THE UNIVERSITY of EDINBURGH
Edinburgh Medical School

Master of Public Health

Dissertation

Title: Emerging evidence on asymptomatic transmission of SARS-CoV-2

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Word Count:
UNCOVER Rapid Review Dissertation: 8988
Reflective Review: 1999

Usher Institute
Population Health Sciences & Informatics

Abstract

Background: We currently face a pandemic caused by the novel virus SARS-CoV-2. Transmission and epidemiology of SARS-CoV-2 are undergoing investigation, however, new evidence is emerging quickly in this rapidly evolving situation. Currently, the risks of asymptomatic transmission are unclear.

Aims: To build on evidence identified within UNCOVER reviews, establishing the current evidence in scientific literature on asymptomatic transmission. A secondary aim is to critically appraise methodologies used within a rapid, emergency context.

Methods: A systematic literature review of reviews was conducted. Three medical and grey literature databases were searched, following a protocol designed according to Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines. Quality assessment of included studies was conducted using Joanna Briggs' Critical Appraisal Skills Programme (CASP) tool for systematic reviews. Results were synthesised narratively.

Results: In the systematic literature search, 329 records were identified after deduplication and four studies, all reviews, were included. Three out of four examined the proportion of asymptomatic infection. Within these studies, key themes were identified from reporting on demographics and setting. Overall the proportion of asymptomatic infection ranged from 11 – 20%. Two out of four studies measured viral load of asymptomatic cases. Evidence reported similar loads to symptomatic cases, however, this was limited and inconclusive. Most evidence was graded low to moderate.

Conclusion: The current evidence for asymptomatic transmission is inconclusive. However, given the unique opportunity for asymptomatic carriers to transmit compared with symptomatic carriers, it remains a significant area for policy attention, to mitigate risks of transmission, pending higher quality studies. Polymerise Chain Reaction (PCR) detection, informing the majority of the current evidence-base, is limited. Ultimately, viral culturing of asymptomatic cases is needed to establish viability and, subsequently, determine true risk through ability to transmit. If this can be established, a multidisciplinary collaboration is recommended to fully assess the risks of asymptomatic transmission.

Acknowledgments

First and foremost, I would like to thank my wonderful supervisor Ruth McQuillan. Thank you, for seeing passion and potential in me at a time when I was lost. You are a joy and I have loved every minute spent collaborating with and learning from your phenomenal expertise. I am beyond grateful for the generosity of your support and bottomless bucket of ideas that kept my spark alive throughout!

Neneh, it feels like your kind-heartedness was the glue that kept us all together through these exceptional circumstances. Thank you, for your unwavering support and caring voice of reassurance.

The team at UNCOVER, I am grateful, more than you'll ever know, for the community and purpose that you provided during the challenging months of lockdown.

My friends within the MPH cohort. Thank you, for the overwhelming amount of love in the short time that we shared together. Truly, you have inspired me the most on this journey.

My number one proof-reader, Mum, I count my stars lucky that you're always there when I need it the most. Thank you, for all that you do for us so freely.

Nanna, thank you so much for our secret that kept me sane cycling in the mountains.

Lastly, Dan. You still made life an adventure the whole time. I am so grateful that we leapt.

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List of Abbreviations

BME - Black, Minority and Ethnic

CASP - Critical Appraisal Skills Programme

COVID-19 - Coronavirus Disease 2019

DE - Data Extraction

HCW - Healthcare Worker

ICU - Intensive Care Unit

MedRxiv - The Preprint Server for Health Services

Medrxivr - app developed for The Preprint Server for Health Services

NPI - Non-pharmaceutical Intervention

PCR - Polymerise Chain Reaction

PECO - Population, Exposure, Comparison, Outcome

PRISMA - Preferred Reporting Items for Systematic review and Meta-Analysis

PRISMA-P - Preferred Reporting Items for Systematic review and Meta-Analysis Protocols

QA - Quality Assessment

RR - Rapid Review

RNA - Ribonucleic Acid

RR - Rapid Review

RT-PCR - Reverse Transcription Polymerase Chain Reaction

SAR - Secondary Attack Rate

SARS-CoV-1 - Severe Acute Respiratory Syndrome Coronavirus 1

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

SR - Systematic Review

UK - United Kingdom

UNCOVER - Usher Network for COVID-19 Evidence Reviews

USA - United States of America

WHO - World Health Organisation

1. Chapter One: Outline of the problem

1.1 Introduction

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organisation (WHO) on 11th March 2020 (WHO, 2020c). The epicentre of the disease is thought to be a seafood market at Wuhan, China, where the first confirmed infections were reported (ProMED, 2020). At the time of writing, there are 32.92 million confirmed cases and over 995,147 confirmed deaths globally (Ritchie et al., 2020).

One of the key challenges presented by COVID-19 is that transmission can be by people displaying no symptoms. Collectively, this group can be termed "non-symptomatic transmitters". Some people will later go on to develop symptoms (pre-symptomatic), however, some will never develop symptoms (asymptomatic). Consequently, mitigation strategies based on identifying and isolating symptomatic cases, which worked so effectively in the SARS-CoV-1 outbreak, cannot be relied upon to eliminate or control this virus.

This dissertation defines asymptomatic COVID-19 infection as follows:

> *Laboratory-confirmed SARS-CoV-2 infection with no symptoms at the time of first clinical assessment nor throughout and to the end of follow-up (Buitrago-Garcia et al., 2020).*

End of follow-up is defined as any of the following:

virological cure, with one or more negative Reverse Transcription Polymerase Chain Reaction (RT-PCR) test results; follow-up for 14 days or more after the last possible exposure to an index case; follow-up for seven days or more after the first RT-PCR positive result (Buitrago-Garcia et al., 2020).

Inherently, the major problem with the nature of asymptomatic infection is that people are unaware they have COVID-19 throughout their infection, meaning they are more likely to transmit the virus to their contacts during their infectious period. Additionally, unaware of their disease status, they are less likely to seek testing, resulting in an underestimate of incidence rates based on antigen testing. Thus, they present significant challenges for

controlling transmission within the community, distinct from those of symptomatic carriers.

On 8th June 2020, WHO official, Maria Van Kerkhove, stated asymptomatic transmission of COVID-19 was "very rare", later clarifying, these cases are much less likely to transmit than symptomatic counterparts (Mandavilli, 2020). Contrarily, similar viral loads have been reported between these groups, implying transmission is possible for both (Hoxha et al., 2020). The reproduction number estimates the total number of cases infected by one index case. Epidemiological modelling studies have suggested the exponential global spread is likely attributable to an R0 as high as 12 if asymptomatic cases are also included in calculations (Aguilar et al., 2020).

Whether asymptomatic cases will transmit the virus depends on interaction between a range of different factors. For instance:

Viral shedding:

- Results from the Princess Diamond cruise ship study found no difference ($p > 0.05$) in virus detection between asymptomatic and symptomatic case cabins (Yamagishi, 2020). The universally accepted test for detecting SARS-CoV-2 viral Ribonucleic Acid (RNA) presence is RT-PCR. A case with a high viral load and high viral shedding is expected to have more viable virus and, subsequently, be at a higher risk of infecting others. However, detecting viral RNA alone cannot demonstrate infectivity. Viral RNA can be live virus (infectivity risk) or fragmented dead virus (no infectivity risk). Investigating viral *viability* requires culturing methods, which show its ability to infect a cell line (Leland and Ginocchio, 2007), helping quantify the proportion of cases transmitted asymptomatically to inform public health and policy.

Opportunity to transmit:

- Intuitively, somebody unaware of their illness will continue as normal, having more contacts than somebody severely ill, and bed bound. Asymptomatic carriers differ significantly behaviourally, compared to severely symptomatic carriers. However, this difference may be less significant between asymptomatic and mildly symptomatic carriers, who are also less likely to alter their movement patterns, especially if they are unable to work from home and

socioeconomic pressures mean they continue to go to work whilst ill. Epidemiological investigations exploring contact tracing between clusters of cases and contacts can help establish how movement patterns differ between asymptomatic and symptomatic cases and who poses highest risk for transmitting. Stratifying these studies further, by sub-populations, could help identify other factors contributing to higher transmission, such as age, activities and context (e.g. socioeconomic status).

There is a trade-off between the efficiency of viral shedding versus the opportunity to transmit. Coughs travel much further than ordinary breathing or speaking (Asadi et al., 2019). Thus, a symptomatic person who is coughing has a wider trajectory to spread the virus more efficiently than an asymptomatic person. However, as above, somebody bed-confined with severe infection may have less opportunity to transmit the virus than asymptomatic or mild cases, still circulating within society. Any environment not within a controlled setting will experience these non-linear dynamics of infection transmission, increasing or decreasing chances of infection depending on setting and individual actors.

An absence of definitive information on the nature of asymptomatic transmission demands high-quality studies, investigating true prevalence, characteristics of asymptomatic infection and transmission dynamics. To create a strong evidence-base for informing important mitigation decisions at policy level, the following questions remain to be answered:

- What is the true proportion of asymptomatic infection?
- What is the viral shedding of asymptomatic cases? Does this correlate with infectivity?
- How do asymptomatic carriers differ in their opportunity to transmit the virus?

Usher Network for COVID-19 Evidence Reviews (UNCOVER) emerged to respond to urgent policy needs arising from the pandemic. Transmission is a key theme in UNCOVER reviews, both explicitly (indoor) and implicitly (facemasks, ethnicity), which asymptomatic transmission emerged from, presenting distinct and significant challenges. This dissertation will build on the work of UNCOVER to focus on this important area.

1.2 Aims

This paper aims to address the following two questions:

1. What evidence is there for asymptomatic transmission of SARS-CoV-2?
2. What are the implications for future research and policy from the evidence on asymptomatic transmission of SARS-CoV-2?

1.3 Methodology

This dissertation follows the following structure:

Firstly, I outline three UNCOVER reviews which I was involved in, identifying why asymptomatic transmission is an important theme within them. I then conduct a systematic review, identifying the existing evidence on asymptomatic transmission of SARS-CoV-2. Lastly, I narratively synthesize key themes before considering implications of findings for future research and policy.

2 Chapter Two: Findings from UNCOVER

2.1 Introduction

UNCOVER originated to respond to urgent requests from policymakers for evidence-based reviews within the context of the novel Coronavirus, presenting great challenges for public health and uncertainties for policymakers.

UNCOVER's aims can be summarised as follows (UNCOVER, 2020):

1. to respond quickly and efficiently to requests from policymakers for evidence reviews on key questions;
2. to not duplicate work being undertaken elsewhere;
3. and to support others' efforts by making methodological resources openly available.

Table 1 and **Table 2** depict my involvement in three UNCOVER reviews and their timelines, respectively.

Review	Search	Title Abstract Screening	Full Text Screening	Quality Appraisal	Data Extraction	Additional Information
Facemasks (Appendix 2a)	-	✓	✓	✓	-	Discussed key themes and provided methodology feedback Involved with sub-review 2: what is the relative effectiveness of medical masks versus non-medical masks or equivalent barriers?
Ethnicity (Appendix 2b)	✓ Key terms discussion	✓	✓	✓	✓	Assisted with write-up of sub-question 3: Are differential rates of relevant comorbid conditions associated with differences in COVID-19 outcomes?
Indoor Transmission (Appendix 2c)	✓ Conducted epidemiological and microbiological searches (Appendix 2ci)	✓ Coordinated all teams	✓ Coordinated all teams	✓ Developed QA tool for cluster studies Conducted all epidemiological QA Coordinated epidemiological & microbiological teams	✓ Developed DE tool for cluster studies (Appendix 2cii) Assisted creating DE tools for fluid mechanics and microbiology Conducted all epidemiological DE Coordinated epidemiological and microbiological teams	Lead coordinator of review, involved in decision-making

Table 1: UNCOVER rapid review involvement. The stages of each review that I was involved in are depicted by ✓

2.1.1 Review timeline

Review	Request status	Duration	Completion date	Additional information
Facemasks (Appendix 2a) Appendix 2a: UNCOVER Facemasks review	✓ Direct request Scottish government	2 days	7th April 2020	-
Ethnicity (Appendix 2b)	✓ Direct request Scottish government	5 days	29th April 2020	-
Indoor Transmission (Appendix 2c)	✗ Not a direct request Internal update on previous UNCOVER work* Applicable to University reopening and facemask recommendations	3 months	15th August 2020	*Previous UNCOVER work: 1. Original "indoor/outdoor transmission" review (Scottish government direct request, duration: <2 days) 2. Following this, "outdoor transmission" review on "gates, stiles and fences" (Department of Agriculture direct request, duration: 2 hours)

Table 2: Timeline for included UNCOVER reviews. Request status depicted by ✓ or ✗

2.2 Aims

This chapter aims:

- to provide an overview of UNCOVER methodology and limitations;
- to critique each review chronologically and provide key reflexive learning points;
- and to provide a narrative of how all reviews relate to the theme of asymptomatic transmission.

2.3 Overview of UNCOVER methodology and limitations

We faced a novel disease and fast-moving pandemic, leaving policymakers and other decision-makers basing rapid decisions based on very limited evidence. Normally, the public health academic community supports policymakers by conducting systematic reviews (SR) on

key policy questions. However, SRs take time (months or more) and UNCOVER was required to provide evidence-reviews within days or weeks. Thus, to save time, we adapted SR methodology utilising the Cochrane Rapid Review Methodology (Garritty C, 2020), omitting or truncating some steps. Key limitations are; we only used one person to screen, extract data and quality assess (although a second person screened rejections). This introduces risk of bias, as different individuals may reach different decisions about the same articles. We also initially restricted searches to English language. Limiting foreign data sources, despite not always significantly affecting overall results (Moher et al., 2000, Jüni et al., 2002), can miss subtle cultural variations between studies conducted in other languages that could offer valuable insight into disease transmission within distinct demographics at higher risk of illness.

Importantly, each UNCOVER review was conducted at a distinct phase of the pandemic. Social contexts and drivers of behaviour and transmission, influencing results of each review, have transformed throughout each phase and will continue to as the pandemic progresses. Subsequently, each review will be critiqued individually and chronologically.

2.4 Critiques of UNCOVER reviews

2.4.1 Facemasks

2.4.1.1 Research question

Does the use of facemasks within the general population make a difference to spread of infection?

2.4.1.2 Summary of key findings

This review found no significant association between wearing facemasks in the community and a reduction in influenza-like illness. The overall quality of included evidence was low.

2.4.1.3 Critique

This review was conducted in a rapid timescale at the beginning of the pandemic. Significant quality appraisal steps were truncated, and screening/assessments not checked by a second

reviewer, amplifying likelihood of bias and missed relevant data.

With no prior evidence on SARS-CoV-2, we had to consider proxy evidence for disease and context. This included influenza-like illnesses and non-pandemic community settings, such as the Hajj pilgrimage. This meant great variability in populations and types of masks being worn, and further variability in those populations' associated mask-wearing behaviours. To date, mask recommendations are to protect others from people who may have COVID-19. However, during the time of the review, emphasis within included studies was on protecting the wearer, examining risk-taking behaviours and also types of PPE within nosocomial settings. Muslims in Hajj studies wore face-coverings for religious reasons not behaviourally associated with preventing disease transmission, whereas healthcare professionals in nosocomial studies wore facemasks as PPE. This is significant as mask-wearing behaviour correlates with other Non-pharmaceutical Intervention (NPI) measures that could impact preventing transmission, such as handwashing. Thus, studies were limited in generalisability. Policymakers were reluctant to act without a firm evidence-base, from evidence not appropriate to a UK pandemic context. It took a significant time for perspectives to shift towards the precautionary principle (Greenhalgh et al., 2020).

2.4.1.4 Reflexive learning points

This review initiated the theme of transmission within UNCOVER, however, uncertain about mode(s) of transmission for SARS-CoV-2, we realised we could not usefully describe facemask effectiveness independently of understanding this. Subsequently, we sought multidisciplinary input to answer overarching questions of future reviews. Without existing expertise in fluid dynamics and microbiology we could not fully assess risks of droplet and aerosol transmission, nor understand whether a facemask would actually mitigate transmission. By endorsing a multidisciplinary approach later in the indoor transmission review, integrating microbiological and mechanistic studies, we enhanced overall topic comprehension.

Our attitudes on investigating transmission with a paucity of evidence synchronised with public discourse. On 6/4/2020, the WHO Expert Panel reported widespread use of facemasks is not evidence-based, carrying "uncertainties and critical risks" (WHO, 2020a), whereas Trish Greenhouse promoted use based on the precautionary principal (Greenhalgh et al., 2020). Using a lack of evidence as rationale against usage seemed misplaced when there was none.

Without RCTs available, we adapted to using a range of different sources of literature. This evolved into using grey literature from media sources in the ethnicity review and motivated the introduction of additional expertise to navigate specific data.

2.4.2 Ethnicity

2.4.2.1 Research question

What is the evidence on ethnic variations in COVID-19 incidence and outcomes?

2.4.2.2 Summary of key findings

Analysis of intensive care unit (ICU) data found Black, Minority and Ethnic (BME) populations more likely to: be admitted to the ICU; require renal and advanced respiratory support and; die. The literature review found evidence of ethnic inequalities in health, housing, employment, and education. Overall quality of evidence was very low.

2.4.2.3 Critique

We included proxy evidence from different countries due to the dearth of evidence on ethnic minorities within a UK and pandemic context. A significant proportion of included studies were from the United States of America (USA), limiting transferability of findings.

Included grey literature was not searched systematically owing to rapid timescale. Peer-reviewed literature routinely follows a prespecified format, however, lack of structure within the grey literature hampered identifying what information was valuable to extract. Reproducibility of results is impacted by this absence in uniformity and quality assessment (QA) being conducted by only one reviewer per article without preformatted tools.

Reproducibility is problematic for grey literature sources. For instance, Google search results are popularity ranked through unique user algorithms (Mahood et al., 2014) and filter based on location. Our expert contributor being USA-based, and inclusion of Americanisms within search strings, could have biased search results.

Grey literature can be neutral or negative, contrasting to positive bias often in academic literature, creating a more balanced view of evidence (Rothstein and Hopewell, 2009).

However, bias is introduced when produced for specific audiences or purposes (Mahood et al., 2014). This applies to the temporal context of this review request, responding to reports that UK's BME groups were disproportionately affected by COVID-19 (Kirby, 2020). On 9/6/2020, the Scottish government committed to understanding the impact of the pandemic within BME communities (Sturgeon, 2020), synchronizing with global protests for "Black Lives Matter" following the death of George Floyd on 25/5/2020 (Burch and Eligon, 2020, Safi, 2020). The media traction this event gained also likely influenced calls for improvements in ethnic reporting to assess health inequalities.

2.4.2.4 Reflexive learning points

Previously, we limited our scope to Randomised Control Trial (RCT) epidemiology, considering scientific evidence on facemasks traditionally. Recognising the need for different sources without traditional evidence available, we utilised a range of grey literature and involved other disciplines for interpreting this data (sociologist expertise). We realised that even relying on preprints could miss important signals during the time lag of emerging scientific evidence within a rapidly evolving context. Using media reports alongside more traditional published and grey literature was useful in this context because they provided an early warning signal. This also impacted our ability to anticipate requests and establish links with expertise in advance.

Our grey literature consisted of preprint academic journals, government data sources and press reports. We mostly found evidence on ethnicity from media articles, offering valuable insight into characteristics of people at risk through rich, contextual details. This later enriched our understanding of factors potentially influencing high transmission in occupational settings within the indoor review (Dyal et al., 2020).

We realised the importance of incorporating ethnic data in health reports and also reporting when data was absent to avoid publication bias. I applied this transparency to my data extraction (DE) tool for epidemiological cluster studies within the indoor review (Appendix 2cii). In future studies, methodological limitations could be resolved through using search engines, such as ProQuest for newspaper articles, in a systematic way as we have with medical database searches.

2.4.3 Indoor transmission

2.4.3.1 Research question

What is the evidence for transmission of SARS-CoV-2 in indoor settings?

2.4.3.2 Summary of key findings

This review found SARS-CoV-2 is mostly transmitted person-to-person, short-range, via mostly respiratory droplets, either directly (airborne) or indirectly (through fomites). Evidence was found in domestic, workplace and community/leisure indoor settings. Overall quality of epidemiological evidence was low.

2.4.3.3 Critique

This review was conducted during a transitional phase, moving from RR to SR evidence. The longer timescale enabled higher quality of evidence, applying greater methodological rigour during QA. However, upon completion the review already warranted an updated search due to exponential growth in emerging evidence.

As mentioned above, we drew on relevant evidence from across three disciplines: epidemiology, microbiology and fluid mechanics. We split into three teams, initially unknown to each other, to assess, extract and synthesise evidence. Fluid mechanics expertise was introduced to understand the physical behaviours of particles under different climatic conditions. However, this team was unfamiliar with SR methodology, highlighted by discrepancies within their initial quality assessments. Disciplinary differences in academic reporting required further discussion to extract knowledge within the appropriate framework. Individuals' backgrounds in controlled laboratory environments, engaging with theoretical principles, became apparent. Contrastingly, we were acting on uncertain premises, on the inability to control for confounders within communities and engaging with various sources and perspectives to formulate evidence for public health. QA tools create systematic structure for interpreting this different data. We applied this systematic reasoning to fluid mechanics, modifying our existing QA tools to create a new one, before incorporating fluid mechanic expert feedback. However, the tool was untested and the expert untrained in

systematic reviews.

Responding to heterogeneity in reporting, I developed DE and QA tools for epidemiological "cluster" studies, adapted from Joanna Briggs' case series tool (JBI, 2020). Synthesising results of studies examining disease clusters allowed us to assess patterns of movement through person-to-person transmission between cases and contacts. Acknowledging that these observational studies are highly susceptible to confounding, I identified a number of features that increased robustness, which I incorporated into the QA tool. For instance, a follow-up period to differentiate between asymptomatic and presymptomatic cases, avoiding misclassification. Developing this tool was problematic, not all cluster studies fitted into corresponding DE tables exactly. Some conducted early in the pandemic may have been missed due to heterogenous reporting and variability in the preliminary definitions of cases and contacts (Tsang et al., 2020).

2.4.3.4 Reflexive learning points

The introduction of new, expert contributors at various stages resulted in time-consuming repeat training and confusion through modification of the original protocol. Although maybe improving our data interpretation abilities, it detracted from overall methodological rigour. Moving forwards, it is important to calculate manpower required from primary search results, enabling initial stronger group cohesion.

The appropriateness of merging different disciplines, and applying systematic techniques, is an open-ended question for future research. Consideration should be given to a possible lack in motivation from laboratory-based disciplines, taking precious time away from their primary research. However, if incorporating multidisciplinary expertise, integrated comprehensive systematic methods training for disciplines, not normally engaging with data in this way, should be used.

Although adapted DE and QA tools enabled greater clarity for users when analysing data, we did not test them prior to use. In future reviews, testing prior beginning will ensure consistency across individuals' approaches and enhance reproducibility.

2.5 Theme within reviews: asymptomatic transmission

The theme of asymptomatic transmission appeared within these reviews. Summaries of evidence, limitations and implications are considered under the following headings:

1. Characteristics of people and environments
2. Mode of transmission
3. Symptom bias

2.5.1 Characteristics of people and environments

The indoor review found that there was higher risk of transmission within communal (care-homes and homeless shelters) than private residential settings. Communal settings were often characterized by shared facilities, problematic for asymptomatic transmission if cases are unaware of the need to enhance hygiene and social distance. Household settings, pivotal in linking different outbreaks by increasing contact numbers, were reported in conjunction with workplace and religious settings (Pung et al., 2020)(religious gatherings (Chaw et al., 2020) and churches (Yong et al., 2020)). Workplaces often represented closed settings, with close proximity for prolonged periods of time (Dyal et al., 2020), seemingly creating unavoidable asymptomatic transmission opportunities.

Behaviours were linked to precaution and compliance with social distancing within the facemask review. Cultural and socio-behavioural factors affecting NPI compliance levels may differ between socio-economic circumstances. The ethnicity review findings suggest individuals experiencing health inequalities through socioeconomic disparities may struggle to self-isolate due to overcrowding or pressure to continue working. Asymptomatic disease is not visible, which can diminish the immediate perceived threat of disease spread. Mitigating this requires educating communities on the full spectrum of COVID-19 illness and risks, providing socioeconomic support where compliance is impossible.

2.5.2 Mode of transmission

Evidence from fluid mechanics studies indicated large respiratory droplets ejected while speaking, coughing and sneezing, land within less than 1-metre, 2-metres and 8-metres from the originator, respectively (Xie et al., 2007). Thus, risk of asymptomatic transmission appears

relatively low. However, overcrowding in closed indoor environments with poor ventilation and shared facilities could increase risk. Additionally, it is theoretically possible for smaller droplets (aerosols) ejected to travel any distance, although this will depend on viability or infectivity.

One report found a Secondary Attack Rate (defined as the probability that an infection occurs among susceptible people within a specific group e.g. household or close-contacts (Liu et al., 2020)) (SAR) of 87% from 61 persons who attended a 2.5-hour choir practice (Hamner et al., 2020). Singing can eject similar quantities of viral particles (order-of-magnitude) to coughing (Asadi et al., 2019). This could be significant for asymptomatic cases, not generating these quantities otherwise. Precautionary measures adopted within environments associated with certain physiological activities could lower transmission risks. Religious settings allow large congregations in close proximity for prolonged periods, often using shared facilities and singing together, conducive asymptomatic transmission potential, both airborne and through fomites.

Some evidence showed a small proportion of 'speech super-emitters' eject significantly (order-of-magnitude) more aerosol particles than others (Asadi et al., 2019), which could explain the high SARs of some outbreaks. If some asymptomatic individuals are super-emitters, this further justifies widespread facemasks use within community, alongside social distancing and enhanced hygiene.

2.5.3 Symptom bias

Asymptomatic cases pose unique challenges for prevention in terms of rapid detection and isolation, limiting case identification strategies determined by symptom presence only. Symptom reports are subject to recall bias; noted for residents and staff in a care-home study, given the general anxiety about COVID-19 (Roxby et al., 2020).

Surveillance and testing must encompass non-symptomatic contacts too, including repeat-testing to mitigate potential for false negative results in asymptomatic cases. Repeat-testing was not always done for quarantined non-symptomatic individuals within the indoor review (Yong et al., 2020, Chaw et al., 2020). Longitudinal testing is also required to distinguish asymptomatic from presymptomatic cases. Inconsistencies were identified in reporting when cases labelled asymptomatic later developed symptoms (Hu et al., 2020).

The incubation period signifies the time elapsed from exposure to developing first symptoms, thus, does not typically apply to asymptomatic cases (Lauer et al., 2020). Studies excluded asymptomatic cases from analyses on incubation period and serial interval (calculated from the former) (Chaw et al., 2020, Cheng et al., 2020). However, uncertainty remains around the period of infectivity for asymptomatic cases, warranting further investigations into asymptomatic populations specifically.

