert transmission from those early in the incubation period who may go undetected by a pre-flight test (reduction in R: 91% (95% UI: 75%, 98%)).

We find that lateral flow tests may be a valuable tool to avert transmission from infected travellers, especially when used repeatedly over the course of 5 or 7 days. Their rapidity may also allow for their use immediately prior to boarding a flight, e.g. as at Stansted airport (19), whereas PCR tests would often require 24 hours to return results. There is evidence that transmission during a flight is possible (20) and that masks may be effective in reducing the risk of transmission (21). Immediate pre-flight rapid tests should be considered to reduce the in-flight transmission risk from currently infectious travellers in combination with the aforementioned measures. There has been concern over the sensitivity of LFTs when compared to the current gold standard PCR test, however they have been shown to detect culturable virus with 97% sensitivity (10), and those who are most likely to transmit to others with 83% sensitivity (22). In addition, while PCR tests are highly sensitive, their ability to detect residual non-viable RNA for several weeks following the infectious period may lead to the continued isolation and disrupted travel of individuals who are no longer infectious (23). Nonetheless, both PCR and LFT may fail to detect infections in the first days following exposure when viral loads are low (with PCR likely to detect infections earlier), leading to the lower estimated effectiveness of a single test either pre- or post-flight. However, despite high reported specificity of lateral flow tests (99.97% in the UK (24)) high volumes of testing will inevitably lead to false positives and, as such, the cost-effectiveness of confirmatory testing with a second lateral flow test or PCR, and potential non-independence thereof, should be assessed with a view to increasing the positive predictive value of testing (25). A further limitation of the reliance on culturability is that while a positive culture indicates sufficient whole virus to cause transmission, a negative culture may not necessarily imply an inability to infect. The relationship between Ct value, culturability and infectivity is key to characterising the ability of tests to detect infectious individuals and reliance on PCR is likely to detect and isolate some individuals well past the end of their infectious period.

Adherence to both quarantine or self-isolation after a positive test or symptom onset is a major component of the effectiveness of all post-flight intervention strategies explored and is one of the least-well characterised components of quarantine, testing and contact tracing systems. We use broadly indicative values for imperfect adherence to quarantine and self-isolation for contact-traced individuals due to a lack of data on rates of adherence of travellers in different countries over the course of the pandemic (26–29). In particular, there are likely cultural and social factors affecting adherence to quarantine and self-isolation (27) and we recognise that estimates of adherence from the UK and Norway may not be transferable to other countries. There is evidence that the rate of adherence to the 14-day quarantine in the absence of symptoms is low, at least in the UK where those self-isolating still report 3.85 (SD: 4.67) non-essential outside trips within the last week (26). However, adherence to self-isolation following a positive test is reportedly higher (86% (12)), although may be biased upwards as a result of this being a requirement under UK law. A recent ONS survey in the UK found that 17% of individuals reported non-adherence to self-isolation guidelines, namely leaving the home (83% of non-adherents) or having visitors for non-permitted reasons. 80% of individuals self-isolating in a household shared with others were unable to fully self-isolate (14) which poses a challenge where poor household isolation and potential low adherence to guidelines for household contacts may result in community transmission linked to an infectious traveller (30). Those who left the home chiefly did so to obtain essential supplies (32%) or to attend work or university (31%) and 30% of respondents who had tested positive either misunderstood or were unaware of the self-isolation requirements, indicating a need for targeted financial and social support, clearer guidance on how to self-isolate, e.g. staying in one room, wearing a mask in common areas (24), and strategies to reduce the risk of transmission under shorter quarantine periods that are more manageable for individuals (31).

There may be a trade-off in the effectiveness of quarantine between its duration and adherence in the population, as shorter quarantines may be easier to adhere to. Managed isolation of travellers in designated facilities such as hotels with regular visits from public health workers, as employed in East Asia and Oceania (32), may minimise possible transmission due to non-adherent persons. This strategy may be considered for countries in which the ratio of possible imported cases to domestic incidence is high (e.g. imported infections may make up the majority of new cases) and where there is a desire to exclude all variants of concern (in which case the threshold for action may be lower). Requiring managed quarantine in designated facilities may also prevent outbreaks within the household of the returning traveller, which are liable to spread further unless the entire household is required to quarantine.

Previous work by Russell and colleagues (3) suggests that an individual country's risk from imported SARS-CoV-2 infections should be considered relative to their domestic incidence, with the required stringency of interventions being proportional to that risk rating. While this principle is still broadly applicable, the emergence of novel variants such as those recently detected in the UK (33,34), South Africa (35), Brazil (36) and India (37) with the potential for greater transmissibility, mortality, and potential for immune escape necessitate the stratification of importation risk and quantifying not just the number of arrivals who may spread the variant,

but how many additional infections are likely to occur. In response, many countries have since implemented more stringent travel restrictions to prevent entry of variants. While we estimate that managed quarantine (with the assumption of complete self-isolation) may reduce the modelled risk to zero, real-world assessment of this policy found outbreaks may still occur (38), which indicates that even strict travel restrictions may be limited to the delay, but not prevention, of the importation of variants (39). If a given variant is already present, local interventions such as contact tracing (2) will be required to limit internal spread. For example, variants such as B.1.1.7 have been detected in many other countries outside of the UK and quickly became the dominant circulating strain in Europe and the USA (40). Testing of incoming travellers may be valuable as a surveillance tool to monitor the incidence of importation of variants; as LFTs detect only the nucleocapsid of SARS-CoV-2, positive lateral-flow tests should be followed up with PCR to monitor for S-gene target failure (for B.1.1.7) or to carry out further genomic analyses. Another factor is the current level of restrictions or population immunity (through infection or vaccination) in the destination country (3,41); imported cases arriving into an $R < 1$ environment will be much less likely to seed new local epidemics than in a $R > 1$ environment.

A limitation of this work, in common with other studies relying on infection fatality ratios to estimate the level of under-ascertainment of cases or infections globally (42), is that under-ascertainment and under-reporting of COVID-19 deaths is also known to be occurring at significant levels in numerous countries (43). Many countries' estimates of the prevalence and incidence of COVID-19 are known, or highly suspected, to be biased downwards, due to death under-ascertainment. This means that any country that is suspected to be underestimating mortality rates of COVID-19, is likely to also underestimate the prevalence and incidence of infection, if such estimates are arrived at using modelling frameworks fit to mortality data — the method used here and the method most global modelling efforts use. Improving global estimates using serological and other surveillance data is ongoing but extremely challenging, given data availability issues and the differences in data quality between different countries. Tools such as Serotracker (44), OpenSky (15) and existing excess deaths databases (45) could provide the tools to arrive at global estimates of death under-ascertainment; but are outside the current scope of this study. The routine testing of travellers, as explored in this study, would allow for the estimation of prevalence in other countries after adjustment for factors such as travel volume.

For clarity and brevity, we have presented the risk ratings for a given country for all incoming travel, and not from specific individual countries. Some countries have chosen to impose restrictions on flights from high-risk origin countries, and relax restrictions on flights from countries considered low-risk in "travel corridors" or "air bridges" (46). Such a strategy is problematic due to the potential for multi-leg flights and mixing with others from high-risk countries in tourist areas of an intermediate country. To allow for country-specific estimates to be calculated, we present relative measures of reduction in infectious entries and their transmission potential by each strategy so that if prevalence and travel volumes from a specific country are known, absolute risk may be simply calculated as the product of prevalence, travel volume and relative reduction. It should be noted that our absolute risk estimates are based on

prevalence and travel volume as of April 2021, and that assessing risk in terms of infectious entries may underestimate the effectiveness of quarantine and testing programmes.

In this report we have shown that existing strategies to reduce SARS-CoV-2 importation such as a 14 day quarantine period for arrivals are effective at reducing transmission risk, and that the duration of quarantine may be reduced to 10 days without, and 5 days with, a PCR or rapid lateral flow antigen test to exit quarantine if negative. Additionally, 5 days of lateral flow tests taken daily could allow for the removal of mandatory quarantine, even under less than perfect adherence. Requiring pre-flight tests as close to departure as possible (i.e, an advantage of rapid tests) may prevent the majority of transmission from infectious would-be travellers. Our findings align with the findings of several other modelling studies for reducing the duration of quarantine in air travel and contact tracing such as Wells et al. (47) and Ashcroft et al. (48). All strategies are however highly dependent on the rate of adherence to quarantine and self-isolation, and improving these rates through financial and social support, and clarity of guidance, will be key to the success of such strategies (27). Managed quarantine on arrival can help minimise the risk of importation of variants of concern from high risk destinations. The risk of infectious arrivals causing ongoing transmission in a given country should be considered relative to domestic incidence (and domestic R), with restrictions on travel having a higher relative impact in countries where the expected number of infectious arrivals exceeds domestic incidence, where a large proportion of the population remains susceptible, and where there is a desire to exclude the importation of variants of concern. Travel restrictions carry significant economic, political, and social costs which must be weighed against the contribution of imported cases to SARS-CoV-2 incidence.

Acknowledgements

The following funding sources are acknowledged as providing funding for the named authors. This research was partly funded by the Bill & Melinda Gates Foundation (OPP1139859: BJQ). This project has received funding from the European Union's Horizon 2020 research and innovation programme - project EpiPose (101003688: WJE). This research was partly funded by the National Institute for Health Research (NIHR) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care (16/136/46: BJQ; 16/137/109: BJQ; PR-OD-1017-20002: WJE). UK MRC (MC_PC_19065 - Covid 19: Understanding the dynamics and drivers of the COVID-19 epidemic using real-time outbreak analytics: SC, WJE). Wellcome Trust (206250/Z/17/Z: TWR; 208812/Z/17/Z: SC, SFlasche; WT098049AIA SJDN). King's Together Rapid COVID-19 Call awards (SJDN, RPG). Huo Family Foundation Award (SP supported by funding granted to SJDN) This publication has been supported by the German Federal Ministry of Health (BMG) COVID-19 Research and development funding to WHO.

The following funding sources are acknowledged as providing funding for the working group authors. This research was partly funded by the Bill & Melinda Gates Foundation (INV-001754: MQ; INV-003174: KP, MJ, YL; INV-016832: SRP; NTD Modelling Consortium OPP1184344: CABP, GFM; OPP1191821: KO'R). BMGF (INV-016832; OPP1157270: KA). CADDE MR/S0195/1 & FAPESP

18/14389-0 (PM). EDCTP2 (RIA2020EF-2983-CSIGN: HPG). ERC Starting Grant (#757699: MQ). ERC (SG 757688: CJVA, KEA). This project has received funding from the European Union's Horizon 2020 research and innovation programme - project EpiPose (101003688: AG, KLM, KP, MJ, RCB, YL). FCDO/Wellcome Trust (Epidemic Preparedness Coronavirus research programme 221303/Z/20/Z: CABP). This research was partly funded by the Global Challenges Research Fund (GCRF) project 'RECAP' managed through RCUK and ESRC (ES/P010873/1: CIJ). HDR UK (MR/S003975/1: RME). HPRU (This research was partly funded by the National Institute for Health Research (NIHR) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care200908: NIB). MRC (MR/N013638/1: EF; MR/V027956/1: WW). Nakajima Foundation (AE). NIHR (16/137/109: FYS, MJ, YL; 1R01AI141534-01A1: DH; NIHR200908: AJK, LACC, RME; NIHR200929: CVM, FGS, MJ, NGD; PR-OD-1017-20002: AR). Royal Society (Dorothy Hodgkin Fellowship: RL). Singapore Ministry of Health (RP). UK DHSC/UK Aid/NIHR (PR-OD-1017-20001: HPG). UK MRC (MC_PC_19065 - Covid 19: Understanding the dynamics and drivers of the COVID-19 epidemic using real-time outbreak analytics: NGD, RME, YL; MR/P014658/1: GMK). UKRI (MR/V028456/1: YJ). Wellcome Trust (206250/Z/17/Z: AJK; 206471/Z/17/Z: OJB; 210758/Z/18/Z: JDM, JH, KS, SA, SFunk, SRM; 221303/Z/20/Z: MK). No funding (DCT, SH).

Data sharing

Code is available at https://github.com/cmmid/covid_quar_test_import_risk for the analysis conducted within this article.

References

1. Burns J, Movsisyan A, Stratil JM, Coenen M, Emmert-Fees KM, Geffert K, et al. Travel-related control measures to contain the COVID-19 pandemic: a rapid review. Cochrane Public Health Group, editor. Cochrane Database Syst Rev [Internet]. 2020 Sep 16 [cited 2020 Dec 21]; Available from: http://doi.wiley.com/10.1002/14651858.CD013717
2. Quilty BJ, Clifford S, Hellewell J, Russell TW, Kucharski AJ, CMMID COVID-19 Working Group, et al. Quarantine and testing strategies in contact tracing for SARS-CoV-2: a modelling study. Lancet Public Health. 2021 Jan 20;
3. Russell TW, Wu JT, Clifford S, Edmunds WJ, Kucharski AJ, Jit M. Effect of internationally imported cases on internal spread of COVID-19: a mathematical modelling study. Lancet Public Health. 2020 Dec;S2468266720302632.
4. Clifford S, Quilty, Billy J, Russell TW, Liu Y, Chan YWD, Pearson CAB, et al. Strategies to reduce the risk of SARS-CoV-2 re-introduction from international travellers: a modelling study. Eurosurveillance. Under Review;
5. Kissler SM, Fauver JR, Mack C, Olesen SW, Tai C, Shiue KY, et al. SARS-CoV-2 viral dynamics in acute infections. medRxiv. 2020 Dec 1;2020.10.21.20217042.
6. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. Lancet Microbe. 2020 Nov;S2666524720301725.
7. McAloon C, Collins Á, Hunt K, Barber A, Byrne AW, Butler F, et al. Incubation period of COVID-19: a rapid systematic review and meta-analysis of observational research. BMJ Open.

2020 Aug;10(8):e039652.
8. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. PLOS Med. 2020 Sep 22;17(9):e1003346.
9. Jefferson T, Spencer EA, Brassey J, Heneghan C. Viral cultures for COVID-19 infectious potential assessment - a systematic review. Clin Infect Dis Off Publ Infect Dis Soc Am. 2020 Dec 3;
10. Pickering S, Batra R, Snell LB, Merrick B, Nebbia G, Douthwaite S, et al. Comparative performance of SARS CoV-2 lateral flow antigen tests demonstrates their utility for high sensitivity detection of infectious virus in clinical specimens. medRxiv. 2021 Mar 2;2021.02.27.21252427.
11. Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. Proc Natl Acad Sci. 2004 Apr 20;101(16):6146–51.
12. Coronavirus and self-isolation after testing positive in England: 1 February to 13 February 2021 [Internet]. GOV.UK. [cited 2021 Apr 9]. Available from: https://www.gov.uk/government/statistics/coronavirus-and-self-isolation-after-testing-positive-in-england-1-february-to-13-february-2021
13. Steens A, Blasio BF de, Veneti L, Gimma A, Edmunds WJ, Zandvoort KV, et al. Poor self-reported adherence to COVID-19-related quarantine/isolation requests, Norway, April to July 2020. Eurosurveillance. 2020 Sep 17;25(37):2001607.
14. Office for National Statistics. Coronavirus and self-isolation after testing positive in England [Internet]. 2021 [cited 2021 Apr 15]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandwellbeing/bulletins/coronavirusandselfisolationaftertestingpositiveinengland/8to13march2021
15. Schafer M, Strohmeier M, Lenders V, Martinovic I, Wilhelm M. Bringing up OpenSky: A large-scale ADS-B sensor network for research. In: IPSN-14 Proceedings of the 13th International Symposium on Information Processing in Sensor Networks [Internet]. Berlin, Germany: IEEE; 2014 [cited 2020 Dec 29]. p. 83–94. Available from: http://ieeexplore.ieee.org/document/6846743/
16. OAG. Coronavirus [Internet]. OAG Aviation Worldwide Ltd.; [cited 2020 Dec 18]. Available from: https://www.oag.com/coronavirus-airline-schedules-data
17. Strohmeier M, Olive X, Lübbe J, Schäfer M, Lenders V. Crowdsourced air traffic data from the OpenSky Network 2019–2020. Earth Syst Sci Data. 2021 Feb 11;13(2):357–66.
18. R: The R Project for Statistical Computing [Internet]. [cited 2021 Apr 16]. Available from: https://www.r-project.org/
19. London Stansted Airport. Pre-departure COVID-19 testing [Internet]. London Stansted Airport; 2021 [cited 2021 May 21]. Available from: https://www.stanstedairport.com/coronavirus/departure-testing/
20. Speake H, Phillips A, Chong T, Sikazwe C, Levy A, Lang J, et al. Flight-Associated Transmission of Severe Acute Respiratory Syndrome Coronavirus 2 Corroborated by Whole-Genome Sequencing - Volume 26, Number 12—December 2020 - Emerging Infectious Diseases journal - CDC. [cited 2021 May 5]; Available from: https://wwwnc.cdc.gov/eid/article/26/12/20-3910_article
21. Nir-Paz R, Grotto I, Strolov I, Salmon A, Mandelboim M, Mendelson E, et al. Absence of in-flight transmission of SARS-CoV-2 likely due to use of face masks on board. J Travel Med [Internet]. 2020 Dec 1 [cited 2021 May 5];27(taaa117). Available from: https://doi.org/10.1093/jtm/taaa117
22. Lee LY, Rozmanowski S, Pang M, Charlett A, Anderson C, Hughes GJ, et al. An observational study of SARS-CoV-2 infectivity by viral load and demographic factors and the utility lateral flow devices to prevent transmission. 2021; Available from:

http://modmedmicro.nsms.ox.ac.uk/wp-content/uploads/2021/01/infectivity_manuscript_20210119_merged.pdf
23. Hellewell J, Russell TW, Matthews R, Severn A, Adam S, Enfield L, et al. Estimating the effectiveness of routine asymptomatic PCR testing at different frequencies for the detection of SARS-CoV-2 infections. BMC Med. 2021 Apr 27;19(1):106.
24. Sebastian Funk, Stefan Flasche. LFD mass testing in English schools - additional evidence of high test specificity [Internet]. CMMID Repository. 2021 [cited 2021 Mar 10]. Available from: https://cmmid.github.io/topics/covid19/mass-testing-schools.html
25. Confirmatory testing with a second lateral flow test may mitigate false positives at low levels of SARS-CoV-2 prevalence in English schools [Internet]. CMMID Repository. 2021 [cited 2021 Apr 16]. Available from: https://cmmid.github.io/topics/covid19/lft_confirm_testing_schools.html
26. Smith LE, Amlôt R, Lambert H, Oliver I, Robin C, Yardley L, et al. Factors associated with adherence to self-isolation and lockdown measures in the UK; a cross-sectional survey. Public Health. 2020 Sep 6;187:41–52.
27. Webster RK, Brooks SK, Smith LE, Woodland L, Wessely S, Rubin GJ. How to improve adherence with quarantine: rapid review of the evidence. Public Health. 2020 May;182:163–9.
28. Smith LE, Potts HWW, Amlot R, Fear NT, Michie S, Rubin J. Adherence to the test, trace and isolate system: results from a time series of 21 nationally representative surveys in the UK (the COVID-19 Rapid Survey of Adherence to Interventions and Responses [CORSAIR] study) [Internet]. Public and Global Health; 2020 Sep [cited 2020 Sep 30]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.09.15.20191957
29. Carlucci L, D'Ambrosio I, Balsamo M. Demographic and Attitudinal Factors of Adherence to Quarantine Guidelines During COVID-19: The Italian Model. Front Psychol [Internet]. 2020 [cited 2020 Dec 29];11. Available from: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.559288/full
30. Department of Health and Social Care. Quarantine and testing if you've been in an amber list country [Internet]. 2021 [cited 2021 May 17]. Available from: https://www.gov.uk/guidance/how-to-quarantine-when-you-arrive-in-england#rules-for-the-people-you-stay-with
31. Reynolds DL, Garay JR, Deamond SL, Moran MK, Gold W, Styra R. Understanding, compliance and psychological impact of the SARS quarantine experience. Epidemiol Infect. 2008 Jul;136(7):997–1007.
32. Han E, Tan MMJ, Turk E, Sridhar D, Leung GM, Shibuya K, et al. Lessons learnt from easing COVID-19 restrictions: an analysis of countries and regions in Asia Pacific and Europe. The Lancet. 2020 Nov 7;396(10261):1525–34.
33. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021 Mar 3;
34. Davies NG, Jarvis CI, Edmunds WJ, Jewell NP, Diaz-Ordaz K, Keogh RH. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. Nature. 2021 Mar 15;1–5.
35. World Health Organization. Statement of the WHO Working Group on COVID-19 Animal Models (WHO-COM) about the UK and South African SARS-CoV-2 new variants. World Health Organization; 2020 Dec.
36. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil | Science [Internet]. [cited 2021 Apr 14]. Available from: https://science.sciencemag.org/content/early/2021/04/13/science.abh2644
37. Public Health England. SARS-CoV-2 variants of concern and variants under investigation [Internet]. 2021 Jul [cited 2021 May 13] p. 39. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/984274/Variants_of_Concern_VOC_Technical_Briefing_10_England.pdf

38. Grout L, Katar A, Ouakrim DA, Summers JA, Kvalsvig A, Baker MG, et al. Estimating the Failure Risk of Quarantine Systems for Preventing COVID-19 Outbreaks in Australia and New Zealand. medRxiv. 2021 Apr 30;2021.02.17.21251946.
39. Clifford S, Pearson CAB, Klepac P, Van Zandvoort K, Quilty BJ, CMMID COVID-19 working group, et al. Effectiveness of interventions targeting air travellers for delaying local outbreaks of SARS-CoV-2. J Travel Med [Internet]. 2020 Aug 20 [cited 2021 Mar 17];27(taaa068). Available from: https://doi.org/10.1093/jtm/taaa068
40. CoVariants [Internet]. [cited 2021 Apr 14]. Available from: https://covariants.org/
41. Quilty BJ, Diamond C, Liu Y, Gibbs H, Russell TW, Jarvis CI, et al. The effect of travel restrictions on the geographical spread of COVID-19 between large cities in China: a modelling study. BMC Med. 2020 Aug 19;18(1):259.
42. Russell TW, Golding N, Hellewell J, Abbott S, Wright L, Pearson CAB, et al. Reconstructing the early global dynamics of under-ascertained COVID-19 cases and infections. BMC Med. 2020 Oct 22;18(1):332.
43. Watson OJ, Alhaffar M, Mehchy Z, Whittaker C, Akil Z, Brazeau NF, et al. Leveraging community mortality indicators to infer COVID-19 mortality and transmission dynamics in Damascus, Syria. Nat Commun. 2021 Apr 22;12(1):2394.
44. Arora RK, Joseph A, Van Wyk J, Rocco S, Atmaja A, May E, et al. SeroTracker: a global SARS-CoV-2 seroprevalence dashboard. Lancet Infect Dis. 2021 Apr;21(4):e75–6.
45. Karlinksy A, Kobak D. The World Mortality Dataset: Tracking excess mortality across countries during the COVID-19 pandemic. medRxiv [Internet]. [cited 2021 Apr 30]; Available from: https://www.medrxiv.org/content/10.1101/2021.01.27.21250604v2
46. UK Government. Coronavirus (COVID-19): travel corridors [Internet]. GOV.UK. [cited 2020 Dec 29]. Available from: https://www.gov.uk/guidance/coronavirus-covid-19-travel-corridors
47. Wells CR, Townsend JP, Pandey A, Moghadas SM, Krieger G, Singer B, et al. Optimal COVID-19 quarantine and testing strategies. Nat Commun. 2021 Jan 7;12(1):356.
48. Ashcroft P, Lehtinen S, Angst DC, Low N, Bonhoeffer S. Quantifying the impact of quarantine duration on COVID-19 transmission. eLife. 2021 Feb 5;10.
49. Linton NM, Kobayashi T, Yang Y, Hayashi K, Akhmetzhanov AR, Jung S mok, et al. Incubation Period and Other Epidemiological Characteristics of 2019 Novel Coronavirus Infections with Right Truncation: A Statistical Analysis of Publicly Available Case Data. J Clin Med. 2020 Feb;9(2):538.
50. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med. 2020 May;26(5):672–5.
51. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis. 2020 Jun;20(6):669–77.

Supplementary appendix

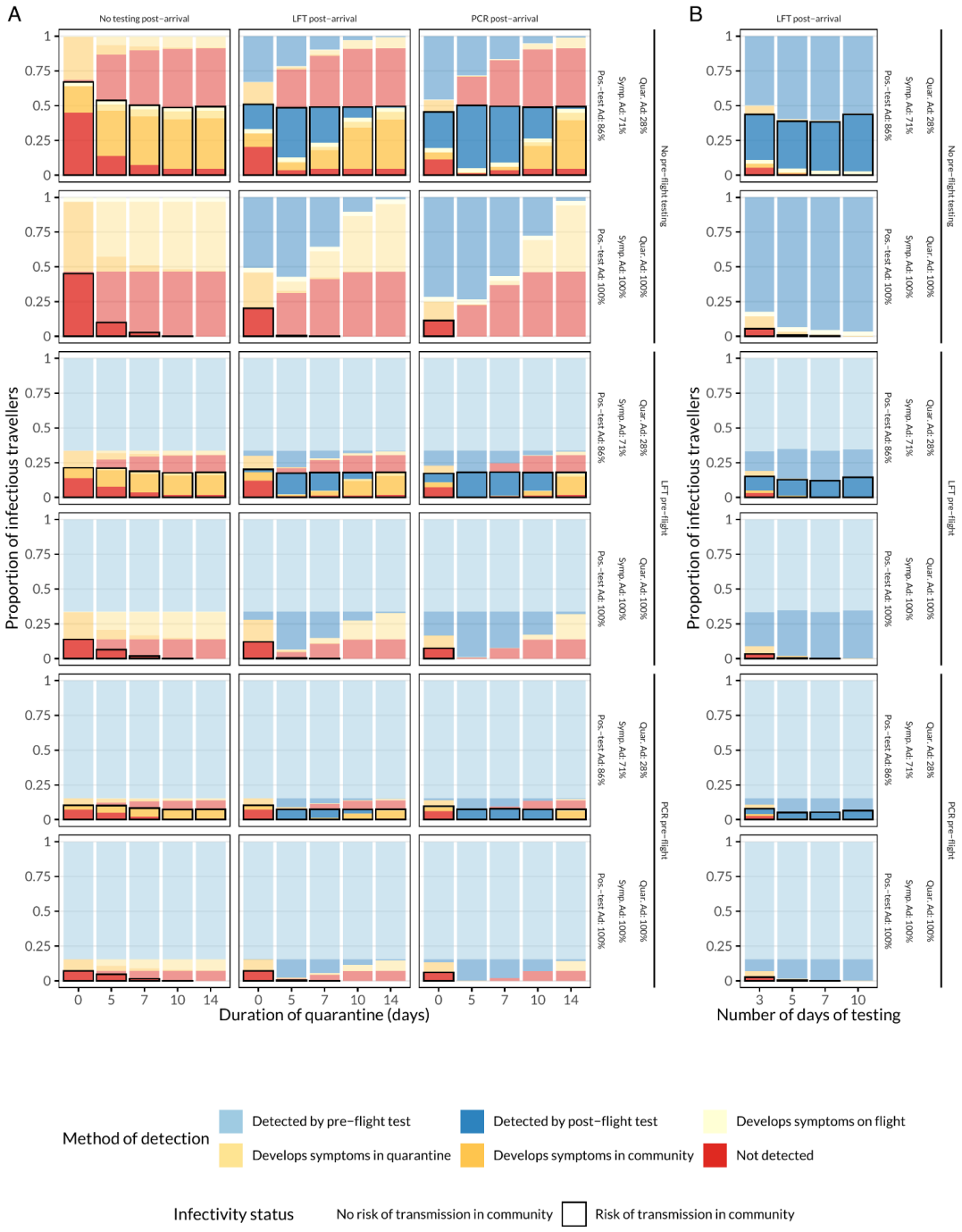


Figure S1: Mean proportion of intending travellers detected at each stage of the quarantine and testing strategies (columns corresponding to either A) quarantine with either no test, Lateral Flow test (LFT), or Polymerase Chain Reaction (PCR) test or B) daily testing). Rows in each plot correspond to either no pre-flight testing, or pre-flight testing with LFT or PCR and either perfect adherence to quarantine and self-isolation guidance, or values derived from literature.

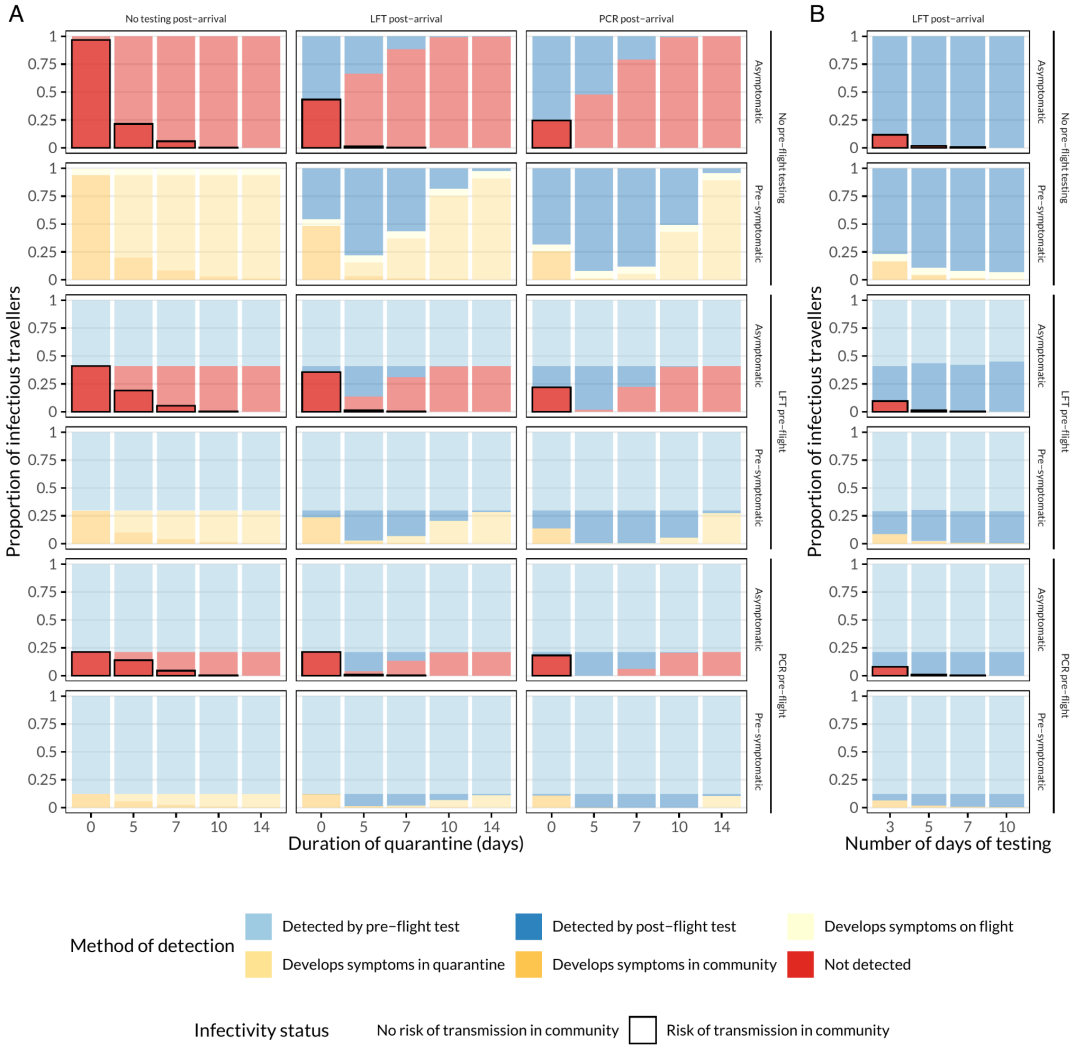


Figure S2: Mean proportion of intending infectious travellers detected at each stage of the quarantine and testing strategies, stratified by whether or not individual is ever symptomatic or always asymptomatic (columns corresponding to either A) quarantine with either no test, Lateral Flow test (LFT), or Polymerase Chain Reaction (PCR) test or B) daily testing). Rows in each plot correspond to either no pre-flight testing, or pre-flight testing with LFT or PCR and either perfect adherence to quarantine and self-isolation guidance, or values derived from literature.

