

SENATE SELECT COMMITTEE ON COVID-19
Australian Government's response to the COVID-19 pandemic
THURSDAY, 25 JUNE 2020

Raina MacIntyre

I would like to add a supplementary statement to Dr Collignon's statement where he refers to me by name *"As to Raina's data, my understanding is that N95 masks, for the vast majority of people, have no benefit over surgical masks but are better than cloth masks. Surgical masks seem to me to be the thing you need to have large numbers of, but obviously you do need N95s for certain people as well. But we need an appropriate stockpile that's looked after adequately."*

I am not certain to what Dr Collignon is referring. To state that N95 respirators are no better than surgical masks "but better than cloth masks" is not aligned with the available scientific evidence. I wish to clarify this, as his use of my name may mislead others to believe I am in agreement with his opinion.

I have published the largest body of randomised clinical trials of masks and respirators in the world, and two large health worker trials which I published show that respirators protect but surgical masks do not. I have attached a systematic review I published in 2020 summarising that and other evidence, as well as the misconstrued argument that surgical masks and respirators are equivalent.

In addition, the WHO-commissioned study by Chu et al in the Lancet (attached) shows that respirators provide 96% protection and surgical masks, 67%. My commentary in the Lancet is also attached, which discusses implications for health workers. I also cite in this commentary the clear evidence that SARS-CoV-2 is aerosol transmitted. The continued denial of this evidence places our health workers at risk. The guidelines should recommend a respirator for health workers caring for COVID-19 patients. A surgical mask is not adequate and places Australian health workers at risk of infection. We should employ the precautionary principle in protecting them.

Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis

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Summary

Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 and is spread person-to-person through close contact. We aimed to investigate the effects of physical distance, face masks, and eye protection on virus transmission in health-care and non-health-care (eg, community) settings.

Methods We did a systematic review and meta-analysis to investigate the optimum distance for avoiding person-to-person virus transmission and to assess the use of face masks and eye protection to prevent transmission of viruses. We obtained data for SARS-CoV-2 and the betacoronaviruses that cause severe acute respiratory syndrome, and Middle East respiratory syndrome from 21 standard WHO-specific and COVID-19-specific sources. We searched these data sources from database inception to May 3, 2020, with no restriction by language, for comparative studies and for contextual factors of acceptability, feasibility, resource use, and equity. We screened records, extracted data, and assessed risk of bias in duplicate. We did frequentist and Bayesian meta-analyses and random-effects meta-regressions. We rated the certainty of evidence according to Cochrane methods and the GRADE approach. This study is registered with PROSPERO, CRD42020177047.

Findings Our search identified 172 observational studies across 16 countries and six continents, with no randomised controlled trials and 44 relevant comparative studies in health-care and non-health-care settings (n=25 697 patients). Transmission of viruses was lower with physical distancing of 1 m or more, compared with a distance of less than 1 m (n=10736, pooled adjusted odds ratio [aOR] 0.18, 95% CI 0.09 to 0.38; risk difference [RD] -10.2%, 95% CI -11.5 to -7.5; moderate certainty); protection was increased as distance was lengthened (change in relative risk [RR] 2.02 per m; $p_{\text{interaction}}=0.041$; moderate certainty). Face mask use could result in a large reduction in risk of infection (n=2647; aOR 0.15, 95% CI 0.07 to 0.34, RD -14.3%, -15.9 to -10.7; low certainty), with stronger associations with N95 or similar respirators compared with disposable surgical masks or similar (eg, reusable 12–16-layer cotton masks; $p_{\text{interaction}}=0.090$; posterior probability >95%, low certainty). Eye protection also was associated with less infection (n=3713; aOR 0.22, 95% CI 0.12 to 0.39, RD -10.6%, 95% CI -12.5 to -7.7; low certainty). Unadjusted studies and subgroup and sensitivity analyses showed similar findings.

Interpretation The findings of this systematic review and meta-analysis support physical distancing of 1 m or more and provide quantitative estimates for models and contact tracing to inform policy. Optimum use of face masks, respirators, and eye protection in public and health-care settings should be informed by these findings and contextual factors. Robust randomised trials are needed to better inform the evidence for these interventions, but this systematic appraisal of currently best available evidence might inform interim guidance.

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Introduction

As of May 28, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 5.85 million individuals worldwide and caused more than 359 000 deaths.¹ Emergency lockdowns have been initiated in countries across the globe, and the effect on health, wellbeing, business, and other aspects of daily life are felt

throughout societies and by individuals. With no effective pharmacological interventions or vaccine available in the imminent future, reducing the rate of infection (ie, flattening the curve) is a priority, and prevention of infection is the best approach to achieve this aim.