3 Chapter Three: A systematic evidence-based literature review

3.1 Introduction

The purpose of this chapter is to describe methodology and results of a literature review investigating evidence for asymptomatic transmission of SARS-CoV-2.

3.1.1 Research question

The following research question was developed to address the aim of this chapter.

- What evidence is there for asymptomatic transmission of SARS-CoV-2?

3.1.2 Methodology

3.1.2.1 Search strategy

This literature search was adapted from a piloted search I had created for a planned UNCOVER review on asymptomatic transmission of SARS-CoV-2. A PECO model was utilised to identify key terms (Population, Exposure, Comparison, Outcome). Search terms for the current review were modified to include reviews only.

Table 3 lists terms deemed appropriate for beginning the search. Appendix 3a displays the finalised search strategies for PubMed, Medrxivr and WHO's COVID-19 database in detail, with Boolean operators.

P	Population	Asymptomatic, Presymptomatic, Paucisymptomatic
E	Exposure	SARS-CoV-2
C	Comparison	Symptoms
O	Outcome	Transmission, Infections, Cluster, Cases, Carrier

Table 3: PECO search terms used in the search strategy

3.1.2.2 Databases

PubMed was chosen as one of the most widely accessible biomedical databases, through its provision of a high proportion of articles from MEDLINE and other National Library of Medicine (NLM) resources, such as PMC (Williamson and Minter, 2019). Limiting searches to MEDLINE records can exclude latest research due to the indexing backlog.

Medrxivr is an interface used to search MedRxiv, utilising a different syntax and updated daily. It captures relevant prepublication articles, resolving problematic searching on MedRxiv associated with searching preprint article sources. Problems concern availability of supporting data and irreproducibility of searches, which can detract from overall reproducibility. Technically, their functionality does not support transparency and, therefore, does not support UNCOVER work as a systematic approach. However, including preprints is important, as publication is often a lengthy process; latest evidence could be missed in indexing backlogs, amplified at present by the exponential growth of evidence in the rapidly evolving pandemic. If included, preprints should be quality assessed with added caution, not having yet been certified through peer-review. Additionally, preprint status should be clearly reported for transparency purposes.

WHO's COVID-19 database is specific to the pandemic, representing a comprehensive multilingual source of global literature; updated daily. While its high proportion of preprints is advantageous for accessing the most current evidence, it should also be treated with associated precautions.

Bibliographical managers Endnote and Zotero were utilised to compile articles retrieved from the databases. All results were then combined in Endnote, where duplicates were removed.

3.1.2.3 Eligibility Criteria

Inclusion criteria

- Reviews on asymptomatic transmission of SARS-CoV-2
- Published in English
- Systematic reviews and rapid reviews
- Meets asymptomatic case criteria:

- *Laboratory-confirmed SARS-CoV-2 infection with no symptoms at the time of first clinical assessment nor throughout and to the end of follow-up (Buitrago-Garcia et al., 2020).*
- *End of follow-up: virological cure, with one or more negative RT-PCR test results; follow-up for 14 days or more after the last possible exposure to an index case; follow-up for seven days or more after the first RT-PCR positive result (Buitrago-Garcia et al., 2020).*

Exclusion criteria

- Reviews not on transmission dynamics or proportion of asymptomatic cases e.g. clinical topographies, focus on treatment or prevention
- No asymptomatic cases according to the inclusion criteria
- Reviews without clear surveillance periods for included studies
- Reviews that limited the demographics in their inclusion criteria e.g. children only
- Non-English reviews
- Modelling-only reviews
- Non-reviews

3.1.2.4 Screening and Quality Assessment

Screening, data extraction and quality assessment was performed in Excel. The different phases of this process are depicted in Figure 1. Data extraction was limited to a minimal set of required data items, appropriated to reviews. Articles were assessed for quality using the Critical Skills Appraisal Programme (CASP) checklist for systematic reviews (CASP, 2018) (Appendix 3b) and graded (**Table 4**). This recognised tool enables assessment of validity by examining bias, rigour, specificity and precision of included studies.

Author	Quality Assessment Grade
Beale *et al.,* 2020	Low
Buitrago-Garcia *et al.,* 2020	Moderate
Byambasuren *et al.,* 2020	Moderate
Walsh *et al.,* 2020	Moderate

Table 4: Quality assessment grades for included reviews

3.1.2.5 Data Extraction

The following data were extracted from included reviews for narrative synthesis: study design, methods, date, country of included studies, asymptomatic case definition, outcome measure, follow-up, test type for COVID-19 diagnosis, demographics, setting, results of interest, author's conclusions, as well as strengths and limitations to enable a thorough assessment of study quality. A summary of the extracted data is included in **Table 5**.

3.2 Results

Four articles were retained for inclusion after quality assessment.

Results can be summarised under the following sub-question headings:

- What is the evidence for the proportion of asymptomatic infection?
    - What evidence is available on demographics or setting?
- What is the evidence for viral shedding of asymptomatic cases?

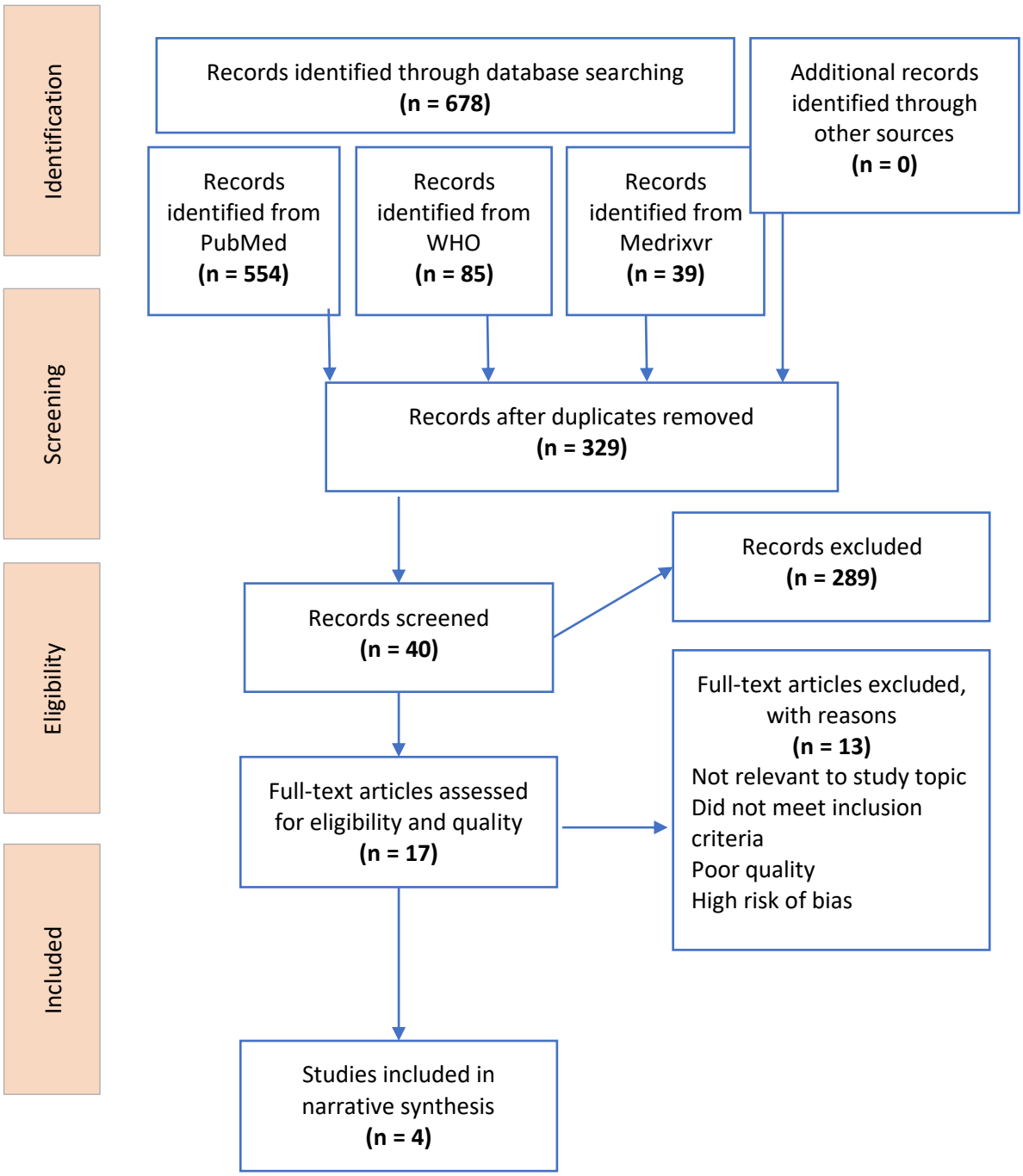

Figure 1: Adapted PRISMA flow diagram (Moher et al., 2009)

Author, date	Study type	Case definitions	Outcome measures	COVID-19 diagnosis test	Follow up period	Results
Beale et al. *5 May 2020* **PREPRINT**	Rapid review & meta-analysis	Asymptomatic and presymptomatic: differentiated through follow-up parameters	(1.) Frequencies of PCR-confirmed infections by symptom status (2.) Cycle threshold values and/or duration of viral shedding by symptom status	PCR only	Range 7-14 days 1 study until 2 consecutive negative swabs (up to 30 days)	(1.) The pooled estimate for the asymptomatic proportion of SARS-CoV-2 infections was 11% (95% CI 4%-18%) (2.) Estimates of baseline viral load similar for asymptomatic and symptomatic cases
Buitrago-Garcia et al. *10 June 2020* *(most recent update/3rd revision)* **PREPRINT**	Rapid living systematic review & meta-analysis	Asymptomatic: Laboratory-confirmed SARS-CoV-2 infection, no symptoms at time of first clinical assessment and no symptoms at end of follow-up Presymptomatic: Laboratory -confirmed SARS-CoV-2 infection, no symptoms at the time of first clinical assessment, developed symptoms by end of follow-up	(1.) Proportion of asymptomatic SARS-CoV-2 infections (2.) Proportion of presymptomatic SARS-CoV-2 infections (3.) Proportion of asymptomatic or presymptomatic transmission (SAR)	RT-PCR	End of follow-up: virological cure, with one or more negative RT-PCR test results; follow-up for 14 days or more after last possible exposure to an index case, or; follow-up for seven days or more after first RT-PCR positive result if date of last exposure could not be determined	(1.) Overall estimate of the proportion of people who become infected with SARS-CoV-2 and remain asymptomatic throughout infection was 20% (95% CI 17–25%, 79 studies) with a prediction interval of 3 to 67% (2.) Proportion of pre-symptomatic could not be summarised, owing to heterogeneity (3.) SAR from asymptomatic infections was slightly lower than from symptomatic infections (relative risk 0.35, 95% CI 0.1–1.27)

Byambasuren et al. *15 May 2020* **PREPRINT**	Systematic review & meta-analysis	Asymptomatic: confirmed via any testing and no symptoms for duration of follow-up to differentiate from presymptomatic cases	(1.) Proportion of asymptomatic SARS-Cov-2 infections (2.) Estimate of community spread from asymptomatic cases	RT-qPCR testing in all and in two cases supplemented with radiological evidence	All cases had follow-up period of at least 7 days to distinguish asymptomatic from presymptomatic	(1.) The proportion of asymptomatic cases ranged from 4% to 41%. Meta-analysis (fixed effect) found overall proportion of asymptomatic cases 15% (95% CI: 12% - 18%) (2.) Lower rates in asymptomatic (0-2.2%) than symptomatic cases (0.8-15.4%)
Walsh et al. *12 May 2020* **PEER-REVIEW**	Rapid review & systematic literature search	Asymptomatic: Remain symptomless throughout duration of disease Presymptomatic: In early stages of disease but symptoms have not yet developed	For asymptomatic, presymptomatic or symptomatic: (1.) Ribonucleic Acid (viral load or detection) during infection (2.) Duration of virus detection (3.) Period of infectiousness/infectivity	Ribonucleic Acid test (50 studies viral load through Rt-PCR)	Follow-up/duration of detection: Start: first confirmed positive test (or symptom onset) End: WHO criteria - two consecutive negative PCR tests 24 h apart	For asymptomatic and presymptomatic: (1.) Evidence for similar viral loads to symptomatic (2.) Estimates varied widely (3.) No study specifically examined duration of infectivity

Table 5: Data extraction for included studies in systematic literature review

3.2.1 What is the evidence for the proportion of asymptomatic infection?

Three out of four included studies reported data on the proportion of asymptomatic cases and found the asymptomatic proportion of SARS-CoV-2 infections to be relatively low. The proportion of asymptomatic cases was calculated through the denominator including all PCR-confirmed cases from the study sample, and the numerator including those who tested positive and had no symptoms throughout follow-up (according to authors' criteria in **Table 5**) (Byambasuren et al., 2020).

- Beale *et al* (2020) found that the pooled estimate for the asymptomatic proportion of SARS-CoV-2 infections was 11% (95% CI 4%-18%);
- Buitrago-Garcia *et al* (2020) found the overall estimate was 20% (95% CI 17–25%, 79 studies) with a prediction interval of 3 to 67%;
- and Byambasuren *et al* (2020) found it to be 15% (95% CI: 12% - 18%) overall, from a fixed-effect meta-analysis.

3.2.2 What evidence is available on demographics of asymptomatic cases or setting for asymptomatic transmission?

A summary of the evidence available on demographics and setting is displayed in **Table 6**. Data extraction was limited to reviews measuring the proportion of asymptomatic infection (Beale et al., 2020, Buitrago-Garcia et al., 2020, Byambasuren et al., 2020).

Review	Age	Sex	Ethnicity	Geographic	Setting
Beale *et al.,* 2020	✓	✓	×	✓	Limited
Buitrago-Garcia *et al.,* 2020	✓	✓	×	✓	✓
Byambasuren *et al.,* 2020	✓	×	×	✓	✓

Table 6: Reporting of demographics and setting within included reviews

Age

All reviews reported on demographics for age of study participants, including when there was none. Only one review had no missing data on mean age for included studies (Byambasuren et al., 2020).

Sex

Two reviews reported on sex distribution of study participants with asymptomatic infection (Beale et al., 2020, Buitrago-Garcia et al., 2020). Data was limited within included studies.

Ethnicity

None of the included reviews reported data on the ethnicity of study participants.

Geography

All reviews reported on geographic location of included studies, detailed in **Table 7**. Overall, the highest sampling frames within each review, from combining included studies according to country, came from China.

Review	No. of studies	No. of countries	Country (no. of studies per country)	Total no. of SARS-CoV-2 cases (asymptomatic cases)	No. of cases per country
Beale *et al.,* 2020	6	5	USA (2) South Korea (1) France (1) Vietnam (1) China (1)	316 (31)	47 & 5 97 6 30 129
Buitrago-Garcia *et al.,* 2020	79	19	China (47) *Other countries not stratified*	6616 (1287)	3802 *Other countries not stratified*
Byambasuren *et al.,* 2020	9	6	China (3) USA (2) Taiwan (1) Brunei Korea (1) Italy (1)	559 (83)	*Not stratified*

Table 7: Reporting of geographic data within included reviews

The highest number of cases (129) reported by Beale et al (2020) was from China. Buitrago-Garcia et al (2020) reported the highest number of studies (47 out of 79) and cases (3802 out of 6832) from China. Although Byambasuren et al (2020) did not stratify their results by case numbers, their highest total sampling frame per study country came from China (14,239 close-contacts out of a total of 21,035 tested).

Setting

All reviews reported on the setting of included studies, **Table 8**. Setting was found in sampling frame or group of participants. Data was stratified differently for each review, however, all identified care-homes/skilled-nursing facilities as one stratum in their reporting of setting (in DE tables or narratively). Two reviews (Beale et al., 2020, Byambasuren et al., 2020) isolated nursing homes/skilled-care facilities as its own category, and one review (Buitrago-Garcia et al., 2020) identified nursing homes narratively within the category “outbreak investigation”.

Review	Setting categories *participant group/sampling frame*
Beale *et al.,* 2020	*"nursing home" or "general public"*
Buitrago-Garcia *et al.,* 2020	*"contact investigation (single/aggregated)", "outbreak investigation", "screening of defined population", "hospitalised (adults/children/adults and children)"*
Byambasuren *et al.,* 2020	*"skilled nursing facilities", "high-risk close-contacts" or "whole district surveillance/screening"*

Table 8: Categories for setting within included reviews

From snowballing references of reviews, settings could be further categorised into; private and communal residential, occupational, community, leisure, religious and nosocomial. All three reviews included studies involving residential, occupational, community, leisure and nosocomial settings (Beale et al., 2020, Buitrago-Garcia et al., 2020, Byambasuren et al., 2020). Two reviews also included studies involving religious settings (Buitrago-Garcia et al., 2020, Byambasuren et al., 2020).

3.2.3 What is the viral load/viral shedding of asymptomatic cases?

Two out of the four included reviews reported data on viral load and viral shedding of asymptomatic cases as measured outcomes (Beale et al., 2020, Walsh et al., 2020). There was no meta-analysis in any of the reviews owing to limited evidence, results were synthesised narratively.

Beale et al (2020) included three studies reporting on viral load through cycle threshold (Ct) values and/or duration of viral shedding by symptom status. They found estimates of baseline viral load to be similar for asymptomatic and symptomatic cases. Detailed reporting of Ct values and epidemiological history of viral shedding by symptom status was limited.

Walsh et al (2020) included seven studies that measured viral load through Ct values of detected RNA in asymptomatic and presymptomatic cases, indicating similar levels compared with symptomatic cases. Eight of their included studies measured duration of viral shedding in asymptomatic or presymptomatic cases. Estimates were varied with an overall range of 1-

23 days from studies combined. None of their included studies definitively measured duration of infectivity.

Additionally, Byambasuren et al (2020) reported from three included studies that Ct values from RT-PCR assays did not differ between asymptomatic and symptomatic individuals. However, this was not a measured outcome.

4 Chapter Four: Discussion

4.1 Introduction

4.1.1 Overview of UNCOVER reviews

This review explored the theme of asymptomatic transmission of SARS-CoV-2, initially identified through involvement in UNCOVER reviews, investigating facemasks, ethnic variation and indoor transmission in relation to COVID-19. The theme mostly appeared in evidence on characteristics of people and environments and mode of transmission. Evidence where asymptomatic transmission appeared here overlapped significantly with evidence generated by the systematic literature search.

4.1.2 Overall findings

This review investigated evidence on asymptomatic transmission and found evidence on the proportion of asymptomatic infection, including demographics of cases and transmission setting; and on viral load of asymptomatic cases. Overall, the proportion of asymptomatic cases was relatively low compared with symptomatic cases. The three reviews investigating this identified cared-living facilities as a setting for asymptomatic transmission. Overall, demographic reporting was limited. Highest sampling frames from combining all included study participants came from China. Data on viral load and shedding of asymptomatic cases was limited and inconclusive from the two reviews investigating this. No evidence available was available on infectivity from viral culturing of asymptomatic SARS-CoV-2 virion.

Limitations of evidence from the systematic search will be evaluated before considering the positioning of all findings within the context of the wider literature.

4.2 Overall limitations of included studies

Three out of four reviews were RRs (Beale et al., 2020, Buitrago-Garcia et al., 2020, Walsh et al., 2020). RRs are limited in their reliability as systematic methodology is truncated due to limited time. Additionally, three reviews were preprints from MedRxiv (Beale et al., 2020, Buitrago-Garcia et al., 2020, Byambasuren et al., 2020), meaning they have not yet been peer-reviewed.

Only one review was graded low quality of evidence (Beale et al., 2020). There were no independent reviewers for rejected articles and studies were restricted to English language only (the other three had no language restrictions (Buitrago-Garcia et al., 2020, Byambasuren et al., 2020, Walsh et al., 2020)). It was also unclear if they included "presymptomatic" as a key search term. If not, this could underestimate the total amount of asymptomatic cases reported in the review.

There were some discrepancies between reviews regarding QA of included studies. One study (Byambasuren et al., 2020) criticised another (Buitrago-Garcia et al., 2020) for including 25 studies in their second update, which they had excluded due to high risk of bias in the sampling frame. This highlights a lack of uniformity in QA methods; standardised QA tools are not sufficiently detailed and heavily depend on user judgment and expertise. Adaptations can introduce more objectivity, assisting with minimising user judgment, and can encourage transparency of reporting, often requiring primary data collection to be released in full (Byambasuren et al., 2020).

All reviews used different QA tools. Two reviews (Beale et al., 2020, Buitrago-Garcia et al., 2020) used Joanna Briggs' tool for prevalence studies, one adapted it (Buitrago-Garcia et al., 2020). Another (Byambasuren et al., 2020) used a combination of tools, adapting key signalling questions (e.g. sampling frame, case definition of asymptomatic, length of follow-up etc.). The remaining review (Walsh et al., 2020) used Cochrane Risk of Bias tool for RCTs, Risk Of Bias In Non randomised studies of intervention tool (ROBINS-I), and adapted tools for other studies from related tools (no details reported).

Lastly, the rapidly evolving nature of the pandemic correlates with an exponential growth in emerging evidence. One review (Buitrago-Garcia et al., 2020) was conducted a month later than the other three reviews. Social contexts and drivers of behaviour and transmission are likely to have changed during this period of time. Additionally, as time progresses more

individuals are tested, inevitably resulting in an increase in case numbers. Thus, findings should be carefully considered in the temporal context that they were conducted in.

4.3 Limitations of the evidence

4.3.1.1 Proportion of asymptomatic

Study type

All three reviews reporting evidence on the proportion of asymptomatic infection were preprints from MedRxiv (Beale et al., 2020, Buitrago-Garcia et al., 2020, Byambasuren et al., 2020) and have not yet undergone peer-review, thus, findings should be interpreted with caution. All had a wide range of confidence intervals, implying a great degree of uncertainty from results lacking in precision (Beale: 4–18%; Buitrago-Garcia: 17–25%; Byambasuren: 12–18%).

Eligibility criteria

The inclusion of family contact investigations with at least one asymptomatic individual could create an overestimate of the asymptomatic proportion. It is possible that the higher proportion of asymptomatic infection reported in Buitrago-Garcia et al (2020) (20%) is due to this. The low end of their total sampling frame (single contact investigation: range 2-15 cases) that included family investigations contrasts with sampling frames for Beale et al (2020) and Byambasuren et al (2020), who excluded studies with <5 positive cases and/or <20 total cases or small cluster studies (not specified numerically), respectively.

Selection bias

The nature of asymptomatic infection is inherently problematic for identification strategies as cases are unaware that they are sick. They are not prompted to get tested and often only identified subsequently from symptomatic cases. To avoid selection bias based on symptom, one review (Byambasuren et al., 2020) excluded studies with sampling frame determined by symptoms and another review (Beale et al., 2020) excluded healthcare settings. It is unlikely

that proportions of asymptomatic infections in hospitals are generalisable to community settings; inclusion would likely create an underestimate of asymptomatic infection overall.

Only one review actually stated exclusion of studies with no data on asymptomatic cases within their eligibility criteria (Byambasuren et al., 2020), however, none of the other reviews reported data on clusters without any asymptomatic cases either. This introduces selection bias and is significant for generalisability of results, as findings may not accurately reflect proportions of asymptomatic infection in the wider community.

PCR testing

All reviews only included studies which used PCR testing to determine diagnosis. However, PCR testing is not uniform between countries (Subbaraman, 2020). RT-PCR assays used for the UK's COVID-19 testing programme have been verified by Public Health England and indicate over 95% sensitivity and specificity (Mayers and Baker, 2020). This means (under laboratory conditions) tests should never show more than 5% false positive or 5% false negative results. Authors did not consider the possible impact of these RT-PCR results in calculations, which would underestimate and overestimate the proportion of asymptomatic infections, respectively. Uniformity in reports repeat-testing participants improves accuracy of findings from results based on PCR. However, four included studies in Byambasuren et al (2020) did not retest asymptomatic cases for RT-qPCR status, diminishing accuracy of findings.

Reporting bias

The proportion of presymptomatic infection could not be summarised by Buitrago-Garcia et al (2020) owing to heterogeneity. If this was underrepresented, authors may have overestimated the proportion of asymptomatic infection. Additionally, none of the reviews stratified on symptom classification.

4.3.1.2 Demographics and setting

All three reviews investigating proportion of asymptomatic infection transparently reported primary data for age, geography and setting, including when this was not available (Beale et al., 2020, Buitrago-Garcia et al., 2020, Byambasuren et al., 2020). None reported data on

ethnicity and data on sex was especially limited. This underreporting of ethnic data is significant for establishing risks in minority communities.

Geography

The total number of cases and contacts identified gives insight into how countries differ in their testing and tracing capacities and how this might impact results. Owing to inherent identification difficulties, identifying asymptomatic cases partly relies on countries' testing and tracing (TT) abilities. Tracking contacts in a timely manner can halt transmission chains and shorten epidemiological history, improving overall accuracy of findings. China has become renowned for its TT capabilities, consistent with reviews' highest total sampling frames by country originating from here.

Setting

Reporting on population sampling frames, which included data on setting, was heterogenous. However, all study settings involved some degree of communality or close proximity between multiple cases. Different settings were also often representative of discrete sub-populations.

Identifying the overlap of included studies between reviews revealed a lack of uniformity in classification for epidemiological studies. For example, an epidemiological investigation of 24 COVID-19 patients associated with a supermarket cluster (Tian et al., 2020) was categorised as an outbreak in one study (Buitrago-Garcia et al., 2020) and a close-contact investigation in another (Byambasuren et al., 2020). There are no defined criteria for what constitutes a close-contact investigation versus an outbreak investigation. This subjectivity within categorisation, through variability in reporting, is problematic when trying to make meaningful cross-comparisons based on setting type. Identifying high-risk settings becomes a time-consuming process of decoding authors' categories, often requiring snowballing of references to trace the epidemiological history with accuracy.

4.3.1.3 *Viral load*

This review found evidence on the viral load of asymptomatic cases to be a similar quantity to viral load of symptomatic cases. However, data was limited and of low quality in both reviews that measured this outcome (Beale et al., 2020, Walsh et al., 2020) and, thus, inconclusive. Only seven out of 113 included studies in Walsh et al (2020) measured viral load for asymptomatic infection, and three of six included studies in Beale et al (2020) One review (Walsh et al., 2020) combined their reporting of asymptomatic and presymptomatic, indicative of general underreporting for these groups. This resulted in a lack of clarity in establishing any differences that might exist between them.

Data was limited to PCR tests, which are only able to detect presence of viral RNA, not establish infectivity. This is problematic as tests could be identifying dead virus, which is not infective. None of their included studies had cultured virion of asymptomatic cases, which is necessary to establish potential for infectivity. One review (Walsh et al., 2020) measured the outcome duration of infectivity, however, this was calculated through duration of viral shedding (established through consecutive PCR tests), which may not correlate with infectivity.