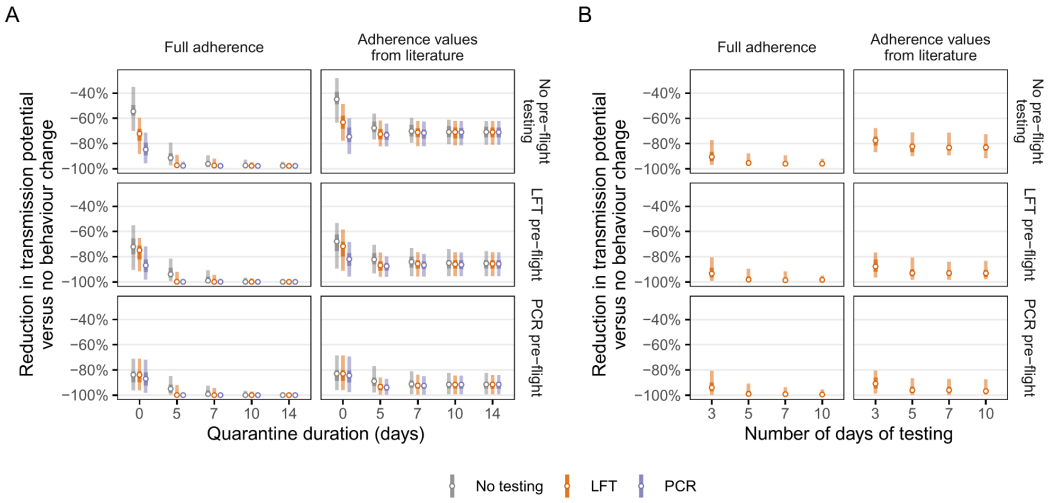


Figure S3: Change in transmission potential of infectious arrivals entering the community, including the effect of symptomatic self-isolation. Self-isolation only with full adherence (top row of plots) or adherence values from literature (28% of individuals adhering to quarantine, 71% of individuals adhering to post-symptom onset self-isolation, and 86% adhering to post-positive test isolation, bottom row of plots), and with or without pre-flight tests. A) Quarantine of varying durations with or without testing with LFTs and PCR. B) Daily testing without quarantine with lateral-flow tests, with self-isolation only upon a positive test result. Vertical lines represent 95% (outer) and 50% (inner) uncertainty intervals around medians (points). Note discrete x-axis values for quarantine duration and number of days of testing.

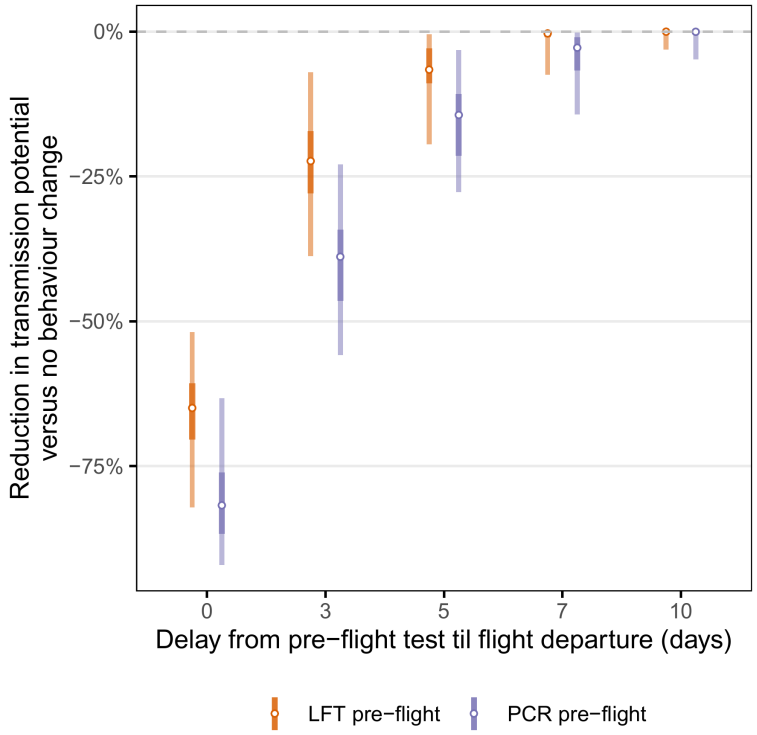
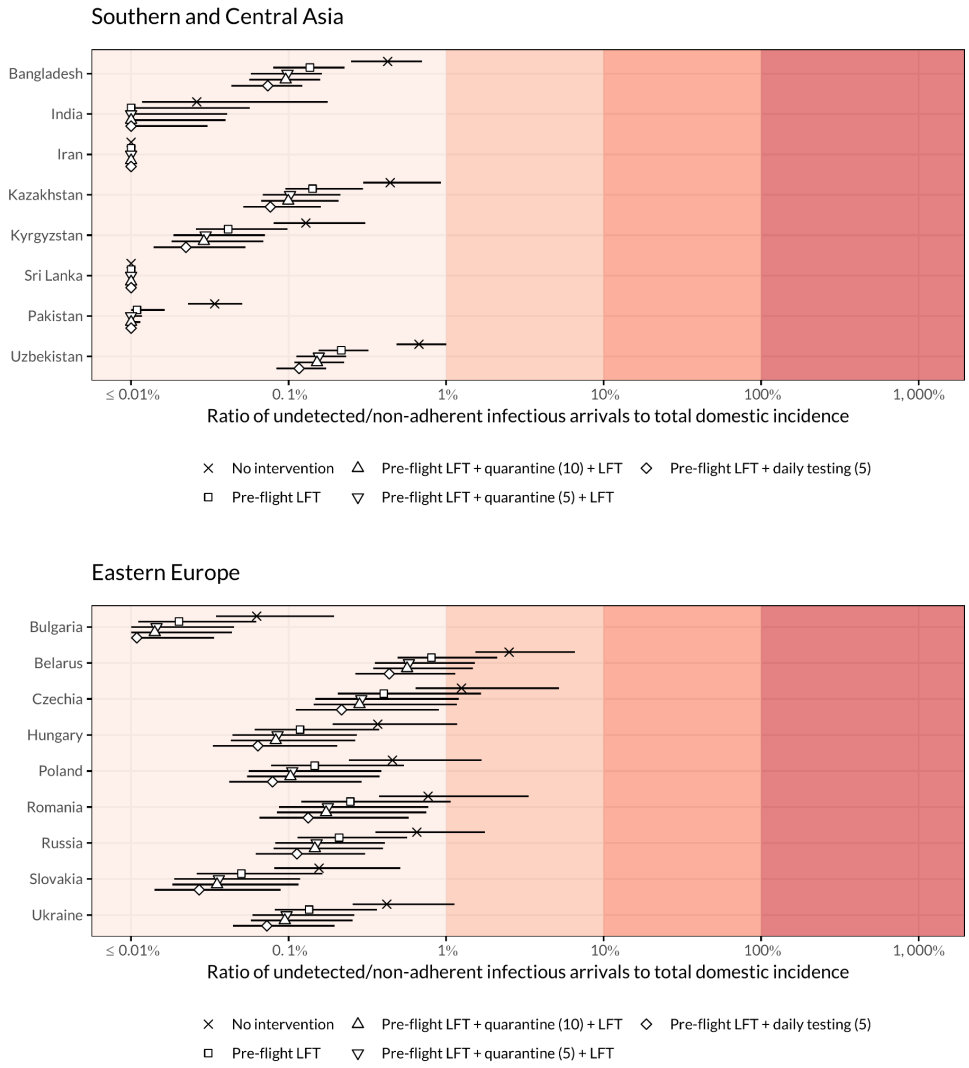
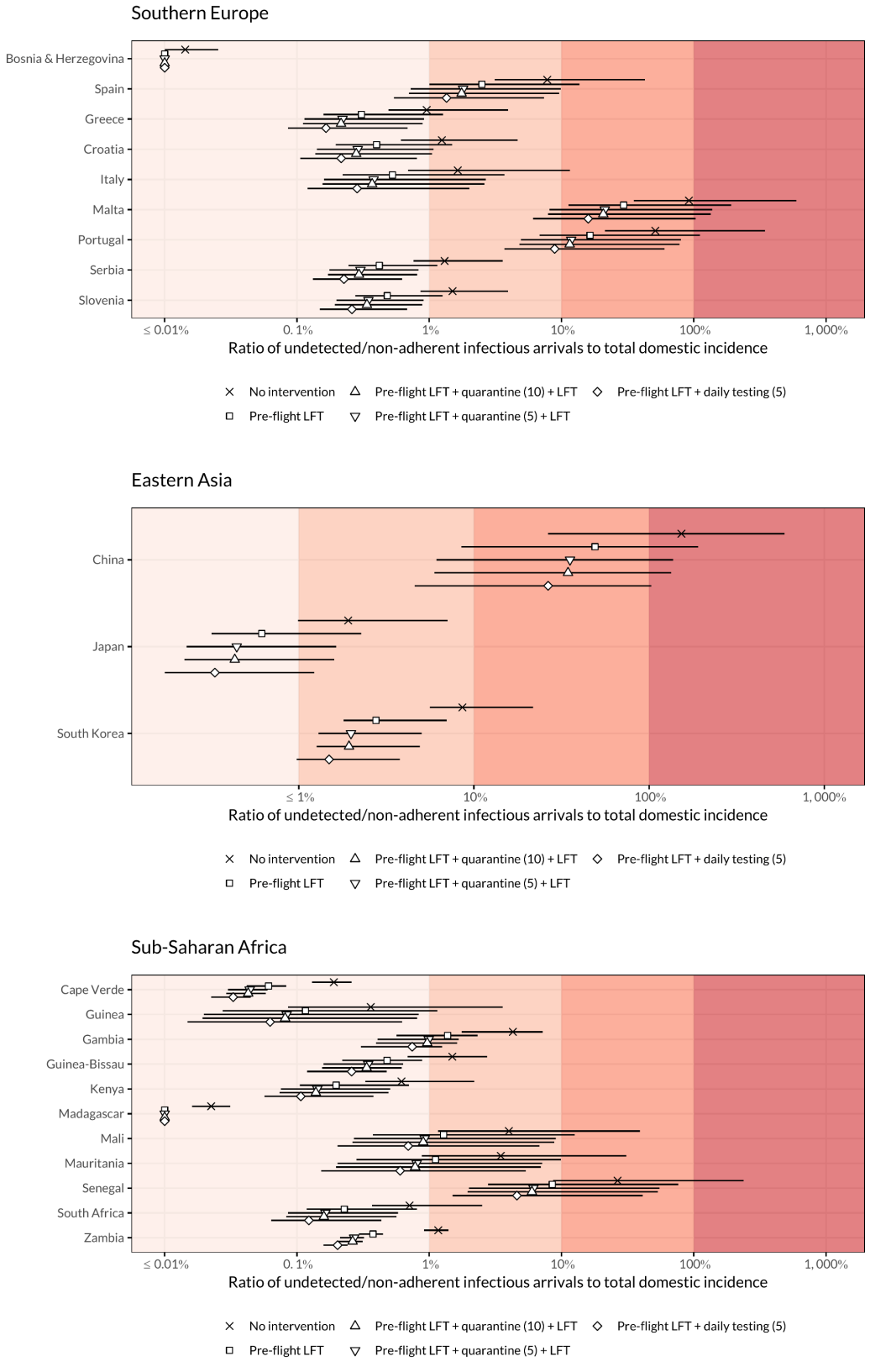
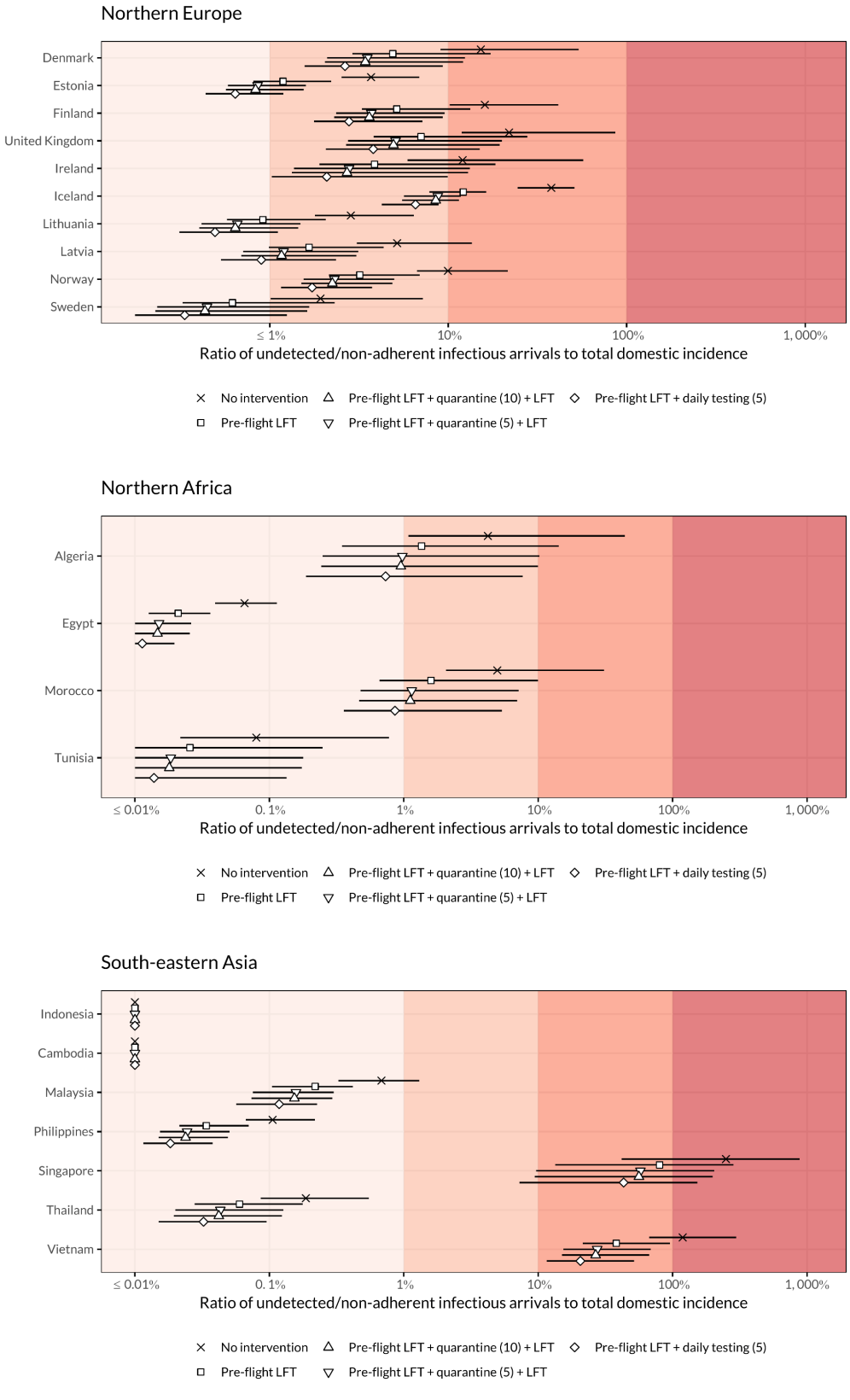
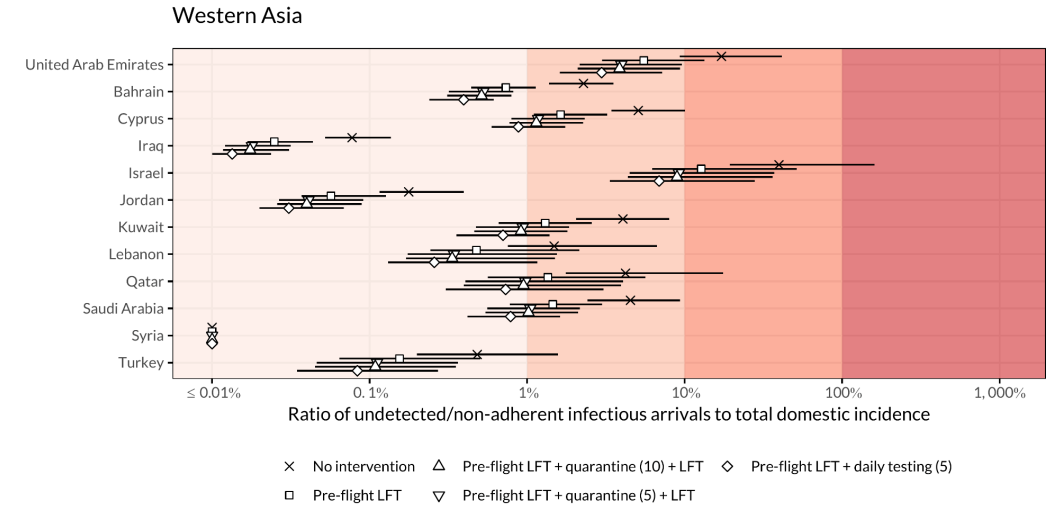


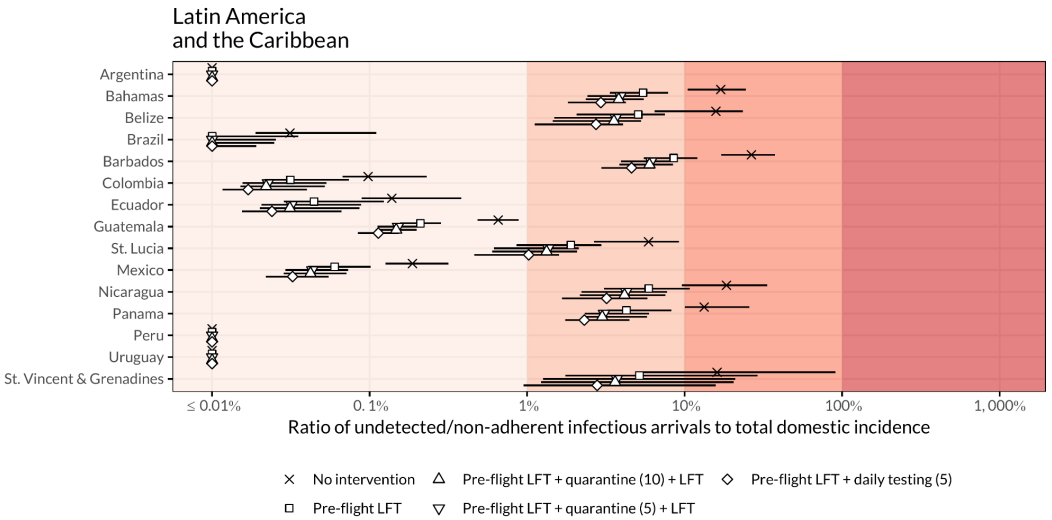
Figure S4: Change in transmission potential of infectious arrivals with different delays from a pre-flight test until boarding a flight. Vertical lines represent 95% (outer) and 50% (inner) uncertainty intervals around medians (points).




Southern Europe
Bosnia & Herzegovina
Spain
Greece
Croatia
Italy
Malta
Portugal
Serbia
Slovenia
≤ 0.01%
0. 1%
1%
10%
100%
1, 000%
Ratio of undetected/non-adherent infectious arrivals to total domestic incidence
No intervention
Pre-flight LFT + quarantine (10) + LFT
Pre-flight LFT + daily testing (5)
Pre-flight LFT
Pre-flight LFT + quarantine (5) + LFT
Eastern Asia
China
Japan
South Korea
≤ 1%
10%
100%
1, 000%
Ratio of undetected/non-adherent infectious arrivals to total domestic incidence
No intervention
Pre-flight LFT + quarantine (10) + LFT
Pre-flight LFT + daily testing (5)
Pre-flight LFT
Pre-flight LFT + quarantine (5) + LFT
Sub-Saharan Africa
Cape Verde
Guinea
Gambia
Guinea-Bissau
Kenya
Madagascar
Mali
Mauritania
Senegal
South Africa
Zambia
≤ 0.01%
0. 1%
1%
10%
100%
1, 000%
Ratio of undetected/non-adherent infectious arrivals to total domestic incidence
No intervention
Pre-flight LFT + quarantine (10) + LFT
Pre-flight LFT + daily testing (5)
Pre-flight LFT
Pre-flight LFT + quarantine (5) + LFT


Northern Europe
Denmark
Estonia
Finland
United Kingdom
Ireland
Iceland
Lithuania
Latvia
Norway
Sweden
≤ 1%
10%
100%
1, 000%
Ratio of undetected/non-adherent infectious arrivals to total domestic incidence
No intervention
Pre-flight LFT
Pre-flight LFT + quarantine (10) + LFT
Pre-flight LFT + quarantine (5) + LFT
Pre-flight LFT + daily testing (5)
Northern Africa
Algeria
Egypt
Morocco
Tunisia
≤ 0.01%
0. 1%
1%
10%
100%
1, 000%
Ratio of undetected/non-adherent infectious arrivals to total domestic incidence
No intervention
Pre-flight LFT
Pre-flight LFT + quarantine (10) + LFT
Pre-flight LFT + quarantine (5) + LFT
Pre-flight LFT + daily testing (5)
South-eastern Asia
Indonesia
Cambodia
Malaysia
Philippines
Singapore
Thailand
Vietnam
≤ 0.01%
0. 1%
1%
10%
100%
1, 000%
Ratio of undetected/non-adherent infectious arrivals to total domestic incidence
No intervention
Pre-flight LFT
Pre-flight LFT + quarantine (10) + LFT
Pre-flight LFT + quarantine (5) + LFT
Pre-flight LFT + daily testing (5)


Western Asia
United Arab Emirates
Bahrain
Cyprus
Iraq
Israel
Jordan
Kuwait
Lebanon
Qatar
Saudi Arabia
Syria
Turkey
≤ 0.01%
0. 1%
1%
10%
100%
1, 000%
Ratio of undetected/non-adherent infectious arrivals to total domestic incidence
No intervention
Pre-flight LFT
Pre-flight LFT + quarantine (10) + LFT
Pre-flight LFT + quarantine (5) + LFT
Pre-flight LFT + daily testing (5)


Latin America
and the Caribbean
Argentina
Bahamas
Belize
Brazil
Barbados
Colombia
Ecuador
Guatemala
St. Lucia
Mexico
Nicaragua
Panama
Peru
Uruguay
St. Vincent & Grenadines
≤ 0.01%
0. 1%
1%
10%
100%
1, 000%
Ratio of undetected/non-adherent infectious arrivals to total domestic incidence
No intervention
Pre-flight LFT
Pre-flight LFT + quarantine (10) + LFT
Pre-flight LFT + quarantine (5) + LFT
Pre-flight LFT + daily testing (5)

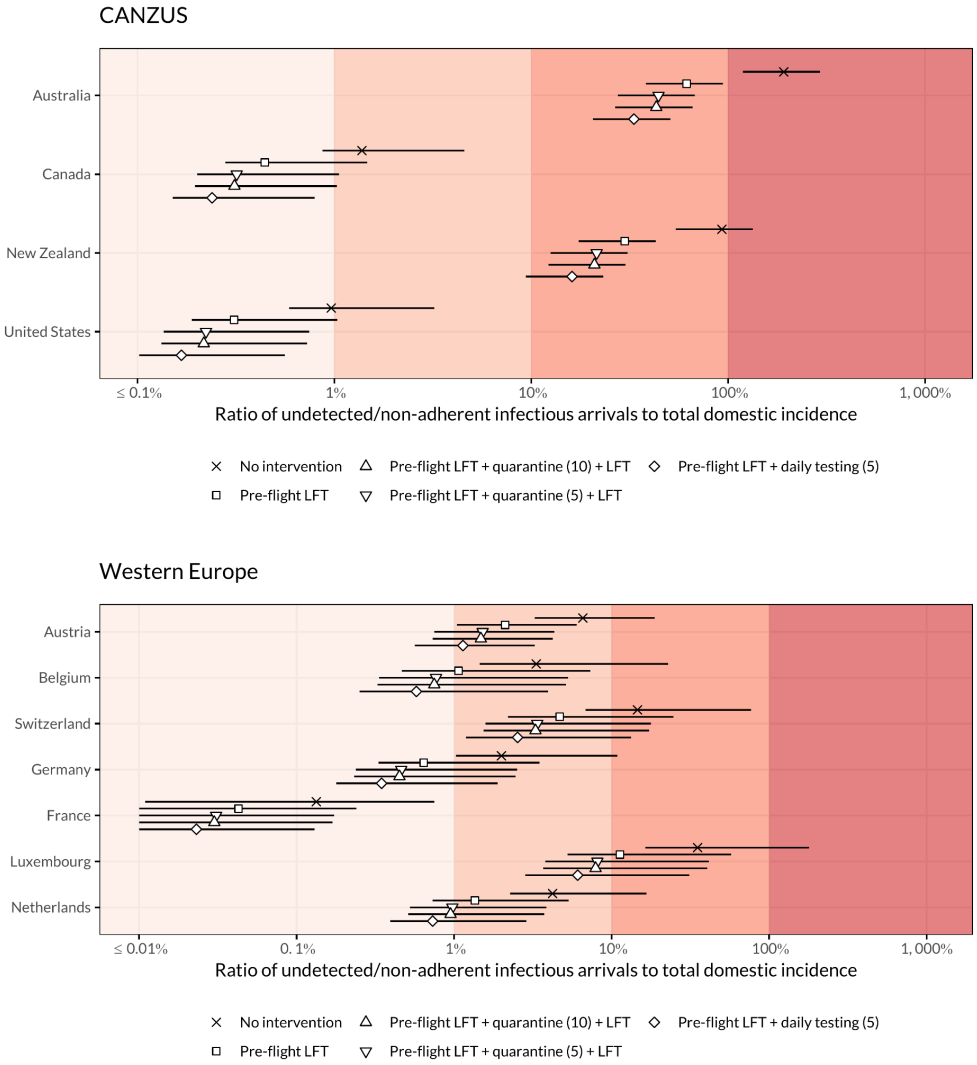


Figure S5: Effectiveness of four testing and/or quarantine strategies, compared to no intervention as of April 2021. Risk is derived as the ratio of new infectious arrivals to domestic incidence, expressed as a percentage. Results are shown for all included countries for the following strategies in increasing order of reduction of entries: no intervention; pre-flight LFT with no further quarantine or testing; pre-flight LFT followed by five days of quarantine with an LFT at exit; pre-flight LFT with ten days of quarantine and an LFT at exit; pre-flight LFT followed by daily LFT for five days. Points represent median risk, with the horizontal line showing the 95% UI; where the median or endpoint of the UI is less than 0.1%, the value is shown as "≤0.1%".

Table S1: Median risk of importation of the B.1.1.7 (diamonds) variant of concern and non-B.1.1.7 (circles) variants from the United Kingdom as a proportion of total domestic incidence. Filled points indicate baseline rates of importation, and open points represent the impact of the intervention scenario (pre-flight LFT, 5 day quarantine with LFT at exit).