SARS-CoV-2 spreads person-to-person through close contact and causes COVID-19. It has not been solved if

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See Online for appendix

Research in context

Evidence before this study

We searched 21 databases and resources from inception to May 3, 2020, with no restriction by language, for studies of any design evaluating physical distancing, face masks, and eye protection to prevent transmission of the viruses that cause COVID-19 and related diseases (eg, severe acute respiratory syndrome [SARS] and Middle East respiratory syndrome [MERS]) between infected individuals and people close to them (eg, household members, caregivers, and health-care workers). Previous related meta-analyses have focused on randomised trials and reported imprecise data for common respiratory viruses such as seasonal influenza, rather than the pandemic and epidemic betacoronaviruses causative of COVID-19 (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), SARS (SARS-CoV), or MERS (MERS-CoV). Other meta-analyses have focused on interventions in the health-care setting and have not included non-health-care (eg, community) settings. Our search did not retrieve any systematic review of information on physical distancing, face masks, or eye protection to prevent transmission of SARS-CoV-2, SARS-CoV, and MERS-CoV.

Added value of this study

We did a systematic review of 172 observational studies in health-care and non-health-care settings across 16 countries and six continents; 44 comparative studies were included in a meta-analysis, including 25 697 patients with COVID-19, SARS, or MERS. Our findings are, to the best of our knowledge, the first to rapidly synthesise all direct information on COVID-19 and, therefore, provide the best available evidence to inform optimum use of three common and simple interventions to help reduce the rate of infection and inform non-pharmaceutical interventions, including pandemic mitigation in non-health-care settings. Physical distancing of 1 m or more was associated with a much lower risk of infection, as was use of face masks (including N95 respirators or similar and surgical or similar masks [eg, 12–16-layer cotton or gauze masks]) and eye protection (eg, goggles or face shields). Added benefits are likely with even larger physical distances (eg, 2 m or more based on modelling) and might be present with N95 or similar respirators versus medical masks or similar. Across 24 studies in health-care and non-health-care settings of contextual factors to consider when formulating recommendations, most stakeholders found these

personal protection strategies acceptable, feasible, and reassuring but noted harms and contextual challenges, including frequent discomfort and facial skin breakdown, high resource use linked with the potential to decrease equity, increased difficulty communicating clearly, and perceived reduced empathy of care providers by those they were caring for.

Implications of all the available evidence

In view of inconsistent guidelines by various organisations based on limited information, our findings provide some clarification and have implications for multiple stakeholders. The risk for infection is highly dependent on distance to the individual infected and the type of face mask and eye protection worn. From a policy and public health perspective, current policies of at least 1 m physical distancing seem to be strongly associated with a large protective effect, and distances of 2 m could be more effective. These data could also facilitate harmonisation of the definition of exposed (eg, within 2 m), which has implications for contact tracing. The quantitative estimates provided here should inform disease-modelling studies, which are important for planning pandemic response efforts. Policy makers around the world should strive to promptly and adequately address equity implications for groups with currently limited access to face masks and eye protection. For health-care workers and administrators, our findings suggest that N95 respirators might be more strongly associated with protection from viral transmission than surgical masks. Both N95 and surgical masks have a stronger association with protection compared with single-layer masks. Eye protection might also add substantial protection. For the general public, evidence shows that physical distancing of more than 1 m is highly effective and that face masks are associated with protection, even in non-health-care settings, with either disposable surgical masks or reusable 12–16-layer cotton ones, although much of this evidence was on mask use within households and among contacts of cases. Eye protection is typically underconsidered and can be effective in community settings. However, no intervention, even when properly used, was associated with complete protection from infection. Other basic measures (eg, hand hygiene) are still needed in addition to physical distancing and use of face masks and eye protection.

SARS-CoV-2 might spread through aerosols from respiratory droplets; so far, air sampling has found virus RNA in some studies^{2–4} but not in others.^{5–8} However, finding RNA virus is not necessarily indicative of replication-competent and infection-competent (viable) virus that could be transmissible. The distance from a patient that the virus is infective, and the optimum person-to-person physical distance, is uncertain. For the currently foreseeable future (ie, until a safe and effective vaccine or treatment becomes available), COVID-19 prevention will continue to rely on non-pharmaceutical interventions, including pandemic mitigation in community settings.⁹

Thus, quantitative assessment of physical distancing is relevant to inform safe interaction and care of patients with SARS-CoV-2 in both health-care and non-health-care settings. The definition of close contact or potentially exposed helps to risk stratify, contact trace, and develop guidance documents, but these definitions differ around the globe.

To contain widespread infection and to reduce morbidity and mortality among health-care workers and others in contact with potentially infected people, jurisdictions have issued conflicting advice about physical or social distancing. Use of face masks with or

without eye protection to achieve additional protection is debated in the mainstream media and by public health authorities, in particular the use of face masks for the general population;¹⁰ moreover, optimum use of face masks in health-care settings, which have been used for decades for infection prevention, is facing challenges amid personal protective equipment (PPE) shortages.¹¹

Any recommendations about social or physical distancing, and the use of face masks, should be based on the best available evidence. Evidence has been reviewed for other respiratory viral infections, mainly seasonal influenza,^{12,13} but no comprehensive review is available of information on SARS-CoV-2 or related betacoronaviruses that have caused epidemics, such as severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS). We, therefore, systematically reviewed the effect of physical distance, face masks, and eye protection on transmission of SARS-CoV-2, SARS-CoV, and MERS-CoV.