Duration of viral shedding was not stratified on symptom status. The poor reporting on symptoms throughout highlights a lack of clarity surrounding whether a correlation between symptomatology and severity of viral shedding exists. Greater uniformity in reporting, stratifying primary data based on symptoms, would assist with establishing this

4.4 Strengths and limitations of the process

Strengths of this review include methodological rigour within a short timescale. Thorough quality assessment identified risk bias and reported on this transparently. Any reviews that did not transparently QA their included studies were excluded. Clear eligibility criteria ensured studies had accurately identified asymptomatic infection and clearly defined parameters of follow-up (detailed in **Table 5**) using validated COVID-19 detections methods (PCR testing), differentiating asymptomatic from presymptomatic infection.

This review was conducted by only one reviewer, without an independent reviewer to check rejections, quality assurance is limited. Overall quality of evidence was graded moderate to

low. The CASP QA tool for systematic reviews (2018) used may lack appropriateness to the rapid and scoping reviews captured by the search. It is likely more current evidence from individual reports and case series was missed by only including reviews.

4.5 Links to wider literature: evidence versus opportunity to transmit

Given the great uncertainties that remain, it is not possible to fully evaluate the risks of asymptomatic transmission without multidisciplinary consideration. Often, different approaches within scientific literature require each others' answers to assess the overall impact of their evidence for public health. Providing answers often involves a dynamic interaction between multiple disciplines. Questions may be structured as: "Given what we know about "X", what is the opportunity for asymptomatic cases to transmit?"

Within this dissertation, this manifests as the following:

- Given the evidence that was found on: proportion; demographics and setting; and infectiousness, of asymptomatic cases, how does this interact with their overall opportunity to transmit?

Questions will be considered within the context of the wider literature, encompassing epidemiological, microbiological and mechanistic approaches.

4.5.1.1 Proportion of asymptomatic versus opportunity to transmit

Variability in symptomology

Evidence indicated the proportion of asymptomatic cases out of the overall total number of confirmed cases (asymptomatic and symptomatic (including presymptomatic) combined) was relatively low. However, included reviews did not report on categories of symptoms. Dichotomising cases into symptomatic or asymptomatic classifications oversimplifies the spectrum of illness for COVID-19 while not stratifying symptoms of symptomatic cases introduces reporting bias. This can extend to misclassification of cases presenting unusual symptoms. Our understanding of what constitutes a symptom has changed significantly throughout the course of the pandemic. Human beings often impose categorical variables to understand novel information, however, the evolution of the pandemic has continued to reveal the continuous spectrum of illness and nonlinear dynamics of disease transmission.

Initially, COVID-19 was categorised into mild, moderate and severe illness (WHO, 2020b). As time has passed, variability between individual symptomology, ranging from asymptomatic to severe disease, has continued to fluctuate. Distinguishing between carriers presenting very mild symptoms and those who are asymptomatic has become increasingly difficult as new symptom classifications have emerged, such as anosmia and ageusia (Costa et al., 2020). Both asymptomatic and mild cases present significant challenges for identification, making it likely that studies conducted earlier in the pandemic investigating proportions of infection based on symptoms may have significantly underestimated numbers of asymptomatic, presymptomatic and paucisymptomatic cases.

Behavioural differences

The great degree of variability between symptomologies, which depends on host, invites significant differences in symptom-associated behavioural risk-factors. Asymptomatic individuals are likely to behave very differently to symptomatic individuals through lack of awareness of illness. These behaviours are likely to differ between different symptomologies and also each person, dependent on individual threshold for illness. This applies to mild cases especially as the UK enters winter, when normal viruses like the common cold will begin circulating and people will experience mild symptoms of illness. This could result in misclassification, through self-diagnosis, of COVID-19 with other illnesses. Depending on personal traits, some individuals will think they need to self-isolate while others may disregard the impact of their illness. Compliance with this precautionary measure will likely interact with socioeconomic position, if individuals are unable to take time off work due to financial pressures. This, combined with a lack of education on risks, could also affect compliance of close-contacts to self-isolate, if cohabiting with potential COVID-19 cases. Problematic, as it presents an opportunity for asymptomatic transmission within households and the workplace.

K value

The behavioural differences between symptomologies mean that even low proportions of asymptomatic infection still warrant policy attention (Byambasuren et al.). They illustrate we cannot assume individual cases have the same transmission potential and will create the same

transmission patterns, mirrored subsequently by their contacts, which is what the R value assumes. The *K value* measures the difference in how many people each COVID-19 case infects. The smaller the *K value*, the lower the number of people who are transmitting the disease to others is. This means there are more individuals who are "super-spreading" (Sneppen et al., 2020), each individually infecting higher numbers of people. Thus, although this review did not find evidence of total asymptomatic proportion to be high, the potential for asymptomatic transmission cannot be evaluated on proportion alone when considering the impact of "super-spreaders". Evaluating this involves considering a range of different factors at both the individual and population level, for instance, investigations on characteristics of people and environments that facilitate outbreaks.

4.5.1.2 Demographics and setting as opportunity to transmit

This review found evidence of significant variability between the proportion of asymptomatic infection and study population or study setting, indicating that opportunity for asymptomatic transmission is context dependent.

Evidence on study setting involved some degree of communality or close proximity between multiple cases. Evidence on transmission in residential, occupational, community, leisure and nosocomial settings was apparent throughout. This reflects evidence from the indoor review; settings of individuals gathered in closer proximity for prolonged periods of time were generally associated with a higher risk of transmission.

Evidence on residential settings, both private (household) and communal (care-homes) was reported throughout. This supports evidence from the indoor review; higher SARs were found in communal residential contexts (range, 18 % to 62 % amongst residents of care homes, shelters for homeless people, cruise ship) than in households (pooled SAR 11 %, 95 % CI 9, 13). While transmission can be mitigated in the household through self-isolation, indicated by lower SARs reported (Burke et al., 2020), this may not apply to asymptomatic transmission when individuals fail to perceive a need to self-isolate. This problem is augmented in overcrowded households. Clarity on close-contact definitions may mitigate the challenge of unawareness, by establishing potential asymptomatic cases. However, in communal and overcrowded residential settings, individuals may still be unable to effectively enact NPI measures or be uncompliant without a perceivable threat of illness.

The separate reporting of nursing homes and skilled-nursing facilities in included studies of this review highlighted this setting as a potential hotspot for outbreaks. Care-homes present unique challenges as unique living environments where contact is unavoidable between staff members, and residents requiring assisted care. Opportunity for asymptomatic transmission between residents is increased through close proximity of living arrangements and shared communal activities, as well as through healthcare workers (HCW) being close-contacts of multiple residents and sometimes working across multiple care-home sites (Tinsley, 2020). Kennelly et al found over a quarter of nursing home staff were asymptomatic (27.1%; 89/329) (Kennelly et al., 2020). HCW have a distinct opportunity to spread the virus, with significantly longer path lengths (Kim and Jiang, 2020), compared to residents, often elderly and limited in movement. Thus, contrasting behavioural differences between sub-population clusters will likely manifest in different dispersion of disease.

Residential settings acting as a "transmission link" between outbreak clusters (Yong et al., 2020) is significant for asymptomatic transmission in demographics experiencing health inequalities from overcrowding. People from BME backgrounds comprise 17% of the social-care workforce (IS, 2020). There is evidence that indicates correlation between overcrowding and ethnic variation and socioeconomic position. Overcrowding is much more prevalent in BME households (30% of Bangladeshi households and 15% of African (Black), compared to 2% of white British households (Haque, 2020) and these households are often multigenerational. BME and socially disadvantaged groups have been found less able to comply with NPI measures, such as self-isolation (Atchison et al., 2020). This could also place BME nursing home staff at higher risk of inducing longer transmission chains.

A combination of socioeconomic pressures to continue working and overcrowded households to return to on overcrowded public transport (Goldbaum and Rogers Cook, 2020) could result in a very long chain of transmission through a high number of contacts per individual case. This is indicative of the importance of investigations on the *K value*, stratified by the unique transmission dynamics of sub-populations within certain settings. The unique behaviours of asymptomatic carriers compared to symptomatic carriers within these settings will likely result in significant variability between their dispersion patterns.

4.5.1.3 Infectiousness versus opportunity to transmit

Assessing the impact of the proportion and demographics of asymptomatic cases, or setting of asymptomatic transmission, involve epidemiological approaches that can only establish correlation, not causality. Ultimately, microbiological studies are required to establish whether asymptomatic cases are actually infectious.

This review found evidence that viral load is similar between asymptomatic and symptomatic cases. There were no statistically significant differences found between Ct values of asymptomatic cases and symptomatic cases, suggesting transmission from asymptomatic carriers is possible. However, low sample sizes resulted in lacking numerical detail on Ct values (Beale et al., 2020). Moreover, findings should be interpreted with caution as infectivity was not definitively measured (Byambasuren et al., 2020); PCR sampling can only detect viral presence and high viral load does not necessarily correlate with infectiousness.

There is some evidence that suggests a relationship between viral load and symptomology. In certain settings, evidence has indicated that the immune system can be overwhelmed by the amount of virus, explaining why some HCWs have been vulnerable to severe disease manifestation (Wu and McGoogan, 2020). If this relationship exists, although more likely to transmit through greater opportunities, asymptomatic cases would be unlikely to make their immediate contacts seriously ill. Nevertheless, with significant behavioural differences affecting their movement patterns, asymptomatic cases may still act as significant drivers of transmission within the community, even if first generation contacts are not severely affected.

Results on viral load or infectivity are not sufficient to establish transmission risk taken alone. Someone might be infectious but not necessarily infect someone else. The opportunity for that viral particle to transmit will depend on its mode of transmission in conjunction with the environment it is in. This requires interpretation of a combination of mechanistic studies and epidemiological studies. Some epidemiological studies have investigated sub-populations, such as residents in care-homes and found no significant difference between the mean Ct values across the four symptom status groups ($p = 0.3$) (Kimball et al., 2020). However, great variability found between certain demographics e.g. children and the elderly (Davies et al., 2020), highlights the need for further investigations into sub-populations.

Microbiological and mechanistic evidence from the indoor review indicates that symptomatic cases with higher viral loads are more likely to spread the virus effectively than asymptomatic cases. However, evidence that asymptomatic cases have high viral loads in their nasal secretions suggests they can silently and efficiently spread the disease (Hosoki et al., 2020). This is a major difference in transmission between SARS-CoV-1 and SARS-CoV-2, the former having significantly more lower respiratory tract involvement (Woelfel et al., 2020). From an epidemiological perspective, those showing no or very little symptoms may be just as dangerous for viral spread, as they are likely to have a greater number of contacts to those with more severe symptoms. Notably, this is context dependent as severely affected vulnerable populations may be experiencing overcrowding through socioeconomic inequalities.

4.6 Implications for further research and policy and practice

4.6.1 Further research

Resolving uncertainties that remain requires interdisciplinary collaboration, to fully understand the opportunities for asymptomatic transmission and implications for policy. This will entail investigations on asymptomatic infection from microbiological, mechanistic and epidemiological approaches. Viral culturing of asymptomatic infection is an area where further studies are required urgently. Without this, our infection prevention strategies for asymptomatic cases remain uncertain.

Since most included evidence was graded low to moderate, further higher quality studies are warranted. Epidemiological studies should incorporate appropriate modifications to increase robustness when assessing evidence highly susceptible to confounding, such as clearly outlined surveillance periods for follow-up.

Greater uniformity overall in reporting for infectious disease outbreaks is required to assess true impact of disease transmission. Clarity in case definitions, clearly outlining parameters that determine classification, will help establish this. Transparent reporting of primary data on any variability in symptomology at the individual level will help to minimise reporting bias and recognise any patterns in unusual symptoms, which could result in misclassification later

on. Adapting quality assessment tools where no universally accepted model exists will help minimise user judgment. In future disease outbreaks, pre-piloted data extraction tools, containing questions helping users identify exactly what data is valuable, will assist with streamlining review processes supporting time pressed decision-makers. Stratifying results based on demographics and study setting, where possible, will enable greater ease in assessing differing transmission patterns. Further epidemiological investigations into movement patterns of disease clusters of specific sub-populations or closed settings are warranted to establish vulnerable at-risk populations.

Since distinct populations are often associated with specific closed environments (e.g. elderly in care-homes, children in nurseries, adolescents in universities/night-clubs) this also warrants investigations into the mechanisms of transmission within these environments, which will also influence opportunities for transmission.

4.6.2 Policy and practice

A steady increase in case numbers has logically followed the increase in UK-wide testing, despite death rates stabilising (Heneghan and Jefferson, 2020). However, importantly, this reflects the number of detected cases, which is not the same as cases rising (Heneghan and Jefferson, 2020). The impact of false positives and false negatives on results for the total number of cases remains. Additionally, estimated sensitivity and specificity for PCR tests is likely to have been estimated in study populations only including symptomatic cases (Byambasuren et al., 2020), thus, implications for asymptomatic cases are unclear.

Case definitions will determine who gets tested, so it is important to identify which infected individuals are at high risk of transmitting (McArthur et al., 2020). Given their unique opportunities to transmit, asymptomatic cases must be clearly defined for this reason.

The way we define a case has changed from identifying people with symptoms, who have then been tested and found positive, to a case simply being a PCR positive result, irrespective of symptom identification (Mahase, 2020). However, a positive PCR result taken alone is problematic due to false positives. This can add to scaremongering through case reports, which may eventually result in distrust towards health services and authorities for not accurately representing effects of disease. A binary Yes/No approach to interpretating RT-PCR results, unvalidated against viral culture, could risk false positives, segregating people no

longer infectious from society (Jefferson et al., 2020). Considering testing data alone seems insufficient to direct local lockdowns (Mahase, 2020). Contact tracing of close-contacts is one remedy for false negatives, however close-contact definitions should be carefully publicly outlined alongside case definitions in test and trace strategies, in order to guard against asymptomatic transmission through false negatives.

More young people are likely to test positive as restrictions ease because they will be out socialising, whereas older generations, often with comorbidities, will likely continue self-isolating or shielding. If tests are identifying a younger generation, the virus may not be attenuating in the same way as with an older generation, background immunity could be a possibility (Mahase, 2020). Batch testing of sub-populations would be one cost-effective way of identifying the prevalence and impact of disease between different populations. It can also help accurately assess proportions of asymptomatic versus symptomatic cases. Individuals can be systematically repeat-tested throughout a period of follow-up, to distinguish asymptomatic from presymptomatic, for example, one hundred university students, care-home residents, or nursery school children. If any cases are positive, testing of all one hundred participants should be repeated at consecutive intervals; at 7 days and 14 days, from the initial test. In reporting, symptoms should be stratified, assisting with differentiating asymptomatic individuals from unusual mild symptoms.

Although widespread viral culturing methods are unrealistic on a large scale, the significant paucity in evidence on infectivity of asymptomatic cases should be prioritised within further investigations, such as batch testing. Ultimately, this will determine the risk of asymptomatic transmission, effectively informing policy strategies. However, until further evidence presents, given the unique opportunity for asymptomatic cases to transmit, the precautionary principle, through widespread use of facemasks and social distancing within communities, is warranted.

5 Chapter Five: Conclusion

This review investigated evidence on asymptomatic transmissions of SARS-CoV-2 and found evidence on proportion of infection, characteristics of demographics and setting, and viral load.

Estimates on the proportion of asymptomatic infections detected by PCR testing ranged from 11% (Beale et al., 2020) to 20% (Buitrago-Garcia et al., 2020). However, studies combined a variety of different sampling frames for population and setting, and selection and reporting bias against symptoms was found, thus, data was inconclusive. Further robust epidemiological evidence is needed to understand the true prevalence of asymptomatic infection and its impact for driving overall transmission. Batch testing of sub-populations presents one cost-effective way of accurately identifying proportions based on symptoms, minimising selection bias through follow-up, while potentially gaining valuable insight into population-specific transmission driving behaviours. This will be useful information for guiding lockdowns and reopening, however, microbiological investigations into viral culturing of asymptomatic infection should also be prioritised, to determine infectiousness, which underpins any risk assessment.

The low proportions of asymptomatic infection reflected in findings, if confirmed to be infectious, still warrant policy attention due to carriers' unique opportunity for dispersion, presented through inherent behavioural differences to symptomatic carriers.

This dissertation recommends future multidisciplinary approaches for assessing the risk of asymptomatic transmission, which reflects the overall nonlinear dynamics disease transmission. While key uncertainties remain, precautionary policy on widespread facemask usage and social distancing within closed environments is warranted.

6 Reflective Review

Dissertation overview

My dissertation is an UNCOVER COVID-19 Rapid Review Dissertation on asymptomatic transmission of SARS-CoV-2. I followed this theme with a degree of curiosity throughout my involvement with UNCOVER before systematically reviewing the literature on it.

Choice of method and possible bias

I did not imagine at the beginning of the MPH that I would be pursuing a dissertation on infectious disease, let alone amidst a global pandemic. I remember in one of the first lectures we were asked to keep our hands up if our first degree had not been named yet, to capture the diversity of the cohort. My hand stayed up right until the end, "Philosophy". Here to change the world.

Without a medical background, I felt set apart from the majority of my colleagues and battled with self-doubt over what was possible for my dissertation. My first tutor tried to persuade me towards a qualitative dissertation on the effects of yoga on mental health, using my position as a yoga teacher as a gateway. However, when the pandemic hit, I pushed back. It seemed inappropriate to be asking for peoples' time in this way; the same people who had lost their jobs, studios, practice and, ultimately, faith. The universal state of panic; followed by a prolonged state of grief, presented conversations that I couldn't ignore. I wanted to use my studies to engage with something that was immediate and useful, with real-world impact. When the opportunity of UNCOVER was presented to me, I had already dropped my worldly commitments and slipped into isolation in my childhood home. Uprooted from my life in Edinburgh, I desperately needed direction and purpose in lockdown; I gave UNCOVER all the time I had, I owed it for re-engaging me.

What struck me most during the initial uproar of panic; was people's inability to show empathy for others while their own life was in turmoil. It seemed like even my friends had lost their capacity to offer support. I could see that people really needed one another, but how could they usefully offer support while the ground they stood on shook? When the

theme asymptomatic transmission was identified within UNCOVER, I was fascinated by what it meant for this. I wondered how you could you induce empathy at a population-level, for what was also an invisible illness, to protect the vulnerable. Having experienced a total absence of this concern on a personal level, I was driven to continue to identify the role of asymptomatic transmission within each review. Already accustomed to unforeseeable changes in my dissertation, I was unattached to my topic and happy to let it unfold organically. I continued to prioritise urgent requests within the politically pressed landscape, asymptomatic transmission in the back of my mind. Charged by the potential of its usefulness to UNCOVER, I worked productively for long hours, my only obligation, remaining at home.

I recognised that my compassionate nature, combined with a tendency for obsession and overthinking, could be a recipe for bias in my research on asymptomatic transmission. This coupled with paranoia induced by lockdown and scaremongering from the media. Thankfully, the extensive work within UNCOVER trained me to view data neutrally. In retrospect, my decision to sign out of all social media shortly before officially beginning my dissertation aided this. I became aware of how much my emotions were directing my perceptions. Engaging with *Black Lives Matter* protests on Instagram was interfering with neutral judgement on the Ethnicity Review. I signed out of Instagram; trading it for the *Calm* meditation app (a habit I've continued). When it came to reviewing literature on asymptomatic transmission for my dissertation, which had grown and evolved exponentially since I identified with the theme, I felt neutral. I had been reunited with my partner back in Scotland (after 100 days apart), feeling calmer having regained control through independence and distance from the data. My drive gained from UNCOVER, to be as rigorous as possible in my methods, remained, paying close attention to detail and privileged by a longer timescale to conduct the work, no longer in an emergency phase.

<u>Challenges</u>

The passionate immersion, to conduct the research in an urgent manner, was very quickly replaced as we moved into the second phase of pandemic research, as rapid reviews began to take a more systematic format. My drive stumbled at this hurdle; it was difficult to slow down and contemplate my own research goals as I still felt this inherent urgency. I was heavily invested emotionally in UNCOVER. For me, deferring my focus from UNCOVER meant moving

away from an ease of purpose that came from working together towards a common goal and a real sense of community through collaboration. Prioritising my own work, in the lonely task of individual research, was daunting. Although my supervisor continually reminded me of the usefulness of my dissertation type and topic, it took a while for me to see its potential beyond my role in UNCOVER, no longer directly responding to decision-makers. This resulted in a delay beginning, as I was adamant to fulfil my existing (over-) commitments within UNCOVER. I had adapted to the continual changes of the pandemic, evolving my research orientation with it. However, I was not decisive in areas where I did have an element of control, such as choosing a dissertation topic, and had effectively delayed decision-making on my dissertation direction until the last minute.

Life during lockdown presented its own challenges, which, in retrospect, would have been difficult enough by themselves, without conducting rapid research and a dissertation during this time. The lockdown situation in Wales was different to the rest of the UK throughout my UNCOVER involvement. It was day number 80 of Welsh lockdown when I signed out of social media. The rest of the world was opening up, friends' lives were visibly beginning again online, even my partner, living next-door in England, was allowed out. Meanwhile, nothing had changed in Wales. I was still confined to the study and my evening walks were becoming rather surreal in 3-dimensional space, after the extensive time spent during the day at the computer screen. I started to lose a grip on reality and turned inward in the isolation, living like a caged bird on Groundhog Day. The distance from the real-world continued as UNCOVER supervisors became busier and more members were introduced to the work. I lost the feeling of personal connection on calls that I had cherished so much in the earlier days. This feeling of disconnection began to affect my ability at times to connect on a personal level with my team on the indoor review. Despite others not noticing this, I was troubled, believing that this ability for deeper connection constitutes a key part of my identity. Still promoting mental health for others during this time, by hosting a free online weekly yoga session for the MPH cohort, I recognised how much I lacked credibility in this by not prioritising my own. The constant reminder that there was always somebody worse off than you and a real-world project to contribute towards, had made it easy to avoid my emotions until they boiled over.

Personal growth and lessons learned

Within my dissertation journey I transitioned from student, to researcher, to lead review coordinator. Initial feelings of guilt, from not being able to help in the same immediate way as doctors on the front line, certainly played a role in the pace at which I opened myself up to research. However, while my new-found purpose provided a great distraction at first, it soon began to take its toll. I felt obliged to fulfil my desire to progress and often overcommitted. Reminding myself that I am *a part of* and not the *whole* process became a useful tool in approaching future reviews.

My role within UNCOVER had evolved from responding to urgent policy requests to coordinating a cross-discipline review team investigating Indoor Transmission. In learning how to act as a catalyst between contributors during this, I quickly became aware of the multidimensionality required for effective problem solving. I can see now how much I had cherished the contact and support in the earlier days, it motivated me to check in on team members' performance at regular intervals and create comprehensive summaries of tasks. This maintenance of clarity and continuity within the team, adding to group cohesion, is something I would endeavour to bring to another leadership role.

Having been amongst the first students to join UNCOVER, I was well versed in the methodologies and aware of time pressures within a rapid context. I became concerned that the efforts of the indoor transmission review teams would go to waste if the review was not completed in a timely manner. Naturally empathetic, I felt burdened relaying news that work needed redoing as new evidence emerged across disciplines of our team, or if another team was facing other constraints and unable to prioritise completion of their tasks, that we were reliant on to move forwards. I was aware of the time devoted within the epidemiology and microbiology teams and didn't want their motivation to dwindle or to feel forgotten. By maintaining some sense of pace and inclusion through regular team updates, I managed to still create some space for the real-world impact that drove all our efforts. Unfortunately, when the work was completed, as I had suspected, it already needed updating. At first, I was very disappointed and felt a little responsible for my team, who had been heavily emotionally invested in the work. However, this process was perhaps one of the greatest learning curves applicable to public health that I could have experienced. Often it is the case that by the time robust evidence-based medicine reaches policy to initiate change, policy itself has already

moved on. Being receptive to the constant change and dynamics of public health and policy was a vital lesson, that the pandemic had condensed what might have previously been learned over years within a career, within the space of a few months. I saw this dynamism mirrored in the nature of disease we were investigating too. Processing these lessons enabled me to positively view what we had created as an incredible resource, which reflected the sincere benefits enabling different disciplines to dynamically interact with one another, endorsing a multidisciplinary approach to understanding a problem. Acknowledging this appreciation as a huge success within the team carried us forwards with vitality, yet humbled, as cogs in an ever-evolving process.

Future directions

So, what now? The philosopher in me still answers first and foremost, "I want to change the world". Truthfully, I am still facing the uncertainties of the pandemic, letting go of plans taken away from me. However, this experience has only confirmed my pursuit of a career where I am responsible for delivering real-world outcomes. From both working alongside and responding to politicians, I have continually craved involvement in the conversation resting above the data, as a decision-maker. I am currently awaiting feedback on roles I have applied for at the Department of Health and Social Care. The roles motivated me, presenting opportunities to build on the work I have developed within UNCOVER. They too are characterised by a combination of analysis, dynamically engaging with people across different sectors, and serving public health outcomes.

This experience has highlighted my deep value of interpersonal connection. I am seeking balance between the positive feedback of moving people on an individual level, when teaching, and affecting their lives on a population-level. Having learnt the importance of putting my own oxygen mask on first, to be able to maximise my worldly contribution, I realise I must also prioritise workplace conditions that will determine by own well-being

Overall, this experience has redefined my future directions. It has taught me to let go and not hold on so tightly to my desired outcomes, which I used to carve in stone, and to lean in with an open mind because, ultimately, everything will change, and *resilience* is built from adaptability.

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8 Appendices

8.1 Appendix 1

8.1.1 Appendix 1a: Level 1 MPHEG ethics oversight letter

MPH ETHICS GROUP
Tel: +44 (0)131 651 1832
email: mph.ethics@ed.ac.uk

10 August 2020

[redacted]

[redacted]

Re: Asymptomatic transmission of SARS-CoV-2. Application No MPH023a

This letter is to confirm that the Ethics Self-Audit (Overview) section of the MPH Ethics Form, completed by you with respect to the above study, demonstrates that the proposed research poses no reasonably foreseeable ethical risks.

Within our research governance process, this means that the research proposed does not require formal ethics review – i.e. it can be considered to be 'exempt'.

You may forward this letter to any collaborating data owner who requires reassurance as to ethical oversight of the research proposed, together with the form completed.

Please be aware that this outcome is in respect of the above research, as described in the application submitted to the MPH Ethics group. If there is in the future *a change* to the study design/protocol/methods, you should check whether the previous self-audit 'exempt' outcome applies, and if not, contact MPH Ethics group immediately explaining that you now need to submit an application for ethics approval.

Best wishes with your research.