Country	Month	Incidence	Risk: B-1.1.7, Intervention	Risk: B-1.1.7, No intervention	Risk: Non-B.1.1.7, Intervention	Risk: Non-B.1.1.7, No intervention
Israel	Oct-2020	2548 (2448, 3028)	1% (1%, 1%)	3% (2%, 3%)	7% (5%, 8%)	29% (23%, 33%)

	Nov-2020	916 (881, 1035)	7% (6%, 8%)	29% (24%, 33%)	5% (4%, 6%)	22% (18%, 25%)
	Dec-2020	3341 (3215, 3762)	3% (2%, 3%)	13% (11%, 15%)	0% (0%, 0%)	1% (1%, 1%)
	Jan-2021	8218 (7933, 9071)	1% (0%, 1%)	2% (2%, 2%)	0% (0%, 0%)	0% (0%, 0%)
	Feb-2021	5170 (4980, 5707)	0% (0%, 0%)	1% (1%, 1%)	0% (0%, 0%)	0% (0%, 0%)
	Mar-2021	1948 (1873, 2202)	0% (0%, 0%)	2% (1%, 2%)	0% (0%, 0%)	0% (0%, 0%)
	Apr-2021	210 (182, 265)	2% (1%, 3%)	9% (6%, 11%)	0% (0%, 0%)	0% (0%, 0%)
Luxembourg	Oct-2020	298 (291, 306)	4% (4%, 5%)	18% (16%, 20%)	40% (37%, 45%)	175% (159%, 197%)
	Nov-2020	587 (585, 590)	9% (9%, 10%)	40% (37%, 44%)	7% (6%, 8%)	30% (28%, 33%)
	Dec-2020	379 (379, 379)	20% (19%, 22%)	88% (82%, 96%)	1% (1%, 1%)	5% (4%, 5%)
	Jan-2021	128 (128, 128)	24% (22%, 26%)	102% (95%, 112%)	0% (0%, 0%)	1% (1%, 1%)
	Feb-2021	171 (169, 174)	3% (3%, 4%)	14% (13%, 15%)	0% (0%, 0%)	0% (0%, 0%)
	Mar-2021	225 (211, 231)	2% (2%, 2%)	8% (7%, 9%)	0% (0%, 0%)	0% (0%, 0%)
	Apr-2021	193 (186, 213)	1% (1%, 2%)	6% (5%, 7%)	0% (0%, 0%)	0% (0%, 0%)
Mexico	Oct-2020	11003 (5863, 20045)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	1% (0%, 2%)
	Nov-2020	11523 (6286, 20250)	0% (0%, 0%)	0% (0%, 1%)	0% (0%, 0%)	0% (0%, 1%)
	Dec-2020	18111 (10082, 30891)	0% (0%, 0%)	1% (0%, 1%)	0% (0%, 0%)	0% (0%, 0%)
	Jan-2021	25056 (14134, 41888)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
	Feb-2021	14034 (7953, 23354)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
	Mar-2021	8666 (4902, 14393)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
	Apr-2021	22466 (21251, 26837)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
Russia	Oct-2020	21055 (19174, 25546)	0% (0%, 0%)	1% (0%, 1%)	1% (1%, 2%)	6% (5%, 7%)
	Nov-2020	34199 (30555, 41745)	0% (0%, 0%)	2% (1%, 2%)	0% (0%, 0%)	1% (1%, 2%)
	Dec-2020	42301 (37706, 51865)	0% (0%, 1%)	2% (1%, 2%)	0% (0%, 0%)	0% (0%, 0%)
	Jan-2021	34291 (30401, 41742)	0% (0%, 0%)	1% (0%, 1%)	0% (0%, 0%)	0% (0%, 0%)
	Feb-2021	22447 (19459, 27410)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
	Mar-2021	16175 (13660, 19843)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
	Apr-2021	24095 (22569, 28340)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)	0% (0%, 0%)
Singapore	Oct-2020	8 (8, 8)	145% (133%, 159%)	626% (575%, 688%)	1426% (1311%, 1569%)	6169% (5672%, 6787%)
	Nov-2020	7 (7, 7)	1072% (970%, 1181%)	4637% (4197%, 5110%)	808% (731%, 890%)	3494% (3163%, 3851%)
	Dec-2020	12 (12, 13)	740% (662%, 817%)	3203% (2862%, 3536%)	39% (35%, 43%)	169% (151%, 186%)
	Jan-2021	30 (30, 31)	167% (150%, 185%)	724% (651%, 799%)	1% (1%, 1%)	4% (4%, 5%)
	Feb-2021	14 (14, 15)	116% (105%, 128%)	502% (452%, 554%)	1% (1%, 1%)	1% (1%, 1%)

	Mar-2021	14 (14, 15)	47% (41%, 52%)	202% (179%, 224%)	1% (1%, 1%)	1% (1%, 1%)
	Apr-2021	30 (25, 99)	14% (4%, 18%)	59% (17%, 77%)	0% (0%, 0%)	0% (0%, 0%)
United States	Oct-2020	99436 (79389, 159221)	0% (0%, 0%)	1% (1%, 1%)	2% (1%, 3%)	9% (5%, 12%)
	Nov-2020	203352 (185395, 332406)	1% (0%, 1%)	2% (1%, 3%)	0% (0%, 0%)	2% (1%, 2%)
	Dec-2020	242440 (223245, 394123)	1% (0%, 1%)	3% (2%, 3%)	0% (0%, 0%)	0% (0%, 0%)
	Jan-2021	217736 (200523, 350709)	0% (0%, 0%)	2% (1%, 2%)	0% (0%, 0%)	0% (0%, 0%)
	Feb-2021	93273 (85894, 148276)	0% (0%, 0%)	1% (1%, 2%)	0% (0%, 0%)	0% (0%, 0%)
	Mar-2021	63588 (58514, 101879)	0% (0%, 0%)	1% (0%, 1%)	0% (0%, 0%)	0% (0%, 0%)
	Apr-2021	62935 (62825, 63006)	0% (0%, 0%)	0% (0%, 1%)	0% (0%, 0%)	0% (0%, 0%)

Detailed methodology: estimating time-varying under-ascertainment rates each day, for each country

We estimate prevalence and incidence for each country (with greater than 10 deaths in total). To do so, we estimate the level of under-ascertainment of symptomatic cases according to the methods in (42) within a fully Bayesian framework. The result of the inference is a time-dependent posterior distribution, representing the level of case ascertainment for each country. We then adjust the confirmed cases for each country using the median of the posterior distribution on each day, and the lower and upper 95% credible intervals. This process results in a 95% credible interval of the true number of symptomatic cases for each country. When considering all infections and not just symptomatic cases, we perform a final step adjusting for potential asymptomatic and presymptomatic infections. We assume that between 26% and 37% of infections are asymptomatic (8).

To estimate the proportion of symptomatic cases ascertained over time, we fit a Gaussian process to a statistical Bayesian model for daily new deaths. The likelihood of the model, written in its simplest form, is given by

$$\begin{aligned} \mathrm{D}_{c,t} &\sim \mathrm{Poisson}(\lambda_{c,t}), \\ \lambda_{c,t} &= \mathrm{bCFR}\frac{\mathrm{dC}_{c,t}}{a^*_{c,t}}, \end{aligned}$$

where $\mathrm{D}_{c,t}$ is the number of daily deaths for country c on day t. We assume a Poisson observation process, with a rate given by $\lambda_{c,t}$, the product of the assumed true baseline case fatality ratio bCFR and the total number of cases with a known outcome by day t. The true number of cases is given by "adjusting" the ascertained number of cases $\mathrm{dC}_{c,t}$ with the

ascertainment rate $a^*_{c,t}$. Specifically, the ratio of the two gives the true number of symptomatic cases in country c on day t. With the ascertainment rate defined in the likelihood function as a parameter, we are able to use the confirmed death data to fit our model and infer a time-dependent posterior distribution for this parameter.

The time-dependent ascertainment rate is defined as

$$\Phi^{-1}(a^*_{c,t}) = f_c(t) + \epsilon_{c,t},$$
$$\epsilon_{c,t} \sim N(0, \sigma^2_{c,1}),$$

where $f_c(t)$ is a nonparametric function of time for country c, $\epsilon_{c,t}$ are independent normally distributed random variables to attempt to explain daily variation in ascertainment for country c and finally $\Phi^{-1}(x)$ is the inverse of the probit function mapping the ascertainment rate to the unit interval - the range of supported values of the ascertainment rate. We model $f_c(t)$ as a realisation of a univariate zero-mean Gaussian process:

$$f_c(t) \sim \mathcal{GP}(\mathbf{0}, k(t, t'; \theta_c)).$$

The details of this Gaussian process, for example the specific parameterisation of the covariance matrix and the kernel function and the priors used can be found in the study which originally developed this model (42).

Adjusting for under-ascertainment

Firstly, we impute corresponding dates to the ascertainment estimates for each country. We do so by assuming the delay from confirmation to death follows the mean of an estimated distribution from the literature of 13 days (49). We have, at this stage, effectively produced a time series of daily ascertainment rates, if we consider only the median and the lower/upper 95% credible intervals of the posterior distribution. Finally, we adjust the confirmed cases on each day using the ascertainment estimates.

Estimating infections

We estimate the total number of infections from the adjusted symptomatic case curves for each country (adjusted for under-ascertainment) by inflating them using estimates from a systematic review of the number of asymptomatic infections overall. The range given is 26% - 37% (8).

Incidence and prevalence estimates

To estimate incidence for each country, we calculated the mean number of infections over the same time period as the time period considered for the expected number of imported cases (which depends on the specific scenario). This time period is typically either a week or a month depending on what exactly is being considered. However, our inference framework provides us with a crude incidence estimate for each country on each day. Therefore, we are able to perform ad-hoc calculations within the same framework over arbitrary time periods, if the traveller data

used to estimate expected numbers of imported cases is over a different time period or of a different temporal resolution. Prevalence was then calculated as the cumulative incidence of the previous 10 day period (the mean duration of the infectious period (50)).

Sources of uncertainty

Several sources of uncertainty are captured in our final uncertainty range:

- the inferred infectious period, with an uncertainty range reported in Table 1 of the main text of Russell et al. (2020) (3).
- the assumed proportion of asymptomatic infections, with an assumed range of [26%, 37%].
- the confirmation-to-death distribution, with an uncertainty range with a 95% CI of (8.7, 20.9) that we integrate over in the Gaussian process fitting procedure (49).

Limitations of our methods

We summarise the limitations of the original study here briefly and we discuss the limitations of the additional steps - extending the methods in (42) - employed in this study to arrive at prevalence estimates in detail. We do so, as the original study (42) which develops and describes the under-ascertainment model includes a verbose description of the limitations of the methods, up to the point of estimating incidence, in the Discussion section of the main text. Furthermore, the original study goes into more detail about such limitations in its Supplementary Material.

Estimating under-ascertainment

In order to estimate under-ascertainment in a flexible manner, we assume a global baseline severity of COVID-19 of 1.4%, with the range 1.1% – 1.7% comprising the standard deviation of a normally-distributed prior on the baseline CFR. It is known that CFR of COVID-19 varies between locations. However, given that our analysis is on the scale of countries, and the uncertainty in the estimate is included in the final 95% credible intervals of our reported results (along with other sources of uncertainty), the effects of the assumption are relatively minor. We do however perform an additional sensitivity analysis in the original study (42), whereby we adjust the baseline CFR value for each country based on the underlying age-distribution of each country, using age-stratified CFR estimates (51). In doing so, we test the sensitivity of the model to the assumed CFR value. We find that our conclusions are broadly unchanged, and our cumulative incidence estimates are in good agreement with available seroprevalence results (42). For other limitations of these estimates, please refer to the main text and supplementary material of the original study (42).

Estimating incidence and prevalence

Extending the methods of (42) — whereby the resulting outputs of the mathematical model are posterior distributions for adjusted incidence over time for all countries (adjusted for under-ascertainment) — to arrive at prevalence estimates adds some limitations to the final estimates. The most pertinent of which is the additional assumptions about timing. Given that

the outputs of the original model take the form of incidence measurements, and our estimates are on the scale of countries, whereby estimates are bound to be crude for a multitude of reasons, we use cumulative incidence as a proxy measure for prevalence. To do so, we sum the recent incidence levels over the mean of an estimated distribution for the time-to-infectiousness and infectious periods (which sum to 10 days (50)) to arrive at prevalence estimates. We include the time-to-infectiousness distribution to allow for some level of presymptomatic transmission (50).

Incorporating these distributions into the otherwise fully Bayesian framework would alleviate this as a limitation of our study. However, in doing so, some of the desirable scalability and flexibility of the model as it stands would be lost, as additional assumptions about recovery and death rates would be required, which have been shown to vary significantly globally. In an attempt to keep the analysis scalable and parsimonious, applied in the same way globally, we opt for the simple adjustment to arrive at prevalence. In doing so, we are producing relatively crude estimates. However, we believe that the uncertainty included in the model as to the true proportion of asymptomatic infections – the source of most of the uncertainty in the 95% lower and upper credible intervals of the results reported – overshadows any additional minor error introduced by using cumulative incidence over the infectious period as a proxy for prevalence.

3. Controlling community spread

3.1 Quarantine and testing strategies in contact tracing for SARS-CoV-2: a modelling study

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	1703195	**Title**	Mr
First Name(s)	Billy		
Surname/Family Name	Quilty		
Thesis Title	Modelling the effectiveness of quarantine and testing strategies during the COVID-19 pandemic		
Primary Supervisor	Stefan Flasche		

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?	The Lancet Public Health		
When was the work published?	20 January 2021		
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?*	**Yes**	Was the work subject to academic peer review?	**Yes**

*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?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	Choose an item.

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)	I co-led the conceptualisation of this work following SPI-M and NHS Test and Trace discussions. I then co-led in the development and analysis of the individual-based contact tracing and testing model, production of results and figures, and the writing of the draft mansucript.

SECTION E

Student Signature	Billy Quilty
Date	7/02/2023

Supervisor Signature	Stefan Flasche
Date	7/02/2023

Quarantine and testing strategies in contact tracing for SARS-CoV-2: a modelling study

Billy J Quilty, Samuel Clifford*, Joel Hellewell†, Timothy W Russell†, Adam J Kucharski, Stefan Flasche, W John Edmunds, on behalf of the Centre for the Mathematical Modelling of Infectious Diseases COVID-19 working group‡*

Summary

Background In most countries, contacts of confirmed COVID-19 cases are asked to quarantine for 14 days after exposure to limit asymptomatic onward transmission. While theoretically effective, this policy places a substantial social and economic burden on both the individual and wider society, which might result in low adherence and reduced policy effectiveness. We aimed to assess the merit of testing contacts to avert onward transmission and to replace or reduce the length of quarantine for uninfected contacts.

Methods We used an agent-based model to simulate the viral load dynamics of exposed contacts, and their potential for onward transmission in different quarantine and testing strategies. We compared the performance of quarantines of differing durations, testing with either PCR or lateral flow antigen (LFA) tests at the end of quarantine, and daily LFA testing without quarantine, against the current 14-day quarantine strategy. We also investigated the effect of contact tracing delays and adherence to both quarantine and self-isolation on the effectiveness of each strategy.

Findings Assuming moderate levels of adherence to quarantine and self-isolation, self-isolation on symptom onset alone can prevent 35% (95% uncertainty interval [UI] 10–59) of onward transmission potential from secondary cases. 14 days of post-exposure quarantine reduces transmission by 48% (95% UI 18–79). Quarantine with release after a negative PCR test 7 days after exposure might avert a similar proportion (50%, 95% UI 23–80; risk ratio [RR] 1·02, 95% UI 0·88–1·41) to that of the 14-day quarantine period, as would quarantine with a negative LFA test 7 days after exposure (49%, 95% UI 20–78; RR 1·00, 0·82–1·28) or daily LFA testing without quarantine for 5 days after tracing (50%, 95% UI 24–79; RR 1·04, 0·69–1·79) if all tests are returned negative. A stronger effect might be possible if individuals isolate more strictly after a positive test and if contacts can be notified faster.

Interpretation Testing might allow for a substantial reduction in the length of, or replacement of, quarantine in the control of onwards transmission from contacts of SARS-CoV-2-infected individuals. Decreasing test and trace delays and increasing adherence will further increase the effectiveness of these strategies. Further research is required to empirically evaluate the potential costs (increased transmission risk, false reassurance) and benefits (reduction in the burden of quarantine, increased adherence) of such strategies before adoption as policy.

Funding National Institute for Health Research, UK Research and Innovation, Wellcome Trust, EU Horizon 2021, and the Bill & Melinda Gates Foundation.

Lancet Public Health 2021; 6: e175–83

Published Online January 20, 2021 https://doi.org/10.1016/S2468-2667(20)30308-X

This online publication has been corrected. The corrected version first appeared at thelancet.com/public-health on May 18, 2021

*Contributed equally

†Contributed equally

‡Working group members are listed in the appendix

Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, London, UK (B J Quilty MSc, S Clifford PhD, J Hellewell PhD, T W Russell PhD, A J Kucharski PhD, Prof S Flasche PhD, Prof W J Edmunds PhD, CMMID COVID-19 working group)

Correspondence to: Mr Billy J Quilty, Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK **billy.quilty@lshtm.ac.uk**

or

Dr Samuel Clifford, Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK **sam.clifford@lshtm.ac.uk**

See Online for appendix

Introduction

To break transmission chains of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causative agent of COVID-19, testing of cases and tracing and quarantine of their contacts has been used as a key non-pharmaceutical intervention in many countries. This measure aims to prevent onward transmission from secondary infections (individuals infected by an index case), and has been used successfully to prevent new outbreaks in countries such as South Korea, without the need for lockdown-style measures. As of November, 2020, guidance in the UK was that contact-traced individuals must quarantine from the moment they are traced until 14 days have elapsed from their exposure to the index case. 14 days is the upper bound for the incubation period of the virus,[1] when more than 95% of eventually symptomatic individuals will have developed symptoms and should subsequently enter a further period of self-isolation (10 days in the UK). However, there is growing evidence that many contacts of cases are unable to effectively quarantine for the entirety of this period, particularly those unable to work from home, or those caring for vulnerable people.[2] The increasing availability of testing, particularly rapid, low-cost lateral flow antigen (LFA) tests,[3,4] opens up the possibility of shorter periods of quarantine when combined with a negative test on exit (a test and release strategy), or even the avoidance of quarantine entirely if it is replaced with daily testing. If effective, both these strategies have the potential to substantially reduce the burden of quarantine on uninfected contacts, which could simultaneously improve quarantine adherence and reduce the economic, personal, financial, and social costs of the current policy.

Research in context

Evidence before this study

During the COVID-19 pandemic, a standard 14-day quarantine period from the day a contact was exposed to an index case has been required in the UK and elsewhere. This approach aims to avert onward transmission during infected contacts' presymptomatic period. This strategy, although a crucial part of the global pandemic response to interrupt transmission chains, places considerable social, financial, and economic pressure on quarantining individuals and society. A search of the literature on Dec 3, 2020, using the terms "quarantine AND test* AND (COVID* OR SARS*) AND effect* AND contact tracing" returned 59 results on PubMed and 1934 results on medRxiv; however, no study had investigated the effect of heterogeneity in viral load or the effectiveness of daily testing without quarantine.

Added value of this study

We modelled the individual severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load trajectories of the contacts of confirmed cases to calculate the effect of a range of quarantine and testing strategies. To the best of our knowledge, this is the first analysis of possible strategies to reduce or replace the quarantine requirement through rapid antigen testing. We found that quarantine until a PCR or lateral flow antigen test on day 7 after exposure (with early release if negative) might avert as much transmission as the 14-day quarantine period. Additionally, daily repeated lateral flow antigen testing of traced contacts for 5 days, with isolation only after a positive test, might allow for the quarantine requirement to be removed if participation in and adherence to self-isolation after a positive test is higher than that of quarantine in the absence of symptoms.

Implications of all the available evidence

The ability to identify and isolate infected individuals rapidly and comprehensively is crucial to reduce the incidence of SARS-CoV-2. Testing contacts of confirmed cases might enable the required quarantine periods for uninfected individuals to be substantially shortened, which could dampen the economic and social impact, while potentially increasing compliance. Further research (such as field trials) should be done to evaluate the potential costs (false reassurance, increased transmission risk) and benefits (reduction in quarantine burden, enhanced case detection, increased compliance) of such a policy.

RT-PCR involves amplification and quantification of viral RNA within a nose or throat sample, with a low cycle threshold (Ct) value indicating the presence of greater quantities of viral genetic material and hence a greater likelihood of being infected.[5] Due to the amplification step, PCR is highly sensitive and specific to the presence of SARS-CoV-2 viral RNA, but requires samples to be sent to a laboratory for processing before return of a result—a process that currently takes an average of 2 days in the UK.[6] In contrast, LFA tests are pregnancy test-style, point-of-care devices that test for the presence of SARS-CoV-2 antigen and allow for return of results within 15–30 min. LFA tests are reportedly substantially cheaper, and might be produced and distributed more easily and frequently, than PCR tests;[3] however, the absence of an amplification step results in a lower sensitivity than PCR tests. Despite this decreased sensitivity, the speed at which results are available might allow for repeated testing of individuals, which could enable faster isolation of cases and reduced transmission potential even if the ability to detect infections is lower than with PCR testing.

Testing of traced contacts might detect incubating and asymptomatic cases, allowing for a reduction in the post-exposure quarantine period from 14 days. Key to this is the timing of testing, because testing contacts too early or too late in their infection might lead to false-negative results. Another crucial factor is the delay in testing and tracing—ie, how long has passed since exposure to the index case to the isolation of their contacts—because approximately half of SARS-CoV-2 transmission occurs before the onset of symptoms.[7] Additionally, the current 14-day quarantine period is poorly adhered to by contacts of cases, with only 10·9% reporting that they did not leave the house in the 14 days after exposure to the index case.[8] Reducing the length of the quarantine period might increase adherence and therefore avert more transmission overall.

Here, we aimed to evaluate the effect of different quarantine and testing strategies on reducing onward transmission from traced secondary infections using a mathematical model to simulate viral load dynamics, tracing and testing timings, and other relevant parameters. We varied the required post-exposure quarantine period, and the timing, number, and type of tests (standard PCR tests or rapid LFA tests). We also investigated the effect of reducing testing and tracing delays, and the effect of reduced adherence to quarantine. As an alternative to quarantine, we considered daily testing on being traced as a contact, and estimated the number of consecutive daily tests required before leaving isolation that would result in a similar reduction in transmission to that achieved by quarantine.

Methods

Contact tracing model of infected individuals

We used a stochastic, individual-based model to simulate an individual's exposure time, viral load trajectory, symptom onset, and tracing and testing timings. The model was specified in such a way as to focus on the cases' infectivity, rather than the number of additional cases generated, and, as such, is independent of the number of secondary or further cases generated.

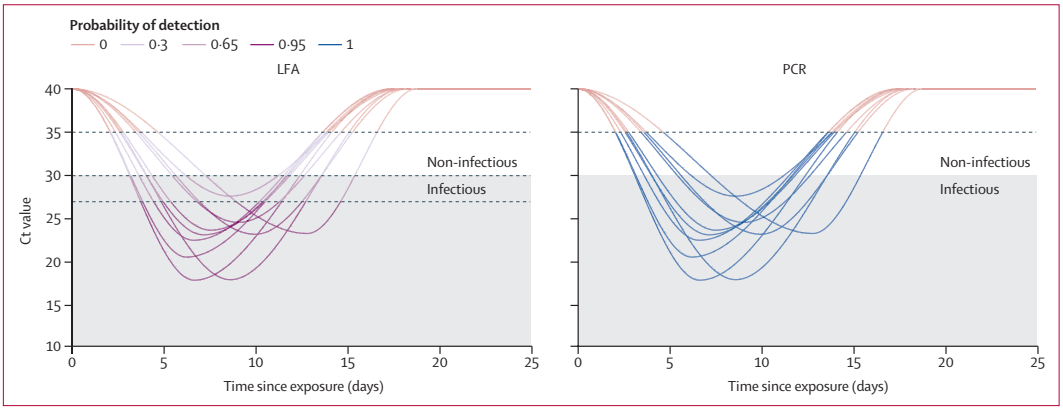


Figure 1: **Simulated Ct curves for ten individuals infected with SARS-CoV-2**
Dashed lines represent thresholds for detection probabilities[9] and the shaded region, with boundary at Ct 30, indicates the time during which individuals are considered infectious. One of the individuals never reaches Ct 30 and hence they are considered to not be infectious; however, they will be detectable by PCR and with probability 0·3 for LFA during $t \in (5–13)$. Ct=cycle threshold. SARS-CoV-2=severe acute respiratory syndrome coronavirus disease 2. LFA=lateral flow antigen.

For each individual in the model (index cases and secondary cases), we simulated a viral load trajectory of Ct values over the course of infection (figure 1) using published data to inform our choice of parameters. Each curve is parameterised by a baseline Ct level, a peak Ct value, and an end time, representing a return to baseline. We assumed a baseline Ct of 40 on exposure (ie, negative for SARS-CoV-2). The timing of the peak Ct was sampled from the incubation period (time from exposure to onset of symptoms) using the pooled log-normal distribution from a published meta-analysis.[10] The peak Ct value is normally distributed with mean 22·3 and SD of 4·2[9] and the time of cessation of viral shedding, a return to baseline, is parameterised as normally distributed with mean 17 days after exposure and SD of 0·94 days for symptomatic individuals,[11] with asymptomatic individuals having a duration that is 40% shorter.[10] The peak and end times are drawn, for each individual, in such a way that each individual is at the same quantile, q, in the cumulative densities of each distribution; this guarantees that the ordering of peak and end is maintained and that there are no rapid returns to baseline Ct after a slow transition to peak Ct. We then fit a cubic Hermite spline[12] to the generated exposure, peak, and end values for each individual, constraining the slope of the curve to be zero at each of them, to simulate viral load kinetics (in Ct) over the course of infection. We assumed that an individual is infectious during the time period that their Ct value is less than 30.[13] If an individual's Ct trajectory does not drop below 30, they are considered to never be infectious and therefore not relevant for transmission. We assumed individuals are uniformly infectious during this period of Ct less than 30.

We simulated index cases as individuals who become exposed, then infectious, at which point they begin exposing their contacts and generating secondary cases. Once the index cases develop symptoms, they begin a period of self-isolation when they are unable to generate additional secondary cases. We assumed that 1 day after symptom onset, they seek out and have a PCR test that is returned positive, which begins the process of contact tracing. Based on the latest National Health Service test and trace data, we assumed that it takes a delay of 3 days from the sample being taken to contacts being instructed to quarantine.[14] To investigate the effect of faster contact tracing (eg, through rapid testing and application-based tracing[15]), we considered halved delays (1·5 days) and instant test and trace (0 days) as a sensitivity analysis.

Quarantine and testing strategies

We assumed that all contacts are successfully identified and traced and, that once traced, are subject to one of several strategies designed to avert onward transmission. In the quarantine-based strategy, we investigated quarantine durations of 0 days, 3 days, 5 days, 7 days, 10 days, and 14 days post exposure to the index case, with either no testing or testing with PCR or LFA tests on the final day of the specified quarantine period (to highlight the effect of said test at the end of quarantine). However, if the end-of-quarantine test is scheduled to occur before the time of the secondary case's tracing, we assumed that they are tested as soon as they are traced; hence, a 0-day quarantine with a test will be equivalent to an immediate test and release strategy. In the daily testing strategy, contacts are required to take an LFA test every day for 1 day, 3 days, 5 days, 7 days, 10 days, or 14 days after they are traced and are not required to quarantine unless they either develop symptoms or test positive. Secondary cases displaying symptoms at any point post exposure, or testing positive at any time, will then isolate until 10 days have passed since onset of symptoms.[16] Given that asymptomatic secondary cases never develop symptoms, they will self-isolate only if

	Description	Value	Source
Incubation period	Time from exposure to onset of symptoms	Log-normal (log-mean 1·63, log-SD 0·5), median 5·1 days, IQR 3·9–6·7 days, 95% CI 2·3–11·5 days	McAloon and colleagues[10]
Infectious period	Time for which Ct is less than 30	Symptomatic individuals mean 7·56 days, SD 1·54 days; asymptomatic individuals mean 4·32 days, SD 1·09 days	Derived
Asymptomatic fraction of secondary cases, *a*	Proportion of infections that are asymptomatic	Beta (alpha 51, beta 115), median 0·31, IQR 0·28–0·33, 95% CI 0·24–0·38	Derived from quantile matching 95% prediction interval[17]

Ct=cycle threshold.

Table: **Model parameters and their values in simulation of cases' infection histories and testing**

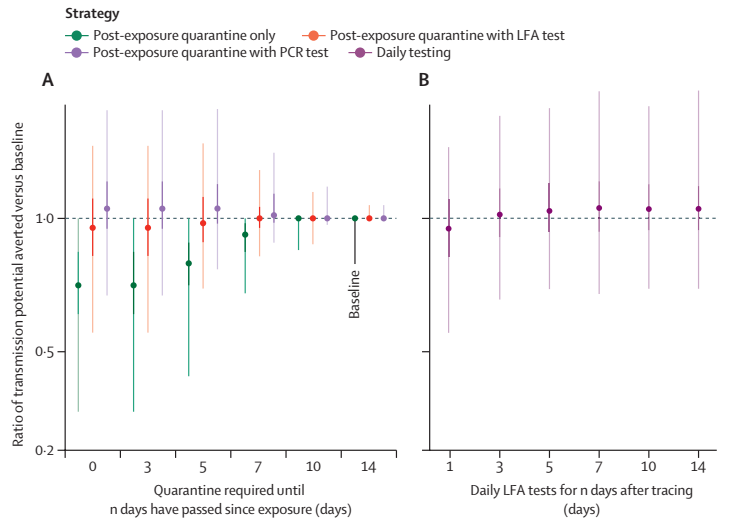


Figure 2: **Transmission potential averted with quarantine-based strategies and daily testing strategies**
Ratio was calculated as the sum of days of secondary cases' infectious periods spent in quarantine or self-isolation divided by the sum of days of secondary cases' infectious periods. Ratios are shown for each strategy versus the baseline of 14 days' quarantine with no testing, for quarantine-based strategies (quarantine required from time of tracing until n days have passed since exposure, either with or without a test on the final day; A) and daily testing strategies (daily LFA tests without quarantine for n days from tracing, isolating only after a positive test result; B). Quarantine and self-isolation adherence were assumed to be 50% and 67%, respectively. The delay from an index case's positive test until the tracing of secondary cases was assumed to be 3 days (current average).[16] Central bars indicate the median ratio for a given strategy, with 95% and 50% uncertainty intervals indicated by light and dark shaded bars, respectively. LFA=lateral flow antigen.

they test positive. We sampled the proportion of secondary infections that are asymptomatic from a beta distribution, which has a median of 31% (95% CI 24–38;[17] table). Further details on the model parameters are provided in the table.

The probability of detecting an infected and possibly infectious individual depends on their Ct value at the time of testing, and is drawn from their individual Ct trajectory (figure 1). For PCR, we assumed that the probability of detection is 100% for Ct below 35 and 0% above 35. For LFA, we approximated the probability of detection is 95% for Ct below 27, 65% for Ct from 27 to 30, 30% for Ct from 30 to 35, and 0% above 35, approximated based on the results of the Innova rapid antigen test evaluation.[4] As a sensitivity analysis to investigate the effect of lower Innova LFA sensitivity, we used the probability of detection for a given Ct as reported in the Liverpool Mass Testing Pilot.[18]

As a moderate baseline scenario, we assumed that 50% of individuals adhere to quarantine and 67% adhere to self-isolation guidelines. To investigate the effect of increased or reduced adherence to quarantine and self-isolation on the effectiveness of the programme, we considered adherences of 100% and 0% for post-tracing quarantine, and 100% and 0% for self-isolation after a positive test or symptom onset. We assumed adherence as a binary variable (adhering or not-adhering) for each individual by sampling from a Bernoulli distribution with the probability given by the proportion adhering.

Transmission potential

For each secondary case, we considered the infectious period as the period of time when the individual's Ct values are less than 30. We then calculated the amount of the infectious period spent in quarantine, or in self-isolation due to onset of symptoms or after a positive test, as transmission potential averted. Assuming that the majority of SARS-CoV-2 transmission is driven by superspreading events,[19] we report the uncertainty associated with the average secondary transmission potential averted per superspreading event by simulating 1000 index cases with ten secondary cases. We calculated the median and inner 50% and 95% ranges for the sum of the secondary cases' infectious periods spent in quarantine or self-isolation divided by the sum of secondary cases' infectious periods if there were no quarantine or self-isolation requirements. Because the model considers averting this transmission rather than focusing on the generation of additional cases, the average amount of infectivity in secondary cases averted by quarantine or testing, or both, is independent of the number of additional cases generated, and the choice of the number of secondary cases affects the width of the uncertainty intervals (UIs; here we consider a reasonable upper bound on secondary cases based on superspreading, as mentioned, in an attempt to faithfully characterise real-world uncertainty). We also calculated the risk ratio (RR) of transmission averted by the given strategy compared with the baseline scenario (a 14-day quarantine period with no testing, 3 days from testing of the index case to tracing, 50% adherence to quarantine, and 67% adherence to self-isolation).