Methods

Search strategy and selection criteria

To inform WHO guidance documents, on March 25, 2020, we did a rapid systematic review.¹⁴ We created a large international collaborative and we used Cochrane methods¹⁵ and the GRADE approach.¹⁶ We prospectively submitted the systematic review protocol for registration on PROSPERO (CRD42020177047; appendix pp 23–29). We have followed PRISMA¹⁷ and MOOSE¹⁸ reporting guidelines (appendix pp 30–33).

From database inception to May 3, 2020, we searched for studies of any design and in any setting that included patients with WHO-defined confirmed or probable COVID-19, SARS, or MERS, and people in close contact with them, comparing distances between people and COVID-19 infected patients of 1 m or larger with smaller distances, with or without a face mask on the patient, or with or without a face mask, eye protection, or both on the exposed individual. The aim of our systematic review was for quantitative assessment to ascertain the physical distance associated with reduced risk of acquiring infection when caring for an individual infected with SARS-CoV-2, SARS-CoV, or MERS-CoV. Our definition of face masks included surgical masks and N95 respirators, among others; eye protection included visors, faceshields, and goggles, among others.

We searched (up to March 26, 2020) MEDLINE (using the Ovid platform), PubMed, Embase, CINAHL (using the Ovid platform), the Cochrane Library, COVID-19 Open Research Dataset Challenge, COVID-19 Research Database (WHO), Epistemonikos (for relevant systematic reviews addressing MERS and SARS, and its COVID-19 Living Overview of the Evidence platform), EPPI Centre living systematic map of the evidence, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, relevant documents on the websites of governmental and other relevant organisations, reference lists of included

papers, and relevant systematic reviews.^{19,20} We hand-searched (up to May 3, 2020) preprint servers (bioRxiv, medRxiv, and Social Science Research Network First Look) and coronavirus resource centres of *The Lancet*, *JAMA*, and *N Engl J Med* (appendix pp 3–5). We did not limit our search by language. We initially could not obtain three full texts for evaluation, but we obtained them through interlibrary loan or contacting a study author. We did not restrict our search to any quantitative cutoff for distance.

Data collection

We screened titles and abstracts, reviewed full texts, extracted data, and assessed risk of bias by two authors and independently, using standardised prepiloted forms (Covidence; Veritas Health Innovation, Melbourne, VIC, Australia), and we cross-checked screening results using artificial intelligence (Evidence Prime, Hamilton, ON, Canada). We resolved disagreements by consensus. We extracted data for study identifier, study design, setting, population characteristics, intervention and comparator characteristics, quantitative outcomes, source of funding