Yours sincerely

Helen Walker

Helen Walker
MPH Ethics Group Administrator

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8.2 Appendix

8.2.1 Appendix 2a: UNCOVER Facemasks review

UNCOVER

Usher Network for COVID-19 Evidence Reviews

Review: Does the use of face masks in the general population make a difference to spread of infection?

Date: 7 April 2020 Version: 003-01

Review Question: Does the use of face masks in the general population make a difference to spread of infection?

Date of review: 7 April 2020

Review produced by UNCOVER https://www.ed.ac.uk/usher/uncover

Answer

- Based on the evidence from three recent systematic reviews and meta-analyses [including our re-analysis focusing on community trials] wearing face masks in the community was not significantly associated with a reduction in episodes of influenza-like illness [ILI]; the overall assessment of the quality was classified as low.
- Jefferson 2020 [re-analysed]: 7 RCTs in the general population with ILI outcome [OR (95% CI) 0.92 (0.87, 1.07)]
- Xiao 2020: 10 RCTs in non-healthcare settings with pandemic influenza outcomes [OR (95% CI) 0.97 (0.79, 1.18]
- Brainard 2020: various study designs with respiratory illness outcome; OR (95% CI): 0.94 (0.75, 1.19)
- SARS-CoV-2 is transmissible by contact and droplets [aerodynamic diameter >5µm]. SARS-CoV-2 can be detectable and viable in aerosols [aerodynamic diameter ≤5µm], suggesting possible transmission routes by aerosols. However, there is little current evidence demonstrating actual aerosol transmission episodes by SARS-CoV-2.
- The quality of the evidence on face mask effectiveness is moderate to low. See table 1. Many of the cohort and cross-sectional studies rely on self-reported symptoms not confirmed clinically or using lab tests. There is very little information on duration or frequency of use or correct usage of masks.
- Whilst some of the RCTs specify the type of mask used, many of the studies do not define the type of mask or the materials masks are made from. This makes it difficult to evaluate the evidence.
- Mask-wearing alone, in the absence of other preventive measures, is unlikely to be effective, yet most studies do not take this into account. Many studies did not gather information on general hygiene and other relevant health behaviours (e.g. hand sanitiser, hand-washing). Many of the studies do not make a distinction between indoor and outdoor settings.
- Much of the evidence is not generalizable to a UK community setting. For example, 8 of the 24 studies focus on face mask use during the annual hajj pilgrimage in Saudi Arabia – a very specific context in very different climatic conditions. The influence of cultural and socio-behavioural factors (e.g. fear, stigma, altruism) on levels of compliance during a pandemic may differ meaningfully from other circumstances.
- There is little evidence on the behavioural aspects of facemask use. The most-studied aspect relates to frequency / consistency of use, with more consistent use linked to a greater reported protective effect (although this must be taken in the context of our overall findings which failed to find a clear protective effect of facemasks). One study found that facemasks contribute to an increased sense of isolation.
- Public health awareness campaigns [Aiello-2010], specific education [Barasheed-2016] and provision of free facemasks [Alabdeen-2005] all appeared to incentivise greater uptake of facemasks. There were little data on how long people can be expected to comply with requirements to wear a facemask. One review reported that "in one study, rates of self-reported adherence were found to decline over a 5-day period" [PHE-2014].

Conclusion

- **This review found mixed and low quality evidence on the use of face masks to prevent community transmission of respiratory illness, with much of the evidence generated in very different contexts from the UK. Key issues are the need for better quality research in community settings, which focuses not only on evaluating different types of mask but also on evaluating adherence (duration and frequency of mask use, correct procedure for putting on and removing masks) and the use of masks in conjunction with hand hygiene.**

Note: This review was conducted very quickly, and as such has the following weaknesses: full text screening, extracted data and quality assessment were not checked by a second reviewer, thus introducing a risk of bias. We will continue to update and refine this review going forward.

Reviewers note that the WHO Expert Panel reported on 6/4/2020 that “the wide use of masks by healthy people in the community setting is not supported by current evidence and carries uncertainties and critical risks”.

Background and Aims

Current UK advice advises that "respiratory etiquette when coughing or sneezing" and social distancing of at least 2m apart should give sufficient protection against transmission from viruses carried in droplets which evaporate or fall to the ground within that distance. However, recent data has suggested that exhalation, coughing and sneezing can carry liquid droplets / aerosols over larger distances and has led to renewed interest in the role of facemasks to limit transmission risk. If there were a general recommendation to wear face masks indoor when symptomatic, or outdoors in public is there evidence to suggest that this may help slow the spread of coronavirus? Could wearing a mask be as effective as social distancing? The WHO Expert Panel on this topic reported on 6/4/2020 that "the wide use of masks by healthy people in the community setting is not supported by current evidence and carries uncertainties and critical risks". This is in contrast to US CDC who recommended the US public wear cloth coverings in pharmacies, groceries and other public places where social distancing is hard to maintain.

Background policy relevance

- Can the use of masks prevent transmission of SARS-COV-2?
- Do masks reduce the virus shedding in respiratory droplets and/ or aerosols?
- Is there a difference between different types of masks (eg surgical or home-made masks)?
- Are there behavioural aspects of face mask wearing by the general population that relate to compliance or risk taking behaviour that are relevant?

Methods:
We adapted rapid review methods outlined by the Cochrane Collaboration. We sought publications in four main inter-connected areas:

- sub-review 1: what is the effectiveness of face masks in preventing respiratory transmission in the community?
- sub-review 2: what is the relative effectiveness of medical masks versus non-medical masks or equivalent barriers?
- sub-review 3: what important behavioural aspects of wearing masks in terms of compliance with advice and impact on risk taking behaviour can be identified?
- sub-review 4: what is known about the nature and spread of respiratory airway particles?

Literature Search: We excluded publications focusing only on health care settings, modelling data, animal models, and articles providing commentary but no data. We focused on studies reporting on COVID-19 but included data from other related respiratory viruses, where appropriate. We became aware that a number of recent existing reviews on related relevant topics. Since there is currently no register of existing reviews we compiled this from websites of partners taking part in the WHO Evidence Collaborative and identified ~170 COVID-19 evidence reviews, including some on use of face masks. We searched the literature for prior reviews and evidence summaries on facemasks to prevent transmission of infection. We appraised the 14 prior reviews/summaries found, and for this update rapid review selected the three most recent, on-topic, and robust quality [Jefferson 2020, Brainard 2020, Xiao 2020] for updating and re-analysis. We sought publications with data on face masks of any study design and of published or pre-published status by updating the literature searches of three systematic reviews. The search was limited to publications from the date onward that each of the systematic review had stopped their search. We searched the databases used in the prior reviews (PubMed, Medline, Embase, Scopus, CENTRAL, CINAHL) and augmented the methods by including a search for pre-prints on medRxiv. The searches were carried out by one reviewer (MD). From the updated search results set, we excluded publications published before 2020, from nosocomial settings, modelling data, animal models, providing commentary but no data. All component studies of the three systematic reviews were included in this update. There were no language limitations as part of the search, but due to time and resource constraints, non-English publications were not included in analysis

Sub-review 1: What is the effectiveness of face masks in preventing respiratory transmission in the community?

Background

Community face mask use was part of successful control policies in China, South Korea and Vietnam, but it is not possible to disentangle their separate contribution to reducing transmission. This rapid review was carried out to establish whether there is evidence for the use of face masks in the general population to reduce the spread of infection with SARS-COV-2.

Methods

We adapted rapid review methods outlined by the Cochrane Collaboration. We searched the literature for prior reviews and evidence summaries on facemasks to prevent transmission of infection. We appraised the 14 prior reviews/summaries found, and for this update rapid review selected the three most recent, on-topic, and robust quality [Jefferson 2020, Brainard 2020, Xiao 2020] for updating and re-analysis. We sought publications with data on face masks of any study design and of published or pre-published status by updating the literature searches of three systematic reviews. The search was limited to publications from the date onward that each of the systematic review had stopped their search. We searched the databases used in the prior reviews (PubMed, Medline, Embase, Scopus, CENTRAL, CINAHL) and augmented the methods by including a search for pre-prints on medRxiv. The searches were carried out by one reviewer (MD). From the updated search results set, we excluded publications published before 2020, from nosocomial settings, modelling data, animal models, providing commentary but no data. All component studies of the three systematic reviews were included in this update.

Screening was shared between three reviewers (MG, XL, WX). Each new title, abstract and full text was screened by one reviewer (MG). References of previous systematic reviews were searched by two reviewers (XL, WX). No new studies meeting the inclusion criteria were identified.

Results

- A total of 766 new results was found from the database searching, reduced to 81 after removal of duplicates and pre-2020 publications. We excluded 72 records by screening titles and abstracts and a further 9 at the full text screen/quality assessment phase, leaving 0 new articles for inclusion in the final review. The key findings from this rapid review were:
- Of the three high quality recent reviews we scrutinised in detail, two included only RCTs [Jefferson 2020, Xiao 2020], whereas Brainard 2020 included population studies too. We ran updated literature searches for these reviews to identify new studies. No new studies meeting inclusion criteria were identified.
- All component studies of the three systematic reviews were included for analysis in this update.
- Jefferson 2020 included 9 RCTs (7 in the general population and 2 in health care workers) and reported that there was no reduction of Influenza-like illness (ILI) for masks compared to no masks [Random effects OR (95% CI): 0.93 (0.83, 1.05)].
- We re-ran a random effects meta-analysis restricting to the 7 RCTs conducted in the general population from Jefferson 2020 and also found no significant reduction of ILI [OR (95% CI): 0.92 (0.87, 1.07)]. Risk of bias analysis using the Cochrane tool done by Jefferson et al indicated that there was high or unknown risk of bias in relation to performance, detection and reporting bias.
- Xiao 2020 evaluated environmental and personal protective measures for pandemic influenza in non-healthcare settings. They run a fixed effect meta-analysis of 10 RCTs of community use of face masks (with or without hand hygiene measures) and they reported a no significant reduction of ILI [Fixed effect OR (95% CI): 0.92 (0.75, 1.12)]. We repeated the analysis using random effects meta-analysis and the result was similar [Random effects OR (95%CI): 0.97 (0.79, 1.18)]. The study quality of the

included studies was evaluated using GRADE by Xiao et al and the overall assessment of the quality was classified as low.

- Brainard 2020 included all study designs on facemasks and similar barriers to prevent respiratory illness. Based on random effects meta-analyses on RCTs, they concluded that wearing face masks can be very slightly protective against primary infection from casual community contact, but this was not significant, and the evidence was classified as low certainty-evidence using the Cochrane risk assessment [Random effects OR (95% CI): 0.94 (0.75, 1.19)]. Similar were the findings for the prevention of household infections when both infected and uninfected members wear face masks.

Conclusion

Based on the evidence from three recent systematic reviews and meta-analyses wearing face masks in the community is not significantly associated with a reduction in ILI and the overall assessment of the quality was classified as low.

Sub-review 2: what is the relative effectiveness of medical masks versus non-medical masks or equivalent barriers?

Background

This review evaluates the evidence on the effectiveness of facemasks for preventing respiratory infection in community settings.

Method

We adapted rapid review methods outlined by the Cochrane Collaboration. We sought published or pre-published observational or intervention studies, investigating face masks or respirators to prevent the transmission of respiratory viruses in community settings. Facemasks could be surgical, medical, N95 respirators, homemade, improvised or repurposed (e.g. DIY masks) made of any material. Included studies had to report a measure of respiratory virus infection and/or its consequences (e.g. days off work, complications, hospital admission, deaths). We excluded case series, case reports, review articles, guidelines, discussions, regulations, debates, and commentaries. We also excluded publications which investigated the prevention of transmission to/from clinically trained persons in clinical settings, studies based on mathematical modelling, and studies investigating transmission from non-humans

We searched the literature for prior reviews and evidence summaries on facemasks to prevent transmission of infection. We appraised the 14 prior reviews/summaries found, and for this update rapid review selected the three most recent, on-topic, and robust quality [Jefferson 2020, Brainard 2020, Xiao 2020] for updating and re-analysis. We sought publications with data on face masks of any study design and of published or pre-published status by updating the literature searches of three systematic reviews. The search was limited to publications from the date onward that each of the systematic review had stopped their search. We searched the databases used in the prior reviews (PubMed, Medline, Embase, Scopus, CENTRAL, CINAHL) and augmented the methods by including a search for pre-prints on medRxiv. The searches were carried out by one reviewer (MD). From the updated search results set, we excluded publications published before 2020, from nosocomial settings, modelling data, animal models, providing commentary but no data. All component studies of the three systematic reviews were included in this update.

Title and abstract screening was by three people, each person screening a third of the studies. A second person checked all rejected studies. Where the second reviewer disagreed with the decision of the first reviewer, the paper was retained for full text screening. Full text screening was again split between the three reviewers. Data extraction and quality appraisal were conducted by a different reviewer from the reviewer who conducted the screening. We used the following quality assessment checklists: CASP checklist for randomised controlled trials, cohort and case-control studies and Joanna Briggs checklists for case series and cross-sectional studies.

Results

We identified a total of 182 studies (107 were primary studies from the 3 key systematic reviews and 78 were studies identified in our update search. We rejected 125 through screening titles and abstracts and a further 32 when reviewing full texts. Reasons for rejection at full text screen were: not meeting inclusion and exclusion criteria (n=18), not primary studies (n=6), full text not available (n=8). We retained 25 studies for detailed analysis and quality appraisal. Key findings were that:

- The quality of the evidence on face mask effectiveness is moderate to low. See table 1.
- Many of the cohort and cross-sectional studies rely on self-reported symptoms not confirmed clinically or using lab tests.
- There is very little information on duration or frequency of use or correct usage of masks.
- Whilst some of the RCTs specify the type of mask used, many of the studies do not define the type of mask or the materials masks are made from. This makes it difficult to evaluate the evidence.
- Mask-wearing alone, in the absence of other preventive measures, is unlikely to be effective, yet most studies do not take this into account. Many studies did not gather information on general hygiene and other relevant health behaviours (e.g. hand sanitiser, hand-washing)
- Many of the studies do not make a distinction between indoor and outdoor settings.
- Much of the evidence is not generalizable to a UK community setting. For example, 8 of the 24 studies focus on face mask use during the annual hajj pilgrimage in Saudia Arabia – a very specific context in very different climatic conditions. Only one lack of transferability between different populations.
- Of the seven studies of moderate quality (table 3) – i.e. the strongest evidence found – three reported no evidence of effectiveness of face masks, whilst 4 reported some evidence of effectiveness. However a key consideration is the difference between evidence of effectiveness in a controlled study and the evidence of effectiveness in real life situations, where compliance may not be optimum.

Table 1: Summary of study designs and evidence quality (GRADE criteria)

Study ID	Study design	Quality assessment
Aiello-2010	RCT	Moderate
Aiello-2012	cRCT	Moderate
Alfelali-2019	cRCT	Moderate
MacIntyre-2009	cRCT	Moderate
MacIntyre-2016	cRCT	Moderate
Simmerman-2011	RCT	Moderate
Suess-2012	cRCT	Moderate
Barasheed-2014	cRCT	Low
Cowling-2009	cRCT	Low
Al-Jasser-2013	Cohort	Low
Balaban-2012	Cohort	Low
Choudhry-2006	Cohort	Low
Gautret-2011	Cohort	Low
Gautret-2015	Cohort	Very low
Larson-2010	Cohort	Very low
Wu-2004	Case-control	Low
Emamian-2013	Case-control	Very low
Zhang-2013b	Case-control	Very low
Kim-2011	Cross-sectional	Low
Uchida-2017	Cross-sectional	Low
Deris-2010	Cross-sectional	Very low
Hashim-2016	Cross-sectional	Very low
Wu-2016	Cross-sectional	Very low
Ma-2020	Experiment	Difficult to evaluate

Conclusions

This review found mixed and low quality evidence on the use of face masks to prevent community transmission of respiratory illness, with much of the evidence generated in very different contexts from the UK. Key issues are the need for better quality research in community settings, which focuses not only on evaluating different types of mask but also on evaluating adherence (duration and frequency of mask use, correct procedure for putting on and removing masks). This review was conducted very quickly, and as such has the following weaknesses: full text screening, extracted data and quality assessment were not checked by a second reviewer, thus introducing a risk of bias; We will continue to update and refine this review going forward.

Sub-review 3 - what evidence is there for the role of behavioural factors on the effectiveness of face mask use in the community?

Background

We looked at behavioural factors that are linked directly to facemask use: Is the facemask put on and taken off correctly? How often do people wear facemasks? Does this change over time? Do the population comply with advice on their use?

Methods

For the full review, we adapted rapid review methods outlined by the Cochrane Collaboration. We

searched the literature for prior reviews and evidence summaries on facemasks to prevent transmission and appraised the 14 prior reviews and summaries found.
These reviews were screened by three reviewers (EMS, MP, AN) for relevance to our sub-question (behavioural aspects of facemask use) and 11 were identified that met our inclusion criteria. The primary studies within these reviews were then taken forward for title & abstract, and subsequent full-text, screening.

Screening Criteria: We included studies that considered:

- How masks are used (e.g. whether people are putting them on or taking them off safely) and whether this alters their effectiveness;
- How mask use affects other relevant protective or risk-taking behaviours;
- Whether mask use changes in the long term; and
- What behavioural interventions (e.g. training, communications) may affect mask use.
- We excluded studies that considered:
- Mask use among healthcare workers or in care settings only.

Screening and Data Extraction

- 84 primary studies were identified from the reference lists of the relevant reviews. 8 studies were excluded because full-text was unavailable, and 2 because they were not in English, by the team who retrieved the studies (RMQ, LG and YB).
- 74 studies remained to be screened. Of these, 9 were prioritised by MP for data extraction, based on our full-text screening of the existing reviews. Data extraction was carried out by two reviewers (MP and AN).
- Title and abstract screening was carried out by one reviewer (EMS) for the other 65 studies, based on our inclusion criteria. 30 studies were included at this stage. Exclusions were checked by a second reviewer (MP), and one further study was included for data extraction.
- Data extraction on these 31 studies was carried out by three reviewers (EMS, AN and MP). 9 further studies were excluded as a result of full-text screening, principally because they did not include any investigation of the behavioural aspects of mask use.

Quality assessment
We carried out a quality assessment of the remaining 22 reviews based on templates adapted from the CASP checklists for critical appraisal.

Results
The key findings from this rapid review were:

- Behavioural aspects of mask use have not been a primary focus of any study on the effectiveness of facemasks. A small number of studies compare the effectiveness of occasional vs regular facemask use, but these terms are not clearly defined and the studies depend on self-reporting of compliance.
- The limited evidence base suggests that regular/consistent use of masks may be more protective than irregular use (but within the context of a wider literature which is inconclusive about the general protective effect of masks). However, the difference between ‘consistent’ and ‘irregular’ use is not clearly defined in existing studies, and is therefore of limited use in developing guidance.
- One review found that adherence to facemask use tended to drop off after five days. Another found that adherence depended on health beliefs and perception of risk.
- Reported concerns that people may wear masks ‘incorrectly’, and therefore ineffectively, in the community are a feature of the literature, but there do not appear to be any studies which assess the extent to which this actually happens, nor how it impacts on effectiveness.

- One study found that people who wore facemasks appeared to have increased compliance with hand hygiene practices. Of concern, however, the same study found an increased rate of respiratory infection among non-vaccinated people who wore facemasks. The evidence is not strong enough to allow us to conclude that facemask use encourages either protective or risk-taking behaviours, but these findings certainly suggest that a degree of caution should be applied.
- A small number of studies found that behavioural incentives – including specific training, public health awareness campaigns, and provision of free face masks – encouraged uptake of masks.
- One study addressed the barriers to use of facemasks, and found that masks contributed to a sense of isolation from others (as well as discomfort and difficulty breathing). This study was not carried out in the context of a pandemic, with mass distancing and 'lockdown', but the possible mental health implications of this finding may require some consideration in this context.
- Most of the studies looking at the use of masks in community settings relate to very specific contexts: schools, university halls of residence, and, most frequently, the Hajj. The Hajj in particular is a unique, time-limited event. Care should be taken when generalising from these studies to the community in general.

Conclusions

- There is little evidence on the behavioural aspects of facemask use, and most studies relate to unique, defined contexts (predominantly the Hajj). The aspect most frequently studied relates to frequency / consistency of use, and it is suggested that more consistent use is linked with a more protective effect (although this must be taken in the context of overall findings about the [limited] protective effect of facemasks).
- One study found that facemasks contribute to an increased sense of isolation, while another found higher rates of respiratory infection among some participants who wore a facemask, which may hint at a link between facemask use and risk-taking behaviours. Neither of these findings is supported by substantial or robust evidence, but both might merit further research in order to inform a full appraisal of the costs vs benefits of facemask use in community settings.

Sub-review 4: what is the mode of transmission of SARS-CoV-2 and other common respiratory pathogens?

Background

This rapid review was conducted to address the question of whether an understanding of SARS-CoV-2 transmission routes can help inform decisions regarding community use of face masks.

Methods

Two working strands were conducted in parallel to address the question.

- Strand 1 searched for original studies and reviews that reported the mode of transmission of coronaviruses, including SARS-CoV-2, MERS-CoV, SARS-CoV-1, and seasonal coronaviruses (i.e. NL63, 229E, OC43 and HKU1).
- Strand 2 searched for existing reviews that reported the mode of transmission of common human respiratory pathogens.

Inclusion criteria

- Reviews and commentaries that reported evidence-based findings of the mode of transmission of coronaviruses (including SARS-CoV-1, SARS-CoV-2, MERS-CoV

and seasonal CoVs) and other respiratory pathogens among general human population; OR

- Any published original studies that reported findings of the mode of transmission of coronaviruses

Exclusion criteria

- Animal-based models

As studies applied different approaches to infer mode of transmission, we grouped the approaches into three levels based on the strength of the evidence:

- Level 1. Pathogen being detectable (in aerosols, droplets or surfaces);
- Level 2. Pathogen being detectable and viable;
- Level 3. Actual transmission events being confirmed. All studies were extracted to an extraction template attached in Appendix.2.

Results

A total of 25 studies were included and their findings were summarised in Table 1. Key findings include:

- All respiratory pathogens included in the review can be transmitted by direct/indirect contact and droplets.
- Measles, influenza virus and adenovirus are known to be transmissible by aerosols.
- SARS-CoV-2 can be detected and is viable in aerosols but with no direct evidence of transmission via aerosols.

Conclusions

- SARS-CoV-2 is transmissible by contact and droplets.
- SARS-CoV-2 can be detectable and viable in aerosols, suggesting possible transmission routes by aerosols. However, little evidence is available so far demonstrating actual aerosol transmission episode by SARS-CoV-2.

Table 2. Summary of findings on mode of transmission of common human respiratory pathogens

Pathogen	Contact[1]	ref	Droplets	ref	Aerosols					
					Detectable	ref	Viable	ref	Transmission events[2]	ref
Measles	yes	Kutter, 2019; Shiu, 2019	mixed	Kutter, 2019; Shiu, 2019	not known		not known		yes	Kutter, 2019; Shiu, 2019
Parainfluenza virus	yes	Kutter, 2019	yes	Kutter, 2019	not known		not known		not known	
Human metapneumovirus	yes	Kutter, 2019; Shiu, 2019	yes	Kutter, 2019	not known		not known		not known	
Respiratory syncytial virus	yes	Nam, 2019; Shiu, 2019; Kutter, 2019	yes	Nam, 2019; Shiu 2019; Kutter, 2019	not known		not known		not known	
Influenza virus	yes	Public Health England-2014, 2014; SAunders, 2017; Otter, 2016; Kutter, 2019; Moghadami, 2017	yes	Shiu, 2019; Moghadami, 2017; Kutter, 2019; Otter 2016; Saunders, 2017; Public Health England-2014, 2014; macIntyre, 2015; Leung 2020; Cowling 2010	yes	Leung, 2020	yes	Cowling, 2010; macIntyre, 2015, Public Health England-2014, 2014	mixed	Shiu, 2019
Human rhinovirus	yes	Kutter, 2019	yes	Leung, 2020; Kutter 2019	yes	Leung, 2020; Kutter, 2019	not known		yes	Kutter, 2019
Coronavirus (CoV), seasonal	not known	–	yes	Leung, 2020	yes	Leung, 2020	not known		not known	
Adenovirus	yes	Kutter, 2019	yes	Kutter, 2019	not known		not known		yes	Kutter,2019
SARS-CoV-1	yes	Shiu,2019;Kutter 2019;Adhikari 2020; Hugonnet 2004; Otter 2016	yes	Shiu,2019;Kutter 2019; Huggonet 2004; Otter 2016	not known		yes	Huggonet 2004; Shiu, 2019; Kutter 2019; Doremala,2020	not known	
MERS-CoV	yes	Shapiro 2016; Adhikari 2020; Otter 2016	Yes	Raoult2020;Kilerby 2020;Shapiro2016; Otter 2016	yes	Shapiro 2016	not known		not known	
SARS-CoV-2	**yes**	Di Wu,2020; Peng 2020;Hui 2020; Adhikari 2020; Rothan 2020; Jeffersen 2020; Greenhalgh 2020	**yes**	Di Wu 2020; Wang 2020; Raoult 2020; Liu 2020;Peng 2020;Hui 2020; adhikari 2020; Rothan 2020;Wilder-Smith; Jeffersen 2020; Greenhalgh 2020; Bourouiba 2020	**yes**	Liu 2020; Bourouiba 2020	**yes**	van Doremalen,2020;Adhikari 2020	**not known**	

SARS = Severe acute respiratory syndrome; MERS = Middle East respiratory syndrome; ref = reference

[1] Transmission by contact includes direct contact (person to person) and indirect contact via a contaminated object.

[2] Transmission event is defined by the transmission of a pathogen via a specific route (e.g. aerosols), causing human infection

RR- face mask review keywords and key references

Sub-review 1 What is the effectiveness of face masks in preventing respiratory transmission in the community?

Keywords
Masks, Respiratory Protective Devices, Personal Protective Equipment, Primary Prevention.

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Sub-review 2: what is the relative effectiveness of medical masks versus non-medical masks or equivalent barriers?

Keywords
COVID-19; coronavirus; SARS-CoV-2; transmission; face masks; community

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8.2.2 Appendix 2b: UNCOVER Ethnicity review

UNCOVER

Usher Network for COVID-19 Evidence Reviews

Review: What is the evidence on ethnic variations in COVID-19 incidence and outcomes?

Date: 29 April 2020 Version: 013-01

Title: What is the evidence on ethnic variations in COVID-19 incidence and outcomes?

Date of review: 29 April 2020

Names and contact details of reviewers, including mobile of lead reviewer: Dr Ruth McQuillan (Ruth.McQuillan@ed.ac.uk) Marshall Dozier, Prof Evropi Theodoratou, Dr Xue Li, Emilie McSwiggan, Lara Goodwin, Durga Kulkarni, Dr Gwenetta Curry.