In our calculation of the transmission potential averted, we considered that in the case that no transmission is averted, an individual will be as infectious as if there were no testing or quarantine. In such a case, that individual is likely to go on to infect a number of additional individuals, R, which is distributed with mean R_0 and dispersion k. With a fraction, a, of their infectivity prevented, an

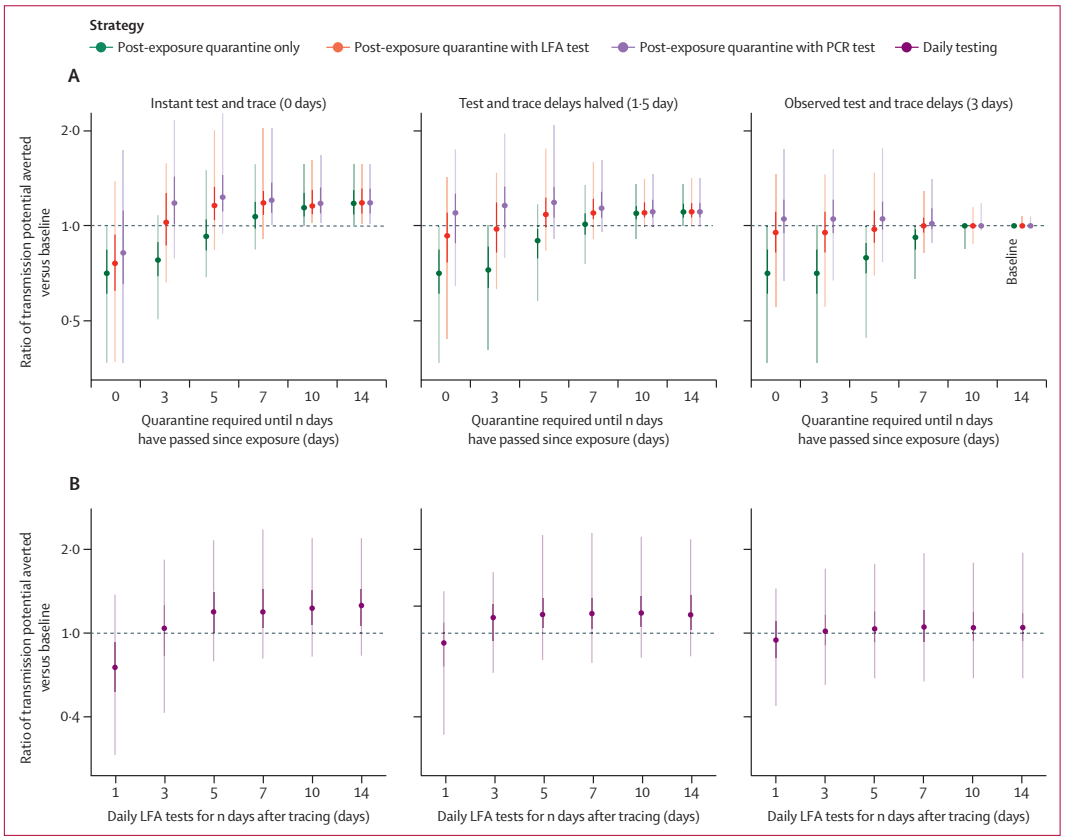


***Figure 3*: Transmission potential averted with reduced test and trace delays**

Ratio was calculated as the sum of days of secondary cases' infectious periods spent in quarantine or self-isolation divided by the sum of days of secondary cases' infectious periods. Ratios are shown for each strategy versus the baseline of 14 days' quarantine with no testing, for quarantine-based strategies (quarantine required from time of tracing until n days have passed since exposure, either with or without a test on the final day; A) and daily testing strategies (daily LFA tests without quarantine for n days from tracing, isolating only after a positive test result; B). Quarantine and self-isolation adherence were assumed to be 50% and 67%, respectively. The delay from an index case's positive test until the tracing of secondary cases was assumed to be 3 days (current average[16]) in the baseline scenario, with halved and eliminated delays investigated. Central bars indicate the median ratio for a given strategy, with 95% and 50% uncertainty intervals indicated by light and dark shaded bars, respectively. LFA=lateral flow antigen.

infectious individual is expected to infect $(1-a)R$ individuals. Hence, the transmission potential averted can be thought of as a linear scaling of R.

The model was coded in R, version 4.0.3, and the entire code required to reproduce this analysis is available online.

For the **code to reproduce analysis** see https://github.com/cmmid/pcr_test_trace

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all of the data and the final responsibility to submit for publication.

Results

According to our model, relying only on 67% of eventually symptomatic people self-isolating on developing symptoms, 35% (95% UI 10–59) of transmission might be averted from secondary infections, with an RR of 0·71 (95% UI 0·37–1·00) compared with the baseline scenario. By tracing contacts and instructing them to self-isolate for a period of time after their last exposure to the index case, additional transmission might be averted from asymptomatic and presymptomatic secondary cases (figure 2; appendix p 1). The amount of transmission averted rises to 43% (95% UI 16–68) with an RR of 0·92 (95% UI 0·68–1·00) at 7 days post exposure; to 46% (95% UI 18–77) with an RR of 1·00 (95% UI 0·85–1·07) at 10 days post exposure; and to 48% (95% UI 18–79, baseline) at 14 days post exposure.

The amount of transmission potential averted can be increased if LFA or PCR testing is done on the final day of quarantine (or on tracing, if the specified quarantine period ends before a case is traced) and people who receive a negative result are released. The introduction of an

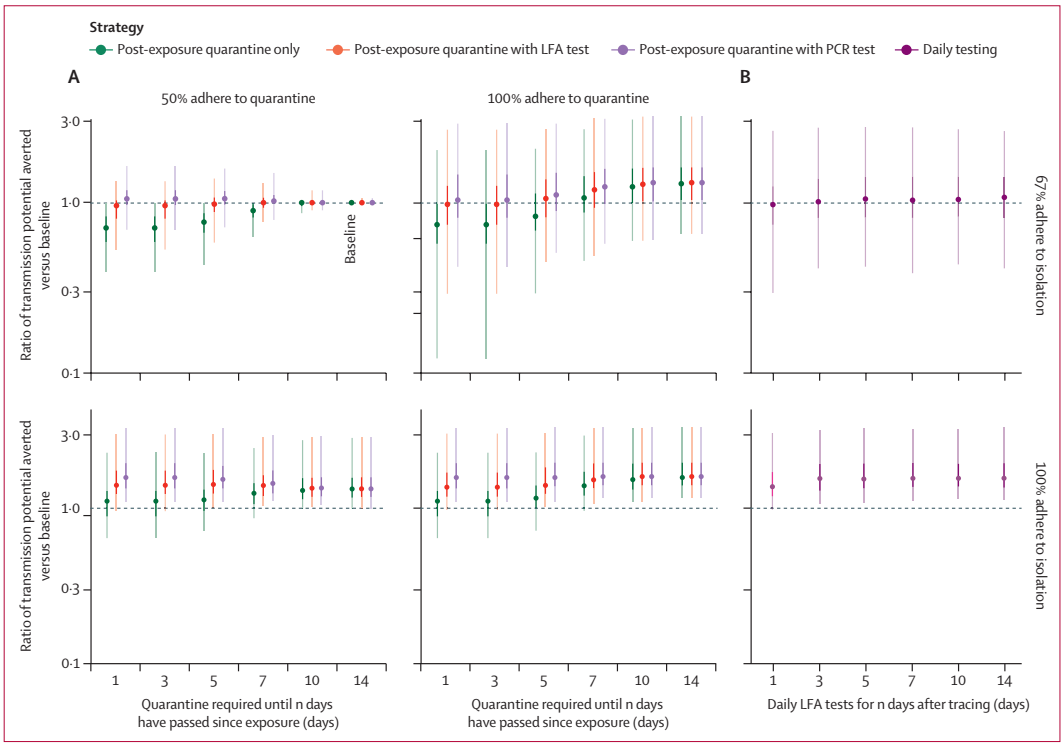


Figure 4: **Transmission potential averted with increased adherence to self-isolation and quarantine**
Ratio was calculated as the sum of days of secondary cases' infectious periods spent in quarantine or self-isolation divided by the sum of days of secondary cases' infectious periods. Ratios are shown for each strategy versus the baseline of 14 days' quarantine with no testing, for quarantine-based strategies (quarantine required from time of tracing until n days have passed since exposure, either with or without a test on the final day; A) and daily testing strategies (daily LFA tests without quarantine for n days from tracing, isolating only after a positive test result; B). Quarantine and self-isolation adherence were assumed to be 50% and 67%, respectively, in the baseline scenario, with 100% explored for both. The delay from an index case's positive test until the tracing of secondary cases was assumed to be 3 days (current average).[16] Central bars indicate the median ratio for a given strategy, with 95% and 50% uncertainty intervals indicated by light and dark shaded bars, respectively. LFA=lateral flow antigen.

immediate test is estimated to avert 46% (95% UI 19–71) of transmission with an LFA test (RR 0·95, 95% UI 0·55–1·46) and 52% (95% UI 24–81) of transmission with a PCR test (RR 1·05, 95% UI 0·67–1·75; figure 2; appendix p 1). However, the greater time spent in quarantine waiting for a PCR test result might avert additional transmission, although these delays might not be desirable features of a test and trace system. Shorter quarantines with a test on the final day might avert a similar amount of transmission to that of the current 14-day quarantine without a test—ie, 7 days with an LFA test (49%, 95% UI 20–78; RR 1·00, 95% UI 0·82–1·28), 10 days with an LFA test (48%, 95% UI 18–80; RR 1·00, 95% UI 0·87–1·15), 7 days with a PCR test (50%, 95% UI 23–80; RR 1·02, 95% UI 0·88–1·41), and 10 days with a PCR test (48%, 95% UI 18–80; RR 1·00, 95% UI 0·97–1·18). As the quarantine period increases in length, the relative contribution of a test is lessened, as the majority of the infectious period has been spent in quarantine. With 14 days of mandatory quarantine, 48% (95% UI 18–79, baseline) of transmission is averted with no testing, and 48% (95% UI 18–82) of transmission is averted (RR 1·00, 95% UI 1·00–1·07) with either a PCR or LFA test (figure 2). Shorter quarantines with tests to release might avert a similar amount of transmission (or greater with PCR) to that of a 14-day quarantine as a result of a high probability of detection soon after tracing and greater adherence to self-isolation after a positive test than to quarantine alone.

If traced contacts are required to take a daily LFA test for n days after tracing instead of entering quarantine, 5 days of testing might avert 50% (95% UI 24–79; RR 1·04, 95% UI 0·69–1·79) of transmission, with additional days of testing averting a similar amount (figure 2).

Our model suggest that if test and trace delays (ie, the time from the index case having a test to the tracing of their contacts) can be reduced, shorter quarantines might become more viable, because the proportion of the infectious period spent in the community before tracing decreases (figure 3; appendix p 2). For example, if test and trace delays can be reduced to zero (ie, through digital contact tracing), the median RR of a 7-day quarantine with no testing might exceed the effect of the 14-day

quarantine with a 3-day test and trace delay (53%, 95% UI 23–76; RR 1·07, 95% UI 0·84–1·57). The effect of daily testing strategies might also exceed the effect of the current 14-day strategy with zero delays (5 days of LFA testing 59%, 95% UI 30–85; RR 1·20, 95% UI 0·80–2·17); however, because secondary infections will be traced earlier in their infection when viral loads are lower, the likelihood of false negatives increases, and additional days of testing (ie, 7–10 days) might be required (figure 3; appendix p 2).

We found that if rates of adherence to quarantine and self-isolation can be boosted, substantial increases in effect over that of the baseline 14-day quarantine policy might be achieved, assuming that in the baseline scenario, 50% of individuals adhere to quarantine and 67% of individuals adhere to post-symptom or post-positive test self-isolation (figure 4; appendix p 3). For example, if individuals adhere perfectly to self-isolation after a positive test in a daily testing scenario, 5 days of testing with LFA after tracing might avert 80% (95% UI 61–91) of transmission (RR 1·56, 95% UI 1·11–4·22).

If more conservative estimates of LFA sensitivity are used,[18] LFA tests might be less efficacious, yet still avert an approximately equal amount of transmission, with quarantine and a negative LFA test at 7 days post exposure averting 45% (95% UI 18–71; RR 1·00, 95% UI 0·82–1·28) and 5 days of LFA testing without quarantine averting 43% (95% UI 22–66; RR 0·89 95% UI 0·59–1·30; appendix p 4).

Discussion

Using a model combining SARS-CoV-2 viral load dynamics with a range of possible quarantine and testing strategies for contact tracing, we estimate that the recommended 14 days of quarantine after last exposure from a confirmed case can prevent 48% (95% UI 18–79) of onward transmission from secondary cases, assuming 50% adherence to quarantine and a total delay of 3 days from the index case having a test to the tracing of their contacts. Assuming the same level of adherence for quarantine and 67% adherence to self-isolation after symptom onset or a positive test, an LFA test 7 days after exposure with quarantine from tracing until testing or alternatively daily testing with LFA tests for 5 days after tracing might avert a similar proportion to that of the 14-day quarantine (RR 1·00, 95% UI 0·82–1·28 and RR 1·04, 95% UI 0·69–1·79, respectively), if all tests are negative, potentially allowing for the reduction of or removal of the quarantine requirement for traced contacts. In strategies requiring quarantine, the additional benefit of testing diminishes with longer quarantine durations, because infectious people spend a greater proportion of their infectious period in quarantine and have a higher probability of developing symptoms (if ever symptomatic) and self-isolating. PCR testing performs better than LFA testing (by averting a greater amount of transmission); however, PCR testing might be limited by the requirement to process samples in a laboratory, a process which has inherent delays (24 h minimum) and logistical limitations (transporting of samples, requirement for skilled staff).

We found that the effectiveness of contact tracing can be limited by low adherence to quarantine and isolation. Data on adherence rates are sparse. A UK survey found that only 10·9% of contacts adhere to quarantine and 18·2% adhere to self-isolation;[8] however, adherence was defined as not leaving the house at all in the 14 days, with most breaches being brief and of low transmission risk—eg, solo outdoor exercise. Hence, we assumed a higher, moderate baseline of 50% of individuals fully adhering to quarantine (and therefore having their transmission potential reduced to zero), which we assumed increased to 67% for self-isolation after symptom onset or a positive test, which might better reflect the rate of public involvement in contact tracing. It is possible that some of the factors inhibiting adherence to the current 14-day quarantine are difficulty in completing fully due to social and financial burdens, and low perception of the risk to others given an unknown case status.[20] As such, reducing the duration of quarantine and increasing the use of tests to compensate might raise adherence by making it easier to complete a full term, and by making cases aware that they might be infectious. Investigating this assumption in our modelling, we found that raised adherence increases the benefit of both short quarantines with testing (at the end of quarantine) and daily testing, beyond that of the current 14-day quarantine. As well as the boost in adherence, which might arise through these strategies, effort should be made to increase adherence through other methods, such as increasing trust in government and public health advice; producing clear guidance on the specified contact tracing protocol; increasing the perceived importance of quarantine in reducing transmission; building strong local and social support networks; and increasing the level of income support and provision of other supplies.[20] Further work on COVID-19 quarantine adherence is required to understand how quarantined individuals behave and whether isolation of cases and suspected cases in hotels or hospitals might be considered to prevent onward transmission.

The ability of any contact tracing programme to minimise the transmission potential of secondary cases is limited substantially by delays from the testing of index cases to the tracing of their contacts, because secondary cases might have been transmitting for a number of days in the community during the time that contact tracing is taking place. If these delays can be reduced through the adoption of rapid testing, rapid digital contact tracing,[15] or both, a greater overall proportion of transmission might be averted; eg, with a 14-day quarantine, 58% (95% UI 29–84) of transmission might be averted from secondary cases if contacts can be notified as soon as a case is tested (assuming the same baseline assumptions for adherence). As such, great emphasis should be put on monitoring and reducing the time taken to reach secondary cases.

However, if such reductions are achieved, a proportionally longer quarantine period or greater number of days of testing will be required to ensure that quarantine or testing overlaps with the period when contacts are most infectious.

Our study has several limitations. In this analysis, we have focused on the potential for quarantine and testing to reduce the transmission potential of traced secondary infections and have not evaluated the number, and cost, of tests that might be required, nor the possibility of false positives, which—despite the high specificity of PCR and LFA—might arise in mass testing of asymptomatic individuals. However, in the context of contact tracing, where prevalence of SARS-CoV-2 among contacts of confirmed cases is likely to be higher than among the general public, this is unlikely to lead to a low positive predictive value. Due to a lack of currently available data, we have assumed that index cases seek out and take a PCR test 1 day after the onset of symptoms. We do not consider other aspects of the test and trace system that might result in poor outcomes, such as the fraction of index cases that do not engage with the service,[21] variation in the number of cases generated by each index case,[22] or the proportion of secondary cases missed by tracers.[23] Additionally, we do not consider the quarantine, or testing of the contacts of contacts (ie, household members) who test positive, or both, which might constitute a substantial additional effect. For our assumptions of adherence to quarantine and self-isolation, we selected static, moderate values of the proportion of contacts who adhere to each. It is probable that adherence varies (eg, between individuals and waning with the duration of quarantine); however, in the absence of suitable data on the functional form of such changes in adherence, we take a parsimonious approach to modelling adherence.

For **code and data** see https://github.com/cmmid/quar_test_contact_tracing

One of the simplifying assumptions we have made is that the Ct curve is a reasonable proxy for both probability of detection by testing (with both PCR and LFA) and potential for transmission. Alternative parameterisations of transmission potential are possible,[24] but unresolved challenges in comparing testing approaches with the transmission potential based on a combination of an incubation period[9] and infectivity relative to onset of symptoms[25] include the need to convert from PCR sensitivity curves[26,27] to LFA in such a way that the timing and height of the two curves are matched meaningfully. A more complete picture of daily testing would require mapping a curve of viral load to one of test sensitivity and one of infectivity. Additionally, while we model viral load and the sensitivity of LFA relative to Ct by PCR in line with the University of Oxford and Public Health England evaluation,[4] Ct values might not be directly comparable between laboratories if different RT-PCR platforms are used.[5] As such, we have provided a sensitivity analysis using the lower reported sensitivities of LFA in the Liverpool Mass Testing Pilot[18] and discussion of results in the context of other studies (appendix p 4).

We have shown that quarantine with a test on day 7 post exposure or 5 days of LFA tests could reduce the transmission potential from secondary cases notified through contact tracing to similar levels to that of a 14-day quarantine without testing. However, factoring in structural issues in contact tracing, such as testing and tracing delays and poor adherence of traced cases, greatly reduces the ability of quarantine and testing to reduce onward transmission, and addressing these should be a focus of policy.

Contributors

BJQ, SC, SF, WJE, AJK, JH, and TWR conceived the study and wrote the report. BJQ and SC led the design, development, and analysis of the model. BJQ and SC accessed and verified the data. All authors read and approved the final Article. All members of the Centre for the Mathematical Modelling of Infectious Diseases COVID-19 working group contributed to the processing, cleaning, and interpretation of data, interpreted findings, contributed towards the writing of the Article, and approved the work for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The entire code and data required to reproduce this analysis are available online.

Acknowledgments

This research was partly funded by the UK National Institute for Health Research (NIHR). BJQ is funded by NIHR grants 16/137/109 and 16/136/46 from the UK Government to support global health research. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the UK Department of Health and Social Care. BJQ is also supported in part by a grant from the Bill & Melinda Gates Foundation (OPP1139859). This research was also funded by UK Research and Innovation (grant MC_PC_19065 to SC and WJE), and partly funded by the Wellcome Trust (Sir Henry Dale Fellowship, grant 208812/Z/17/Z to SF and SC; grant 206250/Z/17/Z to AJK and TWR; and grant 210758/Z/18/Z to JH). This project received funding from the EU's Horizon 2020 research and innovation programme (project EpiPose to WJE).

References

1 Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020; **382:** 1199–207.

2 Wright L, Steptoe A, Fancourt D. What predicts adherence to COVID-19 government guidelines? Longitudinal analyses of 51,000 UK adults. *medRxiv* 2020; published online Oct 21. https://doi.org/10.1101/2020.10.19.20215376 (preprint).

3 WHO. Antigen-detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays. https://www.who.int/publications-detail-redirect/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays (accessed Nov 11, 2020).

4 University of Oxford. Oxford University and PHE confirm high-sensitivity of Lateral Flow Tests following extensive clinical evaluation. https://www.ox.ac.uk/news/2020-11-11-oxford-university-and-phe-confirm-high-sensitivity-lateral-flow-tests-following (accessed Nov 15, 2020).

5 Public Health England. Understanding cycle threshold (Ct) in SARS-CoV-2 RT-PCR: a guide for health protection terms. https://www.gov.uk/government/publications/cycle-threshold-ct-in-sars-cov-2-rt-pcr (accessed Dec 17, 2020).

6 UK Government. NHS test and trace (England) and coronavirus testing (UK) statistics: 22 October to 28 October. https://www.gov.uk/government/publications/nhs-test-and-trace-england-and-coronavirus-testing-uk-statistics-22-october-to-28-october (accessed Nov 10, 2020).

7 Ashcroft P, Huisman JS, Lehtinen S, et al. COVID-19 infectivity profile correction. *Swiss Med Wkly* 2020; **150:** w20336.

8 Smith LE, Potts HWW, Amlot R, Fear NT, Michie S, Rubin J. Adherence to the test, trace and isolate system: results from a time series of 21 nationally representative surveys in the UK (the COVID-19 Rapid Survey of Adherence to Interventions and Responses [CORSAIR] study). *medRxiv* 2020; published online Sept 18. https://doi.org/10.1101/2020.09.15.20191957 (preprint).

9 Kissler SM, Fauver JR, Mack C, et al. SARS-CoV-2 viral dynamics in acute infections. *medRxiv* 2020; published online Dec 1. https://doi.org/10.1101/2020.10.21.20217042 (preprint).

10 McAloon C, Collins Á, Hunt K, et al. Incubation period of COVID-19: a rapid systematic review and meta-analysis of observational research. *BMJ Open* 2020; **10:** e039652.

11 Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe* 2020; published online Nov 19. https://doi.org/10.1016/S2666-5247(20)30172-5.

12 Dougherty RL, Edelman AS, Hyman JM. Nonnegativity-, monotonicity-, or convexity-preserving cubic and quintic Hermite interpolation. *Math Comput* 1989; **52:** 471–471.

13 Singanayagam A, Patel M, Charlett A, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. *Euro Surveill* 2020; **25:** 2001483.

14 UK Government. NHS Test and Trace (England) and coronavirus testing (UK) statistics: 12 November to 18 November. https://www.gov.uk/government/publications/nhs-test-and-trace-england-and-coronavirus-testing-uk-statistics-12-november-to-18-november (accessed Dec 2, 2020).

15 Kretzschmar ME, Rozhnova G, Bootsma MCJ, van Boven M, van de Wijgert JHHM, Bonten MJM. Impact of delays on effectiveness of contact tracing strategies for COVID-19: a modelling study. *Lancet Public Health* 2020; **5:** e452–59.

16 UK Government. How long to self-isolate. National Health Service, 2020 https://www.nhs.uk/conditions/coronavirus-covid-19/self-isolation-and-treatment/how-long-to-self-isolate/ (accessed Aug 10, 2020).

17 Buitrago-Garcia DC, Egli-Gany D, Counotte MJ, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: a living systematic review and meta-analysis. *PLoS Med* 2020; **17:** e1003346.

18 University of Liverpool. Liverpool Covid-SMART Pilot—coronavirus (COVID-19). https://www.liverpool.ac.uk/coronavirus/research-and-analysis/covid-smart-pilot/ (accessed Dec 24, 2020).

19 Adam DC, Wu P, Wong JY, et al. Clustering and superspreading potential of SARS-CoV-2 infections in Hong Kong. *Nat Med* 2020; **26:** 1714–19.

20 Webster RK, Brooks SK, Smith LE, Woodland L, Wessely S, Rubin GJ. How to improve adherence with quarantine: rapid review of the evidence. *Public Health* 2020; **182:** 163–69.

21 O'Dowd A. COVID-19: UK test and trace system still missing 80% target for reaching contacts. *BMJ* 2020; **370:** m2875.

22 Endo A, Abbott S, Kucharski AJ, Funk S. Estimating the overdispersion in COVID-19 transmission using outbreak sizes outside China. *Wellcome Open Res* 2020; **5:** 67.

23 Keeling MJ, Hollingsworth TD, Read JM. Efficacy of contact tracing for the containment of the 2019 novel coronavirus (COVID-19). *J Epidemiol Community Health* 2020; **74:** 861–66.

24 Clifford S, Quilty BJ, Russell TW, et al. Strategies to reduce the risk of SARS-CoV-2 re-introduction from international travellers. *medRxiv* 2020; published online July 25. https://doi.org/10.1101/2020.07.24.20161281 (preprint).

25 He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med* 2020; **26:** 672–75.

26 Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polymerase chain reaction-based SARS-CoV-2 tests by time since exposure. *Ann Intern Med* 2020; **173:** 262–67.

27 Hellewell J, Russell TW. The SAFER Investigators and Field Study Team, et al. Estimating effectiveness of frequent PCR testing at different intervals for detection of SARS-CoV-2 infections. Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine. https://cmmid.github.io/topics/covid19/pcr-positivity-over-time.html (accessed Nov 11, 2020).

THE LANCET
Public Health

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

This online publication has been corrected. The corrected version first appeared at thelancet.com/public-health on May 18, 2021.

Supplement to: Quilty BJ, Clifford S, Hellewell J, et al. Quarantine and testing strategies in contact tracing for SARS-CoV-2: a modelling study. *Lancet Public Health* 2021; published online Jan 20. https://doi.org/10.1016/S2468-2667(20)30308-X.

Supplementary appendix

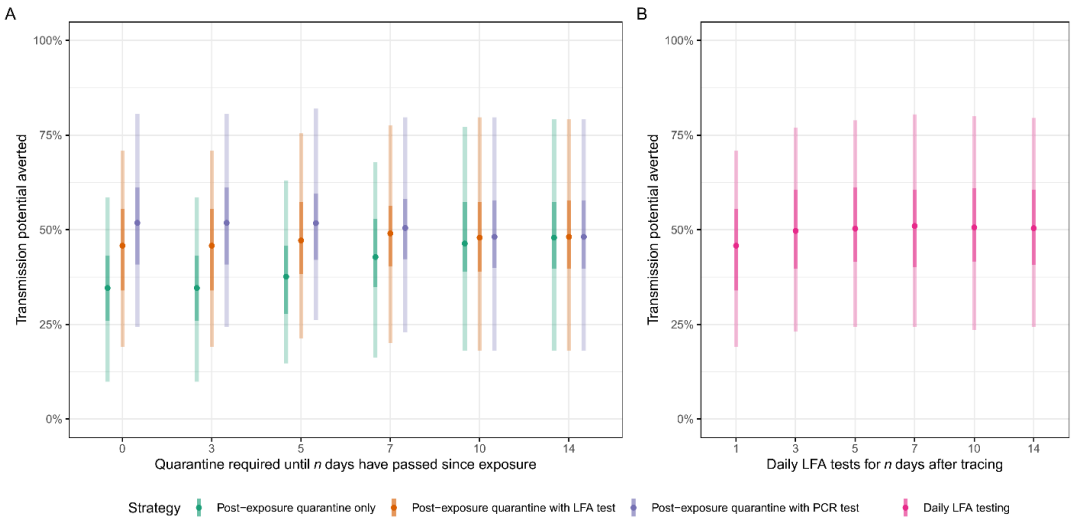


Figure S1: **Transmission potential averted** (sum of days of secondary cases' infectious periods spent in quarantine or self-isolation/ sum of days of secondary cases' infectious periods) for each strategy with quarantine-based strategies (quarantine required from time of tracing until *n* days have passed since exposure, either with or without a test on the final day) in **A** and daily testing strategies (daily lateral-flow antigen tests without quarantine for *n* days from tracing, isolating only upon a positive test result) in **B**. Quarantine and self-isolation adherence assumed to be 50% and 67%, respectively. The delay from index case's positive test until the tracing of secondary cases is assumed to be 3 days (current average). Central bars indicate the median ratio for a given strategy, with 95% and 50% uncertainty intervals indicated by light and dark shaded bars, respectively.

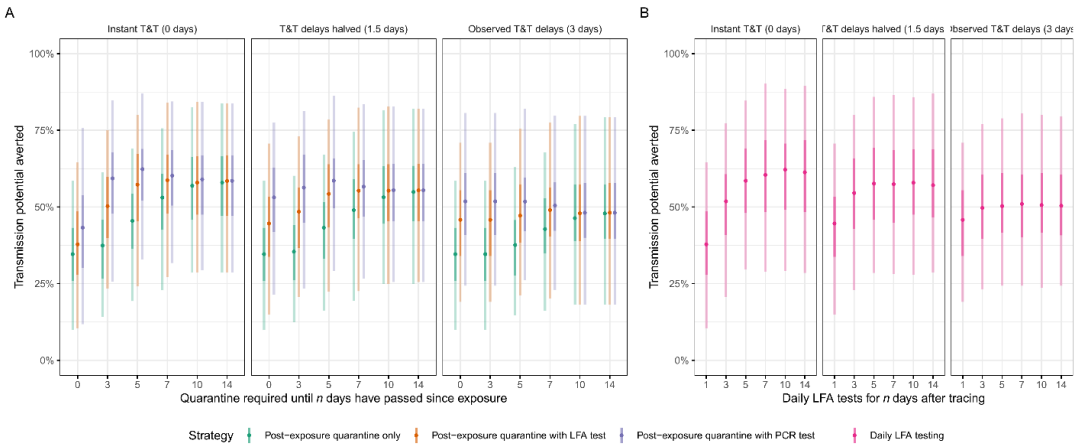


Figure S2: **Transmission potential averted with reduced test and trace delays** (sum of days of secondary cases' infectious periods spent in quarantine or self-isolation/ sum of days of secondary cases' infectious periods) for each strategy with quarantine-based strategies (quarantine required from time of tracing until *n* days have passed since exposure, either with or without a test on the final day) in **A** and daily testing strategies (daily lateral-flow antigen tests without quarantine for *n* days from tracing, isolating only upon a positive test result) in **B**. Quarantine and self-isolation adherence assumed to be 50% and 67%, respectively. The delay from index case's positive test until the tracing of secondary cases is assumed to be 3 days (current average), with sensitivity analysis with halved delays or instant Test & Trace. Central bars indicate the median ratio for a given strategy, with 95% and 50% uncertainty intervals indicated by light and dark shaded bars, respectively.