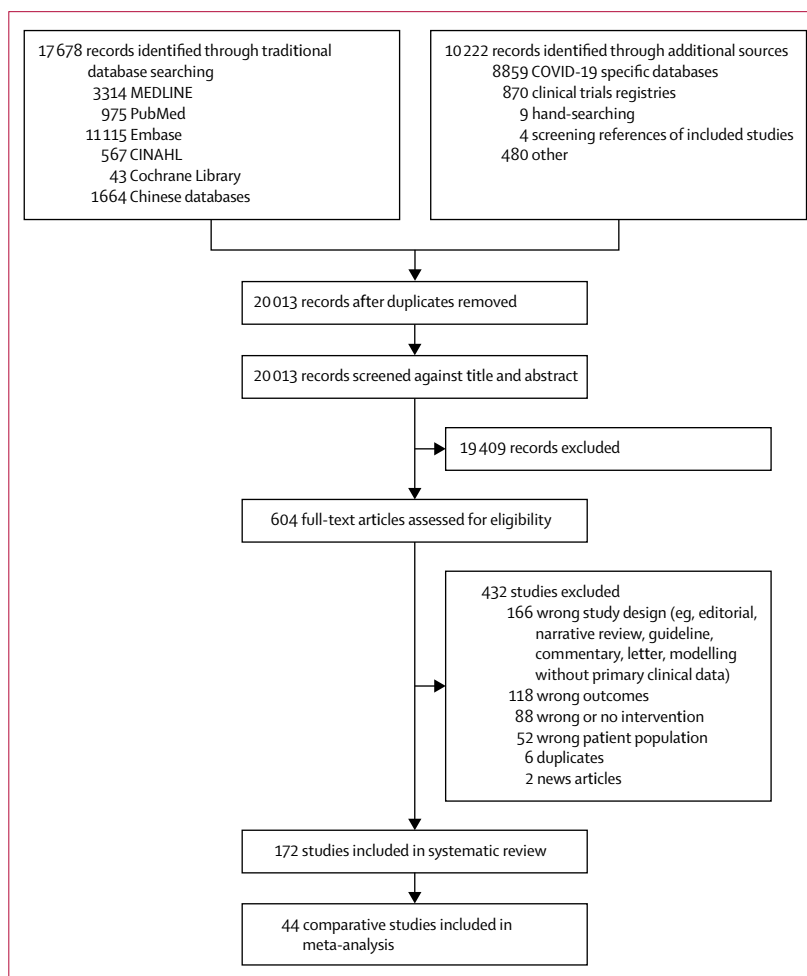


Figure 1: Study selection

	Population size (n)	Country	Setting	Disease caused by virus	Case definition (WHO)	Adjusted estimates	Risk of bias*
Alraddadi et al (2016) ³⁴	283	Saudi Arabia	Health care	MERS	Confirmed	Yes	*****
Arwady et al (2016) ³⁵	79	Saudi Arabia	Non-health care (household and family contacts)	MERS	Confirmed	No	*****
Bai et al (2020) ³⁶	118	China	Health care	COVID-19	Confirmed	No	*****
Burke et al (2020) ³⁷	338	USA	Health care and non-health care (including household and community)	COVID-19	Confirmed	No	****
Caputo et al (2006) ³⁸	33	Canada	Health care	SARS	Confirmed	No	*****
Chen et al (2009) ³⁹	758	China	Health care	SARS	Confirmed	Yes	*****
Cheng et al (2020) ⁴⁰	226	China	Non-health care (household and family contacts)	COVID-19	Confirmed	No	*****
Ha et al (2004) ⁴¹	117	Vietnam	Health care	SARS	Confirmed	No	**
Hall et al (2014) ⁴²	48	Saudi Arabia	Health care	MERS	Confirmed	No	***
Heinzerling et al (2020) ⁴⁴	37	USA	Health care	COVID-19	Confirmed	No	****
Ho et al (2004) ⁴⁵	372	Taiwan	Health care	SARS	Confirmed	No	*****
Ki et al (2019) ⁴⁷	446	South Korea	Health care	MERS	Confirmed	No	*****
Kim et al (2016) ⁴⁸	9	South Korea	Health care	MERS	Confirmed	No	*****
Kim et al (2016) ⁴⁹	1169	South Korea	Health care	MERS	Confirmed	No	*****
Lau et al (2004) ⁵⁰	2270	China	Non-health care (households)	SARS	Probable	Yes	*****
Liu et al (2009) ⁵¹	477	China	Health care	SARS	Confirmed	Yes	*****
Liu et al (2020) ⁵²	20	China	Non-health care (close contacts)	COVID-19	Confirmed	No	*****
Loeb et al (2004) ⁵³	43	Canada	Health care	SARS	Confirmed	No	**
Ma et al (2004) ⁵⁴	426	China	Health care	SARS	Confirmed	Yes	*****
Nishiura et al (2005) ⁵⁵	115	Vietnam	Health care	SARS	Confirmed	Yes	*****
Nishiyama et al (2008) ⁵⁶	146	Vietnam	Health care	SARS	Confirmed	Yes	*****
Olsen et al (2003) ⁵⁷	304	China	Non-health care (airplane)	SARS	Confirmed	No	*****
Park et al (2004) ⁵⁸	110	USA	Health care	SARS	Confirmed	No	*****
Park et al (2016) ⁵⁹	80	South Korea	Health care	MERS	Confirmed and probable	No	***
Peck et al (2004) ⁶⁰	26	USA	Health care	SARS	Confirmed	No	*****
Pei et al (2006) ⁶¹	443	China	Health care	SARS	Confirmed	No	*****
Rea et al (2007) ⁶²	8662	Canada	Non-health care (community contacts)	SARS	Probable	No	****
Reuss et al (2014) ⁶³	81	Germany	Health care	MERS	Confirmed	No	*****
Reynolds et al (2006) ⁶⁴	153	Vietnam	Health care	SARS	Confirmed	No	***
Ryu et al (2019) ⁶⁵	34	South Korea	Health care	MERS	Confirmed	No	*****
Scales et al (2003) ⁶⁶	69	Canada	Health care	SARS	Probable	No	**
Seto et al (2003) ⁶⁷	254	China	Health care	SARS	Confirmed	Yes	*****
Teleman et al (2004) ⁶⁸	86	Singapore	Health care	SARS	Confirmed	Yes	*****
Tuan et al (2007) ⁶⁹	212	Vietnam	Non-health care (household and community contacts)	SARS	Confirmed	Yes	*****
Van Kerkhove et al (2019) ⁴⁶	828	Saudi Arabia	Non-health care (dormitory)	MERS	Confirmed	Yes	*****
Wang et al (2020) ⁴³	493	China	Health care	COVID-19	Confirmed	Yes	****

(Table 1 continues on next page)

	n	Country	Setting	Disease caused by virus	Case definition (WHO)	Adjusted estimates	Risk of bias*
(Continued from previous page)							
Wang et al (2020) ²⁰	5442	China	Health care	COVID-19	Confirmed	No	*****
Wiboonchutikul et al (2016) ²¹	38	Thailand	Health care	MERS	Confirmed	No	*****
Wilder-Smith et al (2005) ²²	80	Singapore	Health care	SARS	Confirmed	No	*****
Wong et al (2004) ²³	66	China	Health care	SARS	Confirmed	No	*****
Wu et al (2004) ²⁴	375	China	Non-health care (community)	SARS	Confirmed	Yes	*****
Yin et al (2004) ²⁵	257	China	Health care	SARS	Confirmed	Yes	*****
Yu et al (2005) ²⁶	74	China	Health care	SARS	Confirmed	No	*****
Yu et al (2007) ²⁷	124 wards	China	Health care	SARS	Confirmed	Yes	*****

Across studies, mean age was 30–60 years. SARS—severe acute respiratory syndrome. MERS—Middle East respiratory syndrome. *The Newcastle-Ottawa Scale was used for the risk of bias assessment, with more stars equalling lower risk.