Background and Aims

The effects of COVID-19 on the health of racial and ethnic minority groups is still emerging; however, current data from around the world indicate that racial and ethnic minority groups may be disproportionately affected. This rapid review assesses the latest available data on incidence, severity and mortality from the UK and around the world and seeks to answer the following questions:

- **Sub-question 1**: What is the evidence for differences in COVID-19 incidence and outcomes (hospitalisation, ICU admission, death)? Is the emerging evidence from the UK in line with that from other countries?
- **Sub-question 2**: Health differences between racial and ethnic groups are multifactorial, with deep structural inequalities driving disadvantage in economic and social conditions. Are differences in living and working conditions among ethnic groups associated with differences in COVID-19 incidence and outcomes?
- **Sub-question 3**: Are differential rates of relevant comorbid conditions associated with differences in COVID-19 outcomes?

A note on terminology: We are using internationally recognized terminology and definitions for race and ethnicity outlined by Johnson and others (2019).

Methods

There are two parts to this paper: an analysis of data collected by the UK Intensive Care National Audit & Research Centre (INARC) and a rapid review of the literature on ethnicity and COVID-19.

Methods: Analysis of ICU data (ICNARC): We analysed data in relation to the different ethnic groups (white, all ethnic minorities and more specifically for Asian and Black ethnic minorities) and various indicators as reported by the ICNARC report on COVID-19 in critical care published on 24 April 2020 (INARC, 2020). We applied Pearson's chi-squared test (χ^2) to evaluate whether observed differences between the different ethnic groups in relation to the type of respiratory support, type of renal support and death after ICU admission occurred by chance. We also tested whether differences in the observed ethnic distributions for COVID-19 ICU admissions and ICU admission for non-COVID-19 viral pneumonia (occurred in 2017-2019) are due to chance. Finally we compared the ethnic distributions of ICU admissions with the ethnic distributions of the underlying general population (ONS, 2018) Analyses were conducted using Stata 12.

Methods: Literature review: As a starting point, we looked for prior reviews. MD scrutinised COVID-19 resource collections (e.g. Cochrane – see appendix for full list) and searched Google for prior reviews on the impact of the pandemic on ethnic groups. Eight grey literature and journal publications were identified and reference lists were screened for inclusion in this review. We contacted experts in the field to find out about ongoing or completed reviews.

PubMed and medRxiv were searched on 26 and 28 April 2020 with entry date limits from late 2019. Full search histories are provided in the appendix.

The initial search on 26 April was a scoping search using a limited set of terms; through collaborative identification of key concepts relevant to the populations of interest a highly sensitive search was created for PubMed, and a slightly more sensitive search was created for medRxiv within search functionality limitations.

The results from the search on 26 April (123 total) were all screened. The results of the more sensitive search on 28 April (841 before deduplication) were too numerous to screen in a rapid review timescale, so we prioritised for the first version of the rapid review those publications with BAME terms (Black, Asian, minority, ethnic) in titles or abstracts (31 new results). The remaining 751 results unique to the more sensitive search will be screened and incorporated into the next update of this rapid review.

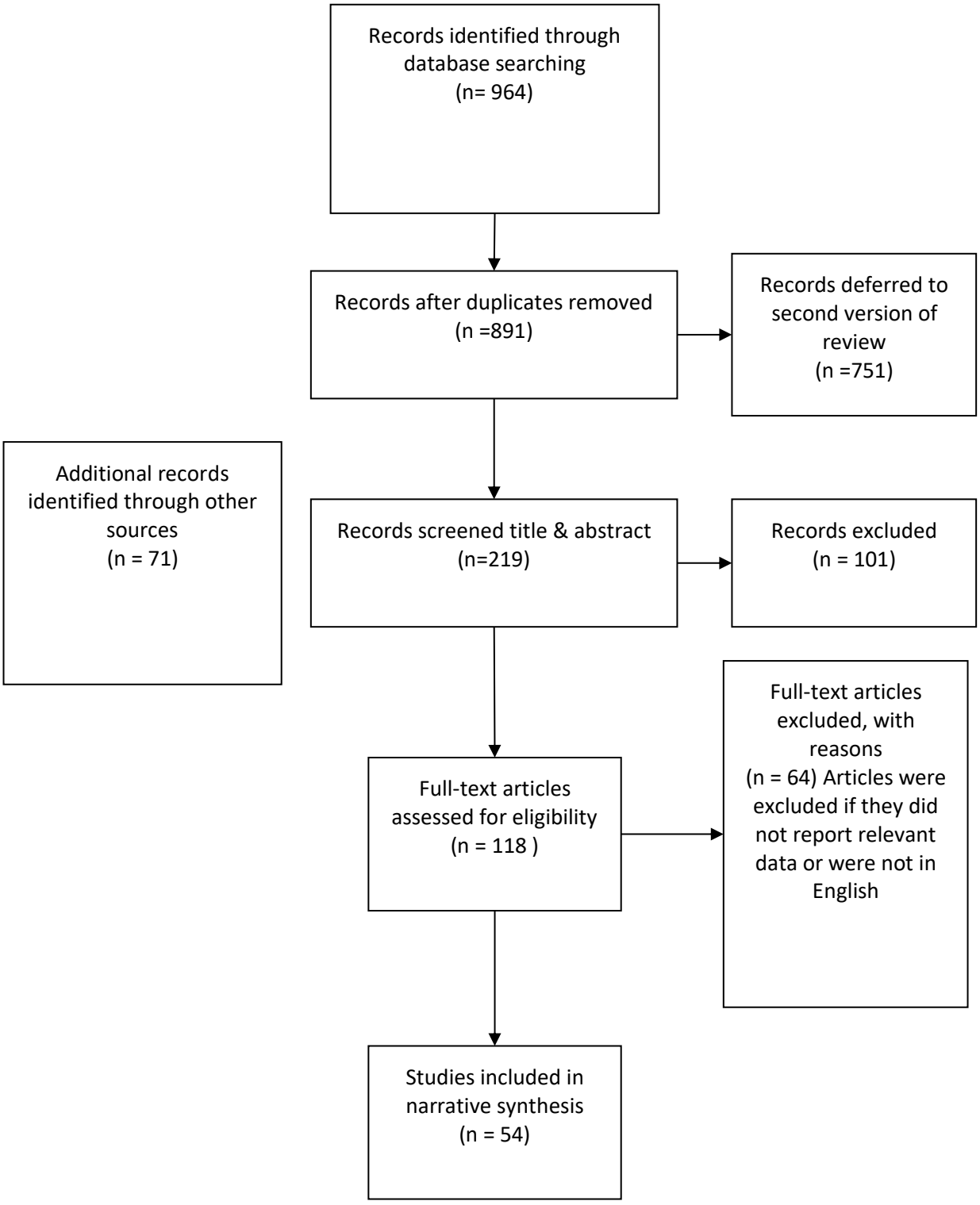
The titles and abstracts of all identified articles were screened by one reviewer (GC, DK, LG, EM, RM). Rejections were reviewed by a second reviewer (GC, DK, LG, EM, RM) and any discrepancies were retained for full text screening. Full texts were screened by one reviewer (GC, DK, LG, EM, RM). Rejections were reviewed by a second reviewer (GC, DK, LG, EM, RM) and any disagreements were resolved through discussion. Because of time pressure and the heterogeneity of the literature, quality assessment was conducted simultaneously with data extraction and without using standardised tools. Data were summarised thematically and reported narratively.

Results

Literature search: A total of 891 unique articles were identified by the literature search; however because of time pressure, a second, more focused search was conducted to reduce the number of articles requiring screening. Additional relevant articles were identified through searching the reference lists of key articles. The titles and abstracts of 219 articles were screened and 101 were rejected at this stage. A further 64 were removed at full text screen, leaving 54 to be analysed. Results are summarised in the following sections.

Evidence quality: Using the GRADE criteria, we rated the overall quality of the evidence from the literature review as **very low**.

Prisma flow diagram of publications screening and appraisal



Results: Sub-question 1: What is the evidence for ethnic differences in COVID-19 incidence and outcomes (hospitalisation, ICU admission, death)? Is the emerging evidence from the UK in line with that from other countries? Results below are split into two parts.

- Firstly, we present the results of an analysis of UK ICU data, comparing ethnic groups for a range of ICU outcomes.
- Secondly, we present the results of a rapid review of the literature on this topic.

Results of analysis of ICU data (ICNARC): Results of the ICNARC data are presented in Tables 1-5. When compared to ICU patients with white ethnicity, ethnic minorities, have a higher proportion than expected for needing advanced respiratory support (p=1.02e-09), for needing any renal support (p=2.68e-09) and for dying after admitting to ICU with COVID-19 (p=0.0001). Also ethnic minorities have a higher proportion than expected by chance to be admitted to ICU when compared to ICU admissions of non-COVID-19 viral pneumonia from 2017-2019 (p=3.82e-183) and to the underlying general population (p=1.37e-87). Similar were the findings when we restricted the analysis to patients of Asian or Black ethnicity. This analysis is descriptive and it was not adjusted for potential confounding factors including age, sex, obesity and other comorbidities (that could explain these findings), due to no access to individual level data. ICNARC have also not undertaken multivariable analyses of risk factors for critical care outcomes for ICU patients with confirmed COVID-19 due to any bias of reporting from early data. They highlight in their report that such analysis is underway and we will update our findings with any new results that become available.

Table 1 Ethnicity of patients critically ill with confirmed COVID-19 that received advanced respiratory support (n=2423) versus those that received only basic respiratory support (n=1007)

Ethnicity	**Advanced Respiratory Support**	**Only basic respiratory support**	**Pearson's chi square p-value[1]**
	N (%)	**N (%)**	
White	1589 (65.6%)	768 (76.3%)	
All ethnic minorities	834 (34.4%)	239 (23.8%)	1.02e-09
Asian	*374 (15.4%)*	*116 (11.5%)*	*0.0001*
Black	*281 (11.6%)*	*70 (7.0%)*	*2.39e-06*

[1] P-values represent the following comparisons: All ethnic minorities versus white, Asian versus White, Black versus White

Table 2 Ethnicity of patients critically ill with confirmed COVID-19 that received any renal support (n=795) versus those that did not receive any renal support (n=2766)

Ethnicity	**Patients**	**Patients not**	**Pearson's chi**

	receiving any renal support	receiving any renal support	square p-value[1]
	N (%)	**N (%)**	
White	477 (60%)	1969 (71.2%)	
All ethnic minorities	318 (40%)	797 (28.8%)	2.68e-09
Asian	*132 (16.6%)*	*378 (13.7%)*	*0.001*
Black	*131 (16.5%)*	*233 (8.4%)*	*1.67e-12*

[1] P-values represent the following comparisons: All ethnic minorities versus white, Asian versus White, Black versus White

Table 3 Ethnicity of patients critically ill with confirmed COVID-19 that were discharged alive (n=1820) versus those that died (n=1863)

Ethnicity	Discharged alive	Died	Pearson's chi square p-value[1]
	N (%)	**N (%)**	
White	1306 (71.8%)	1227 (65.9%)	
All ethnic minorities	514 (28.2%)	636 (34.1%)	0.0001
Asian	218 (12.0%)	299 (16.0%)	*0.0001*
Black	165 (9.1%)	208 (11.2%)	*0.009*

[1] P-values represent the following comparisons: All ethnic minorities versus white, Asian versus White, Black versus White

Table 4 Ethnicity of patients critically ill with confirmed COVID-19 (n=5993) compared to a historic cohort of patients critically ill with viral pneumonia (non-COVID-19) during the years 2017-19 (n=5600).

Ethnicity	Critically ill with COVID-19	Critically ill with non-COVID-19 viral pneumonia 2017-2019	Pearson's chi square p-value[1]
	N (%)	**N (%)**	
White	3938 (65.7%)	4951 (88.4%)	
All ethnic minorities	2055 (34.3%)	649 (11.6%)	3.82e-183
Asian	*925 (15.4%)*	*325 (5.8%)*	*5.93e-86*
Black	*639 (10.6%)*	*155 (2.8%)*	*6.59e-85*

[1] P-values represent the following comparisons: All ethnic minorities versus white, Asian versus White, Black versus White

Table 5 Ethnicity of patients critically ill with confirmed COVID-19 (n=5993) compared to the English/ Wales/ N.Ireland population ethnicity.

Ethnicity	Critically ill with COVID-	English/Wales/ N. Ireland	Pearson's chi square p-

	19	population[1]	value[2]
	N (%)	**N (%)**	
White	3938 (65.7%)	46707655 (76.6%)	
All ethnic minorities	2055 (34.3%)	14289796 (23.4%)	1.37e-87
Asian	*925 (15.4%)*	7437014(12.2%)	*1.17e-26*
Black	*639 (10.6%)*	3968540 (6.5%)	*1.46e-53*

[1] Estimates based on INCNARC reported percentages and current population estimates obtained by ONS 2018 estimates.

[2]P-values represent the following comparisons: All ethnic minorities versus white, Asian versus White, Black versus White

Results of rapid literature review for sub-question 1: We found seven relevant studies, two from the UK and five from the USA. The overall quality of the evidence is graded as **very low**. The two UK studies are of most relevance to the UK population.

Niedzwiedz et al (2020) conducted a cohort study on the relative risk of covid-19 infection by ethnic group, linking UK Biobank data with SARS-CoV-2 test results held by Public Health England. UK Biobank recruited 40 – 70 year olds in 2006 – 2010 from the general population. In this study, they present data for 1474 UK Biobank participants who tested positive for SARS-CoV-2 between 16 March and 13 April 2020. The study found that (self-defined) black, south Asian and white Irish people were more likely to have confirmed infection (RR 4.01 (95%CI 2.92-5.12); RR 2.11 (95%CI 1.43-3.10); and RR 1.60 (95% CI 1.08-2.38) respectively) and were more likely to be hospitalised compared to white British people. The study also found that area-based measures of socioeconomic deprivation and having no qualifications were consistently associated with a higher risk of confirmed infection (RR 1.91 (95%CI 1.53-2.38); and RR 2.26 (95%CI 1.76-2.90) respectively). However, even after controlling for this, some minority ethnic groups have a higher risk of confirmed SARS-CoV-2 infection. Strengths of this study are that it is a very large, well-conducted cohort study of long standing. Limitations are that data on self-defined ethnicity and socio-economic variables were collected some years ago and may no longer be valid. Another limitation is that the study population may not reflect the broader UK population.

de Noronha (2020) analysed actual vs expected hospital deaths during the pandemic period to 21 April 2020. Data on actual hospital deaths by ethnic group were compared with expected hospital deaths, which were estimated using census 2011 data on ethnicity. The study found that for all ethnic groups other than white British and white Irish, the number of deaths exceeded what would be expected for that age group. The mixed and Indian ethnic groups were more than twice as likely to die; Pakistani, Bangladeshi and black Caribbean nearly three times as likely, black African more than four times as likely and other black and other ethnic group nearly eight times as likely. A strength of this analysis is that it is based on actual hospital deaths. A limitation is that expected deaths are based on 2011 census data, which may be out of date. The article provides very little information on methodology, around 9% of actual deaths had no ethnicity recorded and the results do not report confidence intervals or p-values.

The following five studies were conducted in USA, so are not directly applicable to the UK context.

Three (Guha et al, 2020; Li et al, 2020 and Maroko et al, 2020) are ecological studies, which are prone to confounding and which cannot be used to draw inferences at the individual level. Guha et al (2020) found that the proportion of African American residents in a zip code area was significantly associated with increased likelihood of cases of COVID-19, although a sensitivity analysis suggested that this might be explained by population density. Li et al (2020) found that counties with a higher

proportion of African American residents had higher COVID-19 incidence and mortality rates and that this was not driven by socio-economic factors (p = 0.008). Maroko et al (2020) found that cold spots (areas in New York City and Chicago with low rates of people testing positive for SARS-CoV-2) had significantly higher proportions of non-Hispanic white residents and more workers in managerial occupations. Hotspots had higher percentages of people of colour and foreign-born people. However this study did not adjust for potential confounders.

The other two US articles (Badawi et al, 2020 and Garg et al, 2020) report on hospital-based studies conducted in March 2020. Both can only provide a snapshot from an early point in what is a highly dynamic and fast-moving pandemic. Badawi et al (2020) conducted a descriptive study of ICU patients across New York City, comparing the patient population immediately before the pandemic (2019) with the patient population during the pandemic (between March 23 and April 6, 2020). Data are from 186 ICU beds from 14 ICUs and 9 hospitals using a tele-ICU monitoring system, representing 10,714 patients in 2019 and 465 patients during the pandemic period. They found that the proportion of patients with Hispanic ethnicity doubled (7.8% to 16.6%; p<0.01). The proportion of African American patients increased from 16.6 % to 20.6 % but the difference was non-significant. Garg et al (2020) report age-stratified hospitalisation rates and clinical data for laboratory-confirmed COVID-19 cases admitted from 1 – 30 March 2020, the first month of US surveillance. Data are from 99 counties in 14 states (California, Colorado, Connecticut, Georgia, Iowa, Maryland, Michigan, Minnesota, New Mexico, New York, Ohio, Oregon, Tennessee, and Utah). Among 580 hospitalized COVID-19 patients with race/ethnicity data, approximately 45% were white (compared to 59% of the general population in the sample counties), 33% were black (compared to 18% of the general population), and 8% were Hispanic (compared to 14% in the general population). Data are preliminary and should be interpreted with caution. Data on ethnicity were missing for many cases.

Results: Sub-question 2: Health differences between racial and ethnic groups are multifactorial, with deep structural inequalities driving disadvantage in economic and social conditions. Are differences in living and working conditions among ethnic groups associated with differences in COVID-19 incidence and outcomes?

Living conditions: Recent data show that London and Birmingham have become COVID19 hotspots and both have areas of extreme overcrowding. Birmingham has one of the highest proportions of families sharing with elderly relatives in the country, with nearly 29,000 over 70s living with working-age households (Wall 2020). Thirty percent of Bangladeshi household and 15% of African (Black) households are overcrowded, compared to only 2% of white British households (Haque, 2020). Black, Bangladeshi, and Pakistani origin populations in the UK have poverty rates, after housing costs, are as high as 50%. Previous studies have found ethnic inequalities in health, housing, employment, and education across England and Wales (Lymperopoulou, 2017). These inequalities create conditions that disadvantage minority populations and make them more susceptible to illnesses. While the UK COVID19 data is limited, the current findings are concerning, they also closely resemble the United States data for racial minorities. David Williams' research demonstrates how the history of racial residential segregation exacerbates white-Black health disparities in the US (Williams, 2001). Black people are more likely to live in neighbourhoods without access to quality healthcare, grocery stores and safe places to exercise.

In addition to drawing on the academic literature, it is important also to pay attention to news

reports because of the fast-moving nature of this epidemic. Newspapers are often the first to pick up and report important indicators and although we must be cautious in how we interpret such evidence because it may lack rigour, it is equally important not to ignore important early warning signals coming from this quarter. One newspaper article from New York City (NYC), USA compared two ZIP codes with substantially different rates of COVID-19 and found that the hardest-hit areas were the overcrowded Black and Latino communities (Malone 2020). Another US newspaper article reported that as the lockdown procedures were put in place there has been a reduction in train services, leading to crowded conditions on subways in NYC, which reduces the ability of people to exercise social distancing on their way to work (Goldbaum 2020). Although caution must be exercised when drawing conclusions on the basis of data from other countries, factors such as living in crowded inner-city areas, being dependent on public transport and having to leave home to go to work every day are just as relevant in UK and in US ethnic minority populations (see next section below).

Working conditions: We found 19 studies and articles relating to ethnic variations in working patterns and employment conditions (of which 7 relate to the UK, 10 to the USA, and 2 to other countries), which might affect risk factors for Covid-19. Many of these were newspaper articles or summaries of official data, rather than academic studies, and the general quality of data was **very low**.

Workforce data from the UK show significant disadvantage and inequalities in employment, with Black and minority ethnic (BME) groups twice as likely as others to be unemployed or in precarious employment (Haque-2020). Conversely, although people from BAME backgrounds make up over 12% of the working-age population, they represent only 6% of top-management positions (Haque-2020), thus missing out on the possible protective effect of those roles, as data from the US suggests that areas with lower rates of Covid-19 infections have more workers in managerial occupations (Maroko-2010).

People from BAME backgrounds are more likely to work in occupations with higher exposure risk, such as cleaners, public transport and retail (IS-2020). 40% of doctors and 20% of nurses in the NHS, and 17% of the social care workforce, are people from BME backgrounds (IS-2020).

Many of these are jobs that have been classified as "essential work", which are not possible to do remotely (Thebault-2020; Malone-2020). Workers in essential roles share more time with others, and are invariably more exposed to risk (Tomer-2020). Atchison-2020 found that the ability to adopt and comply with certain protective measures, including self-isolation, is lower in black and minority ethnic groups, and in the most economically disadvantaged groups in the UK.

The exigencies of “essential work” are reflected in two US reports (Goldbaum-2020; Valentino-de-Vries-2020) which described movements of people: both finding that people in poorer areas, or from poorer socioeconomic groups, continue to use public transport, including during the working week, to a greater extent than their richer counterparts. Thus it is not only the work, but the need to get to and from work, which may disproportionately expose people from ethnic minority backgrounds to risk.

Finally, Liem-2020 identifies specific risks faced by migrant domestic workers in Hong Kong, which include being tied to their employer, and therefore limited in their ability to adopt social distancing and other protective measures. Dyer-2020 reports that undocumented immigrants in the USA may feel unable to report Covid-19 symptoms because of their immigration status. Neither of these are from the UK context, and care should be taken in generalising their results; however, both highlight that immigration and employment status can be closely linked, and may combine to increase risk of

exposure to Covid-19 in certain circumstances.

Results: Sub-question 3: Are differential rates of relevant comorbid conditions associated with differences in COVID-19 outcomes?

Patients with certain pre-existing cardiovascular disease or diabetes are at increased risk of complications and death from covid-19 (Li et al, 2020; Ruan et al, 2020, Chen et al, 2020; Lippi et al, 2020). There are differential rates of these conditions in ethnic minority populations, which may translate into poorer outcomes. Adams et al (2020) analysed 2017 Behavioral Risk Factor Surveillance System (BRFSS) data to estimate the proportion of the US population with comorbidities that make them vulnerable to COVID-19 complications. They found that significantly more black and native American than white and Hispanic respondents reported having at least one of six chronic conditions associated with adverse COVID-19 outcomes. The six conditions are: cardiovascular disease, chronic obstructive pulmonary disease (COPD), diabetes, asthma, hypertension, and/or cancer other than skin. Whilst 48% (95% CI 47.7 – 48.4) of white respondents reported having at least one of these conditions, the comparable proportions were 52.1% (51.1 – 53.1) for blacks; 35.5% (34.5 – 36.5) for Hispanics and 55.5% (52.9 – 58.1) for native Americans. This study had limitations: the response rate was low, it was a telephone survey and it excluded nursing home residents, so the results may not be representative of the wider population. This was a US study, so is not directly applicable to a UK population; however the findings are consistent with UK data showing that ethnic minority populations have higher rates of cardiovascular disease (Khunti et al, 2020) and diabetes (Khunti et al, 2020; Tillin et al, 2013). Tillin et al (2013) found that diabetes prevalence was greater in South Asians and African Caribbeans than in Europeans.

Discussion:

This rapid evidence review involves two elements: an analysis of intensive care data (INARC, 2020) and a rapid literature review. Our analysis of ICU data found evidence that, when compared to the general population, BAME people are more likely to be **admitted to ICU**. When compared to ICU patients in the UK with white ethnicity, BAME people are more likely to **require renal support and advanced respiratory support** and are more likely to **die**. Findings were similar when the analysis was restricted to patients of Asian or Black ethnicity. These differences were highly statistically significant. Longitudinal UK Biobank evidence (Niedzwiedz et al, 2020) found that BAME people were more likely to have confirmed infection and to be **admitted to hospital** compared with white British people.

Increased risk of hospitalisation, ICU admission, ICU advanced support and death from COVID-19 correlates with **higher rates of cardiovascular disease** (Adams, 2020; Khunti et al, 2020) and **diabetes** (Khunti et al, 2020; Tillin et al, 2013; Adams, 2020) among BAME people. Data from China show that patients with pre-existing cardiovascular disease or diabetes are at increased risk of complications and death from covid-19 (Li et al, 2020; Ruan et al, 2020, Chen et al, 2020; Lippi et al, 2020).

Previous studies have found **ethnic inequalities in health, housing, employment, and education** across England and Wales (Lymperopoulou, 2017). These inequalities create conditions that disadvantage minority populations and make them more susceptible to illnesses. **Household**

overcrowding is much more prevalent in BAME than in white households (Haque, 2020). Data from the UK is consistent with emerging evidence from USA, where newspaper reports suggest that the areas hardest hit by COVID-19 are overcrowded inner city Black and Latino communities (Malone 2020). **Living in an overcrowded community** creates vulnerability by making social distancing more difficult to achieve, for example whilst using public transport (Goldbaum 2020).

Workforce data from the UK show significant disadvantage and inequalities in employment, with Black and minority ethnic (BME) groups twice as likely as others to be **unemployed or in precarious employment** and much **less likely to be able to work remotely** (Haque, 2020). People from BAME backgrounds are more likely to work in **essential occupations with higher exposure risk**, such as health and social care and cleaning (IS, 2020). A recent cross-sectional survey (Atchison, 2020) found that BAME and economically disadvantaged people are **less able to adopt and comply with protective measures, such as self-isolation**. Again, this is consistent with emerging evidence from USA, where two recent reports (Goldbaum, 2020; Valentino-de-Vries, 2020) found that people in poorer areas, or from poorer socioeconomic groups, continue to use public transport, including during the working week, to a greater extent than their richer counterparts. Thus it is not only the work, but the **need to get to and from work**, which may disproportionately expose people from ethnic minority backgrounds to risk.

This review has a number of **limitations**. In order to meet the very tight deadline for this study, various strategies were employed which may reduce quality of the review. The search strategy was limited so it is possible that some key articles have been missed. Data extraction and quality assessment were conducted by one person per article, so this may have biased the results. For the ICU data analysis (INARC, 2020), we did not have access to individual-level data so it was not possible to adjust for potential confounding factors including age, sex, obesity and other comorbidities. ICNARC are in the process of conducting multivariable analyses of risk factors for critical care outcomes for ICU patients with confirmed COVID-19. We will update our findings with any new results that become available. The **overall quality of the evidence from the literature was very low**. In the middle of a novel and fast-moving pandemic, much of the evidence does little more than provide a **snap-shot in time**. We decided to include selected newspaper reports, particularly those reporting on innovative real-time data sources (e.g. the New York Times report by Valentino de Vries et al (2020), which reports on population movement behaviour using data from 15 million cell phones across USA). Although it is essential to interpret newspaper reports with caution, it is equally important not to ignore important early warning signals coming from this quarter. We are committed to reviewing the literature on this topic regularly as new data emerge, to refining and improving review quality and to focusing future reviews on marginalised refugee and asylum-seeker populations not covered explicitly by this review.