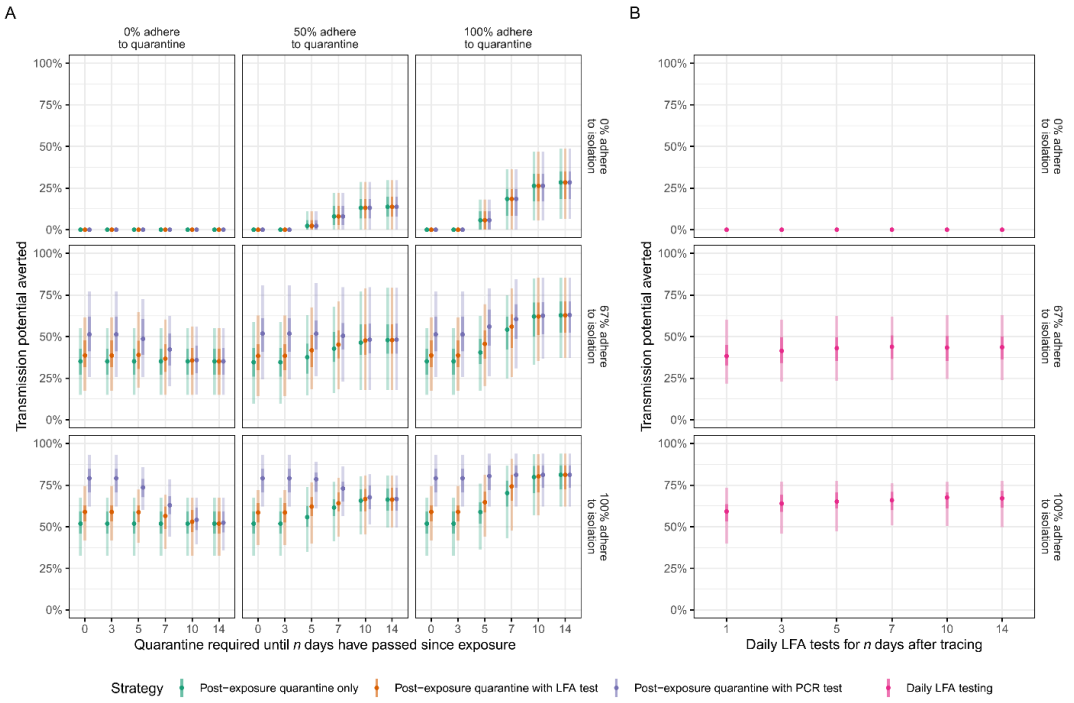


Figure S3: **Transmission potential averted with reduced or increased adherence** (sum of days of secondary cases' infectious periods spent in quarantine or self-isolation/ sum of days of secondary cases' infectious periods) for each strategy with quarantine-based strategies (quarantine required from time of tracing until *n* days have passed since exposure, either with or without a test on the final day) in **A** and daily testing strategies (daily lateral-flow antigen tests without quarantine for *n* days from tracing, isolating only upon a positive test result) in **B**. Quarantine and self-isolation adherence assumed to be 50% and 67%, respectively in the base case, with sensitivity analysis values of 0% and 100% for each. The delay from index case's positive test until the tracing of secondary cases is assumed to be 3 days (current average). Central bars indicate the median ratio for a given strategy, with 95% and 50% uncertainty intervals indicated by light and dark shaded bars, respectively.

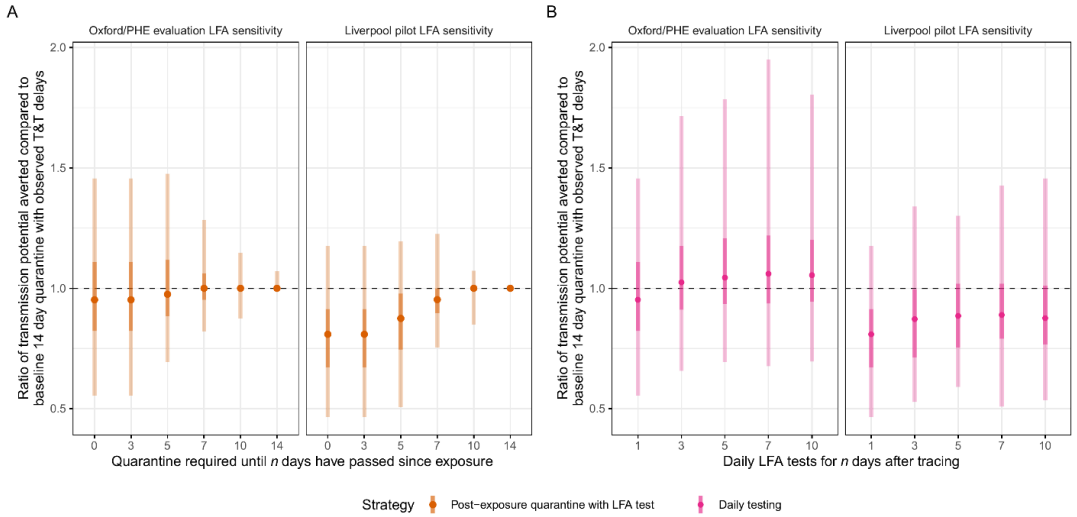


Figure S4: **Ratio of transmission potential averted with values of sensitivity reported in the Liverpool mass asymptomatic testing trial** (sum of days of secondary cases' infectious periods spent in quarantine or self-isolation/ sum of days of secondary cases' infectious periods) for each strategy vs the baseline of 14 days quarantine with no testing, with quarantine-based strategies (quarantine required from time of tracing until *n* days have passed since exposure, either with or without a test on the final day) in **A** and daily testing strategies (daily lateral-flow antigen tests without quarantine for *n* days from tracing, isolating only upon a positive test result) in **B**. Quarantine and self-isolation adherence assumed to be 50% and 67%, respectively, in the baseline scenario. The delay from index case's positive test until the tracing of secondary cases is assumed to be 3 days (current average). Central bars indicate the median ratio for a given strategy, with 95% and 50% uncertainty intervals indicated by light and dark shaded bars, respectively.

Group authorship

The following authors were part of the Centre for Mathematical Modelling of Infectious Disease COVID-19 Working Group: Alicia Rosello, Kevin van Zandvoort, Yung-Wai Desmond Chan, Rachel Lowe, Jack Williams, Hamish P Gibbs, James D Munday, Naomi R Waterlow, Rosalind M Eggo, Gwenan M Knight, Amy Gimma, Simon R Procter, Damien C Tully, Emily S Nightingale, Petra Klepac, Kiesha Prem, Fiona Yueqian Sun, Kaja Abbas, Alicia Showering, Akira Endo, Sebastian Funk, Anna M Foss, Thibaut Jombart, Sam Abbott, Rosanna C Barnard, Yang Liu, Carl A B Pearson, Katharine Sherratt, Christopher I Jarvis, Matthew Quaife, Katherine E. Atkins, Oliver Brady, C Julian Villabona-Arenas, Sophie R Meakin, Graham Medley, Frank G Sandmann, David Simons, Mark Jit, Nicholas G. Davies, Nikos I Bosse.

Affiliation: Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London WC1E 7HT, United Kingdom

3.2 Assessing the contribution of variation in viral load and daily contact rates to heterogeneity in SARS-CoV-2 transmission and the effectiveness of targeted testing strategies in the UK

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	1703195	**Title**	Mr
First Name(s)	Billy		
Surname/Family Name	Quilty		
Thesis Title	Modelling the effectiveness of quarantine and testing strategies during the COVID-19 pandemic		
Primary Supervisor	Stefan Flasche		

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?	Wellcome Open Research
Please list the paper's authors in the intended authorship order:	Billy J Quilty, Lloyd AC Chapman, James Munday, Kerry LM Wong, Amy Gimma, Suzanne Pickering, Stuart JD Neil, Rui Pedro Galão, W John Edmunds, Christopher I Jarvis, Adam J Kucharski on behalf of the CMMID COVID-19 Working Group

Stage of publication	**Not yet 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)	I co-led in the conceptualisation of this work which was derived from two SPI-M reports. I then led in the formulation, development and analysis of the individual-based viral load model which incorporated the Comix and BBC Pandemic contact distributions processed by co-authors. I then co-led in the writing of the first draft.

SECTION E

Student Signature	Billy Quilty
Date	07/02/2023

Supervisor Signature	Stefan Flasche
Date	07/02/2023

Assessing the contribution of variation in viral load and daily contact rates to heterogeneity in SARS-CoV-2 transmission and the effectiveness of targeted testing strategies in the UK

Billy J Quilty[1], Lloyd AC Chapman[1], James Munday[1], Kerry LM Wong[1], Amy Gimma[1], Suzanne Pickering[2], Stuart JD Neil[2], Rui Pedro Galão[2], W John Edmunds[1], Christopher I Jarvis[1], Adam J Kucharski[1] on behalf of the CMMID COVID-19 Working Group

[1] CMMID Covid-19 Working Group, London School of Hygiene and Tropical Medicine
[2] Department of Infectious Diseases, School of Immunology & Microbial Sciences, King's College London

Abstract

Background
SARS-CoV-2 spreads through superspreading, with a minority of individuals responsible for the majority of transmission, though the drivers of such heterogeneity are unclear. In this study we aimed to assess the contribution of variation in viral load and daily contact rates to heterogeneity in transmission, and estimate the effectiveness of targeted control strategies involving rapid testing to reduce transmission through the prevention of superspreading events.
Methods
We evaluated the extent of variation in contact rates from the BBC Pandemic and Comix contact surveys (conducted prior to and during the pandemic respectively) between individuals and over time. We then incorporated this into a mathematical model along with varying viral load progression, and simulated transmission events. We then estimated the mean reproduction number (R) and the overdispersion parameter *k* throughout the pandemic in the UK in 2020, as well as the effect of frequent and pre-event testing on these outcomes.
Findings
The proportion of individuals reporting over 20 daily contacts decreased from 13.7% pre-pandemic to 0.4% during the 1st lockdown in March to June 2020 before increasing to 6.1% when restrictions relaxed and schools reopened in September 2020. There was an increase the variation in contacts compared to pre-pandemic. Heterogeneity in contacts was found to contribute most to heterogeneity in the reproduction number, as a high number of contacts are a necessary prerequisite to infecting a large number of people, and as infected individuals were estimated to go through a highly infectious period of 2 days (95% CI: 0, 6 days) on average regardless of individual variation in viral load progression. We estimated that regular testing every 3 days with adherence, or pre-event testing with an event size threshold of 20, could reduce R below 1 through a reduction in superspreading events, provided uptake/adherence exceeding 80% for pre-pandemic levels of contacts and 50% for relaxed restrictions with schools open.
Interpretation
Restrictions enacted during the COVID-19 pandemic in the UK led to a substantial decrease in the occurrence of high contact events overall, though some remained, leading to an increase in the variation in contact rates from person-to-person. Heterogeneity in contacts likely drives heterogeneity in the secondary case distribution of SARS-CoV-2. Regular or pre-event lateral flow testing could provide a targeted way to reduce R through a reduction in superspreading events, provided moderate-to-high uptake/adherence.

Introduction

Transmission of SARS-CoV-2 occurs primarily through superspreading, with 20% of infections generating around 80% of secondary infections[1]. A review and meta-regression by Chen et al.[2] indicates that substantial variation in the respiratory viral load of individuals infected with SARS-CoV-2 is a primary driver of overdispersion in secondary infection generation. However as most studies cited measure viral load at one point over the course of infection, it is difficult to determine whether this is due to some individuals being more infectious than others generally ("wrong person") or whether most individuals pass through a highly infectious period which happens to coincide with a period of high contact ("wrong time"). High contact rates are a necessary prerequisite for infecting a high number of people, and hence the potential for superspreading should vary over the course of the pandemic as restrictions on contacts were enacted and relaxed. Despite the accumulation of immunity to SARS-CoV-2 through vaccination and infection, the emergence of more transmissible and immune evasive variants such as Omicron and easing of restrictions means superspreading may remain common feature of transmission.

In this paper, we reconstruct the secondary infection distribution of SARS-CoV-2 using a model of intra- and inter-host heterogeneity in infectiousness derived from viral load trajectories and infectivity combined with data on reported numbers of daily contacts from two social contact surveys in the UK. While previous models of superspreading of SARS-CoV-2 have either fitted to summary data on key epidemiological metrics, such as the mean reproduction number and distributions of individual-level numbers of secondary cases from contact tracing studies[3] to estimate social contact rates or considered a wide range of plausible contact rates[4], here we estimate the secondary infection distribution directly from data on social contacts gathered prior to and during the pandemic in the UK. This allows us to characterise variation in the secondary infection distribution over time under different levels of restrictions on contacts. We also consider the impact of lateral flow tests (able to detect individuals with high viral loads when they are most likely to be infectious[5,6]) taken regularly or before events on R and the potential for superspreading with differing levels of adherence and background contact rates.

The distribution of the number of secondary infections generated by each infectious individual can be characterised in terms of the mean number of secondary infections R and an overdispersion parameter k that represents the variation in the number of secondary infections (with smaller values of k representing greater variation). Even if the mean number of secondary infections R is below 1, there may still be a considerable probability of 1 or more secondary infections if k is small. We estimate the utility of regular rapid lateral-flow antigen tests (LFTs) on reducing R and the potential for superspreading events (by decreasing variation in numbers of secondary infections, i.e. increasing k).

Methods

Contact data

BBC Pandemic survey

The BBC Pandemic contact survey was conducted between September 2017 and December 2018 as part of a BBC Four documentary and involved over 40,000 participants (full details published elsewhere[7,8]). Participants used an app to record their personal basic demographic information and the number of social contacts they made during the previous 24 hour period, as well information such as as the contact's age, type of interaction, and setting (home, work, school, other).

CoMix survey

The CoMix survey was a behavioural survey launched on 24th of March 2020 to gather social and behavioural data to aid the response to the COVID-19 pandemic. Full details have been published elsewhere [9,10]. Briefly, however, the contact survey was based on the POLYMOD contact survey [11]. The sample is broadly representative of the UK adult population. Participants were invited to respond to the survey once every two weeks. Weekly data was collected by running two alternating panels. Parents completed the survey on behalf of children (17 years old or younger). Participants recorded direct, face-to-face contacts made on the previous day, specifying certain characteristics for each contact including the age and sex of the contact, whether contact was physical (skin-to-skin contact), and where contact occurred (e.g. at home, work, while undertaking leisure activities, etc.).

On the 24th May 2020 Comix included the ability to record an estimated mass contacts count in situations where it would be infeasible to record the detailed information of all contacts made, such as large gatherings. As the BBC Pandemic survey did not include this option, potentially truncating the true contact distribution, as a sensitivity analysis we investigated the effect on R and k of imputing a heavier tail for the BBC Pandemic survey. We assumed that the tail of this distribution, those reporting over 250 contacts, would follow a negative exponential form, and hence used maximum likelihood estimation to estimate the rate parameter for the number of contacts reported in relaxed restrictions time periods, i.e, when high numbers of contacts were possible and common ("Relaxed restrictions", "School reopening" and "Step 2 + schools") from the Comix survey. We then imputed the tail of the BBC Pandemic survey by sampling proportionally from the resultant distribution.

Analysis of social contact data

We calculated the percentage of participants reporting over than 5, 10, 20, 50, 100, and 200 contacts in the 24-hour period prior to filling in the survey. We compared these percentages over time to assess changes over the previous year. We also calculated these percentages from nine time periods over the previous year representing different levels of restrictions (Table 1).

We compared contact distributions (overall and stratified by household/out of household) for the BBC Pandemic survey (here referred to as Pre-pandemic) and Comix surveys for nine indicative time periods as defined in previous work[9,10]. For plotting contact distributions, we calculated the percentage of participants in each time period who reported a certain number of contacts to account for differences in numbers of participants per time period. We fitted negative binomial distributions to numbers of total daily contacts in the different time periods to estimate the mean and dispersion of the contact distributions.

Reconstruction of secondary infection distribution

We simulated 10000 individual respiratory viral load trajectories of index cases over the course of infection as a piecewise linear function defined by a proliferation phase (days from exposure to peak), clearance phase (days from peak to cessation) and peak viral load, with these three parameters drawn from distributions from Kissler et al. 2021[12]. Viral load (in cycle threshold (Ct) units) was assumed to be Ct 40 (negative) at exposure and cessation of shedding, with a peak viral load of Ct 22.4 (95% CI: 20.7, 24.0). All viral load parameters were assumed to be Normally distributed and values were sampled for independently per individual. We then estimate the probability of infectiousness for a given viral load (in Ct) by fitting a logistic regression model to the probability of culturing virus at that viral load[13], producing an infectiousness trajectory (Figure 1).

To simulate secondary infections, we first randomly sample a number (and duration) of contacts from empirical contact distributions (the BBC Pandemic contact survey[7,8,14] and Comix contact surveys[9]) with each index case having N_1 household contacts and N_2 daily non-household contacts (work, school and “other” contacts). Each household and non-household contact has a duration (defined as the proportion of a 24 hour period spent at home or outside of the home respectively also

independently sampled from Comix (Figure S2)). Household contacts are sampled once per index case, whereas non-household contacts are sampled daily. The infection process for each contact is modelled as Bernoulli with the probability of infection equal to the infectiousness of the index case on the day of contact multiplied by the duration of contact parameter. We assumed uniform susceptibility of individuals in the model which does not vary by, for example, age.

We then estimate the corresponding R (mean number of secondary cases) and k (overdispersion in the number of secondary cases) by fitting a negative binomial distribution to the number of secondary cases.

Simulation of interventions

We also estimate the impact of regular testing every 3 days with LFTs (with detection calculated by fitting a logistic regression model to the probability of detection with LFTs given viral load[13], with individuals self-isolating at-home upon their first positive test (i.e, reduce the number of work, school and casual contacts to zero after the date of the positive test while leaving home contacts unchanged).

The code and data for this study can be found at https://github.com/bquilty25/superspreading_testing.

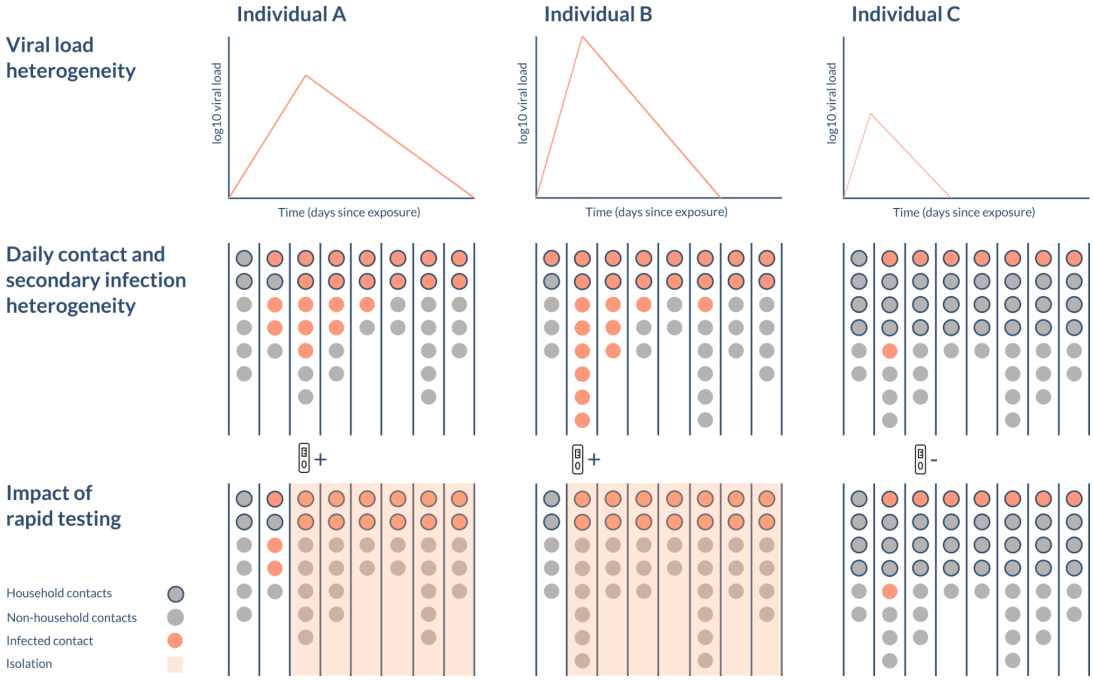


Figure 1: Schematic of the model. The viral load and number of daily contacts (circles) varies from person-to-person and over time, influencing the number of secondary infections (stratified by household (outlined) and non-household (no outline)) they generate. The viral load at time of testing also determines the likelihood they will test positive and subsequently isolate.

Results

Changes in the distribution of social contacts

Figure 2A and Table 1 show the proportions of survey participants in the UK reporting more than a certain number of contacts (5, 10, 20, 50, 100 and 200) in the previous day over time, both pre-pandemic (BBC Pandemic) and from Comix for the 9 time periods during the survey with different

levels of restrictions. The proportion of individuals reporting more than 20 contacts in a day was substantially lower during the pandemic compared to the pre-pandemic period (13.7%), varying from a low of 0.4% during the first lockdown from March to June 2020 to a peak of and 6.1% in September 2020, when restrictions were most relaxed and schools reopened. The proportion of individuals reporting over 100 and 200 contacts was lower in the pre-pandemic BBC Pandemic contact survey compared to periods of relaxed restrictions due to differences in the reporting of high contact events. Overall, people reporting more than 50, 100, or 200 contacts make up <3% of the total survey sample.

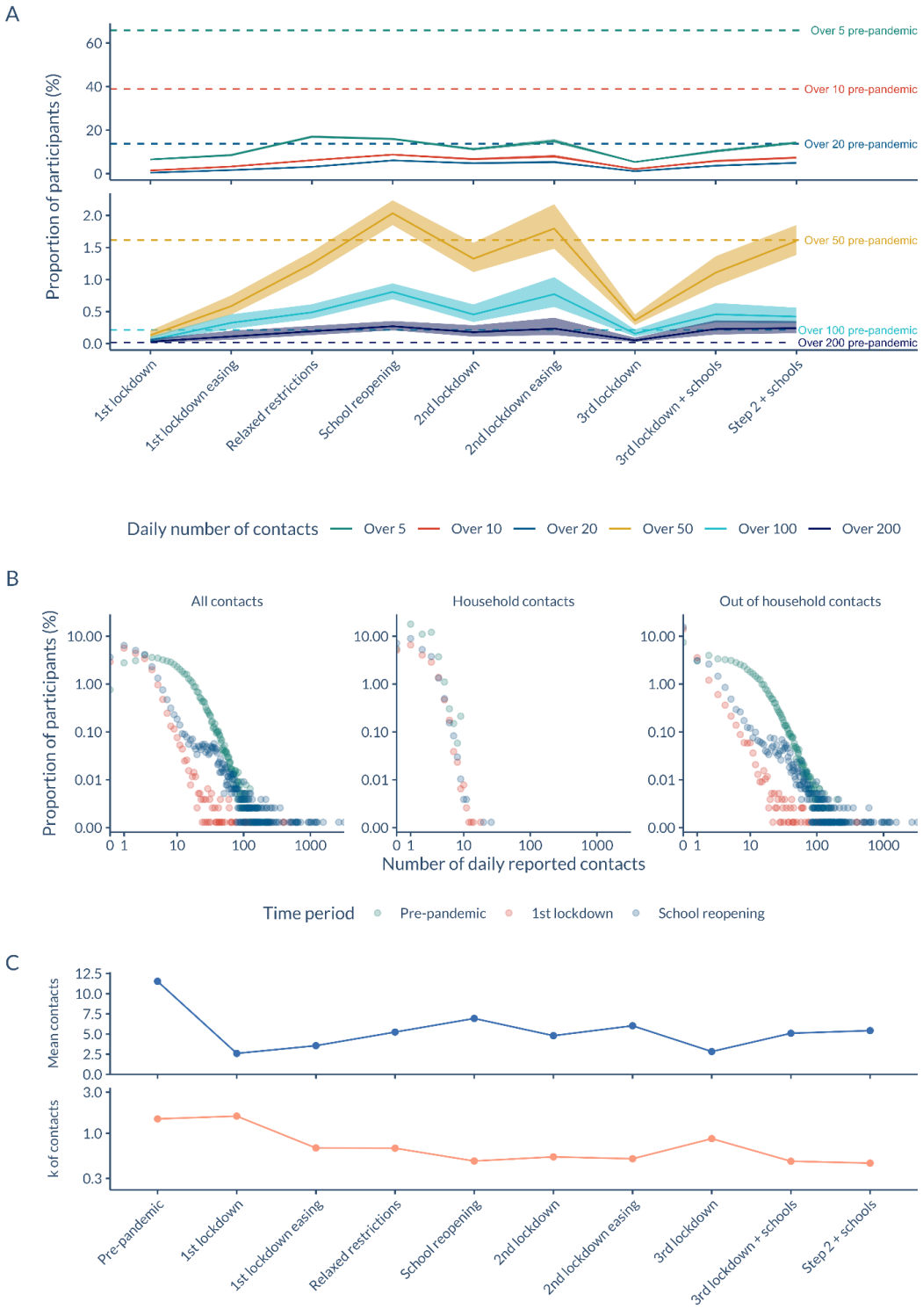


Figure 2: A. Proportion of participants reporting over 5, 10, 20, 50, 100, and 200 daily contacts during the pandemic in the UK, with dashed horizontal lines indicating the proportion of participants reporting over that value from the 2018 BBC Pandemic contact survey. Median and 95% binomial confidence intervals shown. B. Distribution of the number of reported daily contacts for three indicative timepoints before and during the pandemic in the UK in 2020. C. Mean and k of contacts during the time periods.

Table 1. Percentage of participants with more than a certain number of contacts in different time periods based on lockdowns and different levels of restrictions in the UK over the past year.

Time period	From	To	N	Over 5 (%)	Over 10 (%)	Over 20 (%)	Over 50 (%)	Over 100 (%)	Over 200 (%)
Pre-pandemic (BBC Pandemic)	01/09/2017	01/12/2018	40162	65.8	38.9	13.7	1.6	0.2	0
Lockdown 1	23/03/2020	03/06/2020	15906	6.6	1.5	0.5	0.1	0.1	0
Lockdown 1 easing	04/06/2020	29/07/2020	10651	8.6	3.3	1.7	0.6	0.3	0.1
Relaxed restrictions	30/07/2020	03/09/2020	15415	17.6	6.4	3.2	1.3	0.5	0.2
School reopening	04/09/2020	24/10/2020	20759	16.7	9	6.2	2.1	0.8	0.3
Lockdown 2	05/11/2020	02/12/2020	10008	11.9	6.9	4.9	1.3	0.5	0.2
Lockdown 2 easing	03/12/2020	19/12/2020	5898	16.1	8.1	5.4	1.8	0.8	0.2
Lockdown 3	05/01/2021	07/03/2021	21542	5.6	2.2	1.2	0.4	0.2	0.1
Lockdown 3 + schools	08/03/2021	31/03/2021	8452	10.8	5.9	3.7	1.2	0.5	0.2
Step 2 + schools	16/04/2021	16/05/2021	1771	16.6	8	5	1.9	0.7	0.3

The estimated mean and *k* (lower values indicating more overdispersion (variation) in the distribution) of numbers of daily contacts in the UK were lower than that observed pre-pandemic, with mean daily contacts averaging ~6 during the pandemic compared to ~12 pre-pandemic, and *k* averaging ~0.6 during the pandemic compared to ~1.5 pre-pandemic, indicating individuals having on average lower, but more varied, numbers of daily contacts. These values also changed considerably across the different periods of restrictions in a similar pattern to the proportion of participants with high numbers of contacts, with the mean number of daily contacts ranging from ~3 during the first lockdown to ~7 when schools reopened in September 2020, with similar drops during the third lockdown, though less so during the second lockdown when schools remained open (Figure 2C). *K* of contact rates were similar pre-pandemic and during the first lockdown (1.5 and 1.6 respectively) then became lower (more varied) following the easing of the first lockdown, where *k* averaged ~0.6 (Figure 2C). Stratifying contacts by household/non-household revealed contact rates within the household remained stable throughout, with changing non-household contact rates driving much of the variation in the mean and *k* of daily contacts over the course of the pandemic (Figure S2). Both the mean and *k* of out-of-household daily contacts remained lower than pre-pandemic contact rates Contact durations in Comix differed significantly between household and non-household contacts, with a median duration of 45 minutes (95% CI: 0, 720 minutes) for out of household contacts compared to 720 minutes (12 hours) (95% CI: 15, 1440 minutes) for household contacts (Figure S2).

Variation in viral load and infectivity over the course of infection

Analysis by Kissler et al. of densely sampled viral load trajectories in individuals infected with SARS-CoV-2 suggested substantial variation between individuals in the duration of proliferation and clearance phases of infection, and lowest Ct value (inversely correlated with peak viral load) (Figure

3A). By mapping viral load to infectivity via a logistic function based on viral load and culture (representing live, infectious virus) from Pickering et al. (Figure 3B), calculating P(infectivity) by day (Figure 3C), then integrating under the infectivity curve, we can reproduce substantial heterogeneity in individual infectiousness as reported by Ke et al., with a >54 fold difference in individual-level infectivity between the 2.5% and 97.5% percentiles of the individual-level distribution (0.11 and 6.09, a.u, respectively) and a shape parameter of a Gamma distribution of 1.55. Individuals had viral loads high enough to cause infections (had culturable virus) for a median of 2 days (95% CI: 0, 6 days). A substantial proportion (18.7%) were estimated to be infectious for zero days, though the remainder were infectious for at least one day and theoretically capable of causing superspreading events (Figure 3).

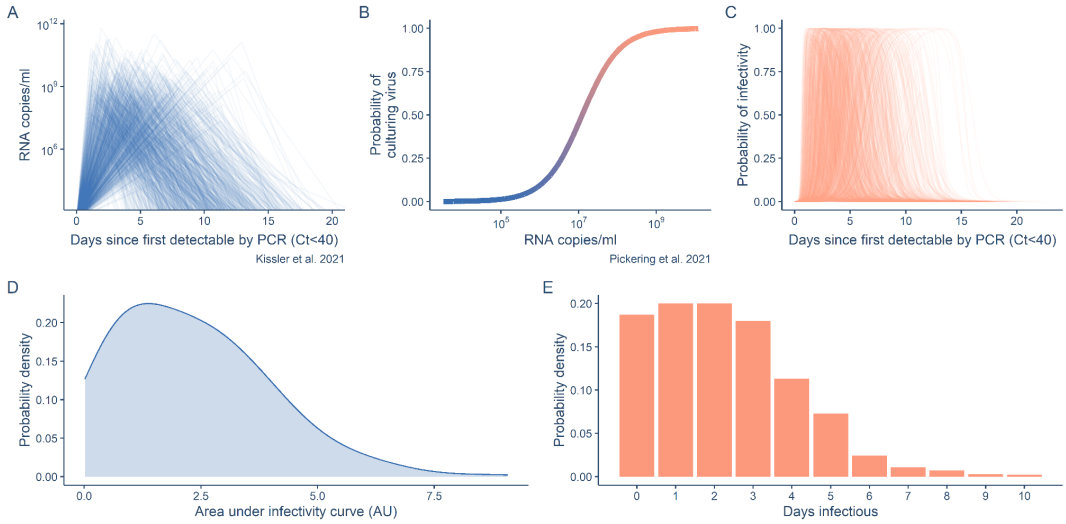


Figure 3: Variation in viral load progression and infectivity. A. Individual-level viral load trajectories. B. Logistic model for probability of culturing virus given a certain viral load. C. Probability of infectivity over time. D. Area under the infectivity curve. E. Distribution of the number of days for which individuals are infectious.