Table 1: Characteristics of included comparative studies

and reported conflicts of interests, ethics approval, study limitations, and other important comments.

Outcomes

Outcomes of interest were risk of transmission (ie, WHO-defined confirmed or probable COVID-19, SARS, or MERS) to people in health-care or non-health-care settings by those infected; hospitalisation; intensive care unit admission; death; time to recovery; adverse effects of interventions; and contextual factors such as acceptability, feasibility, effect on equity, and resource considerations related to the interventions of interest. However, data were only available to analyse intervention effects for transmission and contextual factors. Consistent with WHO, studies generally defined confirmed cases with laboratory confirmation (with or without symptoms) and probable cases with clinical evidence of the respective infection (ie, suspected to be infected) but for whom confirmatory testing either had not yet been done for any reason or was inconclusive.

Data analysis

Our search did not identify any randomised trials of COVID-19, SARS, or MERS. We did a meta-analysis of associations by pooling risk ratios (RRs) or adjusted odds ratios (aORs) depending on availability of these data from observational studies, using DerSimonian and Laird random-effects models. We adjusted for variables including age, sex, and severity of source case; these variables were not the same across studies. Because between-study heterogeneity can be misleadingly large when quantified by I^2 during meta-analysis of observational studies,^{21,22} we used GRADE guidance to assess between-study heterogeneity.²¹ Throughout, we present RRs as unadjusted estimates and aORs as adjusted estimates.

We used the Newcastle-Ottawa scale to rate risk of bias for comparative non-randomised studies corresponding

to every study's design (cohort or case-control).^{23,24} We planned to use the Cochrane Risk of Bias tool 2.0 for randomised trials,²⁵ but our search did not identify any eligible randomised trials. We synthesised data in both narrative and tabular formats. We graded the certainty of evidence using the GRADE approach. We used the GRADEpro app to rate evidence and present it in GRADE evidence profiles and summary of findings tables^{26,27} using standardised terms.^{28,29}

We analysed data for subgroup effects by virus type, intervention (different distances or face mask types), and setting (health care vs non-health care). Among the studies assessing physical distancing measures to prevent viral transmission, the intervention varied (eg, direct physical contact [0 m], 1 m, or 2 m). We, therefore, analysed the effect of distance on the size of the associations by random-effects univariate meta-regressions, using restricted maximum likelihood, and we present mean effects and 95% CIs. We calculated tests for interaction using a minimum of 10 000 Monte Carlo random permutations to avoid spurious findings.³⁰ We formally assessed the credibility of potential effect-modifiers using GRADE guidance.²¹ We did two sensitivity analyses to test the robustness of our findings. First, we used Bayesian meta-analyses to reinterpret the included studies considering priors derived from the effect point estimate and variance from a meta-analysis of ten randomised trials evaluating face mask use versus no face mask use to prevent influenza-like illness in health-care workers.³¹ Second, we used Bayesian meta-analyses to reinterpret the efficacy of N95 respirators versus medical masks on preventing influenza-like illness after seasonal viral (mostly influenza) infection.¹³ For these sensitivity analyses, we used hybrid Metropolis-Hastings and Gibbs sampling, a 10 000 sample burn-in, 40 000 Markov chain Monte Carlo samples, and we tested non-informative and sceptical priors (eg, four time variance)^{32,33} to inform