The UNCOVER network is committed to responding quickly and impartially to requests from policymakers for evidence reviews. This document has therefore been produced in a short timescale and has not been externally peer-reviewed

Key references:

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Appendix:

COVID-19 evidence summary sites scrutinised 26 April 2020 for prior reviews:

- Cochrane Collaboration COVID Rapid Reviews https://covidrapidreviews.cochrane.org/
- COVID reviews question bank hosted by Cochrane https://covidrapidreviews.cochrane.org/search/site
- CEBM at Oxford (primary care focus): https://www.cebm.net/covid-19/
- EvidenceAid https://www.evidenceaid.org/coronavirus-covid-19-evidence-collection/
- HIQA (Health Information and Quality Authority in Ireland) https://www.hiqa.ie/reports-and-publications/health-technology-assessments?tid_1=All&field_hta_topics_target_id=112
- Joanna Briggs Institute https://joannabriggs.org/ebp/covid-19
- NICE https://www.nice.org.uk/covid-19
- Saw Swee Hock School of Public Health https://sph.nus.edu.sg/covid-19/research/
- WHO Country & Technical Guidance - Coronavirus disease (COVID-19) https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance

Google search for grey literature and prior reviews

Advanced search: covid-19 AND (ethnic OR racial OR minority) filetype:pdf

Search histories

PubMed search date 2020-04-26
Credit: PubMed COVID-19 search string (Shokraneh 2020)
72 results
(race OR racial OR ethnic* OR migrant* OR refugee* OR displaced OR minorit*) AND (("Betacoronavirus"[Mesh] OR "Coronavirus Infections"[MH] OR "Spike Glycoprotein, COVID-19 Virus"[NM] OR "COVID-19"[NM] OR "Coronavirus"[MH] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[NM] OR 2019nCoV[ALL] OR Betacoronavirus*[ALL] OR Corona Virus*[ALL] OR Coronavirus*[ALL] OR Coronovirus*[ALL] OR CoV[ALL] OR CoV2[ALL] OR COVID[ALL] OR COVID19[ALL] OR COVID-19[ALL] OR HCoV-19[ALL] OR nCoV[ALL] OR "SARS CoV 2"[ALL] OR SARS2[ALL] OR SARSCoV[ALL] OR SARS-CoV[ALL] OR SARS-CoV-2[ALL] OR Severe Acute Respiratory Syndrome CoV*[ALL]) AND ((2019/11/17[EDAT] : 3000[EDAT]) OR (2019/11/17[PDAT] : 3000[PDAT])))

medRxiv via https://mcguinlu.shinyapps.io/medrxivr/ search date 2020-04-26
51 results
topic1 <- c("[Rr]ace", "[Rr]acial", "[Ee]thnic", "[Mm]igrant", "[Rr]efugee", "[Dd]isplaced", "[Mm]inorit")
topic2 <- c("COVID-19", "coronavirus ", "SARS-CoV-2 ", "2019-nCoV")
mx_results <- mx_search(query, from.date =20191130, to.date =20200426, NOT = c(""), deduplicate = TRUE)

PubMed search date 2020-04-28
Credit: PubMed COVID-19 search string (Shokraneh 2020)
527 results
"Ethnic Groups"[Mesh] OR Socioeconomic Factors[MeSH Terms] "social determinant*"[Text Word] OR occupation*[Text Word] OR movement[Title/Abstract] OR public transport[MeSH Terms] OR Demography[MeSH Terms] OR demographic[Title/Abstract] OR smoking[MeSH Terms] OR smoker*[Title/Abstract] OR diabet*[Title/Abstract] OR hypertens*[Title/Abstract] OR obes*[Title/Abstract] OR overweight[Title/Abstract] OR beta-Thalassemia[MeSH Terms] OR "beta-Thalassemia"[Title/Abstract] OR "beta thalassaemia"[Title/Abstract] OR comorbidity[MeSH Terms] OR "underlying condition*"[Title/Abstract] OR comorbidit*[Title/Abstract] OR Overweight[MeSH Terms] OR Obesity[MeSH Terms] OR Hypertension[MeSH Terms] OR Diabetes Mellitus[MeSH Terms] OR "sickle cell"[Title/Abstract] OR Anemia, Sickle Cell[MeSH Terms] OR genetic[Title/Abstract] OR Genetic Predisposition to Disease[MeSH Terms] OR "care home*"[Title/Abstract] OR "nursing home*"[Title/Abstract] OR Residential Facilities[MeSH Terms] OR life style[MeSH Terms] OR (Health Behavior[MeSH Terms] OR depriv*[Title/Abstract] OR poverty[MeSH Terms] OR "gig economy"[Title/Abstract] OR ((work*[Title/Abstract] OR employment[Title/Abstract]) AND (insecur*[Title/Abstract] OR precari*[Title/Abstract] OR temporary[Title/Abstract])) OR (migrant*[Title/Abstract] OR refugee*[Title/Abstract] OR asylum[Title/Abstract] OR immigrant*[Title/Abstract] OR ethnic* [Title/Abstract] OR racial [Title/Abstract] OR "displaced person*"[Title/Abstract] OR Refugees[MeSH Terms] OR Emigrants and Immigrants[MeSH Terms] OR Transients and Migrants[MeSH Terms]) OR ("multiple tenancy" OR "House in multiple occupation" OR "multiple occupancy hous*" OR (accommodation AND (breakfast OR hostel OR rental)) OR "food desert*"[Title/Abstract] OR "food bank*"[Title/Abstract] OR Urban Population[MeSH Terms] OR Over-crowding[Title/Abstract] OR Over-crowded[Title/Abstract] OR Multi-generational[Title/Abstract] OR Housing[MeSH Terms] OR access*[Title/Abstract] OR equit*[Title/Abstract] OR disparit*[Title/Abstract] OR Health Services Accessibility[MeSH Terms] OR Healthcare Disparities[MeSH Terms] OR "language barrier*"[Title/Abstract] OR Punjabi[Title/Abstract] OR Bengali[Title/Abstract] OR Sylheti[Title/Abstract] OR Polish[Title/Abstract] OR Urdu[Title/Abstract] OR Gujarati[Title/Abstract] OR Tamil[Title/Abstract] OR Arabic[Title/Abstract] OR Somali[Title/Abstract] OR Romanian[Title/Abstract] OR Italian[Title/Abstract] OR Turkish[Title/Abstract] OR "communication barriers"[MeSH Terms] OR mistrust[Title/Abstract] OR "cultural mistrust"[Title/Abstract] OR "public transport"[Title/Abstract] OR movement[Title/Abstract]
AND
(("Betacoronavirus"[Mesh] OR "Coronavirus Infections"[MH] OR "Spike Glycoprotein, COVID-19 Virus"[NM] OR "COVID-19"[NM] OR "Coronavirus"[MH] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[NM] OR 2019nCoV[ALL] OR Betacoronavirus*[ALL] OR Corona Virus*[ALL] OR Coronavirus*[ALL] OR Coronovirus*[ALL] OR CoV[ALL] OR CoV2[ALL] OR COVID[ALL] OR COVID19[ALL] OR COVID-19[ALL] OR HCoV-19[ALL] OR nCoV[ALL] OR "SARS CoV 2"[ALL] OR SARS2[ALL] OR SARSCoV[ALL] OR SARS-CoV[ALL] OR SARS-CoV-2[ALL] OR Severe Acute Respiratory Syndrome CoV*[ALL]) AND ((2019/11/17[EDAT] : 3000[EDAT]) OR (2019/11/17[PDAT] : 3000[PDAT])))
AND
Epidemiology[MeSH Terms] OR morbidity[MeSH Terms] OR epidemiolog*[Title/Abstract] OR indicence[Title/Abstract] OR prevalence[Title/Abstract] OR prognosis[MeSH Terms] OR "Critical Care Outcomes"[Mesh] OR "Fatal Outcome"[Mesh] OR "Treatment Outcome"[Mesh] OR "Population Health"[Mesh] OR outcome*[Title/Abstract] OR impact[Title/Abstract] OR Hospitalization[MeSH Terms] OR hospitali*[Title/Abstract] OR hospital admission*[Text Word] OR Continuous Positive Airway Pressure[MeSH Terms] OR CPAP[Title/Abstract] OR "Intensive Care Units"[MeSH Terms] OR "Critical Illness"[MeSH Terms] OR "Critical Care"[MeSH Terms] OR "Critical Care Outcomes"[MeSH Terms] OR "intensive care"[Title/Abstract] OR ITU[Title/Abstract] OR ICU[Title/Abstract] OR "critical

care"[Title/Abstract] OR survival[MeSH Subheading] OR mortality[MeSH Subheading] OR surviv*[Title/Abstract] OR death*[Title/Abstract] OR mortality[Title/Abstract]

medRxiv via https://mcguinlu.shinyapps.io/medrxivr/ search date 2020-04-28
314 results
population cluster combined with OR:
[Dd]emographic
[Rr]ace
[Rr]acial
[Ee]thnic
[Mm]igrant
[Rr]efugee
[Dd]isplaced
[Aa]sylum
[Ii]mmigrant
[Mm]inorit
[Oo]ccupation
[Ee]mployment
[Ii]nsecur
[Pp]recari
[Pp]overty
[Dd]epriv
[Cc]omorbid
[Gg]enetic
Covid-19 cluster combined with OR:
COVID-19
[Cc]oronavirus
SARS-CoV-2
2019-nCoV
The two clusters combined together using AND
Date limit 2020-01-01 onward

8.2.3 Appendix 2c: UNCOVER Indoor Transmission review

UNCOVER

Usher Network for COVID-19 Evidence Reviews

Review: What is the evidence for indoor transmission of SARS-CoV-2?

Date: 15 August 2020 Version: 016-01

THE UNIVERSITY of EDINBURGH | usher institute

Title: What is the evidence for indoor transmission of SARS-CoV-2?

Date of review: 15 August 2020

Names and contributions of reviewers: Anderson, N.[8], Attili, A.[7], Barranco Cárceles, S.[7], Dozier, M.[3], Epelle, E.I.[7], Gabl, R.[7], Goodwin, L.[3,4,6,7], Hayward, T.[6,7], Krishan, P.[6,7], McQuillan, R.[1,2], Nolan, G.[6,7], Nundy, M.[6,7], Ostrishko, K.[6,7], Pappa, E.[7], Stajuda, M.[7], Viola, I.M.[5], Zen, S.[7]

[1]Principal Investigator
[2]Wrote paper
[3]Conducted literature searches
[4]Coordination of screening, quality assessment and data extraction (epidemiology and microbiology)
[5]Write-up and coordination of screening, quality assessment and data extraction (mechanistic studies)
[6]Record screening
[7]Quality assessment and data extraction
[8]Conducted meta-analysis

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Introduction

It is well established that SARS-CoV-2 is readily transmitted in indoor environments; however questions remain about the relative importance of different transmission mechanisms, the risks associated with different indoor environments and activities and the role of ventilation and plumbing systems in mitigating or amplifying transmission.

These questions are complex and cannot be answered by one discipline in isolation. It is necessary to draw on a range of disciplinary knowledge and expertise in order to build a complete picture. We therefore sought to identify and integrate evidence from three distinct disciplines, each of which has distinct strengths and limitations: **mechanistic approaches** model the physical behaviour of small and large droplets under different climatic conditions. As modelling studies, they are based on assumptions and do not account for all aspects of the physical reality, and are limited in what they can tell us about the viability or infectivity of particles in 'real-world' conditions. Also included in this category are experiments which investigate particle emission during speech or breathing. These studies can help us understand the mechanisms of droplet and aerosol formation, but do not normally test for the presence or infectivity of viruses in such particles, and so are limited in what they can tell us about the role of these as routes of transmission. **Epidemiological approaches** interrogate descriptive data on case clusters from the early stages of the pandemic to try to identify the most likely routes of transmission. A limitation of these approaches is that data are limited and that observational findings have a high risk of bias. **Microbiological experiments** investigate the viability of the virus under different environmental and time periods under controlled laboratory conditions. The limitation of this sort of study is that the results may not be generalizable to the real world.

The purpose of this review is to integrate evidence from epidemiological, microbiological and fluid mechanics studies on the transmission of SARS-CoV-2 in indoor settings. We set out to answer ten specific questions:

1. What evidence is there for aerosolised transmission?
2. What evidence is there for faecal-oral transmission?
3. What evidence is there regarding the role of ventilation systems in indoor transmission?
4. What evidence is there regarding the role of plumbing systems in indoor transmission?
5. What evidence is there regarding transmission via different indoor surfaces (materials and specific objects)?
6. What evidence is there for the transmission in indoor residential settings?
7. What evidence is there for transmission in indoor workplace settings?
8. What evidence is there for transmission in other indoor settings (social, community, leisure, religious, public transport)?
9. Do particular activities convey greater risk (e.g. shouting, singing, eating together, sharing bedrooms)?
10. What evidence is there for the appropriate length of distancing between people?

Methods

We divided our search strategy into two searches to focus on indoor transmission. The first search focused on epidemiological and microbiological approaches. We searched PubMed and medRxiv between 20-05-2020 and 21-05-2020 (LG). The second search focused on mechanistic and numerical simulation approaches. We searched PubMed, medRxiv, arXiv, Scopus, WHO COVID-19 database, Compendex & Inspec between 20-05-2020 and 21-05-2020 (MD). Full search details are in Appendix 1.

We included articles reporting data on any indoor setting (e.g. domestic, workplace, leisure, public transport, healthcare); any indoor activities (e.g. singing, eating together, sharing living environments); any potential means of transmission (e.g. airborne transmission, surface transmission (fomites), faecal-oral transmission); mechanisms which may influence transmission in indoor environments (e.g. ventilation, air conditioning, plumbing systems). We excluded studies investigating transmission in healthcare settings; studies focusing purely on the clinical characteristics of cases; studies focusing on covid-19 prevention interventions and studies set in schools (transmission in schools and among children is the focus of a separate ongoing review which can be found here [insert link]). Screening criteria for mechanistic studies were adapted to include articles reporting data on any respiratory virus and numerical simulation studies focusing on the mechanisms of transmission.

Title and abstract screening was conducted by one reviewer (LG, GN, RM, PK, TH). Rejections were reviewed by a second reviewer (LG, GN, RM, PK, TH). Full text screening of each article was conducted by one reviewer (LG, GN, PK, TH, RN, KO). A second reviewer screened all excluded full texts (LG, GN, PK, TH, RN, KO). Data extraction and quality assessment for each article was conducted by a single reviewer (LG, GN, PK, TH, RN, KO).

Data extraction was limited to a minimal set of required data items. Due to the highly heterogeneous nature of the study types identified by the searches, it was not possible to assess quality using validated risk of bias tools. Instead, each study was critically appraised individually. Mechanistic and numerical simulation studies were appraised by an expert in the field (IMV, SBC, EP, SZ, MS). Data were synthesised narratively, and meta-analysis was conducted where indicated. Using the GRADE system (Guyatt et al., 2008) a single reviewer RM graded the certainty of the evidence

overall.

In the absence of suitable existing tools, we developed a quality appraisal tool for numerical simulation studies from three sources (American Society of Mechanical Engineers, 2009, 2018; Roache, 2009). We developed a quality appraisal tool for experimental studies (microbiological and fluid mechanics) from several sources (CAMARADES, 2020; Public Health Agency of Canada, 2014; Young & Solomon, 2009). We adapted a quality assessment and data extraction tool for epidemiological outbreak cluster studies from the Joanna Briggs Institute checklist for critically appraising case series (Joanna Briggs Institute, 2020). For other epidemiological study designs, we used Critical Appraisal Skills Programme (CASP) checklists (Critical Appraisal Skills Programme, 2020). Critical appraisal tools are available in appendix 2.

Data on secondary attack rates in households were meta-analysed using a fixed effects model in R 3.6.3 (R Core Team, 2020) using the *rma.uni()* function in the metafor package (Viechtbauer, 2010). I^2 and Cochrane's Q were calculated to assess heterogeneity. For consistency, the same function was used to estimate confidence intervals for SAR in individual studies that were not included in pooled estimates.

Because most of the microbiological evidence on this topic was generated from hospital-based studies, we included microbiological studies which collected samples from both clinical and non-clinical settings. To maximise the transferability and generalisability of these findings to non-clinical indoor settings, we excluded results of samples collected in areas of the hospital such as operating theatres and ICU where aerosol-generating procedures are routinely carried out.

This is an update of two previous rapid reviews (UNCOVER 002-01 – focusing on indoor vs. outdoor transmission, full description of methods available here, literature search conducted 31 March 2020; and UNCOVER 002-02 – focusing on outdoor transmission, full description of methods available here, literature search conducted 30 April 2020). In summary, UNCOVER 002-01 sought publications of any study design providing data on indoor or outdoor transmission and of published or pre-published status, excluding publications from nosocomial settings, modelling data, animal models and articles providing commentary but no data. UNCOVER 002-02 re-examined articles identified by the initial review, using revised screening criteria to include articles that reported data on outdoor transmission, airborne transmission, surface transmission, environmental factors affecting virus transmission (e.g. virus viability and persistence on different surfaces and at different temperatures and levels of humidity). We excluded papers exclusively about indoor transmission. We also excluded statistical modelling studies. A specialist in fluid dynamics (IMV) joined our team to provide expert critical appraisal of the evidence on aerosol vs. droplet transmission through the air.

Results

After the removal of duplicates, a total of 1573 articles were identified. 1447 were rejected through title and abstract screening and a further 60 were rejected at the full-text screening stage and quality assessment stage. 33 did not provide data relevant to study questions, 26 were poor quality and 1 article could not be retrieved. 66 articles were retained for analysis. This information is summarised in the PRISMA diagram (Figure 1). The overall quality of the evidence was graded as low. We report the results on each of our review questions separately, integrating the epidemiological, microbiological and fluid mechanics evidence.

What evidence is there for aerosolised transmission?

We know that SARS-CoV-2 is transmitted through respiratory droplets ejected from the mouth or

nose of an infected individual. Transmission occurs either when these droplets come into direct contact with mucosal membranes in the eyes, nose or mouth of a susceptible individual, or when deposited on a surface and successively transferred to a mucosal membrane through physical contact (i.e. touching a contaminated object and then touching one's nose, mouth or eyes). Respiratory droplets range in size from 0.1 μm (roughly the size of a dust particle) to 1 mm (Mittal, Ni, & Seo, 2020). They behave differently depending on their size.

Larger droplets (diameters of the order of 100 - 1000 μm) follow a ballistic trajectory (i.e. they fall mostly under the influence of gravity) and reach the ground within approximately 1 second and without time to evaporate (Bourouiba, 2020; Bourouiba, Dehandschoewercker, & Bush, 2014; Xie, Li, Chwang, Ho, & Seto, 2007). It is well-established that SARS CoV-2 is transmitted through larger respiratory droplets. The distance they travel before landing depends on (among other factors) how they were generated: those generated from speaking land 1 metre or closer to the speaker (Xie et al., 2007), droplets generated by coughing travel about 2 metres (Bourouiba et al., 2014) before landing, and those generated by sneezing can travel for 8 metres before falling to the ground (Bourouiba, 2020).

Smaller droplets (diameters of the order of 10 μm or smaller) fall so slowly through the air that they have time to evaporate. These very light, desiccated particles, or aerosols, can then remain suspended in the air, potentially indefinitely. Aerosolised particles are ejected in a jet-like flux which, within a few metres, increases in diameter from a few centimetres to tens of centimetres. This flux bends upwards because it is warmer than the surrounding air. Aerosolised particles can travel long distances on air flows – for example, from room to room or in and out of windows within a building or from coach to coach within a train - before eventually landing.

There are also intermediate-sized particles (diameters of the order of 10 – 100 μm), which share some properties of both large droplets and aerosols: being larger and heavier than aerosols, they will fall to the ground more quickly. They may carry a smaller infectious dose than large droplets (Tellier, Li, Cowling, & Tang, 2019).

While the possibility of CoV-2 transmission through aerosol is still uncertain, Li et al demonstrated with numerical simulations that a COVID-19 outbreak in a restaurant in Guangzhou, China, is compatible with aerosol transmission (Y. Li et al., 2020). Furthermore, there is substantial evidence that virus-laden aerosol dispersion played a role in the 2003 SARS-CoV outbreak (Li, Duan, Yu, & Wong, 2005; Li Y., Huang X., & I.T., 2005; Wong et al., 2004; I. T. Yu et al., 2004; I. T. S. Yu, Wong, Chiu, Lee, & Li, 2005). One illustration of the potential risk posed by aerosols was an experiment which showed that aerosols emitted above mid-body height would tend to remain at vertical elevations corresponding to the breathing levels of seated passengers in an aircraft carriage (Poussou & Plesniak, 2012). Aerosol dispersal has also been shown to be possible within a train coach (Yang, Li, Li, & Tu, 2018), between buildings (I. T. Yu et al., 2004) and between floors of a building (Li et al., 2005; Niu & Tung, 2008).

Evidence from fluid mechanics experiments and simulations show that very small, virus-sized particles can remain suspended in the air in aerosols for long periods of time. This does not, however, tell us whether live virus can survive in this state. Laboratory-based microbiological studies have been conducted to explore this question. van Doremalen et al found that the virus remained viable for 3 hours in the aerosolised state (median half-life 1.09 hours, 95 % credible interval 0.64, 2.64), indicating that aerosolised transmission is theoretically possible (van Doremalen et al., 2020). To investigate whether aerosolisation of viral particles might actually be occurring, several hospital-based studies (Guo et al., 2020; Liu, Ning, et al., 2020; Santarpia et al., 2020; Wu et al., 2020; Zhou et al., 2020) and one study which considered modes of transmission in the Diamond

Princess cruise ship (Yamagishi, 2020) collected and analysed environmental samples. Four studies found that SARS-CoV-2 RNA was detectable in the air using air sampling techniques, which is suggestive of aerosolised particles. Positive results included hospital hallways, patient rooms, and pharmacy areas, all of which were accessible by the general public, highlighting potential exposure and transmission risk (Guo et al., 2020; Liu, Ning, et al., 2020; Santarpia et al., 2020; Zhou et al., 2020). Interestingly, Liu et al sampled areas surrounding the two hospitals in their study and found virus RNA detection at the entrance of two department stores where patients frequently walked past to access the hospital, highlighting potential aerosol transmission from clinical to non-clinical areas (Liu, Ning, et al., 2020). However, two studies failed to detect SARS-CoV-2 via air samples (Wu et al., 2020; Yamagishi, 2020). It is also important to note that the detection of viral RNA does not necessarily imply the presence of live virus. Viral RNA can be either live virus, which poses an infectivity risk, but equally it can be fragmented dead virus which does not have the ability to cause infection. To establish whether environmental samples of SARS-CoV-2 pose an infection risk, it is not sufficient simply to detect viral RNA: we need to know whether the virus is viable, a question which can only be answered using laboratory culturing methods (Leland & Ginocchio, 2007).

Taking this evidence together, aerosolised transmission is theoretically possible. SARS-CoV-2 can survive in aerosolised form for up to 3 hours (van Doremalen et al., 2020) so it is *theoretically* possible for an uninfected person to inhale particles of aerosolised virus even after the source of the infection has departed the scene. Whether or not this poses an *actual* infection risk depends, among other factors, on the quantity of virus required to trigger infection, a question which currently remains unanswered. We examined observational epidemiological studies for evidence suggestive of aerosol transmission. The evidence is of poor quality and lacks detail. Most of the epidemiological evidence is compatible with droplet/fomite transmission through close contact. A large outbreak in Washington State, USA, linked to a choir practice is potentially consistent with aerosolised transmission. Xu et al conducted a careful analysis of the outbreak on the Diamond Princess cruise ship (Xu et al., 2020). After 6 February, when passengers were confined to their cabins, passenger transmission was limited to close contacts (sharing a cabin). The absence of any cross-room transmission among passengers after the quarantine period began supports the hypothesis that transmission was via droplets/fomites and not airborne via the air conditioning system.

What evidence is there for faecal-oral transmission?

Other human coronaviruses can be transmitted via the faeces of infected individuals, so it is important to establish whether SARS-CoV-2 can be transmitted in this way. We reviewed seven case series (Jiehao C, Jing X, & Daojiong L, 2020; Ling et al., 2020; W. Wang et al., 2020; Wölfel et al., 2020; Wu Y, Guo C, & Tang L, 2020; Zhang, Wang, & Xue, 2020; W. Zhang et al., 2020), two case reports (Holshue et al., 2020; Tang et al., 2020), and one non-systematic review article (L. Y. Li et al., 2020). Emerging evidence suggests that gastro-intestinal (GI) symptoms in SARS-CoV-2 may be the result of viral invasion of ACE2 expressing enterocytes of ileum and colon, as seen with SARS-CoV (Zhang H, Kang Z, & Gong H, 2020). However, GI symptoms are less common in SARS-CoV-2 than in SARS-CoV or MERS: a review of published studies found that compared to 30% patients with gastro-intestinal symptoms in SARS and MERS, diarrhoea and vomiting occurred in 5.6% (range of estimates 2 - 34), and 4.5 % (range 1 - 10) patients of COVID -19, respectively (L. Y. Li et al., 2020). All ten articles we reviewed reported detection of SARS-CoV-2 viral RNA in faecal samples using RT-PCR. Estimates of the proportion of adult cases with viral RNA detectable in faeces range from 29 % (Ling et al., 2020) to 82 % (W. Wang et al., 2020), although because the studies used different parameters and time frames, it is not possible to draw any firm conclusions from these data. Four case series (Jiehao C et al., 2020; Ling et al., 2020; Wu Y et al., 2020; J. Zhang et al., 2020), one case report (Tang et al., 2020) and one review article (L. Y. Li et al., 2020) reported that SARS-CoV-2 faecal samples still tested positive after throat swabs had turned negative, implying the potential for prolonged

infectivity. Again, though, sample sizes are small and differences in the way that data were collected and reported makes direct comparison difficult. Four case series (Jiehao C et al., 2020; Wu Y et al., 2020; W. Zhang et al., 2020) and one case report (Tang et al., 2020) found that the presence of SARS-CoV-2 viral RNA or live virus in faecal samples was unrelated to the presence of gastro-intestinal symptoms. We also reviewed three studies which collected environmental samples, two in clinical settings (Liu, Ning, et al., 2020; Santarpia et al., 2020) and one in a cruise ship (Yamagishi, 2020), which suggest that aerosolisation of viral particles may occur through toilet flushing. Two studies highlighted the detection of SARS-CoV-2 RNA on the floor surrounding toilets used by confirmed cases, which is consistent with aerosolisation of virus particles through toilet flushing (Santarpia et al., 2020; Yamagishi, 2020). The highest concentration of SARS-CoV-2 RNA detected in air samples by (Liu, Ning, et al., 2020) was in a patient toilet cubicle.