Simulating secondary infections from heterogeneity in contact rates and viral load progression

Simulating secondary infections using an individual-based model based on daily contact rates, contact duration, and daily infectivity derived from viral load, we estimate an R0 (mean initial reproduction number based on UK pre-pandemic contact rates) of 2.3, closely matching contemporaneous estimates[15]. *K* was estimated at 1.2, higher than other estimates (less heterogeneous)[1]. Limiting our analysis to 2020 prior to the widespread emergence of more transmissible variants of SARS-CoV-2 and mass vaccination, during the first national lockdown R was estimated at 0.4 and *k* at 0.5. R rose as lockdown eased (R = 0.6) and restrictions were relaxed in the summer of 2020 (R = 1), before rising above 1 as schools reopened in the autumn (R = 1.5). As with contacts, *k* reduced as the pandemic began, indicating more variability in the secondary case distribution (Figure 4). A sensitivity analysis imputing a heavier tail for for BBC Pandemic based on the tails of relaxed restrictions periods during Comix led to a small increase in our estimate of R0 from 2.3 to 2.5 and a reduction in *k* from 1.2 to 0.9 (Figure S3).

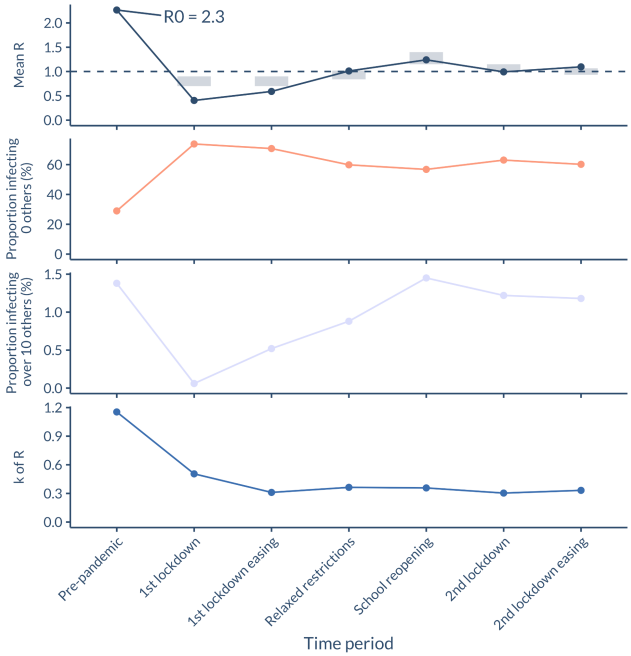


Figure 4. Estimates of the mean and dispersion of negative binomial distributions fitted to simulated secondary case distributions by time period in 2020. The dispersion parameter k gives an indication of the variation inthe secondary case distribution, with smaller values corresponding to greater variation and values less than 1 corresponding to very large variation. Also shown are the tails of the distribution, represented as the proportion of index cases infection over 10 others and 0 others, respectively. Grey boxes in R plot show the average upper and lower bounds (90% confidence interval) of the consensus estimates published SPI-M in the UK for the specified time periods.

Contribution to heterogeneity in secondary infections due to variation in contacts rates and viral load progression

To investigate the contribution of heterogeneity in contact rates and heterogeneity in viral load between individuals to variation in the secondary infection distribution, each was either fixed at its median value or allowed to vary by the full distribution. If both variables are fixed, then R is approximately Poisson with equal mean and variance (very large values of k). If contacts are fixed at their mean but viral load is allowed to vary between individuals, then k is around 2.7. If viral load is fixed at the mean trajectory, but contacts vary, then values of k are approximately equal to that of both variable contacts and variable viral load, indicating that variable numbers of daily contacts, as the denominator in the infection process, are the primary factor required for superspreading rather than some individuals being much more infectious than others (Figure 5).

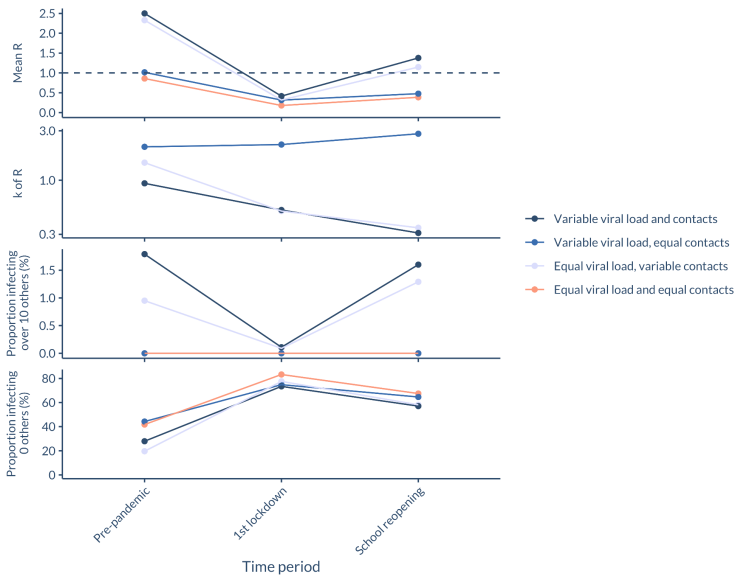
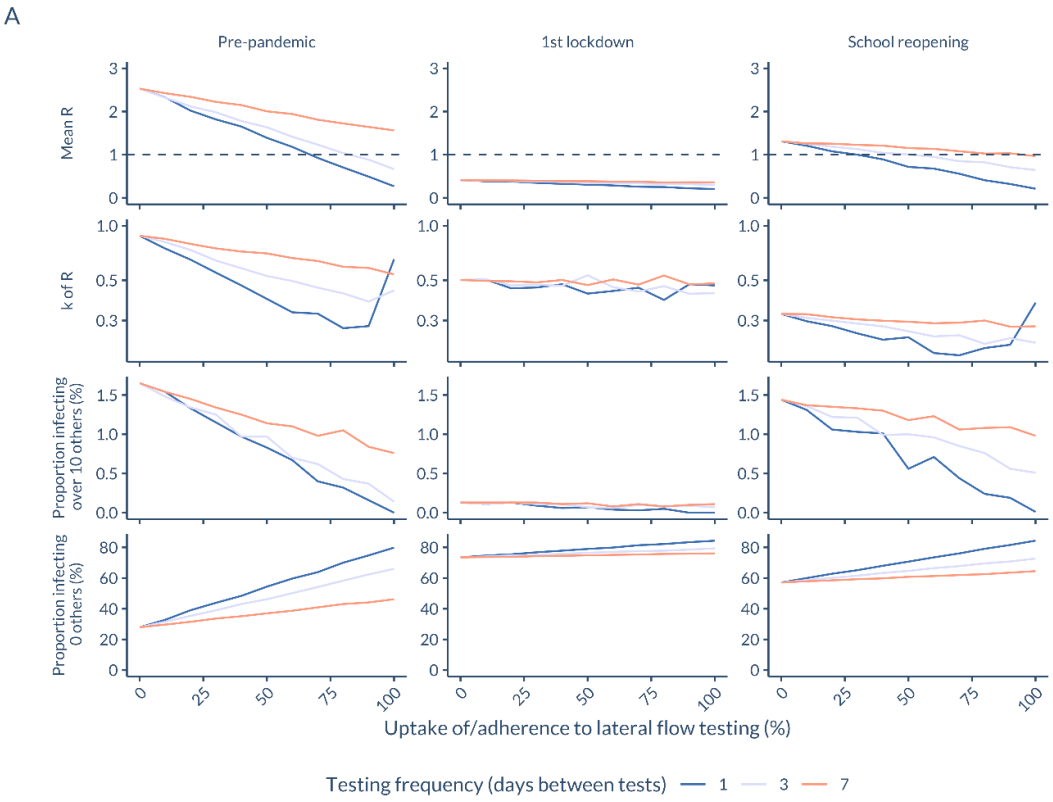


Figure 5. Estimates of the mean and dispersion of negative binomial distributions fitted to total daily contacts by period, with contact rates and viral load trajectories either set at their median or allowed to vary. The dispersion parameter k gives an indication of the variation in numbers of contacts, with smaller values corresponding to greater variation and values less than 1 corresponding to very large variation. Values of k for equal viral load and equal contacts not shown due to being very large (i.e., R is Poisson distributed).

Impact of rapid testing (regular testing vs. pre-event testing)

Finally, we assessed the hypothesis that if those with the highest viral loads are most likely to cause superspreading events, and lateral flow tests are most sensitive towards those with the highest viral loads, then lateral flow tests should be able to prevent superspreading events, here defined as infecting over 10 contacts. We modelled regular (1, 3, and 7 day frequency) and pre-event lateral flow testing (before meeting >=5, >=10, >=20 others) to determine the comparative effectiveness of rapid testing to control transmission, looking at three indicative timepoints before (BBC Pandemic) and during (1st lockdown (March-June) and the reopening of schools (September 2020)) the pandemic, and varying the rate of uptake or adherence to the specified policy. For pre-pandemic levels of contacts, uptake exceeding 60% is required to reduce R below 1 even if testing daily; if testing every 3 days, this must be above 80%; there is no level of uptake to reduce R below 1 if testing weekly (Figure 6A). For lockdown levels of contacts, testing does not appreciably reduce R below its already low level. For contact rates during relaxed restrictions in which schools have reopened, testing every 3 days may reduce R below 1 if uptake exceeds 50% (Figure 6A). Pre-event testing acts similarly, with high uptake necessary to reduce R below 1 for pre-pandemic levels of contact, though is effective in reducing R below 1 even if testing only when attending events exceeding 20 others for moderate levels of adherence during relaxed restrictions with schools open (Figure 6B). Both regular testing and pre-event testing reduce the rate of superspreading as defined as the proportion of individuals infecting over 10 others; however, there is also a substantial increase in the proportion of individuals that infect no one. This results in a decrease in *k* (greater overdispersion in the secondary case distribution) (Figure 6).


A
Pre-pandemic
1st lockdown
School reopening
Mean R
k of R
Proportion infecting over 10 others (%)
Proportion infecting 0 others (%)
Uptake of/adherence to lateral flow testing (%)
Testing frequency (days between tests) 1 3 7

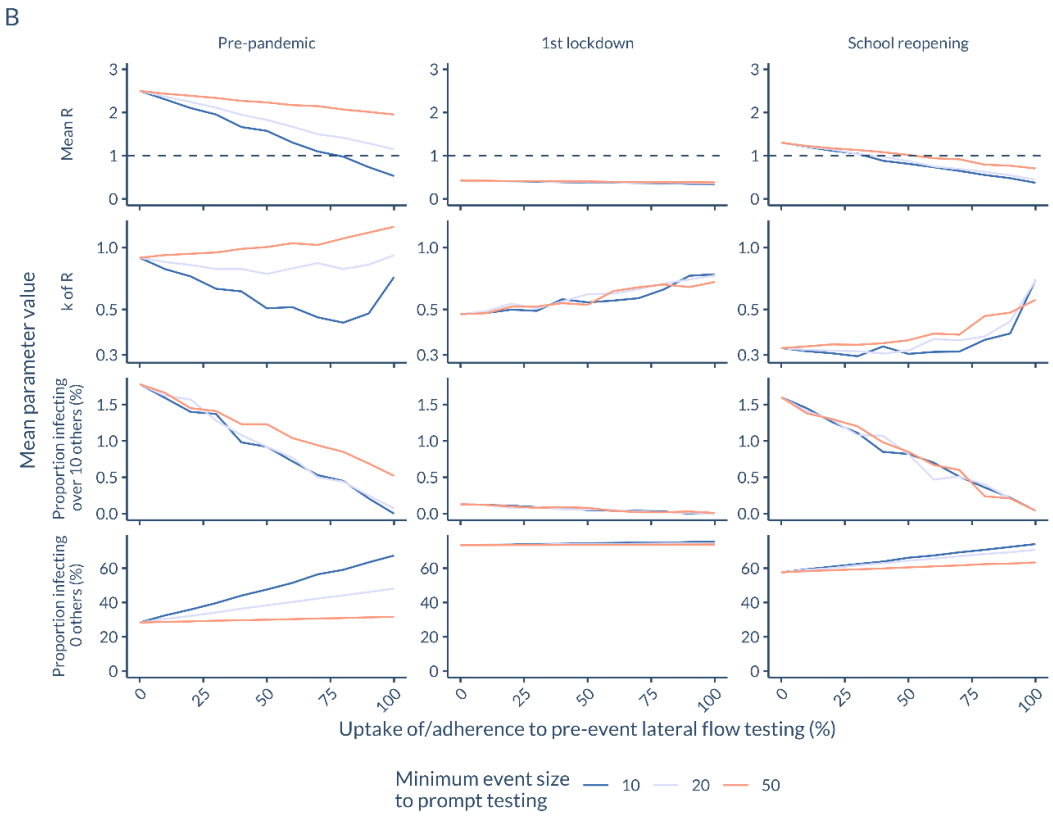

B
Pre-pandemic
1st lockdown
School reopening
Mean parameter value
Mean R
k of R
Proportion infecting over 10 others (%)
Proportion infecting 0 others (%)
Uptake of/adherence to pre-event lateral flow testing (%)
Minimum event size to prompt testing 10 20 50

Figure 6: Effect of regular (A) or pre-event (B) testing on R, *k*, and the proportion infecting 0 or over 10 others for varying levels of uptake/adherence and background contact rates.

Discussion

Daily contact rates became both lower on average (from ~12 per day to ~6 per day) and more overdispersed during the SARS-CoV pandemic in the UK in 2020 as some individuals maintained high contact rates (i.e., essential workers) while others had their number of daily contacts reduced to zero (those working from home). Using an individual-based model incorporating viral load trajectories and reported daily contacts, we find that we can plausibly infer both the mean reproduction number and the degree of overdispersion, *k*, over the course of the SARS-CoV-2 pandemic in the UK, closely matching contemporaneous estimates. *k* of R was estimated higher than that reported by Endo et al. (~0.1)[1], indicating other other factors such as contact closeness, contact setting (e.g. indoor vs. outdoor)[16], or variation in susceptibility (e.g., by age[17]) may further contribute to heterogeneity in transmission of SARS-CoV-2.

Contact heterogeneity was found to contribute more to superspreading than heterogeneity in viral load, as having a high number of contacts is required to infect a large number of people (as the denominator in the infection process), and that despite some individuals having much higher infectious potential than others, most individuals would pass through a high viral load period, with >80% estimated to have viral loads capable of infecting many others on at least one day of their infection. This indicates that superspreading is likely more a case of “wrong place, wrong time” than “wrong person”. Hence if reductions in contact rates can be targetted specifically at infected individuals during this window of high infectivity (e.g., by the daily testing of contacts[18]) then this may result in reductions in transmission while minimising the burden of quarantine. Studies such as Goyal et al.[3] investigating the superspreading nature of SARS-CoV-2 come to simular conclusions; our study differs in that we investigate the impact of changes in contact heterogeneity using real-world contact distributions from before and during the pandemic and estimate infectiousness and LFT detectability using linked data analyses[13]. Our use of reported heterogeneity in viral load trajectories[12] also contributes to a wider estimated distribution for the number of days individuals are likely infectious which closely match empirical daily sampling[19] and human challenge studies[5].

We hypothesised that lateral flow testing, by detecting the individuals with high viral loads when they were most infectious, would reduce transmission through reducing the potential for superspreading. This manifested as a decrease in the proportion infecting over 10 others while as the proportion infecting zero others increased substantially. This, perhaps counter-intuitively, resulted in a decrease in *k* as the relative increase in those infecting zero others exceeded that of the decrease in those infecting over 10 others. Hence, assessment of superspreading via the metric of the overdispersion parameter *k* alone may conceal changes in both the upper and lower tail of the secondary case distribution. Both regular testing and pre-event testing were effective in reducing R given high enough frequency or a low enough event size threshold, respectively, as long as uptake or adherence was high. Testing had the highest relative impact on transmission when contact rates were high (e.g pre-pandemic levels) as there were more potentially preventable exposures, meaning rapid testing could reduce R below the growth threshold of 1 while otherwise maintaining relatively normal contact rates; in contrast, testing during lockdown would have less impact as R was already below 1. This indicates that testing could be an effective, minimally disruptive intervention to reduce transmission if uptake/adherence could be maximised through incentivising use.

Our analysis has several limitations. The Comix contact survey was designed to be comparable to previous contact surveys in the UK, namely BBC Pandemic[7,8,14] and POLYMOD[11]; however, previous surveys required participants to list contacts individually to include other information such as contact age, sex, occupation, etc., meaning it was difficult to include mass contacts such as those one would make for example, at a large gathering, thus truncating the true contact distribution. From 18 May 2020 Comix introduced the option to record mass contacts as a count rather than listing each

individual as its own entry. This means pre- and early pandemic contact distributions are not directly comparable to those conducted later. A sensitivity analysis imputing a heavier tail for for BBC Pandemic based on the tails of relaxed restrictions periods during Comix led to a small increase in our estimate of R0 from 2.3 to 2.5 and a reduction in *k* from 1.2 to 0.9 (Figure S3). We assume that the probability of shedding infectious virus is equal to the probability of culturing virus, which in turn is dependent on intra-host viral load kinetics over the course of infection[13,19]. We focus on an index case and their infections to one other generation, which may underestimate second order effects which may result from considering a full contact network structure[6]. We do not consider other interventions which may have an additional impact on *R* such as vaccination, contact tracing, or self-isolation upon symptom onset. We also do not consider the impact of variants with increased transmissibility, and hence limit our analysis to 2020 before the widespread emergence of Variants of Concern such as Alpha, Delta, or Omicron. We assumed contacts for each individual within household were the same each day, whereas out of household contacts were sampled randomly for each individual per day, which may underestimate the overall contact rates and hence infection potential of specific individuals. We do not account for the possibility that high-contact individuals may make more fleeting contacts with lower transmission probability beyond sampling a duration of contact for each contact. We assume that self-isolating individuals are unable to fully self-isolate from their household members as reported by the majority of those surveyed by the ONS in England in April 2021[20]; further decreases in *R* may be possible if self-isolating individuals isolate themselves from household members.

In conclusion, the superspreading nature of SARS-CoV-2 transmission can be reasonably explained as occurring when an infected individual makes a high number of contacts during a highly infectious period lasting approximately 2 days on average, with over 80% of individuals being infectious enough on at least one day to be capable of causing a superspreading event, given they make a high number of contacts. Changes in the number of contacts observed throughout the pandemic in the Comix contact survey were able to explain changes in the reproduction number, with contact rates becoming more heterogeneous during the pandemic given lockdowns and changes in working practices. Regular or pre-event lateral flow testing may be a way to target individuals when most infectious and hence minimise the burden of NPIs while maximising reduction in transmission rates, provided moderate to high uptake.

Funding

Medical Research Council (MC_PC_19065); European Commission (EpiPose 101003688 - KLMW, AG, WJE); NIHR (CV220-088 - COMIX; 16/137/109 - BJQ, 16/136/46 - BJQ); Bill & Melinda Gates Foundation (OPP1139859 - BJQ); Wellcome Henry Dale Fellowship (206250/Z/17/Z – AJK); HPRU in Modelling & Health Economics (NIHR200908 - AJK; LACC); Wellcome Trust Senior Fellowship (WT098049AIA - SJDN); King's Together Rapid COVID-19 Call - SJDN, RPG; Huo Family Foundation Award - SP, SJDN.

References

1. Endo, A., Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group, Abbott, S., Kucharski, A. J. & Funk, S. Estimating the overdispersion in COVID-19 transmission using outbreak sizes outside China. *Wellcome Open Res.* **5**, 67 (2020).
2. Chen, P. Z. *et al.* Heterogeneity in transmissibility and shedding SARS-CoV-2 via droplets and aerosols. *eLife* **10**, e65774 (2021).
3. Goyal, A., Reeves, D. B., Cardozo-Ojeda, E. F., Schiffer, J. T. & Mayer, B. T. Viral load and

contact heterogeneity predict SARS-CoV-2 transmission and super-spreading events. *eLife* **10**, e63537 (2021).

4. Susswein, Z. & Bansal, S. Characterizing superspreading of SARS-CoV-2 : from mechanism to measurement. *medRxiv* 2020.12.08.20246082 (2020) doi:10.1101/2020.12.08.20246082.
5. Killingley, B. *et al.* Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge. Preprint at https://doi.org/10.21203/rs.3.rs-1121993/v1 (2022).
6. Ke, R. *et al.* Daily longitudinal sampling of SARS-CoV-2 infection reveals substantial heterogeneity in infectiousness. *Nat. Microbiol.* **7**, 640–652 (2022).
7. Klepac, P., Kissler, S. & Gog, J. Contagion! The BBC Four Pandemic - The model behind the documentary. *Epidemics* **24**, 49–59 (2018).
8. Klepac, P. *et al. Contacts in context: large-scale setting-specific social mixing matrices from the BBC Pandemic project*. http://medrxiv.org/lookup/doi/10.1101/2020.02.16.20023754 (2020) doi:10.1101/2020.02.16.20023754.
9. Jarvis, C. I. *et al.* Quantifying the impact of physical distance measures on the transmission of COVID-19 in the UK. *BMC Med.* **18**, 124 (2020).
10. Gimma, A. *et al.* Changes in social contacts in England during the COVID-19 pandemic between March 2020 and March 2021 as measured by the CoMix survey: A repeated cross-sectional study. *PLoS Med.* **19**, e1003907 (2022).
11. Mossong, J. *et al.* Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases. *PLOS Med.* **5**, e74 (2008).
12. Kissler, S. M. *et al.* Viral dynamics of acute SARS-CoV-2 infection and applications to diagnostic and public health strategies. *PLOS Biol.* **19**, e3001333 (2021).
13. Pickering, S. *et al.* Comparative performance of SARS-CoV-2 lateral flow antigen tests and association with detection of infectious virus in clinical specimens: a single-centre laboratory evaluation study. *Lancet Microbe* **2**, e461–e471 (2021).
14. Kucharski, A. J. *et al.* Effectiveness of isolation, testing, contact tracing, and physical distancing on reducing transmission of SARS-CoV-2 in different settings: a mathematical modelling study. *Lancet Infect. Dis.* S1473309920304576 (2020) doi:10.1016/S1473-3099(20)30457-6.
15. Davies, N. G. *et al.* Effects of non-pharmaceutical interventions on COVID-19 cases, deaths, and demand for hospital services in the UK: a modelling study. *Lancet Public Health* **5**, e375–e385 (2020).

16. Frieden, T. R. & Lee, C. T. Identifying and Interrupting Superspreading Events—Implications for Control of Severe Acute Respiratory Syndrome Coronavirus 2. *Emerg. Infect. Dis.* **26**, 1059–1066 (2020).

17. Lau, M. S. Y. *et al.* Characterizing superspreading events and age-specific infectiousness of SARS-CoV-2 transmission in Georgia, USA. *Proc. Natl. Acad. Sci.* **117**, 22430–22435 (2020).

18. Quilty, B. J. *et al.* Quarantine and testing strategies in contact tracing for SARS-CoV-2: a modelling study. *Lancet Public Health* (2021) doi:10.1016/S2468-2667(20)30308-X.

19. Ke, R. *et al. Daily sampling of early SARS-CoV-2 infection reveals substantial heterogeneity in infectiousness*. http://medrxiv.org/lookup/doi/10.1101/2021.07.12.21260208 (2021) doi:10.1101/2021.07.12.21260208.

20. Office for National Statistics. Coronavirus and self-isolation after testing positive in England. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandwellbeing/bulletins/coronavirusandselfisolationaftertestingpositiveinengland/8to13march2021 (2021).

Supplementary material

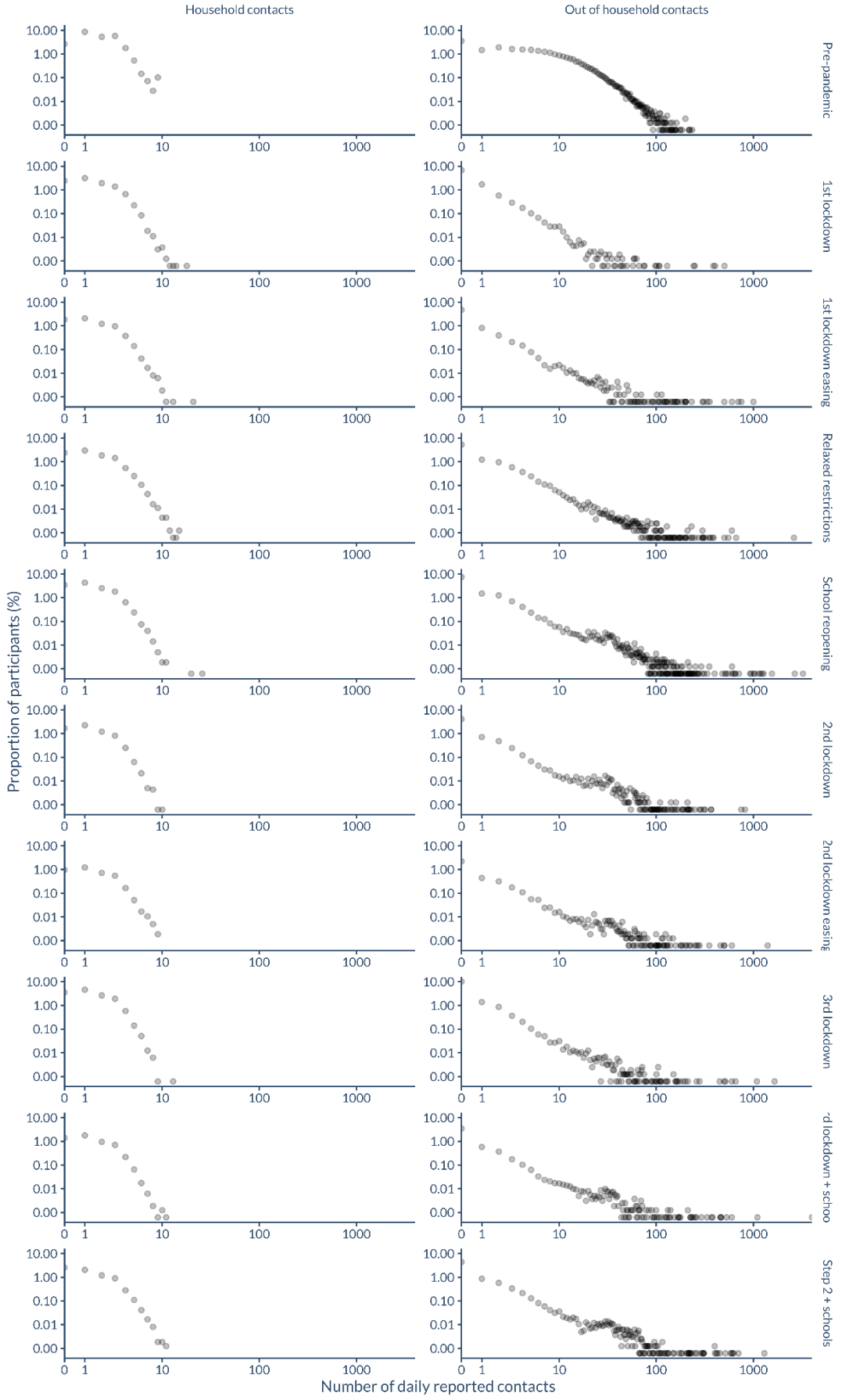

Household contacts
Out of household contacts
Pre-pandemic
1st lockdown
1st lockdown easing
Relaxed restrictions
School reopening
2nd lockdown
2nd lockdown easing
3rd lockdown
-d lockdown + schoo
Step 2 + schools
Proportion of participants (%)
Number of daily reported contacts
10.00
1.00
0.10
0.01
0.00
0
1
10
100
1000

Figure S1. Distribution of the number of reported daily contacts for all timepoints before (BBC Pandemic contact survey) and during (Comix contact survey) the pandemic in the UK in 2020.

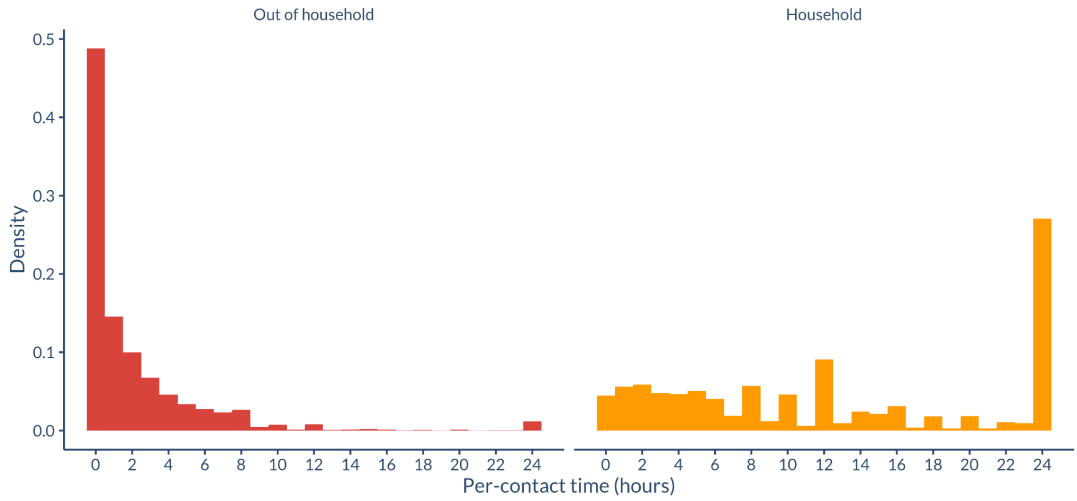


Figure S2: Distribution of the duration of contact for household and out of household contacts from the Comix contact survey in the UK.

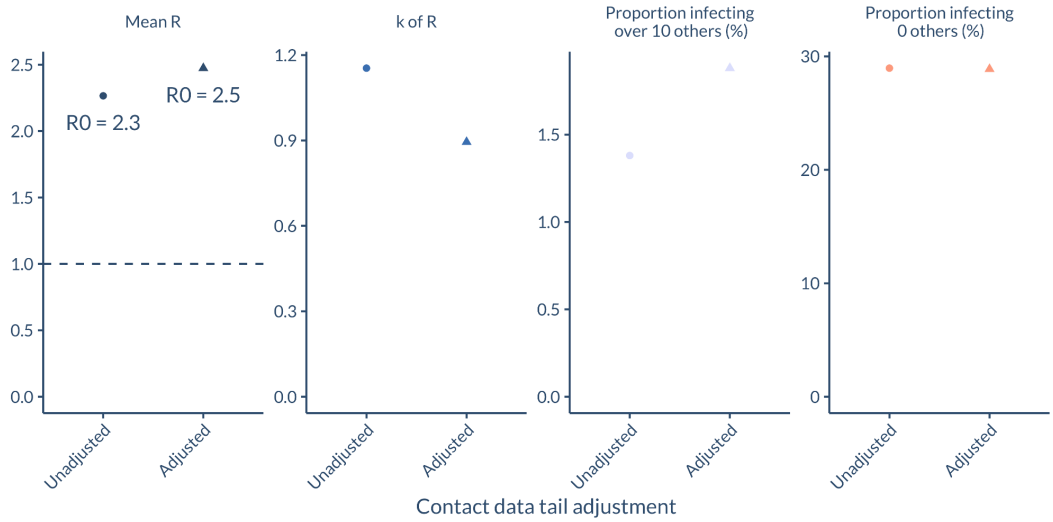


Figure S3: Sensitivity analysis of the effect on R, *k*, and the proportion of infected individuals infecting zero and over 10 others. imputing a heavier tail of the contact distribution for the pre-pandemic BBC Pandemic contact survey, which lacked the ability to record raw counts of high numbers of contacts.