For more on the GRADEpro app see <https://www.grade-pro.org>

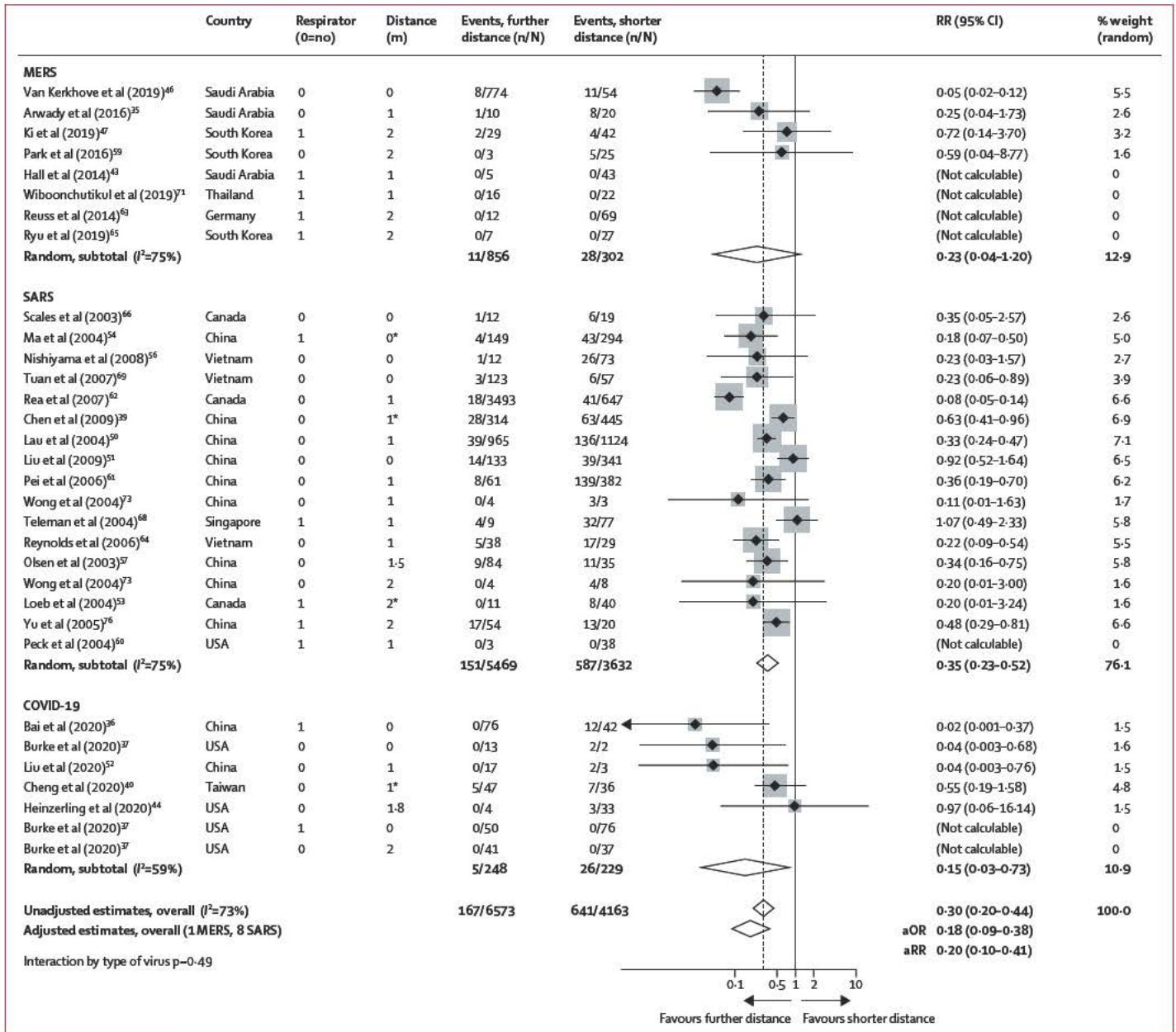


Figure 2: Forest plot showing the association of COVID-19, SARS, or MERS exposure proximity with infection
 SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. aRR=adjusted relative risk. *Estimated values; sensitivity analyses excluding these values did not meaningfully alter findings.

mean estimates of effect, 95% credibility intervals (CrIs), and posterior distributions. We used non-informative hyperpriors to estimate statistical heterogeneity. Model convergence was confirmed in all cases with good mixing in visual inspection of trace plots, autocorrelation plots, histograms, and kernel density estimates in all scenarios. Parameters were blocked, leading to acceptance of approximately 50% and efficiency greater than 1% in all cases (typically about 40%). We did analyses using Stata version 14.3.

Role of the funding source

The funder contributed to defining the scope of the review but otherwise had no role in study design and data collection. Data were interpreted and the report drafted and submitted without funder input, but according to contractual agreement, the funder provided review at the time of final publication. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

	Studies and participants	Relative effect (95% CI)	Anticipated absolute effect (95% CI), eg, chance of viral infection or transmission		Difference (95% CI)	Certainty*	What happens (standardised GRADE terminology) ²⁹
			Comparison group	Intervention group			
Physical distance ≥1 m vs <1 m	Nine adjusted studies (n=7782); 29 unadjusted studies (n=10736)	aOR 0.18 (0.09 to 0.38); unadjusted RR 0.30 (95% CI 0.20 to 0.44)	Shorter distance, 12.8%	Further distance, 2.6% (1.3 to 5.3)	-10.2% (-11.5 to -7.5)	Moderate†	A physical distance of more than 1 m probably results in a large reduction in virus infection; for every 1 m further away in distancing, the relative effect might increase 2.02 times
Face mask vs no face mask	Ten adjusted studies (n=2647); 29 unadjusted studies (n=10170)	aOR 0.15 (0.07 to 0.34); unadjusted RR 0.34 (95% CI 0.26 to 0.45)	No face mask, 17.4%	Face mask, 3.1% (1.5 to 6.7)	-14.3% (-15.9 to -10.7)	Low‡	Medical or surgical face masks might result in a large reduction in virus infection; N95 respirators might be associated with a larger reduction in risk compared with surgical or similar masks§
Eye protection (faceshield, goggles) vs no eye protection	13 unadjusted studies (n=3713)	Unadjusted RR 0.34 (0.22 to 0.52)¶	No eye protection, 16.0%	Eye protection, 5.5% (3.6 to 8.5)	-10.6% (-12.5 to -7.7)	Low	Eye protection might result in a large reduction in virus infection