Taken together, these results suggest that there is potential for transmission via the faeces of an infected person, either through the contamination of surfaces or through aerosolisation; however they should be interpreted with caution. The detection of SARS-CoV-2 viral RNA in faecal samples does not mean that live virus is present or that patients are infectious. Two studies tested faecal samples for the presence of live virus. One detected live virus in all four samples tested (W. Wang et al., 2020); however in a virological analysis of nine cases of COVID-19 who were all part of a single epidemiological cluster in Munich, Germany, Wölfel et al were able to isolate infectious virus from samples taken from patients' throats and lungs, but not from faecal samples, even though these samples had high concentrations of viral RNA (Wölfel et al., 2020).

Conclusions – Transmission mechanisms

Based on the evidence available to date, the most common transmission route for SARS-CoV-2 is person-to-person, short-range spread via mostly respiratory droplets that directly reach recipients either through the air or through touching contaminated surfaces and then transferring the virus on the hands to mucosal membranes. Evidence from numerical simulation and fluid mechanics studies, microbiological laboratory studies and environmental sampling studies suggest that aerosol transmission is theoretically possible and is another potential source of transmission. Evidence from an outbreak linked to a choir practice is also consistent with this. SARS-CoV-2 is potentially transmissible via the faecal-oral route but there is no direct evidence of this.

What evidence is there regarding the role of ventilation systems in indoor transmission?

Air currents, amplified by ventilation systems, are responsible for the dispersal of both aerosols and large droplets within buildings. This can happen in various ways. For example, a study by Chen et al showed that even small differences of temperature between two rooms can cause a two-way flow between the rooms (Chen, Zhao, & Yang, 2011). Li et al conducted a real-scale experiment and a computational fluid dynamics simulation in a restaurant, which showed that there was higher particle concentration in the presence of air recirculation, generated by cold air injected into the room by the air conditioning unit and warm air generated by the people eating in the restaurant (Y. Li et al., 2020). A study by Sung et al discovered that tracer gas was efficiently distributed from room to room along a building corridor, aided by strong air currents entering through open windows (Sung et al., 2018). In a study showing that an upper apartment can contain up to 7 % of the air from the one beneath it, Niu and Tung provide evidence that airborne transmission through ventilation is possible (Niu & Tung, 2008). A study by Li et al showed that during the 2003 SARS outbreak in Hong Kong the ventilation system in the densely populated Amoy Gardens apartment complex contributed to the dispersal of the virus among flats and across different floors and buildings in the complex (Li et al., 2005).

However, ventilation systems are also likely to decrease the concentration of viral particles in the air: the above study on the role of ventilation systems in the SARS outbreak at the Amoy Gardens

complex also suggested that the ventilation system played a fundamental role in mitigating the outbreak by diluting the concentration of virus particles (Li et al., 2005). Yu et al demonstrated, through numerical simulations, that increasing air exchange rates decreases the risk of contamination in a semi-open hospital ward (H. C. Yu, Mui, Wong, & Chu, 2017). In short, ventilation is likely to decrease virus concentration but increases aerosol dispersal, therefore it is likely to decrease virus transmission risk near the source and increase virus transmission risk further away from the source.

What evidence is there regarding the role of plumbing systems in indoor transmission?

There is no direct evidence that SARS-CoV-2 is transmissible via infected faeces; however until this is demonstrated definitively, it is important to understand the potential role of defective plumbing systems, which are thought to have played a role in the transmission of SARS-CoV in a large outbreak in the Amoy Gardens residential complex in Hong Kong in 2003. During this outbreak, 321 cases in the apartment complex were linked to faecal-oral transmission (L. S. Hung, 2003) and there is compelling evidence that this was exacerbated by deficient indoor plumbing systems. Subsequent simulations have demonstrated that aerosols can be generated in vertical soil stack pipes when toilets are flushed and can enter a room due to the suction generated by the ventilation system (Gormley, Aspray, Kelly, & Rodriguez-Gil, 2017; H. C. K. Hung, Chan, Law, Chan, & Wong, 2006; Jack, Cheng, & Lu, 2006; I. T. Yu et al., 2004). In this context, contaminated aerosols originating from breath or sewage are more likely to be warmer than the surrounding air, and so are more likely to travel from the lowest to the highest floors of a building than vice versa. The lower the environmental air temperature, the more significant the aerosol transmission from the lowest floors to the highest floors (Lim, Cho, & Kim, 2011). The study by Gormley et al implies that a functioning U-trap is the only mechanism preventing transportation of aerosolised particles (Gormley et al., 2017). Yet this study states that U-trap failure/depletion can result from a variety of mechanisms and is not unusual. The authors report that most of the buildings where defective U-traps have been found are high occupancy and that two such buildings in the UK are hospitals.

Conclusions: Role of ventilation and plumbing systems in transmission

Air currents are responsible for the dispersal of both aerosols and large droplets within buildings, between different rooms and even between different floors. This dispersal can be amplified by a variety of factors, including ventilation and air conditioning systems, differences of temperature between rooms and air currents entering through open windows.

However, ventilation systems are also likely to dilute the concentration of viral particles in the air and thereby to play a potential role in decreasing transmission. Ventilation systems are likely to decrease virus transmission risk near the source but to increase virus transmission risk further away from the source.

There is no direct evidence that SARS-CoV-2 is transmissible via infected faeces; however until this route of transmission is definitively ruled out, it is important to note that aerosolised particles can be generated in vertical soil stack pipes when toilets are flushed. These particles can then enter a room via ventilation systems and defective plumbing systems – specifically U-trap failure/depletion. This is of particular relevance in high occupancy and high-rise buildings.

What evidence is there regarding transmission via different indoor surfaces (materials and specific objects)?

A fomite is any object that may be contaminated with infectious agents and serve in their transmission. Virus particles from aerosols, droplets or people's hands can contaminate surfaces in this way. If they are then touched by a susceptible person and transported by hands into mucosal membranes, they can cause infection. We looked at the research evidence for fomite transmission

in order to establish the length of time live virus survives on different surfaces and under different environmental conditions and to identify the sorts of objects and surfaces commonly contaminated.

Microbiological evidence on the persistence of live virus on different surfaces or materials comes from two sources: laboratory-based studies which investigate the survival of live virus under carefully controlled environmental conditions ((Chin et al., 2020; Sun et al., 2020; van Doremalen et al., 2020) and studies which collect environmental samples using swabbing techniques and then test them for detection of viral RNA using reverse transcription polymerase chain reaction (RT-PCR) (V. C. C. Cheng et al., 2020; Hirotsu, Maejima, Nakajima, Mochizuki, & Omata, 2020; Jiang et al., 2020; Santarpia et al., 2020; Wu et al., 2020; Yamagishi, 2020; Ye et al., 2020; Zhou et al., 2020). As highlighted above, viral RNA can be either live virus, which poses an infectivity risk, but equally it can be fragmented dead virus which does not have the ability to cause infection. To establish whether environmental samples of SARS-CoV-2 pose an infection risk, it is not sufficient simply to detect viral RNA: we need to know whether the virus is viable. Live virus can be detected through laboratory culturing methods, which give an indication of the presence of live virus in suitable cell lines (Leland & Ginocchio, 2007). Three of the studies attempted to culture live virus from environmental swabs (Santarpia et al., 2020; Yamagishi, 2020; Zhou et al., 2020).

In a laboratory-based study, van Doremalen et al investigated the persistence of SARS-CoV-2 on a variety of different surfaces (van Doremalen et al., 2020). The researchers found that the virus persisted for up to 72 hours after application to plastic (median half-life 6.81 hours, 95 % credible interval5.62, 8.17) and up to 48 hours after application to stainless steel (median half-life 5.63 hours, 95 % credible interval 4.59, 6.86). The virus was found to be more stable on these surfaces than on copper (median half-life 0.774 hours, 95 % credible interval 0.427, 1.19) and cardboard (median half-life 3.46 hours, 95 % credible interval 2.34, 5). After 4 hours, no viable SARS-CoV-2 was detectable on copper and after 24 hours no viable SARS-CoV-2 was detectable on cardboard. Chin et al found that SARS-CoV-2 was more stable on smooth surfaces. No infectious virus could be detected on day 4 (glass and banknote) or day 7 (stainless steel and plastic) (Chin et al., 2020). In the same study the researchers investigated stability at different temperatures and found SARS-COV-2 to be highly stable and able to survive for long periods at low temperatures (4°C), but sensitive to heat: at 4°C, there was only around a 0·7 log-unit reduction of infectious titre on day 14, whereas at 22°C it was detectable at 7 days but not at 14 days. With the incubation temperature increased to 70°C, the time for virus inactivation was reduced to 5 minutes. Using a strain from the nasal-pharyngeal swab of a clinically confirmed COVID-19 patient in Shanghai, Sun et al measured the stability of SARS-CoV-2 in wet (in 100 uL culture medium) and dry (10 uL supernatant on filter paper) environments at room temperature (22°C) each day for 7 days, as well as its stability under acidic conditions to mimic the gastric environment (pH2.2) (Sun et al., 2020). Although the virus survived for 3 days in both the wet and dry environments, the dry environment was less favourable for virus survival. Viable virus was not observed after 4 days in either the wet or dry condition. The authors concluded that COVID-19 virus is highly infectious and high concentrations can also survive under an acidic condition, such as the stomach. Overall, these studies indicate that under highly controlled laboratory conditions, low temperatures and wet environments are most conducive to persistence of SARS-COV-2.

We examined evidence from six hospital-based studies in China (Wu et al., 2020; Ye et al., 2020), Hong Kong (V. C. C. Cheng et al., 2020), Japan (Hirotsu et al., 2020), UK (Zhou et al., 2020) and USA (Santarpia et al., 2020) and two studies from non-clinical settings: a cruise ship moored in Japan (Yamagishi, 2020) and a quarantine hotel in China (Jiang et al., 2020). All eight studies used real-time PCR methods for detection of SARS-CoV-2 from surface samples. This involved detection of viral RNA through targeting different parts of the virus (Sironi et al., 2020). Studies utilised different target genes, all specific for SARS-CoV-2. The RdRp gene assay has been reported to have the highest analytical sensitivity (H. Wang et al., 2020). Furthermore, some studies reported the quantities of

viral RNA in each sample, which gives an indication of the amount of virus present. This is relevant for assessing viral load.

The six hospital-based studies collected swab samples from patient rooms and high-touch surfaces. Telephones, keyboards, doorknobs, elevator buttons, TV controls, water dispenser buttons and toilet floors were the most common areas of SARS-CoV-2 contamination in the hospital-based studies. Zhou et al detected viral RNA in both clinical and public areas of the hospital, although this was significantly more likely to be found in areas of the hospital occupied by covid-19 patients (OR 0.5, 95 % confidence interval 0.2-0.9, p=0.025) (Zhou et al., 2020). They detected viral RNA on 114/218 (52.3 %) of surfaces. These swabs were taken from several different objects, including chairs, computer keyboards and alcohol hand sanitiser dispensers. Hirotsu et al collected 15 environmental samples from rooms occupied by an infected patient (Hirotsu et al., 2020). The samples were collected after thorough cleaning of the area. They did not detect any viral RNA, which provides evidence on the effectiveness of cleaning to reduce transmission. Ye et al also suggested that because they collected samples after new environmental cleaning protocols were introduced, environmental contamination of SARS-CoV-2 may have been previously higher in this Wuhan hospital at the earlier stages of the pandemic and could have contributed to the initial high transmission rate amongst healthcare workers and visitors (Ye et al., 2020).

Two studies investigated virus detection in non-clinical settings: a quarantine hotel in China (Jiang et al., 2020) and a cruise ship in Japan (Yamagishi, 2020), both of which had confirmed SARS-CoV-2 cases in the rooms/cabins. In the cruise ship cabins viral RNA was present on highly touched surfaces in cabins such as the room phone, TV remote and the doorknob before and after spraying with 5 % hydrogen peroxide solution, indicating that wiping surfaces may be more effective at disinfection than only spraying surfaces (Yamagishi, 2020). High virus detection was also observed on bed pillows. Furthermore, Jiang et al detected high viral load on the pillowcase and bed sheet in the room of one confirmed case (Jiang et al., 2020). The results from the cruise ship study also found no difference ($p > 0.05$) in virus detection between symptomatic and asymptomatic case cabins (Yamagishi, 2020). These studies highlight hotspots of virus detection in hospitality settings used to quarantine suspected cases and could be important for infection control in non-clinical settings, to avoid future transmission/outbreaks.

Three studies quantified the amount of virus present by reporting viral load/gene copy data. All three found minimal amounts of viral material, indicating that although the virus was present, there were low levels of contamination in the environment (V. C. C. Cheng et al., 2020; Santarpia et al., 2020; Yamagishi, 2020).

Three studies attempted to culture live virus from environmental samples. Zhou et al were unable to culture any live virus from either air or surface samples and the results in the other two studies were inconclusive (Santarpia et al., 2020; Yamagishi, 2020; Zhou et al., 2020). In these studies, it is not known what time had elapsed between environmental contamination and sample collection: if there was a considerable delay, this could potentially explain the difficulties in isolating live virus. Transport time to the laboratory (Yamagishi, 2020), methodological errors (Yamagishi, 2020), low RNA levels in the samples (Zhou et al., 2020), or virus that is infectious but not culturable in the laboratory (Zhou et al., 2020) have all been suggested as potential reasons for the failure to culture live virus from viral RNA samples. Three studies highlighted the absence of viral culturing methods as an obstacle in demonstrating the infectivity of SARS-CoV-2 positive samples (Guo et al., 2020; Jiang et al., 2020; Liu, Ning, et al., 2020).

Sze-To et al investigated the indirect contact infection risk associated with fabric and non-fabric surfaces (Sze-To, Yang, Kwan, Yu, & Chao, 2014). The researchers used a technique called Lagrangian

simulations, which is a method of tracking the trajectories of particles. They concluded that non-fabric fomites (e.g. hard floors or tables) present higher risk than fabric ones (e.g. carpets).

There is very limited epidemiological evidence on this subject. A contact tracing report on a church outbreak in Singapore reported by Pung et al found that one of the three secondary cases did not have direct contact with the presumed index cases, but occupied the same seat as one of them at a prayer meeting directly following the service but not attended by the index cases (Pung et al., 2020).

Conclusions: transmission via different surfaces and objects

Laboratory-based experiments demonstrate that the length of time SARS-CoV-2 remains viable on surfaces depends on the type of surface and the environmental conditions. Evidence suggests that the virus prefers smooth, non-fabric surfaces, low temperatures and damp conditions. It survives for longer on plastic (detectable for up to 72 hours, with a half-life of approximately 7 hours) and stainless steel (detectable for up to 48 hours, with a half-life of approximately 6 hours) than on cardboard (detectable for up to 24 hours, with a half-life of approximately 3.5 hours). Copper has strong anti-viral properties, with no viable virus detectable after 4 hours and a half-life of less than an hour. Experiments investigating the impact of temperature on the virus show that it highly stable at 4° C (still detectable at 14 days). At 22° C it is detectable at 7 but not at 14 days. At 70° C it is undetectable after 5 minutes. Although the virus persists in both the wet and dry environments, experiments have shown that the dry environment is less favourable for survival. It can also survive under acidic conditions, such as the stomach.

Studies analysing swabs taken from various surfaces and high-touch objects in clinical and non-clinical settings occupied by infected cases detected viral RNA on telephones, keyboards, doorknobs, elevator buttons, TV controls, water dispenser buttons, chairs, toilet floors, bedding and hand sanitiser dispensers. However all three studies which quantified the amount of virus present found minimal amounts of viral material. We found only one epidemiological study which reported explicitly on fomite transmission: a case of secondary transmission through occupying the same seat as the index case, without the infected person coming into direct contact with the index case.

What evidence is there for the transmission of COVID-19 in indoor residential settings?

Twelve studies included data on transmission in residential settings (Bi et al., 2020; Burke et al., 2020; Chan et al., 2020; Chaw et al., 2020; H. Y. Cheng et al., 2020; Fan et al., 2020; Hu et al., 2020; Kim & Jiang, 2020; McMichael et al., 2020; Roxby et al., 2020; Tobolowsky et al., 2020; Xu et al., 2020). These can be split into those focusing on private households and those focusing on communal living facilities, such as care homes and shelters for people experiencing homelessness. Six studies reported on household transmission, with 4 providing data on secondary attack rates (defined as the probability that an infection occurs among susceptible people within a specific group, such as a household or close contacts (Liu, Eggo, & Kucharski, 2020)) (SARs) (Table 1). We conducted a meta-analysis of the SARs for these four studies. The pooled SAR for people living in the same household was 11 % (95 % CI 9, 13) (figure 2).

We found six studies reporting data on transmission in settings with some degree of communality (e.g. communal dining rooms, bathrooms, dormitories or social spaces; food prepared communally or served by staff; staff providing assistance with daily living). These studies involved very different types of population, so it was not appropriate to conduct a meta-analysis. Two articles reported on outbreaks in nursing homes in USA (McMichael et al., 2020) and South Korea (Kim & Jiang, 2020). Tobolowsky et al reported on an outbreak in three affiliated day/overnight shelters for people experiencing homelessness in USA (Tobolowsky et al., 2020); Xu et al described the outbreak on the Diamond Princess cruise ship quarantined off Japan (Xu et al., 2020); Roxby et al reported on an outbreak in an assisted and independent living community in Washington State, USA (Roxby et al.,

2020); and Fan et al reported on Chinese nationals repatriated from Iran in early March 2020 (Fan et al., 2020). Four of the studies provided data for estimating SARs amongst residents (Table 2 - data are reported separately in table 3 for staff working in these settings). The SARs for people living in communal settings were significantly higher than the SARs for households. The highest - 62.3 % (95 % confidence interval 54.0, 70.6) - was in the US care home (although ascertainment of the denominator was not precise). SARs amongst residents of the homeless shelters and passengers on the cruise ship were similar to each other (18 %; 95 % CI 12.6, 23.3 and 19.6 %; 95 % CI 17.6, 20.3 respectively). The lowest SAR - 3.8 %, 95 % confidence interval 0, 7.9 - was in the senior assisted and independent living community in the USA, where elderly residents lived largely independently in separate apartments. The study by Fan et al on Chinese nationals repatriated from Iran provided very little information on potential exposures; however it reported a significant positive correlation between the incidence of COVID-19 infection and residing in a dormitory ($\chi 2 = 4.088$, $p = 0.043$) (Fan et al., 2020).

What evidence is there for the transmission of COVID-19 in indoor workplaces?

Ten studies reported on transmission among workers or at workplaces: care home workers (McMichael et al., 2020), cruise ship crew (Kakimoto et al., 2020; Xu et al., 2020), staff at a shelter for people experiencing homelessness (Tobolowsky et al., 2020), staff at an assisted and independent living community for the elderly (Roxby et al., 2020), workers at meat/poultry processing plants (Dyal et al., 2020); shop workers (Pung et al., 2020); workers at a customer call centre (Kim & Jiang, 2020); workers at a government ministry (Kim & Jiang, 2020) and unspecified workplaces or schools (Burke et al., 2020; Chaw et al., 2020). Five of these studies provided data for the estimation of SARs among staff (Table 3). They range from 3.2 % (95 % CI 0, 7.6) for staff working in the assisted and independent living community to 21 % (95 % CI 8.1, 34.0) for staff working in the shelters for people experiencing homelessness. SARs for staff and residents were not significantly different in the assisted and independent living community or in the shelter; however SARs were significantly higher for residents than for staff on the cruise ship ($p = 0.000017$) and in the care home ($p < 0.00001$). The final study reported in table 3 is from a US contact tracing study, in which the close contacts of travel-related cases at the beginning of the pandemic were traced. No detail about the types of workplace or occupations is provided. There were no secondary cases. We found three workplace studies which did not present sufficient data to estimate SARs but nevertheless provide insight into workplace transmission. Dyal et al present data collected by the US Centers for Disease Control (CDC) on workplace outbreaks in meat and poultry processing facilities across the USA (Dyal et al., 2020). The article presents data from 17 of 23 US states reporting at least one such outbreak, expressing the number of cases in each state as a proportion of all meat and poultry workers employed in the state. In other words, the denominator includes workers in facilities which have not experienced an outbreak, thus under-estimating the impact of such an outbreak on an individual facility. By April 2020 there had been a total of 4913 cases in a total workforce of 130578 in the 17 states who provided full data (3.8 %, 95 % CI 3.7, 3.9). CDC identified a range of key drivers: difficulty in maintaining the 2 metre social distance on the production line at break times and while entering/exiting the facility; difficulty implementing covid-19-specific disinfection guidelines; socioeconomic challenges related to poverty, such as people continuing to work whilst ill, especially where attendance is incentivised and workers living in overcrowded, multigenerational households; communication challenges such as the inaccessibility of health and safety training to non-English speakers and to non-literate workers; sharing of transportation to work; and adherence to correct usage of face coverings. Kakimoto et al report data from part-way through the outbreak among crew of the Diamond Princess cruise ship anchored off Japan (Kakimoto et al., 2020). Results point to the role of close living and working conditions in transmission. Fifteen out of the initial 20 cases among the crew were in food service workers and 16 lived on the same deck. Eight of the 20 shared cabins with fellow crew members and as of 4 March 2020 five of these had developed covid-19. Pung et al conducted a small contact tracing study of an

outbreak in Singapore connected with the visit of a tour group of around 20 tourists from China to a complementary health products shop and to a jewellery shop (Pung et al., 2020). Four assistants in the complementary health products shop and one assistant in the jewellery shop were subsequently confirmed to have COVID-19. Finally, Kim and Jiang report limited information on two workplace outbreaks in South Korea: one in a customer call centre, where 164 people became ill and another in the Ministry of Oceans and Fisheries, where there were 30 cases (Kim & Jiang, 2020). No information is provided about the numbers of close contacts working in these environments, nor on the nature of the workplace involved in the Ministry of Oceans and Fisheries outbreak.

What evidence is there for the transmission of COVID-19 in other indoor settings (social, community, leisure, religious, public transport)?

We found six epidemiological studies reporting on transmission related to social, religious, community or leisure settings. Four studies report on a total of eight outbreaks related to religious gatherings or churches (Chaw et al., 2020; Kim & Jiang, 2020; Pung et al., 2020; Yong et al., 2020). One study reports on two outbreaks in gyms (Kim & Jiang, 2020) and one investigated evidence for transmission in a clinic waiting room (Burke et al., 2020).

Chaw et al report on outbreaks related to the Tablighi Jama'at religious gathering in Malaysia and a subsequent similar gathering in Brunei (Chaw et al., 2020). Both were extended, communal overnight gatherings. Estimated SARs were 25.3 % (95 % CI 15.5, 35.2) and 14.8 % (95 % CI 5.3, 24.3) respectively. Pung et al describe a contact tracing study in a church in Singapore (Pung et al., 2020). The presumed index cases were a couple visiting from China who had attended a service at the church. Three of the 142 contacted attendees at the service subsequently tested positive for SARS-CoV-2 (SAR 2.1; 95 % CI 0, 4.4). Two further articles report on transmission via church services but do not provide sufficient data to estimate SARs. Yong et al describe linked outbreaks in two churches in Singapore (Yong et al., 2020). The presumed index cases at the first church were two Chinese national travellers from Wuhan who attended a service. Five people subsequently became ill. The index case at the second church was a church employee, who is presumed to have contracted the virus whilst hosting a family celebration attended by a symptomatic case from the first church outbreak. Sixteen people became ill. Finally, Kim and Jiang describe four outbreaks linked to churches in South Korea: Shincheonji church (149 cases at the time of publication), River of Grace community church (67 cases), Onchun church (43 cases) and Dongan church (29 cases) (Kim & Jiang, 2020).

This study also reports on two outbreaks connected with gyms in South Korea. At the first, Cheonan-si gym facility, 63 people were reported as contracting the virus. At the second, Cheonan/Asan-si gym, there were 35 reported cases. No further details are provided (Kim & Jiang, 2020).
The study of early travel-related cases in USA by (Burke et al., 2020) followed up 95 people who spent time in clinic waiting rooms with affected individuals. No cases were detected.

Conclusions: transmission in different indoor settings

We found evidence of transmission in domestic, workplace and community/leisure settings. Most of the studies we found were conducted early in the pandemic, when effective and accurate contact tracing was possible. We found higher secondary attack rates in communal residential contexts (care homes, shelters for homeless people, cruise ship) than in households.

We found evidence of workplace outbreaks in a care home, an assisted and independent living community, shelters for homeless people, shops, meat and poultry processing factories, a cruise ship, a business conference, a customer call centre and a government ministry; however few of the studies provided enough detail to allow meaningful comparison of the risks in different settings. Nevertheless, many of the workplace settings where outbreaks have occurred are characterised by

close physical contact and prolonged time spent in crowded indoor spaces. Evidence from the study by Dyal et al on outbreaks in meat and poultry processing plants also highlights the role health inequalities and inadequate social protection play in relation to people continuing to work whilst ill, overcrowded housing and transportation to and from work and inadequate health and safety communication and training, particularly for non-English speakers and non-literate workers (Dyal et al., 2020).

Do particular activities convey greater risk (e.g. shouting, singing, eating together, sharing bedrooms)?

Because SARS-CoV-2 is transmitted through respiratory droplets, activities that increase the emission of droplets convey greater risk. Evidence from fluid mechanics experiments enables us to partition activities into four levels of risk based on the number of droplets ejected (Asadi, Wexler, & Cappa, 2019; Chao et al., 2009; Duguid, 1946; Xie, Li, Sun, & Liu, 2009; Zayas et al., 2012), the least risky being quiet breathing. The next riskiest level is heavy breathing or singing, followed by coughing and finally sneezing. There is a very significant (orders-of-magnitude) difference in risk between each of these levels and the next. There is also evidence that pronouncing some sounds (e.g. need, see) results in the emission of more droplets than others (e.g. hot, mood); however these risk differences are relatively small compared to the risks between, for example, coughing and singing (Asadi S, Wexler AS, Cappa CD, Barreda S, & Bouvier NM, 2020).