4. Discussion

4.1 Summary of findings

In 2020, the outbreak of SARS-CoV-2 resulted in a global pandemic, prompting the implementation of strict non-pharmaceutical interventions (NPIs) on an unprecedented scale. As a novel pathogen there initially was no direct empirical evidence for the effectiveness of such measures; thus, it was crucial to use mathematical modelling to generate estimates of the potential impact of different NPIs and assess their individual and societal costs. These models were utilised to inform evidence-based recommendations in the face of a rapidly evolving situation. This thesis evaluates the effectiveness of various NPIs, including syndromic screening at airports, *cordon sanitaires*, quarantine, and isolation, and proposes novel strategies based on testing, such as test-to-release with PCR and daily contact testing with LFTs, to maximise effectiveness while minimising the burden of NPIs by specifically targeting measures at infectious individuals. The NPIs assessed can be broadly divided into two categories: those designed to prevent geographical spread, such as travel restrictions, and those designed to prevent transmission locally, such as contact tracing.

4.1.1 Preventing or delaying geographical spread

In the first aspect of my research, I assessed the effectiveness of different types of travel restrictions such as border closures and quarantine measures in preventing the spread of infectious diseases between countries or regions. This involved the use of mathematical modelling to simulate the potential impact of different travel restriction scenarios on the potential for importation.

My first published paper (Chapter 2.1) assessed the effectiveness of syndromic screening for fever at airports by simulating a flight from China to the UK. My findings suggested that screening for symptoms at exit and entry would likely miss around half of infected travellers. This was primarily due to the duration of the incubation period (5.2 days on average) reported by Li *et al.* [1] and the proportion asymptomatic (1 in 6) reported by Chan *et al.* [2], which meant that a substantial proportion of individuals would be infected but undetectable by thermal screening due to being either pre- or asymptomatic at the time of screening with the potential

to go on to spark outbreaks in the destination country. Sensitivity analysis, implemented in an interactive R Shiny app [3] indicated that longer incubation period durations relative to the duration of the symptomatic period, greater proportions of asymptomatic infections, and lower sensitivity of entry or exit screening would severely impact the effectiveness of such measures for other pathogens. These findings are in agreement with a 2015 review by Gostic *et al.* [4] which found effectiveness "depends strongly on pathogen natural history and epidemiological features, as well as human factors in implementation and compliance", with screening being relatively less effective for pathogens such as Ebola with longer incubation periods and more effective for pathogens such as influenza with shorter incubation periods (though notably still missing a substantial proportion of infections). Overall, this indicates that syndromic screening of travellers from an outbreak epicentre is unlikely to be effective to prevent importation to other countries for most pathogens, and that if this was the desired goal, then stricter measures such as the quarantining and/or testing of travellers would be required. However, further analysis indicated that such measures could delay an outbreak elsewhere by approximately 8 days in the initial stages of an outbreak when the absolute number of infected travellers was low, though would be shorter in large rapidly growing epidemic [5].

The second analysis conducted (Chapter 2.2) aimed to assess the effectiveness of the cordon sanitaire imposed on Wuhan [6] which aimed to limit spread to other parts of China in the context of the *Chunyun* Spring Festival holiday travel period. Using real-world mobile phone travel data [7] and estimated SARS-CoV-2 prevalence in Wuhan [8], I estimated the rate of exportation over time to other provinces and simulated outbreaks using a branching process model and included counterfactuals of what would have occurred had there been no cordon sanitaire and no *Chunyun*. Based on the volume of outbound travel and likely number of infections in Wuhan in the weeks prior to the imposition of the cordons sanitaires, local transmission likely began in the first week of January in the four cities studied, and that local infections were likely in the thousands by the time the *cordon sanitaires* came into force. While the *cordon sanitaires* rapidly reduced the number of imported cases after it was imposed, local epidemics were likely already underway. I found no appreciable difference in the epidemic progression after this date when compared to the counterfactual scenario of no *cordon sanitaires* in the absence of local R-reducing interventions. Reducing R below 1 to represent the strict non-pharmaceutical

interventions imposed in most of mainland China led to a fall in infections consistent with those observed in regions such as Guangdong [9]. My results indicated that travel restrictions around a disease epicentre are unlikely to contain an outbreak when 1) there is a high volume of outbound travel, 2) there is a growing, mostly undetected epidemic with an R_0 significantly higher than 1, as the probability of a sufficient number of infections being exported to exceed the outbreak threshold is high. Therefore, cities, regions, and countries with a high volume of travel from a disease epicentre should assume that they have undetected epidemics and take appropriate measures to identify cases and limit spread. Other studies estimated the Wuhan cordon sanitaire to have had a modest effect on the epidemic in China, delaying epidemic progression on the order of 3-5 days, but a more marked reduction internationally due to the relatively lower volume of international travel out of Wuhan than within China [10, 11].

The third analysis (Chapter 2.3) assessed the effectiveness of quarantining travellers for differing durations and the marginal utility of testing travellers by PCR. By the middle of 2020 most countries had introduced a 14-day quarantine period for arrivals based on the upper bound of the incubation period where it was assumed that almost all infected individuals would have become symptomatic and hence enter isolation. Such a policy was designed to prevent transmission which may occur from pre-symptomatic individuals [12, 13], though significantly burdened both the individual isolating (the majority of which unlikely to be infected) [14] and economies dependent on travel and tourism through disincentivising travel [15, 16]. Using an individual-based model incorporating the sensitivity of PCR over the course of infection [17], I found that PCR testing could be used to reduce the typical duration of quarantine by half by testing on day 7 post-arrival with minimal loss of effectiveness as measured in terms of transmission potential prevented. The expected rate of importation depends on the product of travel volume and estimated prevalence in the origin country, each of which being difficult to determine accurately and in a timely manner and changing substantially over the course of the pandemic as epidemic waves rose and fell and travel slowly recovered [18]. Furthermore, the potential of arriving infected individuals to cause new chains of transmission would depend on the local transmission rate which would be modulated by factors such as the stringency of local NPIs (e.g. whether the destination country was in lockdown) and the build-up of immunity through infection and vaccination.

The fourth and final analysis on travel measures (Chapter 2.4) assessed expected importation rates given estimated prevalence in an origin country (inferred from case under-ascertainment rates based on reported deaths and the infection fatality rate [19]) and travel volume (from OpenSky [20]), then estimated the fraction prevented by different quarantine and testing regimens, including daily lateral flow testing. Following the approach of Russell *et al.* [18], I calculated the proportion of importations expected under each scenario relative to to domestic incidence to contextualise the relative importance of importations to an ongoing domestic epidemic. Thus, this allowed for individual countries to assess which travel restriction strategy, if any, may be beneficial; for countries with high domestic incidence, the likely ratio of importations to domestic incidence was likely very small, indicating little benefit to implementing stringent travel restrictions, though for countries with low, controlled domestic incidence, importations would make up a substantial proportion of incidence, hence meaning more stringent measures would have a higher relative benefit. This however was complicated by the emergence of new variants of concern - here the international spread of B.1.1.7 (Alpha) was assessed - which could be treated as entirely new pandemics at the outset with countries initially having very low incidence. Testing was found to be beneficial in reducing or replacing (with daily testing) the standard 14-day quarantine period, though depended on assumptions of lower adherence to quarantine relative to that of adherence to isolation following a positive test.

4.1.2 Limiting community spread

The second aspect of my thesis was concerned with the implementation of domestic interventions, namely contact tracing and testing. Contact tracing, which consisted of the identification and quarantine of exposed contacts of cases, had been implemented with varying degrees of success across the world during the middle and latter half of 2020 [21]. Concerns over the time taken to test cases and trace contacts reported by NHS Test & Trace [22] relative to the infectiousness profile for SARS-CoV-2, and reportedly low adherence to the 14-day quarantine period in the UK [23] prompted an analysis into assessing the system's effectiveness and determining if alternative strategies based on the use of rapid testing with LFTs may be beneficial (Chapter 3.1). Accounting for individual-level viral load trajectories from Kissler *et al.* [24], LFT sensitivity given viral load from the University of Oxford/ PHE Porton Down LFT

evaluation [25] and assumptions of the differential rate at which individuals would adhere to quarantine in the absence of symptoms, quarantine in the presence of symptoms, and isolation following a positive test, I found 7 days quarantine followed a PCR or LFT, or alternatively, daily LFTs for 5 days following notification, to be likely non-inferior to a 14-day quarantine without testing. I identified speed as a key factor in the success of contact tracing; delays in the time between index cases taking a PCR test and the subsequent tracing and isolation of contacts would substantially impact its effectiveness, corroborating findings by Kretzschmar *et al.* [26] and Ferretti *et al.* supporting the use of digital contact tracing to shorten these delays [27]. Additionally, the differential rate at which individuals would adhere to quarantine in the absence of symptoms, quarantine in the presence of symptoms, and isolation following a positive test would be important, given their perception of risk in the presence or absence of knowledge of their infection status. This would improve effectiveness by 1) vastly shortening the time to return the index cases test, 2) allowing for the daily testing of contacts, allowing for the avoidance of quarantine if negative, and 3) quickly detecting infectious contacts who could then enter isolation, and be more likely to adhere given they knew their infection status.

The second analysis (Chapter 3.2) on community spread assessed the contribution of heterogeneity in contacts (as measured by the BBC Pandemic [28] and Comix [29] contact surveys in the UK) and viral load (from the longitudinal sampling study by Kissler *et al.* [30]) to heterogeneity in transmission. Restrictions enacted during the pandemic in the UK led to a decrease in average contacts but also an increase in the variation in contact distributions compared to pre-pandemic, likely as a result of the contrasting recommendations of working from home where possible, and essential working plus children attending school. This method allowed for the inference of R and k, the overdispersion parameter of the secondary case distribution, for different periods of the pandemic in the UK, with estimates of R closely matching contemporaneous estimates. Heterogeneity in contacts was found to contribute most to heterogeneity in the reproduction number, as a high number of contacts are a necessary prerequisite to infecting a large number of people, and as most individuals were estimated to go through a highly infectious period of around two days on average regardless of individual variation in viral load progression. I found that lateral flow testing, by rapidly identifying the most infectious cases with high viral loads, could reduce overall transmission in a targeted fashion through

the prevention of superspreading either through regular testing or pre-event testing.

4.2 Research in the context of an ongoing pandemic

My PhD research describes the factors impacting the effectiveness of non-pharmaceutical interventions to reduce transmission of SARS-CoV-2 throughout the COVID-19 pandemic, and identifies pragmatic strategies to both improve effectiveness both in terms of the reduction in transmission as well as a reduction in the burden of restrictions through the use of testing. Many of these findings had direct policy implications. Through my modelling, I highlighted issues with the methods used successfully for past outbreaks of high-consequence infectious disease such as SARS, namely those focused on identifying cases through the appearance of symptoms (e.g. syndromic surveillance at airports), due to the duration of the incubation period, substantial asymptomatic proportion, and high likelihood of pre- and asymptomatic transmission for SARS-CoV-2. As it became apparent that due to these factors SARS-CoV-2 would be unable to be effectively controlled using such "light-touch" measures, leading to the imposition of highly stringent measures such as 14-day quarantines and lockdowns, I identified possible strategies to lessen the burden of such restrictions, namely through the use of testing to identify cases for isolation while allowing for the release or avoidance of quarantine entirely of those not infected. Additionally, I examined the hypothesis that lateral flow tests, by rapidly identifying the most infectious cases with high viral loads before high-contact events, could reduce overall transmission in a targeted fashion through the reduction in the number of superspreading events.

My findings show the importance of speed and timing in control, from when measures such as *cordon sanitaires* should be implemented, to the optimal timing of testing of travellers and contacts of cases, due to the short time between generations of infection. Thus, effort should be made to minimise delays where possible. For testing, this can involve the use of rapid tests over PCR to rapidly return test results, for which their lower relative sensitivity can be offset by frequent repeated usage made feasible due to their low cost and ease of use [31]. Another key factor identified is a lack of adherence, which can substantially limit the effectiveness of NPIs. There may exist an inverse correlation between the stringency of a measure and the rate of adherence, with individuals less able or willing to comply with interventions which carry

greater burdens. Increased adherence may and thus greater effectiveness may be sought through ensuring a package of support [32], or by investigating and implementing alternative, less burdensome, strategies.

These analyses were conducted in real-time as the situation surrounding the pandemic evolved. Analyses conducted earlier in the pandemic (such as Chapter 2.1, conducted in late January 2020) made use of what sparse data there was available, such as the incubation period duration from Li *et al.* [1] and proportion asymptomatic from Chan *et al.* [2]. As such, model parameterisation was constrained by data availability, and typically required sampling from marginal distributions from independent studies. As further studies were conducted over the course of the pandemic that better characterised individual-level dynamics (such as viral load progression from Kissler *et al.* [30] and the Comix contact survey [29]), this allowed for the development of more sophisticated models which could capture dynamics more closely, such as those in Chapter 3.1 and Chapter 3.2). Such models can capture heterogeneity in data, such as variation in viral load and daily contacts, to not only illustrate possible uncertainty in estimated impact but leverage such heterogeneity to guide and target control strategies where they may have the greatest effect whilst minimising negative externalities (e.g., rapid testing to prevent superspreading events).

The often rapidly-changing circumstances often required that policy decisions had to be made equally rapidly, often in situations where the evidence was unclear. The use of mathematical modelling in my analyses meant that these decisions could be made informed by a synthesis of the available evidence within a logical framework. Furthermore, by accounting for uncertainty in the data in my modelling, I was able to communicate that uncertainty in the form of a region of confidence around point estimates to policy-makers. For example, in the modelling assessment of daily lateral flow testing for contacts (henceforth daily contact testing (DCT), Chapter 3.1), the finding on DCT reducing transmission to approximately the same degree as a 10-day quarantine, albeit with wide uncertainty, led to the initiation of several studies assessing DCT on engagement and acceptability [33, 34, 35, 36] as well as randomised controlled trials in schools and the adult population in the UK to assess the impact on transmission [37, 38]. Given the potential benefits of such a policy (allowing uninfected contacts to continue daily activities), these trials allowed for a small potential loss of effectiveness in transmission

terms by assessing DCT on the basis of non-inferiority in secondary attack rates - DCT being not unacceptably less effective than the current strategy of a 10-day quarantine period for contacts in terms of the proportion of their contacts that became infected - with the adult trial using a non-inferiority margin of 1.9% higher attack rates in the DCT arm (derived from the results of the schools trial [37]). The results of these studies were broadly aligned with that of the modelling presented in Chapter (3.1), that DCT was non-inferior to a 10-day quarantine in terms of transmission reduction with evidence of superiority (attack rates in the DCT arm were -1·2% (95% CI –2·3 to –0·2) that of the 10-day quarantine arm, substantially lower than the 1.9% increase non-inferiority margin), possibly due to the rapid detection of cases and increase in cautious behaviour following a positive test. Following these trials, DCT was adopted as national policy in the UK in December 2021 during the Omicron wave and with national uptake reportedly between 50 to 60% [39]. As well as demonstrating the applicability of DCT to control transmission and reduce the adverse effects of quarantine policy, the pipeline of evidence from modelling providing the basis to conduct trials, to eventual adoption as national policy, is a potential template for an evidence-based response to future pandemics.

The aim and intent of travel restrictions also changed significantly over the course of the pandemic. Travel restrictions during the COVID-19 pandemic were initially implemented with the ambition of containing the virus and mitigating or delaying the onset of outbreaks in regions yet unaffected. However, the evolving nature of the pandemic necessitated the reassessment and adaptation of these strategies. Firstly, the global reach of the SARS-CoV-2 virus made it evident that the initial objective of containment had not been entirely successful. By mid-2020, the transmission of the virus was firmly established worldwide, leading to widespread community transmission far beyond the initially identified centres of infection. This realisation implied that the benefit derived from travel restrictions - in terms of preventing new introductions of the virus - had significantly reduced, given the widespread local transmission. Secondly, in response to the global spread and rapidly evolving situation, nations implemented several domestic interventions to control transmission. The relative risk posed by imported cases was therefore altered in the context of these domestic interventions. The third significant development was the emergence of new SARS-CoV-2 variants, which were found to be more transmissible [40], severe [41], and able to evade immunity [42]. The potential for these

novel variants to be imported, and their potential to evade established domestic interventions, brought a renewed focus on the strategic implementation of travel restrictions [43]. Nations needed to consider the evolving risk landscape posed by these variants and balance them against the economic, social, and public health ramifications of continued travel restrictions. However, some travel measures may have additional benefits beyond that of reducing importations, such as testing enabling the estimation of prevalence in other countries, or sequencing of tests allowing for the identification of novel variants [43].

4.3 Limitations

4.3.1 Test sensitivity and infectiousness

A substantial proportion of this thesis is dedicated to the assessment of lateral flow tests. Lateral flow tests became available to order to home through the NHS in the UK in early 2021 following assessment by the University of Oxford/PHE Porton Down [25] and a mass testing trial in Liverpool [44], with the intended use being to take a test twice weekly to detect asymptomatic or pre-symptomatic infections. This policy attracted criticism from some aspects of the scientific community, with concerns over the reported sensitivity of LFTs in the Liverpool trial [45], with the overall reported sensitivity being 53.4% [44]. However, individuals with cycle threshold (Ct) values greater than 25-30 (on an inverse log scale to viral load) were estimated to be unlikely to account for a substantial proportion of onwards transmission [46]; there also exist systematic differences in how PCR assays report Ct values, which can vary substantially between labs [47]. Additionally, PCR, by amplifying viral RNA, is highly sensitive to even very small volumes of genetic material; such RNA can persist for weeks following the cessation of infectiousness, as defined by the generation time as well as the duration of time that live virus can be successfully cultured, as determined by daily longitudinal sampling and human challenge [48, 49, 50]. Such studies found high agreement between LFT positivity and culture, indicating that they may be sensitive and specific for infectious individuals, especially when used repeatedly. Studies involving the repeated collection of samples from individuals over the course of infection with samples tested by multiple diagnostic methods (PCR, LFT, culture) may help with determining the necessary duration of quarantine and isolation and the marginal utility of testing early in an outbreak, such as for Mpox [51].

However, there still remains uncertainty over the relationship between culture and infectiousness (and by extension, LFT sensitivity and infectiousness) for SARS-CoV-2; transmission is a very difficult process to observe directly, and while live virus is a necessary criterion for transmission, culture may be imperfectly sensitive owing to the expertise required to carry out the laboratory process [52]. It may also be possible that a test result from one sampling site (e.g. nose or throat) may miss infections that may have been detected if another was swabbed; for example, it appeared that Omicron became detectable in the throat and mouth before the nose [53]. The relative timings of test positivity with the appearance of symptoms is also unclear, and possibly in flux, with the incubation period appearing to shorten for more recent variants [54], with positive tests anecdotally following several days later. However, this is substantially confounded by the development of immunity over the course of the pandemic through infection and vaccination; it has been hypothesised that pre-existing immunity brings forward the development of symptoms as part of the immune response [55], as evidenced by the incubation period reported for Omicron (3.8 days average) closely matching that of seasonal coronaviruses for which the population has significant prior immunity (3.2 days average) [56]. Further study however is required to confirm such a phenomenon, as it has significant implications for individual's behaviour following the appearance of COVID-19 symptoms but in the absence of a positive test, as well as the duration of quarantine, isolation, and test to exit strategies that typically index "day 0" as the first day of the onset of symptoms [57].

4.3.2 Consideration of population and network effects

The models used in this thesis have primarily been individual-based analyses of one generation of infection (with the exception of paper 2, in which a branching process model was used). This typically consisted of modelling the infectivity and detectability of an infected individual over the course of their infection, with the effectiveness of interventions determined by the truncation of an individual's infectious period through quarantine or isolation following a detection process. The advantage of this model structure is that it allows for the simulation of individual-level heterogeneity in the infectivity and detectability processes through sampling from reported probability distributions, which then translates into uncertainty in the modelled outcome of prevented transmission potential. However, by only modelling one generation I do not account for some emergent properties of an epidemic process, namely the depletion of

the susceptible population through the generation of immunity over the course of (whether that be via infection or vaccination), or network effects.

Early in an epidemic of a novel pathogen it may be reasonable to omit the consideration of a finite susceptible population from a model as almost everyone will be susceptible, with its inclusion in a model having little impact on results (assuming homogeneous mixing; though this may be an overly simplistic assumption, as discussed in the next section). At this stage, where there are few cases, it may be more important to divert computational resources into more closely modelling stochasticity in infections, which can determine the probability of extinction or outbreak probability [58]. However as an epidemic progresses through a population, immunity builds, impacting transmission. The effect of this on the effectiveness of non-pharmaceutical interventions is three-fold. One is that if contacts of cases are no longer susceptible, then there is by definition no transmission to prevent to these individuals, so the maximum effectiveness an intervention such as testing can have is lower. Another is that the effective reproduction number will trend lower due to the build-up of susceptibility; if R is close to but above 1, then even a small effect of an intervention can have an outsized impact by reducing R below 1, leading to a decline in incidence. The third is that as immunity builds, the average severity of infection declines, leading to a change in the cost-effectiveness of strict intervention measures to reduce transmission (i.e., the harms and costs associated with an intervention may come to outweigh the harms and costs associated with infection). The emergence of the Omicron variant (associated with an increase in the rate of reinfection) in late 2021 meant that non-pharmaceutical interventions such as testing would become of use again to reduce transmission as well as ensure key parts of society (such as the healthcare system) continued to function in the face of a large number of people isolating due to infection through strategies such as test to release after initially testing positive for SARS-CoV-2 [59].

Another limitation of modelling a single generation is to not account for population structure and the higher-order dynamics which result from a connected, clustered social contact network. Other studies assessing regular rapid testing and contact tracing such as Pavelka *et al.* [60] and Fyles *et al.* [61] modelled transmission between individuals clustered into households, concluding that given the high risk of transmission within-household compared to between household, it may be more appropriate and effective to treat households as a unit when

quarantining post-positive test. Firth *et al.* [62] modelled contact tracing on a real-world contact network and assessed index case isolation, primary contact tracing (contacts of the index case), and secondary contact tracing (contacts of contacts of the index case), finding that both primary and secondary contact tracing could substantially reduce outbreak size, though in effect generating a "local lockdown" with up to 40-50% of the population in quarantine at the peak of the outbreak, rather than a targeted strategy. A policy testing to release, while reducing the number in quarantine, led to an increase in outbreak size as more individuals again became susceptible to infection. This dynamic of temporary "susceptible thinning" was hypothesised to have been one of the reasons why cases peaked and rapidly fell in the UK during the Euro 2020 football tournament, as high contact rates led to an increase in cases, subsequently followed by a large number of people quarantining of testing themselves as a contact [63]. It is unclear how the effectiveness of rapid testing changes when considering network effects, though it could be possible that available rapid testing leads to earlier and greater awareness of infection risk in contacts and contacts of contacts who then modify their behaviour or test themselves, rapidly controlling outbreaks.

4.3.3 Adherence to NPIs

A critical variable identified in my analyses is the impact of behaviour on the efficacy of public health interventions. Measures such as quarantine, isolation, and testing rely on individuals to comply in order for them to be effective, with low adherence significantly limiting their potential impact. There are many reasons why individuals may comply or not comply with a given measure, including knowledge of disease risk, knowledge of the importance of interventions in reducing transmission, social or cultural norms, access to resources, and individual psychological and emotional factors [32, 14]. One major factor is that of whether individuals have the financial means to self-isolate, which may entail significant loss of income if missing work, especially in countries where sick pay is low or absent. The UK implemented a £500 self-isolation payment scheme, though high rejection rates for applicants (7 in 10 rejected) may have limited its effectiveness [64]. Labour unions have called for sick pay to be a focus of the UK Covid inquiry [65]. Additionally, the changing circumstances of a pandemic require governments and public health authorities to issue new and updated rules and guidance regularly, some of which may be contradictory to previous guidance [66]. These factors have a

measurable effect on adherence, which can fluctuate over time [67]. The assumptions about behaviour in this thesis are simplistic due to the sparsity of data when the analyses were conducted and the difficulty in accurately predicting how individuals and societies may react to novel control measures and other future circumstances, such as the emergence of a more transmissible and severe variant such as Omicron.

The incorporation of behaviour into infectious disease models is an area of growing interest [68, 69, 70], but it poses challenges such as the potential for feedback loops where models based on certain assumptions about cautious behaviour produce optimistic forecasts, which prompt a relaxing of behaviour and subsequently worse real-world outcomes. To improve the accuracy of estimations, communication of public health messages, and the effectiveness of infectious disease control measures, a closer integration between behavioural science and infectious disease dynamics should be sought [69].

4.3.4 Assessing the impact of NPIs for an emerging endemic pathogen

One aspect of dynamics not explored in this work is the overall relevance of NPIs in a pandemic where it becomes apparent that elimination is not possible. Early during the SARS-CoV-2 pandemic a policy of "containment" was pursued as per WHO recommendations for pandemic influenza [71]. Though as large outbreaks began to occur outside of China the focus shifted to "mitigation", i.e., acknowledging the likelihood that a substantial proportion of the global population would eventually become infected with SARS-CoV-2, though attempt to avoid the worst outcomes of such an event (e.g. through slowing infections and "flattening the curve" to prevent a sharp peak leading to health system collapse and substantial morbidity or mortality [72]). The use of lockdowns leading to a decline in incidence in many countries reignited the debate around elimination (or "Zero COVID"), with some countries including Australia, New Zealand, Singapore and China achieving and sustaining elimination for an extended period of time through strict travel restrictions and rapid control of outbreaks. However, the emergence of more transmissible variants of SARS-CoV-2 such as Alpha and Delta meant such outbreaks were unlikely to be controlled, leading to the eventual transition from "Zero COVID" to "living with COVID", i.e., endemicity. As elimination became infeasible with the emergence of Omicron, which was able to partially evade immunity to reinfect those pre-

viously infected as well as those previously vaccinated [42]) any NPI implemented to reduce transmission could not "prevent" infection, though could "delay" infection until a point in the future. This then begs two questions. The first is "how much can we delay?" which is a question that may be answered for specific NPIs or combinations of NPIs using mathematical modelling (e.g. delays from travel restrictions estimated for COVID and pandemic influenza [5, 73, 74]). The second is "what can we use such a delay for?". If infection is certain, then reducing the severity of that eventual infection is paramount, e.g. through the use of vaccines preceding infection, or treatments. However, these must be developed and trialled in a population to determine their safety profile and effectiveness, a process that takes time. Organisations such as CEPI (the Coalition for Epidemic Preparedness Innovations) have set a target for vaccines against a future pandemic to be authorised 100 days after the viral sequence is identified (this took 326 days for SARS-CoV-2) [75]. Thus it follows that if NPIs can be used to suppress transmission until a vaccine is demonstrated to be safe, efficacious, licensed, and administered to a population, then mortality can be minimised. However, the assessment of vaccine efficacy requires that there be infections to prevent; if due to suppression there are few infections then this becomes more difficult to demonstrate (suggestions to circumvent this include human challenge studies or correlates of protection (e.g. antibody generation) [76, 77]). Another possibility is that some countries will have the means to sustain elimination while others may not, a situation likely to be exploited in vaccine development [78]. Nonetheless, interventions such as lockdown and quarantine that may be implemented to delay infections until after vaccine licensure and mass administration will still result in a significant burden on individuals and society, and alternative measures should be sought where possible (e.g. testing).

4.3.5 Generalisability

The emergence of SARS-CoV-2, as well as recent outbreaks of zoonotic diseases such as Mpox (formerly Monkeypox) [79] and Sudan ebola virus in Uganda [80], highlights the likelihood and potential frequency and intensity of future outbreaks of high-consequence infectious diseases. Factors such as climate change and changes in land usage may contribute to this increase [81]. Therefore, significant investment in preparedness for future pandemics is warranted to mitigate their impact. The models used in this thesis provide a foundation for the rapid evaluation of control strategies for future outbreaks by replacing the SARS-CoV-2 pa-

rameter distributions with those of other pathogens; differences in the transmission dynamics and natural history of infection are likely to influence the effectiveness of such strategies. For example, the approximately 50% shorter timescales of influenza generation times compared to SARS-CoV-2 [82] mean reducing delays in detection and isolation are even more important, though policies based on syndromic surveillance may be relatively more effective. However, such data may initially be unavailable at the outset of outbreaks of novel pathogens as it was for SARS-CoV-2, requiring rapid elucidation. My research highlights the importance of studies such as that of infector-infectee pairs in contact tracing to determine key variables such as incubation period, serial interval, and secondary attack rate, as well as daily longitudinal sampling and human challenge studies to examine viral load dynamics on an individual level. Testing samples from individuals with multiple diagnostic methods (including PCR, rapid tests, and culture) ensures test probabilities are internally consistent in terms of methodology (e.g., PCR protocol) and can be assessed conditionally upon each other, an advantage over sampling from marginal distributions from separate studies. This data will be essential for determining the impact and necessary duration of quarantine, isolation, and testing in future pandemic response through mathematical modelling.

4.4 Future work

The COVID-19 pandemic led to the use of quarantine and testing on a level previously unseen. Novel strategies involving self-testing by individuals rather than by medical professionals have opened the door to "decentralized testing" [83] allowing for greater autonomy and rapidity in epidemic response. However, there are still key unknowns about the ways in which individuals use tests and how it impacts behaviour, such as the propensity to quarantine or isolate in the presence or absence of symptoms as well as positive or negative tests. Given results are available instantly to individuals, the marginal utility of formal contact tracing systems above that of informal tracing (in which individuals notify their own contacts) should also be examined. Further research is also needed to examine the social costs and acceptability of quarantine and testing in different demographic groups, and determine strategies to alleviate their burden where possible. While our understanding of the relationship between viral load, infectiousness, and detection has improved due to high-resolution daily longitudinal sampling

and human challenge studies [49, 50, 30], there remain uncertainties around the interaction of such processes with vaccination, prior infection, and new variants of SARS-CoV-2. Additional challenge studies for SARS-CoV-2 are underway assessing these factors as well as the effect of inoculum dose [84] which may improve our understanding of the proxies of transmission. Incorporating the developed aspects of the model (heterogeneity in viral load kinetics, contacts, quarantine and testing behaviour) into a population model with a network structure may allow for the elucidation of higher-order effects such as the depletion of susceptibility (short-term through quarantine in "susceptible thinning" [63] or long-term through immunity), or potential group-level behavioural changes such as that of one individual in a social network testing positive and informing their contacts, who may act more cautiously and begin testing themselves. Applying the model to other pathogens such as pandemic influenza, perhaps assessing strategies such as test-to-treat with antivirals, will be useful to update pandemic preparedness policy [85].