Table based on GRADE approach.^{26–29} Population comprised people possibly exposed to individuals infected with SARS-CoV-2, SARS-CoV, or MERS-CoV. Setting was any health-care or non-health-care setting. Outcomes were infection (laboratory-confirmed or probable) and contextual factors. Risk (95% CI) in intervention group is based on assumed risk in comparison group and relative effect (95% CI) of the intervention. All studies were non-randomised and evaluated using the Newcastle-Ottawa Scale; some studies had a higher risk of bias than did others but no important difference was noted in sensitivity analyses excluding studies at higher risk of bias; we did not further rate down for risk of bias. Although there was a high *I*² value (which can be exaggerated in non-randomised studies)²⁵ and no overlapping CIs, point estimates generally exceeded the thresholds for large effects and we did not rate down for inconsistency. We did not rate down for indirectness for the association between distance and infection because SARS-CoV-2, SARS-CoV, and MERS-CoV all belong to the same family and have each caused epidemics with sufficient similarity; there was also no convincing statistical evidence of effect-modification across viruses; some studies also used bundled interventions but the studies include only those that provide adjusted estimates. aOR=adjusted odds ratio. RR=relative risk. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SARS-CoV=severe acute respiratory syndrome coronavirus. MERS-CoV=Middle East respiratory syndrome coronavirus. *GRADE category of evidence; high certainty (we are very confident that the true effect lies close to that of the estimate of the effect); moderate certainty (we are moderately confident in the effect estimate; the true effect is probably close to the estimate, but it is possibly substantially different); low certainty (our confidence in the effect estimate is limited; the true effect could be substantially different from the estimate of the effect); very low certainty (we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect). †The effect is very large considering the thresholds set by GRADE, particularly at plausible levels of baseline risk, which also mitigated concerns about risk of bias; data also suggest a dose-response gradient, with associations increasing from smaller distances to 2 m and beyond, by meta-regression; we did not rate up for this domain alone but it further supports the decision to rate up in combination with the large effects. ‡The effect is very large, and the certainty of evidence could be rated up, but we made a conservative decision not to because of some inconsistency and risk of bias; hence, although the effect is qualitatively highly certain, the precise quantitative effect is low certainty. §In a subgroup analysis comparing N95 respirators with surgical or similar masks (eg, 12–16-layer cotton), the association was more pronounced in the N95 group (aOR 0.04, 95% CI 0.004–0.30) compared with other masks (0.33, 0.17–0.61; *p*_{interaction}=0.090); there was also support for effect-modification by formal analysis of subgroup credibility. ¶Two studies^{24,75} provided adjusted estimates with *n*=295 in the eye protection group and *n*=406 in the group not wearing eye protection; results were similar to the unadjusted estimate (aOR 0.22, 95% CI 0.12–0.39). ||The effect is large considering the thresholds set by GRADE assuming that ORs translate into similar magnitudes of RR estimates; this mitigates concerns about risk of bias, but we conservatively decided not to rate up for large or very large effects.

Table 2: GRADE summary of findings

Results

We identified 172 studies for our systematic review from 16 countries across six continents (figure 1; appendix pp 6–14, 41–47). Studies were all observational in nature; no randomised trials were identified of any interventions that directly addressed the included study populations. Of the 172 studies, 66 focused on how far a virus can travel by comparing the association of different distances on virus transmission to people (appendix pp 42–44). Of these 66 studies, five were mechanistic, assessing viral RNA, virions, or both cultured from the environment of an infected patient (appendix p 45).

44 studies were comparative^{34–77} and fulfilled criteria for our meta-analysis (*n*=25697; figure 1; table 1). We used these studies rather than case series and qualitative studies (appendix pp 41–47) to inform estimates of effect. 30 studies^{34,37,41–45,47–51,53–56,58–61,64–70,72,74,75} focused on the association between use of various types of face masks and respirators by health-care workers, patients, or both with virus transmission. 13 studies^{34,37–39,47,49,51,54,58,60,61,65,75} addressed the association of eye protection with virus transmission.

Some direct evidence was available for COVID-19 (64 studies, of which seven were comparative in

design),^{36,37,40,41,44,52,70} but most studies reported on SARS (*n*=55) or MERS (*n*=25; appendix pp 6–12). Of the 44 comparative studies, 40 included WHO-defined confirmed cases, one included both confirmed and probable cases, and the remaining three studies included probable cases. There was no effect-modification by case-definition (distance *p*_{interaction}=0.41; mask *p*_{interaction}=0.46; all cases for eye protection were confirmed). Most studies reported on bundled interventions, including different components of PPE and distancing, which was usually addressed by statistical adjustment. The included studies all occurred during recurrent or novel outbreak settings of COVID-19, SARS, or MERS.