We found six descriptive epidemiological studies which describe transmission via daily living activities among people living together in households, although none of the studies provides sufficient detail to pinpoint the risks associated with specific activities. In a contact tracing study of 9 travel-related cases in USA early in the pandemic, Burke et al report on 2 cases resulting from household transmission, both in the spouses of cases (Burke et al., 2020). They suggest that daily living activities such as sharing beds, bathrooms, eating together, face to face contact and spending time in the car together are likely to increase the risk of transmission. Family members cohabiting during case isolation were advised where possible to use separate bedrooms and bathrooms, limit time in same room and affected family members were advised to wear a mask when in the same room as others. The study reported strong compliance in general with these measures, with some evidence that there was higher compliance with isolation measures and less time spent with affected family members in households where there was no transmission. In a high quality, well-conducted study Chaw et al investigated attack rates for different relationships living together in households (Chaw et al., 2020). They found that the highest secondary attack rate was amongst spouses, at 41.94 % (95 % CI, 26.42, 59.24). This compares with 14.12 % (95 % CI, 8.27, 23.08) for children and 2.03 % (95 % CI, 0.69, 5.79) for other relatives (parents, siblings, grandparents, housekeepers, etc.). Cheng et al compared secondary attack rates in household members with non-household family members (H. Y. Cheng et al., 2020). The secondary attack rate in people living in the same household was 19.44 % (95 % CI 9.75, 35.02) compared to 10.64 % (95 % CI 4.63, 22.6) in relatives living apart, although the difference is not significant. Bi et al investigated factors associated with transmission for 391 primary cases in Shenzhen, China (Bi et al., 2020). They tested and followed up 1286 close contacts for 14 days and then retested. Close contacts were defined as people living in the same apartment, sharing a meal, travelling together, or interacting socially with the index case from 2 days before the onset of symptoms. A multivariate regression analysis estimated the OR for household contacts as 6.3 (95 % CI 1.5, 26.3), travelling together 7.1 (95 % CI 1.4, 34.9) and eating meals together 7.13 (95 % CI 0.73, 69.32). The OR for having contact "often" with the index case (compared to having rare or moderate contact) was 8.8 (95 % CI 2.6, 30.1). Two studies (Chan et al., 2020; Hu et al., 2020) did not provide sufficient data to estimate SARs but nevertheless provided narrative evidence on transmission within families living together and on the risks of transmission within households when cases are asymptomatic, and thus not aware of the need for enhanced hygiene and social distancing at home.

The six studies we found which report on transmission in communal contexts are consistent with the conveyance of risk through close contact daily living activities, although again, insufficient detail is provided to identify risks associated with specific activities. It is striking that the SAR reported in the care home (McMichael et al., 2020) is an order of magnitude higher than that reported in the senior assisted and independent living community (Roxby et al., 2020), a much less communal setting, where elderly residents lived largely independently in separate apartments. It is important to note, however, that although the age profile in the two settings is likely to be similar, the residents of the nursing home were likely frailer. Also, ascertainment of the denominator in the care home study was not precise, so these results are uncertain.

Conclusions: transmission risk associated with different activities

Our study found evidence that within households, the risk of transmission was higher between spouses than between other types of relative. We found evidence that effective social distancing to prevent transmission within households is possible, particularly if the isolated person is able to use a separate bathroom, a separate bedroom, minimise time in the same room as other family members and wear a mask where this is unavoidable. However, such measures are challenging in overcrowded housing and do not take into account that many cases are asymptomatic so individuals will be unaware that they are sick and potentially transmitting the virus to others.

We found evidence that activities associated with a higher risk of transmission are those where people gather in close proximity indoors for prolonged periods. Churches and religious gatherings, sharing meals and bathing facilities, close physical contact and activities such as singing together have all been reported in conjunction with outbreaks. In contrast, there have been fewer reports of transmission in relation to more casual, short term social contact, although this may be because such contacts are subject to recall bias and harder to track and trace. Risks associated with travelling with an affected case are difficult to evaluate – the evidence from these studies was limited and non-specific.

What evidence is there for the appropriate length of distancing between people?

There is a general consensus that the main route of CoV-2 transmission is through person-to-person short-range transmission, which occurs through large respiratory droplets ejected while speaking, coughing and sneezing. These droplets land within less than 1 metre, 2 metres and 8 metres from the source, respectively.

There is clear evidence that aerosolised transmission played a role in the 2003 SARS-CoV outbreak (Li et al., 2005; Li Y. et al., 2005; Wong et al., 2004; I. T. Yu et al., 2004; I. T. S. Yu et al., 2005). The evidence is less clear for SARS-CoV-2; however viral RNA has been detected in aerosols (Liu, Ning, et al., 2020) and laboratory studies suggest live virus can survive in this form for up to 3 hours (van Doremalen et al., 2020). Numerical studies have demonstrated that aerosol can travel significant distances, including across different rooms, floors, and also from one building to another. Epidemiological evidence from a large outbreak linked to a choir practice is also compatible with aerosolised transmission across longer distances indoors. However, the longer the travelled distance, the lower the likelihood that the concentration of virus is above the threshold needed to transmit the disease.

Discussion

This review integrates current evidence from epidemiological, microbiological and fluid mechanics perspectives on the transmission of covid-19 in indoor settings.

Most of the epidemiological studies it draws on were conducted early in the pandemic, when effective and accurate contact tracing was possible. We found higher secondary attack rates in communal residential contexts (care homes, shelters for homeless people, cruise ship) than in households. Within households, the risk of transmission was higher between spouses than between other types of relative. This study suggests that effective social distancing to prevent transmission within households is possible, particularly if the isolated person is able to use a separate bathroom, a separate bedroom, minimise time in the same room as other family members and wear a mask where this is unavoidable. However, such measures are challenging in overcrowded housing and do not take into account that many cases are asymptomatic so individuals will be unaware that they are sick and potentially transmitting the virus to others.

We found evidence of workplace outbreaks in a care home, an assisted and independent living community, shelters for homeless people, shops, meat and poultry processing factories, a cruise ship, a business conference, a customer call centre and a government ministry; however few of the studies provided enough detail to allow meaningful comparison. Nevertheless, many of the workplace settings where outbreaks have occurred are characterised by close physical contact and prolonged time spent in crowded indoor spaces. Evidence from the study on outbreaks in meat and poultry processing plants (Dyal et al., 2020) also highlights the role health inequalities and inadequate social protection play in relation to people continuing to work whilst ill, overcrowded housing and transportation to and from work and inadequate health and safety communication and training, particularly for non-English speakers and non-literate workers.

We found evidence that community and social settings associated with a higher risk of transmission are again those where people gather in close proximity indoors for prolonged periods. Churches and religious gatherings, sharing meals and bathing facilities, close physical contact and activities such as singing together have all been reported in conjunction with outbreaks. In contrast, there have been fewer reports of transmission in relation to more casual, short term social contact, although this may be because such contacts are subject to recall bias and harder to track and trace. Risks associated with travelling with an affected case are difficult to evaluate – the evidence from these studies was limited and non-specific.

Most of the studies featured in this review were conducted early in the pandemic (January to April 2020 – see figure 3). During these early stages, before transmission was widely disseminated in communities, it was easier to track discrete outbreaks and to identify chains of transmission with a degree of confidence. The period of lockdown which then followed in many countries effectively reduced transmission in most workplace, social and non-residential community settings. At the time of writing (August 2020) many countries have suppressed the virus to the extent that lockdown measures can be relaxed, and economic and social activity can resume, albeit with strict social distancing measures in place. As this happens, we can anticipate the re-emergence of outbreaks in workplace and social settings. There will be new lessons to learn about high-risk activities and environments and it will be important to update the evidence as it emerges over the coming months. There will inevitably be a time lag whilst the scientific evidence emerges, during which news media can provide a useful early warning system. For example, on 2 July 2020, the Guardian newspaper reported on a spike in workplace outbreaks across England as the lockdown eased (Barr, 2020). A later article in the same newspaper reported on numerous outbreaks in food processing factories during the summer months (Mohdin, 2020) and a 30 June article linked a spike in cases in the English city of Leicester, which resulted in the re-imposition of a local lockdown, to garment and food processing factories in the city (Bland & Campbell, 2020). Many of the factors – workers continuing to come to work whilst sick, workplace and residential overcrowding, a disproportionate impact on minority communities and the failure of employers to institute effective physical

distancing – echo the findings of the report into outbreaks in US meat processing plants (Dyal et al., 2020).

Evidence from microbiological and fluid mechanics studies suggest that aerosolised transmission is theoretically possible and epidemiological evidence from a large outbreak linked to a choir practice is compatible with aerosolised transmission across longer distances indoors. However, many questions remain unanswered and there is some conflicting evidence. We still do not know what quantity of live virus is required to present an infection risk or whether live virus is present sufficient quantities in aerosolised particles to present a risk. Although the investigation of the outbreak amongst choir members was consistent with airborne transmission created by aerosolised droplets generated in the act of singing, the absence of any cross-cabin transmission among passengers on the Diamond Princess cruise ship after the quarantine period began and passengers were confined to their cabins supports the hypothesis that transmission was via droplets/fomites and not airborne via air conditioning in this context.

This review has a number of limitations. Although the focus of this study is transmission of SARS-CoV-2 in indoor, non-clinical settings, most of the microbiological and environmental evidence was generated in clinical contexts because this is where most of this type of study have been conducted to date. Clearly such settings are very different from non-clinical, community contexts: for example, there is a higher risk of transmission via aerosol generating procedures (AGP) and greater numbers of individuals infected with SARS-CoV-2, so virus detection in these settings is likely higher than in non-clinical indoor settings. To maximise the transferability and generalisability of these findings to community settings, we attempted to extract and report only on samples taken from areas of hospitals accessible to visitors and the general public; however this was not always possible, as the studies did not provide information on the extent to which AGPs were carried out in patient rooms. Therefore, these results must be treated with caution in applying them to non-clinical settings.

Although we excluded evidence from animal studies in this review, such studies should perhaps be included in future reviews, as they can potentially provide direct experimental evidence on modes of transmission in a way that is impossible from observational human studies. For example, (Richard M, Kok A, & de Meulder D, 2020) conducted an experiment with ferrets to ascertain whether SARS-CoV-2 could be transmitted efficiently through the air. Donor ferrets were inoculated with a high dose of SARS-CoV-2 taken from a human subject. Each donor ferret was then put into a cage with a healthy ferret (“direct contact”). A second healthy ferret (“indirect recipient”) was housed in a second cage, separated from the first by a space of 10 cm. Air flowed from the infected cage to the initially uninfected cage. The researchers found that the virus was transmitted efficiently by direct contact (from the inoculated ferret to the direct contact ferret) and through the air (from the inoculated ferret to the indirect recipient in a separate cage). The patterns of virus shedding and infectivity in all three types of ferret were similar. This study provides evidence that transmission is possible via direct contact or through the air. Because the indirect recipients were only 10 cm distant from the inoculated ferrets, this study cannot distinguish between droplet and aerosolised transmission but it is possible to envisage an extension of this study which could address such a question by extending the distance separating the infected from the recipient ferret such that any observed transmission would have to occur via aerosolisation of the virus.

Our study also has methodological limitations. Title and abstract and full text screening was conducted by only one reviewer, with a second reviewer screening rejected articles only. Thus this may have biased the studies included in the review. Similarly, the data extraction and quality assessment of each article was conducted by one reviewer only. The quality of the available epidemiological evidence was graded as low, so this makes any conclusions uncertain. In particular, there is significant variability in contact tracing approaches across different countries and even

different regions within countries. Contact tracing of rapidly evolving infectious diseases inevitably contains case ascertainment biases, non-homogenous sampling over time and location, and uncontrolled correlation (Kim & Jiang, 2020). There may be publication bias, with large outbreaks potentially more likely to be reported and investigated than household studies. This review draws on evidence from a wide variety of populations and so not all the results will be directly applicable to a given population. Finally, this review was conducted at particular stage of the pandemic and as such is a snapshot in time: social contexts and drivers of behaviour and transmission will likely evolve and change as the pandemic progresses.

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Funding: The UNCOVER network is a Data-Driven Innovation and Wellcome Trust's Institutional Strategic Support Fund (ISSF3) supported project.

Conflicts of interest: No conflicts of interest are declared in relation to this work.

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8.2.3.1 *Appendix 2ci: Search strategies for epidemiology and microbiology studies within UNCOVER Indoor Transmission review*

PUBMED:

- (("Betacoronavirus"[Mesh] OR "Coronavirus Infections"[MH] OR "Spike Glycoprotein, COVID-19 Virus"[NM] OR "COVID-19"[NM] OR "Coronavirus"[MH] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[NM] OR 2019nCoV[ALL] OR Betacoronavirus*[ALL] OR Corona Virus*[ALL] OR Coronavirus*[ALL] OR Coronovirus*[ALL] OR CoV[ALL] OR CoV2[ALL] OR COVID[ALL] OR COVID19[ALL] OR COVID-19[ALL] OR HCoV-19[ALL] OR nCoV[ALL] OR "SARS CoV 2"[ALL] OR SARS2[ALL] OR SARSCoV[ALL] OR SARS-CoV[ALL] OR SARS-CoV-2[ALL] OR Severe Acute Respiratory Syndrome CoV*[ALL]) AND ((2019/11/17[EDAT] : 3000[EDAT]) OR (2019/11/17[PDAT] : 3000[PDAT])))

  AND

  (("Disease Transmission, Infectious"[Mesh] OR "transmission" [Subheading] OR "Infections"[Mesh:NoExp] OR "Carrier State"[Mesh] OR "transmission"[Text Word] OR "transmissibility"[Text Word] OR infecti*[Text Word] OR contagi*[Text Word] OR outbreak*[Text Word] OR spread*[Text Word] OR "carrier*"[Text Word] OR "cluster"[Text Word] OR "clusters"[Text Word] OR "serial interval"[Text Word] OR "cases"[Text Word])

  AND

  "indoor*"[Text Word] OR "public space*"[Text Word] OR "public transport*"[Text Word] OR "closed facilit*"[Text Word] OR "public facilities"[Text Word] OR "shop*"[Text Word] OR "mall*"[Text Word] OR "shopping centre"[Text Word] OR "shopping center"[Text Word] OR "retail park"[Text Word] OR "restaurant*"[Text Word] OR "eatery"[Text Word] OR "eateries"[Text Word] OR "cafe*"[Text Word] OR "canteen"[Text Word] OR "refectory"[Text Word] OR "bar"[Text Word] OR bars OR "pub"[Text Word] OR "pubs"[Text Word] OR "nightclub*"[Text Word] OR "night-club*"[Text Word] OR "cinema*"[Text Word] OR "theatre*"[Text Word] OR "choir*"[Text Word] OR "museums"[Text Word] OR "gym*"[Text Word] OR "leisure centre"[Text Word] OR "leisure center*"[Text Word] OR "sports centre"[Text Word] OR "sports center"[Text Word] OR "workplace"[Text Word] OR "desk"[Text Word] OR "factory"[Text Word] OR "factories"[Text Word] OR "office*"[Text Word] OR "library"[Text Word] OR "libraries"[Text Word] OR "multiple occupancy"[Text Word] OR "residential"[Text Word] OR (("accommodation"[Text Word] OR "residence"[Text Word]) AND ("temporary"[Text Word] OR "student"[Text Word] OR "living"[Text Word] OR "breakfast"[Text Word] OR "hostel"[Text Word] OR "rental"[Text Word])) OR (("housing"[Text Word] OR "flat"[Text Word]) AND ("tower"[Text Word] OR "block"[Text Word])) OR "multiple tenancy"[Text Word] OR "House in multiple occupation"[Text Word] OR "hotel"[Text Word] OR "prison*"[Text Word] OR "shelter"[Text Word] OR "asylum"[Text Word] OR "refugee camp"[Text Word] OR "care home"[Text Word] OR "residential home"[Text Word] OR "nursing home"[Text Word] OR "washroom"[Text Word] OR "light switch*"[Text Word] OR "door"[Text Word] OR "door handle"[Text Word] OR "toilet"[Text Word] OR "bathroom"[Text Word] OR "sink"[Text Word] OR "tap"[Text Word] OR "elevator"[Text Word] OR "lift"[Text Word] OR "escalator"[Text Word] OR "railing"[Text Word] OR "plastic"[Text Word] OR "glass"[Text Word] OR "metal"[Text Word] OR "surface"[Text Word] OR "public transport"[Text Word] OR "transport*"[Text Word] OR

"car"[Text Word] OR "bus"[Text Word] OR "plane"[Text Word] OR "aeroplane*"[Text Word] OR "airplane*"[Text Word] OR "airport*"[Text Word] OR "ship"[Text Word] OR "boat*"[Text Word] OR "cruise*"[Text Word] OR "taxi*"[Text Word] OR "train"[Text Word] OR "trains"[Text Word] OR "station"[Text Word] OR "subway"[Text Word] OR ("tube"[Text Word] AND "underground"[Text Word]) OR "church"[Text Word] OR "mosque"[Text Word] OR "synagogue"[Text Word] OR "chapel"[Text Word] OR "temple"[Text Word] OR "religious gather*"[Text Word] OR "clinic"[Text Word] OR ("hospital"[Text Word] AND ("ward"[Text Word] OR "room"[Text Word]))

Retrieved 875 results on 20200520.

MedRxiv via https://mcguinlu.shinyapps.io/medrxivr/:

Topic sets below combined internally with OR and between sets with AND

- *Covid terms:*
  COVID-19
  [Cc]oronavirus
  SARS-CoV-2
  2019-nCoV

  AND

  Transmission terms:
  [Cc]ontagi
  [Oo]utbreak
  \\b [Ss]pread
  [Tt]ransmiss
  [Ii]nfect
  [Cc]luster
  [Vv]iral load
  [Cc]arrier
  [Cc]ase
  [Ss]hedding

  AND

  Location terms:
  [Ii]ndoor
  [Ii]nside
  [Ff]acilit
  [Pp]ublic transport
  [Rr]estaurant
  [Ww]orkplace
  [Pp]rison
  [Ss]helter
  [Cc]amp
  [Tt]oilet
  [Bb]athroom
  [Aa]irport

[Aa]irplane
[Cc]ruise
[Rr]eligious
[Oo]bjects
[Dd]oorknob
[Hh]ousehold

Date range from 20191117 - 17th November 2019

Retrieved 82 results on 20200521.

8.2.3.2 Appendix 2cii: Data extraction form for epidemiological "cluster" studies within the Indoor Transmission review

Review	
Which study question does this article address? *(1-10)*	
Study design	
Methods	
Date	
Country/geographic information	
Indoor context *(e.g. household, restaurant, workplace)*	
Case/contact definitions *(a-/pre-/symptomatic, close contacts etc.)*	
Outcome measure *(COVID-19 test type)*	
Description of index case *(if known)*	
Total number of cases/contacts *(stratify on symptom status if possible; e.g. asymptomatic, presymptomatic, symptomatic)*	
Number of secondary cases/contacts	
Number of tertiary cases/contacts *(if known)*	
Surveillance monitoring of cases/contacts *(e.g. quarantine period, contact tracing details)*	
Was there a follow-up test 7 days after first test?	
Demographics of cluster *(age, sex, ethnicity; Yes - specify/No - state)*	
Results of interest	

Author's conclusions	
Strengths of study	
Limitations of study	
QA score	

8.3 Appendix 3

8.3.1 Appendix 3a: Search strategy for systematic literature search on asymptomatic transmission

PUBMED:

Credit: COVID-19 Search string (Shokraneh, 2020)

- (("Betacoronavirus"[Mesh] OR "Coronavirus Infections"[MH] OR "Spike Glycoprotein, COVID-19 Virus"[NM] OR "COVID-19"[NM] OR "Coronavirus"[MH] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[NM] OR "2019nCoV"[ALL] OR "Betacoronavirus*"[ALL] OR "Corona Virus*"[ALL] OR "Coronavirus*"[ALL] OR "Coronovirus*"[ALL] OR "CoV"[ALL] OR "CoV2"[ALL] OR "COVID"[ALL] OR "COVID19"[ALL] OR "COVID-19"[ALL] OR "HCoV-19"[ALL] OR "nCoV"[ALL] OR "SARS CoV 2"[ALL] OR "SARS2"[ALL] OR "SARSCoV"[ALL] OR "SARS-CoV"[ALL] OR "SARS-CoV-2"[ALL] OR "Severe Acute Respiratory Syndrome CoV*"[ALL]) AND ((2019/11/17[EDAT] : 3000[EDAT]) OR (2019/11/17[PDAT] : 3000[PDAT])))

  AND

  ("asymptomatic"[Text Word] OR "presymptomatic"[Text Word] OR "pre-symptomatic"[Text Word] OR "paucisymptomatic"[Text Word] OR "pauci-symptomatic"[Text Word] OR "clinically silent"[Text Word] OR "subclinical"[Text Word] OR ("mild"[Text Word] AND "cases"[Text Word]) OR ("Symptom*"[Text Word] AND ("nonspecific"[Text Word] OR "developed"[Text Word] OR "onset"[Text Word])) OR "Asymptomatic Infections"[Mesh])

  AND

  ("Disease Transmission, Infectious"[Mesh] OR "transmission" [Subheading] OR "Infections"[Mesh:NoExp] OR "Carrier State"[Mesh] OR "transmission"[Text Word] OR "transmissibility"[Text Word] OR "infection*"[Text Word] OR "carrier*"[Text Word] OR "cluster"[Text Word] OR "clusters"[Text Word] OR "serial interval"[Text Word] OR "cases"[Text Word])

  AND

  ("review"[TIAB] OR "rapid review"[TIAB] OR "systematic review"[TIAB])

Retrieved 277 articles after duplicates were removed. 10-07-2020

MedRxiv via https://mcguinlu.shinyapps.io/medrxivr/:

Topic clusters below combined internally with **OR** and between clusters with **AND**

- *Covid cluster*
  COVID-19
  [Cc]oronavirus
  SARS-CoV-2
  2019-nCoV

AND

Population cluster
[Aa]symptomatic
[Pp]resymptomatic
[Pp]re-symptomatic
[Ss]ubclinical
[Ss]ymptom onset
[Pp]aucisymptomatic
[Pp]auci-symptomatic

AND

Study type
[Rr]eview

20191117 - 20200710

Retrieved 39 articles after duplicates were removed. 10-07-2020

WHO COVID-19:

- (tw:((tw: asymptomatic OR presymptomatic OR pre-symptomatic OR subclinical or paucisymptomatic OR "symptom onset" OR "clinically silent" OR ("mild" AND "cases") OR ("symptoms" AND ("nonspecific" OR "developed" or “onset”))))) AND (ti:((ti: review OR "rapid review" OR "systematic review”)))
  Language: English

Retrieved 85 articles after duplicates were removed. 10-07-2020

8.3.2 Appendix 3b: Assessing the quality of studies – CASP

Systematic reviews

Beale et al (2020) - A Rapid Review of the Asymptomatic Proportion of PCR-Confirmed SARS-CoV-2 Infections in Community Setting

1. Did the review address a clearly focused question?	Yes	
2. Did the authors look for the right type of papers?	Yes	Ovid - Medline and EMBASE for peer-reviewed articles, and BioRxiv and MedRxiv for pre-prints
3. Do you think all the important, relevant studies were included?	No	Testing type restricted to PCR only. Unclear if presymptomatic included in search terms.

4. Did the review authors do enough to assess study quality?	Yes	Joanna Briggs' tool for prevalence studies.
5. If the results were combined, was it reasonable to do so?	Yes	
6. What are the overall results of the review?	The asymptomatic proportion of SARS-CoV-2 infections is relatively low when estimated from methodologically-appropriate studies. Further investigation into the degree and duration of infectiousness for asymptomatic infections is warranted	
7. How precise are the results?	Not precise 11% (95% CI 4%-18%)	
8. Can the results be applied to the local population?	Yes	No populations excluded. Demographics limited across studies, age & sex but not always, no ethnicity.
9. Were all important outcomes considered?	Yes	
10. Grade	Low	

Systematic reviews

Buitrago-Garcia et al (2020) - Asymptomatic SARS-CoV-2 infections: a living systematic review and meta-analysis

1. Did the review address a clearly focused question?	Yes	
2. Did the authors look for the right type of papers?	Yes	PubMed, Embase, BioRxiv and MedRxiv
3. Do you think all the important, relevant studies were included?	Yes	
4. Did the review authors do enough to assess study quality?	Yes	Adapted Joanna Briggs' tool.
5. If the results were combined, was it reasonable to do so?	Yes	
6. What are the overall results of the review?	The overall estimate of the proportion of people who become infected with SARS-CoV-2 and remain asymptomatic throughout infection was 20% (95% CI 17-25) with a prediction interval of 3-67% in 79 studies that addressed this review question.	

7. How precise are the results?	Not precise, wide confidence interval (95% CI 17-25) with a prediction interval of 3-67%.	
8. Can the results be applied to the local population?	Yes	Demographics: sex and age, no ethnicity.
9. Were all important outcomes considered?	Yes	
10. Grade	Moderate	

Systematic reviews

Byambasuren et al (2020) - Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: systematic review and meta-analysis

1. Did the review address a clearly focused question?	Yes	
2. Did the authors look for the right type of papers?	Yes	PubMed, Embase, Cochrane COVID-19 trials, and Europe PMC (which covers pre-print platforms such as MedRxiv)
3. Do you think all the important, relevant studies were included?	Yes	
4. Did the review authors do enough to assess study quality?	Yes	Combination of risk of bias tools for prevalence studies and diagnostic accuracy and adapted the key signalling questions on sampling frame, ascertainment of infectious disease status, acceptability of methods to identify denominators, case definition of asymptomatic for the numerator, and length of follow up.
5. If the results were combined, was it reasonable to do so?	Yes	
6. What are the overall results of the review?	Our estimates of the prevalence of asymptomatic COVID-19 cases and asymptomatic transmission rates are lower than many highly publicized studies, but still sufficient to warrant policy attention	
7. How precise are the results?	Not precise, the proportion of asymptomatic cases was 15% (95% CI: 12% - 18%) overall.	
8. Can the results be applied to the local population?	Yes	Demographics: age, no ethnicity.
9. Were all important outcomes considered?	Yes	

10. Grade	Moderate	

Systematic reviews

Walsh et al (2020) - SARS-CoV-2 detection, viral load and infectivity over the course of an infection

1. Did the review address a clearly focused question?	Yes	
2. Did the authors look for the right type of papers?	Yes	PubMed, Europe PubMed Central and EMBASE
3. Do you think all the important, relevant studies were included?	Yes	
4. Did the review authors do enough to assess study quality?	Yes	Cochrane Risk of Bias tool for RCTs, Risk Of Bias In Non randomised studies of intervention tool (ROBINS-I), and where no universally accepted quality appraisal tool existed (e.g. case series, modelling studies) a de-novo tool, adapted from related tools, was used (no details reported).
5. If the results were combined, was it reasonable to do so?	Yes	
6. What are the overall results of the review?	There is a relatively consistent trajectory of SARS-CoV-2 viral load over the course of COVID- 19 from respiratory tract samples, however the duration of infectivity remains uncertain.	
7. How precise are the results?	Unclear. No statistical significance. Very small sample size. 7 studies out of 113 included measured viral load of asymptomatic.	
8. Can the results be applied to the local population?	Yes	Limited demographic reporting, population: adult/children, no ethnicity.
9. Were all important outcomes considered?	Yes	
10. Grade	Moderate	