4.5 Concluding remarks

My PhD research examines the effectiveness of non-pharmaceutical interventions to reduce transmission of SARS-CoV-2 during the COVID-19 pandemic and identifies strategies to improve effectiveness and reduce the burden of restrictions through testing. Through my modelling, I highlighted the limitations of traditional methods of identifying cases through symptoms, such as syndromic surveillance, due to the duration of the incubation period, high proportion of asymptomatic cases, and likelihood of pre- and asymptomatic transmission for SARS-CoV-2. I identified possible strategies to reduce the burden of restrictions such as quarantines and lockdowns by using testing to identify cases for isolation and prevent superspreading through the rapid identification of the most infectious cases with high viral loads. My findings also emphasise the importance of speed and timing in control, the use of rapid tests over PCR, and the inverse correlation between the stringency of a measure and the rate of adherence. Effort should be made to minimise delays and ensure individuals are able to comply with interventions through support and alternative, less burdensome strategies. My research was conducted in real-time as the situation surrounding the pandemic evolved and thus model assumptions were constrained by data availability. As further studies were conducted over the

course of the pandemic, more sophisticated models were developed that capture heterogeneity in the data to guide and target control strategies where they have the greatest effect while minimising negative externalities. This work provides a framework to assess the value of NPIs for future pandemic response.

4.6 References

[1] Q. Li et al. “Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia”. In: *New England Journal of Medicine* (Jan. 2020), NEJMoa2001316. ISSN: 0028-4793, 1533-4406. DOI: 10.1056/NEJMoa2001316. (Visited on 02/20/2020).

[2] J. F.-W. Chan et al. “A Familial Cluster of Pneumonia Associated with the 2019 Novel Coronavirus Indicating Person-to-Person Transmission: A Study of a Family Cluster”. In: *Lancet (London, England)* 395.10223 (Feb. 2020), pp. 514–523. ISSN: 1474-547X. DOI: 10.1016/S0140-6736(20)30154-9.

[3] *Effectiveness of Airport Screening at Detecting Travellers Infected with Novel Coronavirus COVID-19 (Formerly 2019-nCoV)*. https://cmmid.github.io/visualisations/traveller-screening. Mar. 2022. (Visited on 01/02/2023).

[4] K. M. Gostic, A. J. Kucharski, and J. O. Lloyd-Smith. “Effectiveness of Traveller Screening for Emerging Pathogens Is Shaped by Epidemiology and Natural History of Infection”. In: *eLife* 4 (Feb. 2015). Ed. by S. I. Hay, e05564. ISSN: 2050-084X. DOI: 10.7554/eLife.05564. (Visited on 02/20/2020).

[5] S. Clifford, C. A. B. Pearson, P. Klepac, K. Van Zandvoort, B. J. Quilty, CMMID COVID-19 working group, R. M. Eggo, and S. Flasche. “Effectiveness of Interventions Targeting Air Travellers for Delaying Local Outbreaks of SARS-CoV-2”. In: *Journal of Travel Medicine* 27.taaa068 (Aug. 2020). ISSN: 1708-8305. DOI: 10.1093/jtm/taaa068. (Visited on 03/17/2021).

[6] *Coronavirus: Wuhan Shuts Public Transport over Outbreak - BBC News*. https://www.bbc.co.uk/news/world-asia-china-51215348. (Visited on 01/10/2021).

[7] *Home-Baidu Map Insight*. https://huiyan.baidu.com/. (Visited on 01/11/2021).

[8] A. J. Kucharski et al. “Early Dynamics of Transmission and Control of COVID-19: A Mathematical Modelling Study”. In: *The Lancet Infectious Diseases* 20.5 (May 2020), pp. 553–558. ISSN: 1473-3099. DOI: 10.1016/S1473-3099(20)30144-4. (Visited on 12/15/2022).

[9] J. Lu et al. “Genomic Epidemiology of SARS-CoV-2 in Guangdong Province, China”. In: *Cell* 181.5 (May 2020), 997–1003.e9. ISSN: 0092-8674. DOI: 10.1016/j.cell.2020.04.023. (Visited on 02/03/2021).

[10] M. Chinazzi et al. “The Effect of Travel Restrictions on the Spread of the 2019 Novel Coronavirus (COVID-19) Outbreak”. In: *Science* 368.6489 (Apr. 2020), pp. 395–400. DOI: 10.1126/science.aba9757. (Visited on 01/02/2023).

[11] K. A. Grépin, T.-L. Ho, Z. Liu, S. Marion, J. Piper, C. Z. Worsnop, and K. Lee. “Evidence of the Effectiveness of Travel-Related Measures during the Early Phase of the COVID-19 Pandemic: A Rapid Systematic Review”. In: *BMJ Global Health* 6.3 (Mar. 2021), e004537. ISSN: 2059-7908. DOI: 10.1136/bmjgh-2020-004537. (Visited on 01/02/2023).

[12] Y. Liu, S. Funk, and S. Flasche. *The Contribution of Pre-Symptomatic Infection to the Transmission Dynamics of COVID-2019*. Apr. 2020. DOI: 10.12688/wellcomeopenres.15788.1. (Visited on 11/17/2022).

[13] D. Buitrago-Garcia, D. Egli-Gany, M. J. Counotte, S. Hossmann, H. Imeri, A. M. Ipekci, G. Salanti, and N. Low. “Occurrence and Transmission Potential of Asymptomatic and Presymptomatic SARS-CoV-2 Infections: A Living Systematic Review and Meta-Analysis”. In: *PLOS Medicine* 17.9 (Sept. 2020), e1003346. ISSN: 1549-1676. DOI: 10.1371/journal.pmed.1003346. (Visited on 01/11/2021).

[14] S. K. Brooks, R. K. Webster, L. E. Smith, L. Woodland, S. Wessely, N. Greenberg, and G. J. Rubin. “The Psychological Impact of Quarantine and How to Reduce It: Rapid Review of the Evidence”. In: *The Lancet* 395.10227 (Mar. 2020), pp. 912–920. ISSN: 0140-6736, 1474-547X. DOI: 10.1016/S0140-6736(20)30460-8. (Visited on 02/15/2021).

[15] *Traveler Survey Reveals COVID-19 Concerns*. https://www.iata.org/en/pressroom/pr/2020-07-07-01/. (Visited on 02/15/2021).

[16] *COVID-19 and the Aviation Industry: Impact and Policy Responses*. http://www.oecd.org/coronavirus/policy-responses/covid-19-and-the-aviation-industry-impact-and-policy-responses-26d521c1/. (Visited on 02/15/2021).

[17] L. M. Kucirka, S. A. Lauer, O. Laeyendecker, D. Boon, and J. Lessler. “Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction–Based

SARS-CoV-2 Tests by Time Since Exposure". In: *Annals of Internal Medicine* (May 2020), pp. M20–1495. ISSN: 0003-4819, 1539-3704. DOI: 10.7326/M20-1495. (Visited on 08/10/2020).

[18] T. W. Russell, J. T. Wu, S. Clifford, W. J. Edmunds, A. J. Kucharski, and M. Jit. "Effect of Internationally Imported Cases on Internal Spread of COVID-19: A Mathematical Modelling Study". In: *The Lancet Public Health* (Dec. 2020), S2468266720302632. ISSN: 24682667. DOI: 10.1016/S2468-2667(20)30263-2. (Visited on 12/09/2020).

[19] T. W. Russell et al. "Estimating the Infection and Case Fatality Ratio for Coronavirus Disease (COVID-19) Using Age-Adjusted Data from the Outbreak on the Diamond Princess Cruise Ship, February 2020". In: *Eurosurveillance* 25.12 (Mar. 2020), p. 2000256. ISSN: 1560-7917. DOI: 10.2807/1560-7917.ES.2020.25.12.2000256. (Visited on 12/15/2022).

[20] M. Schäfer, M. Strohmeier, V. Lenders, I. Martinovic, and M. Wilhelm. "Bringing up OpenSky: A Large-Scale ADS-B Sensor Network for Research". In: *IPSN-14 Proceedings of the 13th International Symposium on Information Processing in Sensor Networks*. Apr. 2014, pp. 83–94. DOI: 10.1109/IPSN.2014.6846743.

[21] T. R. Mercer and M. Salit. "Testing at Scale during the COVID-19 Pandemic". In: *Nature Reviews Genetics* 22.7 (July 2021), pp. 415–426. ISSN: 1471-0064. DOI: 10.1038/s41576-021-00360-w. (Visited on 01/10/2023).

[22] UK Government. *Weekly NHS Test and Trace Bulletin, England: 20 August to 26 August 2020*. Tech. rep. Department of Health & Social Care, Mar. 2020.

[23] L. E. Smith, H. W. W. Potts, R. Amlot, N. T. Fear, S. Michie, and J. Rubin. *Adherence to the Test, Trace and Isolate System: Results from a Time Series of 21 Nationally Representative Surveys in the UK (the COVID-19 Rapid Survey of Adherence to Interventions and Responses [CORSAIR] Study)*. Preprint. Public and Global Health, Sept. 2020. DOI: 10.1101/2020.09.15.20191957. (Visited on 09/30/2020).

[24] S. M. Kissler et al. "SARS-CoV-2 Viral Dynamics in Acute Infections". In: *medRxiv* (Dec. 2020), p. 2020.10.21.20217042. DOI: 10.1101/2020.10.21.20217042. (Visited on 12/17/2020).

[25] University of Oxford. *Oxford University and PHE Confirm High-Sensitivity of Lateral Flow Tests Following Extensive Clinical Evaluation | University of Oxford*.

https://www.ox.ac.uk/news/2020-11-11-oxford-university-and-phe-confirm-high-sensitivity-lateral-flow-tests-following. (Visited on 11/15/2020).

[26] M. E. Kretzschmar, G. Rozhnova, M. C. J. Bootsma, M. van Boven, J. H. H. M. van de Wijgert, and M. J. M. Bonten. "Impact of Delays on Effectiveness of Contact Tracing Strategies for COVID-19: A Modelling Study". In: *The Lancet Public Health* (July 2020), S2468266720301572. ISSN: 24682667. DOI: 10.1016/S2468-2667(20)30157-2. (Visited on 08/05/2020).

[27] L. Ferretti, C. Wymant, M. Kendall, L. Zhao, A. Nurtay, L. Abeler-Dörner, M. Parker, D. Bonsall, and C. Fraser. "Quantifying SARS-CoV-2 Transmission Suggests Epidemic Control with Digital Contact Tracing". In: *Science (New York, N.y.)* 368.6491 (May 2020), eabb6936. ISSN: 0036-8075. DOI: 10.1126/science.abb6936. (Visited on 01/17/2023).

[28] P. Klepac, A. J. Kucharski, A. J. Conlan, S. Kissler, M. L. Tang, H. Fry, and J. R. Gog. *Contacts in Context: Large-Scale Setting-Specific Social Mixing Matrices from the BBC Pandemic Project*. Preprint. Epidemiology, Feb. 2020. DOI: 10.1101/2020.02.16.20023754. (Visited on 11/26/2021).

[29] C. I. Jarvis et al. "Quantifying the Impact of Physical Distance Measures on the Transmission of COVID-19 in the UK". In: *BMC Medicine* 18.1 (May 2020), p. 124. ISSN: 1741-7015. DOI: 10.1186/s12916-020-01597-8. (Visited on 05/14/2021).

[30] S. M. Kissler et al. "Viral Dynamics of Acute SARS-CoV-2 Infection and Applications to Diagnostic and Public Health Strategies". In: *PLOS Biology* 19.7 (July 2021), e3001333. ISSN: 1545-7885. DOI: 10.1371/journal.pbio.3001333. (Visited on 11/25/2021).

[31] D. B. Larremore, B. Wilder, E. Lester, S. Shehata, J. M. Burke, J. A. Hay, M. Tambe, M. J. Mina, and R. Parker. "Test Sensitivity Is Secondary to Frequency and Turnaround Time for COVID-19 Screening". In: *Science Advances* 7.1 (Jan. 2021), eabd5393. ISSN: 2375-2548. DOI: 10.1126/sciadv.abd5393.

[32] R. K. Webster, S. K. Brooks, L. E. Smith, L. Woodland, S. Wessely, and G. J. Rubin. "How to Improve Adherence with Quarantine: Rapid Review of the Evidence". In: *Public Health* 182 (May 2020), pp. 163–169. ISSN: 0033-3506. DOI: 10.1016/j.puhe.2020.03.007. (Visited on 03/16/2021).

[33] S. Denford, A. F. Martin, N. Love, D. Ready, I. Oliver, R. Amlôt, L. Yardley, and G. J. Rubin. “Engagement With Daily Testing Instead of Self-Isolating in Contacts of Confirmed Cases of SARS-CoV-2: A Qualitative Analysis”. In: *Frontiers in Public Health* 9 (2021). ISSN: 2296-2565. (Visited on 02/06/2023).

[34] E. Marchant, D. Ready, G. Wimbury, R. Smithson, A. Charlett, and I. Oliver. “Determining the Acceptability of Testing Contacts of Confirmed COVID-19 Cases to Improve Secondary Case Ascertainment”. In: *Journal of Public Health* 43.3 (Sept. 2021), e446–e452. ISSN: 1741-3842. DOI: 10.1093/pubmed/fdab079. (Visited on 02/06/2023).

[35] A. F. Martin, S. Denford, N. Love, D. Ready, I. Oliver, R. Amlôt, G. J. Rubin, and L. Yardley. “Engagement with Daily Testing Instead of Self-Isolating in Contacts of Confirmed Cases of SARS-CoV-2”. In: *BMC Public Health* 21.1 (June 2021), p. 1067. ISSN: 1471-2458. DOI: 10.1186/s12889-021-11135-7. (Visited on 02/06/2023).

[36] N. K. Love, D. R. Ready, C. Turner, L. Yardley, G. J. Rubin, S. Hopkins, and I. Oliver. “The Acceptability of Testing Contacts of Confirmed COVID-19 Cases Using Serial, Self-Administered Lateral Flow Devices as an Alternative to Self-Isolation”. In: *Journal of Medical Microbiology* 71.8 (2022), p. 001567. ISSN: 1473-5644. DOI: 10.1099/jmm.0.001567. (Visited on 01/22/2023).

[37] B. C. Young et al. “Daily Testing for Contacts of Individuals with SARS-CoV-2 Infection and Attendance and SARS-CoV-2 Transmission in English Secondary Schools and Colleges: An Open-Label, Cluster-Randomised Trial”. In: *The Lancet* 398.10307 (Oct. 2021), pp. 1217–1229. ISSN: 01406736. DOI: 10.1016/S0140-6736(21)01908-5. (Visited on 03/03/2022).

[38] N. K. Love et al. “Daily Use of Lateral Flow Devices by Contacts of Confirmed COVID-19 Cases to Enable Exemption from Isolation Compared with Standard Self-Isolation to Reduce Onward Transmission of SARS-CoV-2 in England: A Randomised, Controlled, Non-Inferiority Trial”. In: *The Lancet Respiratory Medicine* 10.11 (Nov. 2022), pp. 1074–1085. ISSN: 2213-2600. DOI: 10.1016/S2213-2600(22)00267-3. (Visited on 01/12/2023).

[39] Evaluation and Social Research unit. *Evaluation of Daily Testing for Contacts of COVID-19 Cases (DTCC)*.

[40] N. G. Davies et al. “Estimated Transmissibility and Impact of SARS-CoV-2 Lineage B.1.1.7 in England”. In: *Science* (Mar. 2021). ISSN: 1095-9203. DOI: 10.1126/science.abg3055.

[41] N. G. Davies, C. I. Jarvis, W. J. Edmunds, N. P. Jewell, K. Diaz-Ordaz, and R. H. Keogh. “Increased Mortality in Community-Tested Cases of SARS-CoV-2 Lineage B.1.1.7”. In: *Nature* (Mar. 2021), pp. 1–5. ISSN: 1476-4687. DOI: 10.1038/s41586-021-03426-1. (Visited on 03/15/2021).

[42] J. R. C. Pulliam, C. van Schalkwyk, N. Govender, A. von Gottberg, C. Cohen, M. J. Groome, J. Dushoff, K. Mlisana, and H. Moultrie. “Increased Risk of SARS-CoV-2 Reinfection Associated with Emergence of Omicron in South Africa”. In: *Science (New York, N.Y.)* 376.6593 (May 2022), eabn4947. ISSN: 1095-9203. DOI: 10.1126/science.abn4947.

[43] A. J. Kucharski, M. Jit, J. G. Logan, M. Cotten, S. Clifford, B. J. Quilty, T. W. Russell, R. W. Peeling, M. Antonio, and D. L. Heymann. “Travel Measures in the SARS-CoV-2 Variant Era Need Clear Objectives”. In: *The Lancet* 399.10333 (Apr. 2022), pp. 1367–1369. ISSN: 0140-6736, 1474-547X. DOI: 10.1016/S0140-6736(22)00366-X. (Visited on 01/02/2023).

[44] University of Liverpool. *Liverpool Covid-SMART Pilot - Coronavirus (COVID-19)*. https://www.liverpool.ac.uk/coronavirus/research-and-analysis/covid-smart-pilot/. (Visited on 12/24/2020).

[45] J. Wise. “Covid-19: Concerns Persist about Purpose, Ethics, and Effect of Rapid Testing in Liverpool”. In: *BMJ* 371 (Dec. 2020), p. m4690. ISSN: 1756-1833. DOI: 10.1136/bmj.m4690. (Visited on 01/25/2023).

[46] University of Oxford. *Lateral Flow Devices Detect Most Infectious COVID-19 Cases and Could Allow a Safer Relaxation of the Current Lockdown | University of Oxford*. https://www.ox.ac.uk/news/2021-01-21-lateral-flow-devices-detect-most-infectious-covid-19-cases-and-could-allow-safer. Jan. 2021. (Visited on 02/15/2021).

[47] M. J. Mina, T. E. Peto, M. García-Fiñana, M. G. Semple, and I. E. Buchan. “Clarifying the Evidence on SARS-CoV-2 Antigen Rapid Tests in Public Health Responses to COVID-19”. In: *The Lancet* (Feb. 2021), S0140673621004256. ISSN: 01406736. DOI: 10.1016/S0140-6736(21)00425-6. (Visited on 02/23/2021).

[48] M. Cevik, M. Tate, O. Lloyd, A. E. Maraolo, J. Schafers, and A. Ho. “SARS-CoV-2, SARS-CoV, and MERS-CoV Viral Load Dynamics, Duration of Viral Shedding, and Infectiousness: A Systematic Review and Meta-Analysis”. In: *The Lancet Microbe* (Nov. 2020), S2666524720301725. ISSN: 26665247. DOI: 10.1016/S2666-5247(20)30172-5. (Visited on 12/02/2020).

[49] R. Ke et al. “Daily Longitudinal Sampling of SARS-CoV-2 Infection Reveals Substantial Heterogeneity in Infectiousness”. In: *Nature Microbiology* 7.5 (May 2022), pp. 640–652. ISSN: 2058-5276. DOI: 10.1038/s41564-022-01105-z. (Visited on 12/20/2022).

[50] B. Killingley et al. *Safety, Tolerability and Viral Kinetics during SARS-CoV-2 Human Challenge*. Mar. 2022. DOI: 10.21203/rs.3.rs-1121993/v1. (Visited on 03/03/2022).

[51] C. Suñer et al. *Viral Dynamics in Patients with Monkeypox Infection: A Prospective Cohort Study in Spain*. SSRN Scholarly Paper. Rochester, NY, Oct. 2022. DOI: 10.2139/ssrn.4248017. (Visited on 01/23/2023).

[52] A. Agard et al. “Clinical Comparison and Agreement of PCR, Antigen, and Viral Culture for the Diagnosis of COVID-19: Clinical Agreement Between Diagnostics for COVID19”. In: *Journal of Clinical Virology Plus* 2.3 (Aug. 2022), p. 100099. ISSN: 2667-0380. DOI: 10.1016/j.jcvp.2022.100099. (Visited on 01/23/2023).

[53] A. V. Winnett et al. *Extreme Differences in SARS-CoV-2 Viral Loads among Respiratory Specimen Types during Presumed Pre-Infectious and Infectious Periods*. Jan. 2023. DOI: 10.1101/2022.07.13.22277113. (Visited on 01/23/2023).

[54] Y. Wu, L. Kang, Z. Guo, J. Liu, M. Liu, and W. Liang. “Incubation Period of COVID-19 Caused by Unique SARS-CoV-2 Strains: A Systematic Review and Meta-analysis”. In: *JAMA Network Open* 5.8 (Aug. 2022), e2228008. ISSN: 2574-3805. DOI: 10.1001/jamanetworkopen.2022.28008. (Visited on 01/23/2023).

[55] Michael Mina [@michaelmina_lab]. *IMPORTANT: RAPID TESTS DO WORK WITH OMICRON "But Why Are Some People Staying Negative in the First Days They Have Symptoms??" This Is Expected. Symptoms Don’t = Contagious Virus This Is Literally a Reflection of the Fact That Vaccines Are Doing Their Job! PLEASE READ https://t.co/YBJvNovQXL*. Tweet. Dec. 2021. (Visited on 01/23/2023).

[56] J. Lessler, N. G. Reich, R. Brookmeyer, T. M. Perl, K. E. Nelson, and D. A. Cummings. "Incubation Periods of Acute Respiratory Viral Infections: A Systematic Review". In: *The Lancet. Infectious Diseases* 9.5 (May 2009), pp. 291–300. ISSN: 1473-3099. DOI: 10.1016/S1473-3099(09)70069-6. (Visited on 12/30/2020).

[57] C. Marquez et al. "COVID-19 Symptoms and Duration of Rapid Antigen Test Positivity at a Community Testing and Surveillance Site During Pre-Delta, Delta, and Omicron BA.1 Periods". In: *JAMA Network Open* 5.10 (Oct. 2022), e2235844. ISSN: 2574-3805. DOI: 10.1001/jamanetworkopen.2022.35844. (Visited on 10/13/2022).

[58] M. Hartfield and S. Alizon. "Introducing the Outbreak Threshold in Epidemiology". In: *PLoS Pathogens* 9.6 (June 2013). Ed. by G. F. Rall, e1003277. ISSN: 1553-7374. DOI: 10.1371/journal.ppat.1003277. (Visited on 02/19/2020).

[59] B. J. Quilty, J. R. C. Pulliam, and C. A. B. Pearson. *Test to Release from Isolation after Testing Positive for SARS-CoV-2*. Preprint. Epidemiology, Jan. 2022. DOI: 10.1101/2022.01.04.21268372. (Visited on 01/25/2023).

[60] M. Pavelka et al. "The Impact of Population-Wide Rapid Antigen Testing on SARS-CoV-2 Prevalence in Slovakia". In: *Science* 372.6542 (May 2021), pp. 635–641. DOI: 10.1126/science.abf9648. (Visited on 01/12/2023).

[61] M. Fyles, E. Fearon, C. Overton, University of Manchester COVID-19 Modelling Group, T. Wingfield, G. F. Medley, I. Hall, L. Pellis, and T. House. "Using a Household-Structured Branching Process to Analyse Contact Tracing in the SARS-CoV-2 Pandemic". In: *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 376.1829 (July 2021), p. 20200267. ISSN: 1471-2970. DOI: 10.1098/rstb.2020.0267.

[62] J. A. Firth, J. Hellewell, P. Klepac, S. Kissler, A. J. Kucharski, and L. G. Spurgin. "Using a Real-World Network to Model Localized COVID-19 Control Strategies". In: *Nature Medicine* 26.10 (Oct. 2020), pp. 1616–1622. ISSN: 1546-170X. DOI: 10.1038/s41591-020-1036-8. (Visited on 12/02/2022).

[63] SPI-MO. *Consensus Statement 28th July 2021*. Tech. rep. UK Government, July 21. (Visited on 11/25/2022).

[64] TUC. *High Rejection Rates Show the Self-Isolation Payment Scheme Isn't Fit for Purpose*. https://www.tuc.org.uk/blogs/high-rejection-rates-show-self-isolation-

payment-scheme-isnt-fit-purpose. Text. Feb. 2021. (Visited on 07/05/2023).

[65] The Guardian. “Covid Inquiry Must Examine Impact of UK’s ‘Broken Sick Pay’ System, Says TUC”. In: *The Guardian* (June 2023). ISSN: 0261-3077. (Visited on 07/05/2023).

[66] L. E. Smith, H. W. W. Potts, R. Amlo±t, N. T. Fear, S. Michie, and G. J. Rubin. “Engagement with Protective Behaviours in the UK during the COVID-19 Pandemic: A Series of Cross-Sectional Surveys (the COVID-19 Rapid Survey of Adherence to Interventions and Responses [CORSAIR] Study)”. In: *BMC Public Health* 22.1 (Mar. 2022), p. 475. ISSN: 1471-2458. DOI: 10.1186/s12889-022-12777-x. (Visited on 01/23/2023).

[67] L. E. Smith, H. W. W. Potts, R. Amlo±t, N. T. Fear, S. Michie, and G. J. Rubin. “Intention to Adhere to Test, Trace, and Isolate during the COVID-19 Pandemic (the COVID-19 Rapid Survey of Adherence to Interventions and Responses Study)”. In: *British Journal of Health Psychology* 27.3 (2022), pp. 1100–1118. ISSN: 2044-8287. DOI: 10.1111/bjhp.12576. (Visited on 01/23/2023).

[68] D. Weston, K. Hauck, and R. Amlôt. “Infection Prevention Behaviour and Infectious Disease Modelling: A Review of the Literature and Recommendations for the Future”. In: *BMC Public Health* 18.1 (Mar. 2018), p. 336. ISSN: 1471-2458. DOI: 10.1186/s12889-018-5223-1. (Visited on 01/23/2023).

[69] G. C. Marshall et al. *Public Perceptions and Interactions with UK COVID-19 Test, Trace and Isolate Policies, and Implications for Pandemic Infectious Disease Modelling*. Sept. 2022. DOI: 10.12688/f1000research.124627.1. (Visited on 01/23/2023).

[70] S. Funk, M. Salathé, and V. A. A. Jansen. “Modelling the Influence of Human Behaviour on the Spread of Infectious Diseases: A Review”. In: *Journal of The Royal Society Interface* 7.50 (May 2010), pp. 1247–1256. DOI: 10.1098/rsif.2010.0142. (Visited on 01/23/2023).

[71] World Health Organization. *WHO | WHO Interim Protocol: Rapid Operations to Contain the Initial Emergence of Pandemic Influenza*. Tech. rep. World Health Organization, Oct. 2007. (Visited on 03/15/2021).

[72] S. Roberts. “Flattening the Coronavirus Curve”. In: *The New York Times* (Mar. 2020). ISSN: 0362-4331. (Visited on 01/21/2023).

[73] N. M. Ferguson, D. A. T. Cummings, C. Fraser, J. C. Cajka, P. C. Cooley, and D. S. Burke. “Strategies for Mitigating an Influenza Pandemic”. In: *Nature* 442.7101 (July 2006), pp. 448–452. ISSN: 1476-4687. DOI: 10.1038/nature04795.

[74] B. S. Cooper, R. J. Pitman, W. J. Edmunds, and N. J. Gay. “Delaying the International Spread of Pandemic Influenza”. In: *PLOS Medicine* 3.6 (May 2006), e212. ISSN: 1549-1676. DOI: 10.1371/journal.pmed.0030212. (Visited on 02/05/2023).

[75] M. Saville, J. P. Cramer, M. Downham, A. Hacker, N. Lurie, L. Van der Veken, M. Whelan, and R. Hatchett. “Delivering Pandemic Vaccines in 100 Days — What Will It Take?” In: *New England Journal of Medicine* 387.2 (July 2022), e3. ISSN: 0028-4793. DOI: 10.1056/NEJMp2202669. (Visited on 01/21/2023).

[76] Adam Kucharski [@adamjkucharski]. *There Are Lots of Suggestions That Future Pandemic Strategy Should Be ’Keep Transmission Low and Develop an Efficacious Vaccine within a Few Months’. But This Paper Illustrates the Challenges of Demonstrating Efficacy When Cases Are Low: https://t.co/dpaKLvQTOL*. Tweet. Jan. 2022. (Visited on 01/21/2023).

[77] World Health Organization. *DESIGN OF VACCINE EFFICACY TRIALS TO BE USED DURING PUBLIC HEALTH EMERGENCIES – POINTS OF CONSIDERATIONS AND KEY PRINCIPLES*. (Visited on 01/21/2023).

[78] G. S. Heriot and E. Jamrozik. “Not in My Backyard: COVID-19 Vaccine Development Requires Someone to Be Infected Somewhere”. In: *The Medical Journal of Australia* 214.4 (Mar. 2021), 150–152.e1. ISSN: 0025-729X. DOI: 10.5694/mja2.50930. (Visited on 01/21/2023).

[79] *Mpox (Monkeypox) Outbreak 2022*. https://www.who.int/emergencies/situations/monkeypox-oubreak-2022. (Visited on 01/23/2023).

[80] *Ebola Outbreak 2022 - Uganda*. https://www.who.int/emergencies/situations/ebola-uganda-2022. (Visited on 01/23/2023).

[81] M. Marani, G. G. Katul, W. K. Pan, and A. J. Parolari. “Intensity and Frequency of Extreme Novel Epidemics”. In: *Proceedings of the National Academy of Sciences* 118.35 (Aug. 2021), e2105482118. ISSN: 0027-8424, 1091-6490. DOI:

10.1073/pnas.2105482118. (Visited on 01/23/2023).

[82] F. Carrat, E. Vergu, N. M. Ferguson, M. Lemaitre, S. Cauchemez, S. Leach, and A.-J. Valleron. “Time Lines of Infection and Disease in Human Influenza: A Review of Volunteer Challenge Studies”. In: *American Journal of Epidemiology* 167.7 (Apr. 2008), pp. 775–785. ISSN: 0002-9262. DOI: 10.1093/aje/kwm375. (Visited on 02/05/2023).

[83] J. Budd et al. “Lateral Flow Test Engineering and Lessons Learned from COVID-19”. In: *Nature Reviews Bioengineering* 1.1 (Jan. 2023), pp. 13–31. ISSN: 2731-6092. DOI: 10.1038/s44222-022-00007-3. (Visited on 02/02/2023).

[84] University of Oxford. *A Dose Finding Human Experimental Infection Study With SARS-CoV-2 in Healthy Volunteers With Immunologically Sensitised With Either Previous, SARS-CoV-2 Infection and/or Vaccination Against SARS-CoV2*. Clinical Trial Registration NCT04864548. clinicaltrials.gov, Jan. 2023. (Visited on 02/02/2023).

[85] E. B. Wroe, K. J. Seung, B. K. Baker, and P. E. Farmer. “Test and Treat: A Missing Link in the Global Fight against COVID-19”. In: *The Lancet. Global Health* 10.2 (Feb. 2022), e181–e182. ISSN: 2214-109X. DOI: 10.1016/S2214-109X(21)00568-4. (Visited on 02/07/2023).