Risk of bias was generally low-to-moderate after considering the observational designs (table 1), but both within studies and across studies the overall findings were similar between adjusted and unadjusted estimates. We did not detect strong evidence of publication bias in the body of evidence for any intervention (appendix pp 15–18). As we did not use case series data to inform estimates of effect of each intervention, we did not systematically rate risk of bias of these data. Therefore, we report further only those studies with comparative data.

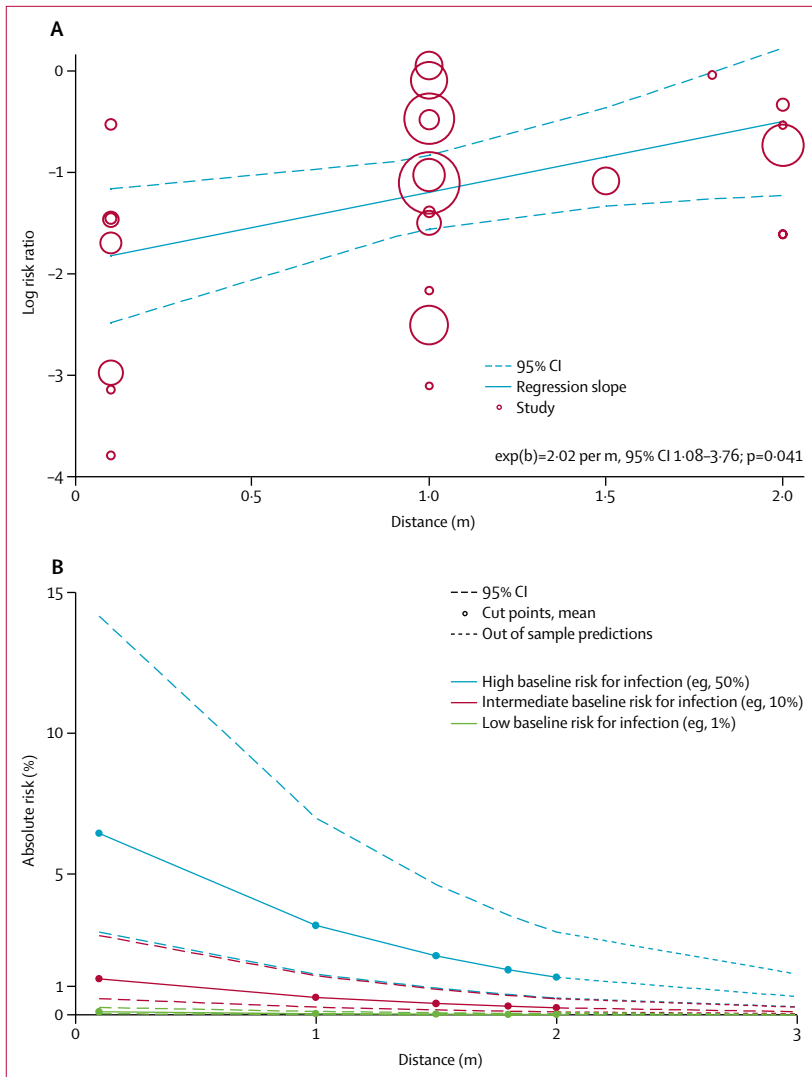


Figure 3: Change in relative risk with increasing distance and absolute risk with increasing distance
 Meta-regression of change in relative risk with increasing distance from an infected individual (A). Absolute risk of transmission from an individual infected with SARS-CoV-2, SARS-CoV, or MERS-CoV with varying baseline risk and increasing distance (B). SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. SARS-CoV=severe acute respiratory syndrome coronavirus. MERS-CoV=Middle East respiratory syndrome coronavirus.

Across 29 unadjusted and nine adjusted studies,^{35-37,39,40,43,44,46,47,50-54,56,57,59-66,68,69,71,73,76} a strong association was found of proximity of the exposed individual with the risk of infection (unadjusted n=10736, RR 0.30, 95% CI 0.20 to 0.44; adjusted n=7782, aOR 0.18, 95% CI 0.09 to 0.38; absolute risk [AR] 12.8% with shorter distance vs 2.6% with further distance, risk difference [RD] -10.2%, 95% CI -11.5 to -7.5; moderate certainty; figure 2; table 2; appendix p 16). Although there were six studies on COVID-19, the association was seen irrespective of causative virus ($p_{\text{interaction}}=0.49$), health-care setting versus non-health-care setting ($p_{\text{interaction}}=0.14$), and by type of face mask ($p_{\text{interaction}}=0.95$; appendix pp 17, 19). However, different studies used different distances for the intervention. By meta-regression, the strength of

association was larger with increasing distance (2.02 change in RR per m, 95% CI 1.08 to 3.76; $p_{\text{interaction}}=0.041$; moderate credibility subgroup effect; figure 3A; table 2). AR values with increasing distance given different degrees of baseline risk are shown in figure 3B, with potential values at 3 m also shown.

Across 29 unadjusted studies and ten adjusted studies,^{34,37,41-45,47-51,53-56,58-61,64-70,72,74,75} the use of both N95 or similar respirators or face masks (eg, disposable surgical masks or similar reusable 12–16-layer cotton masks) by those exposed to infected individuals was associated with a large reduction in risk of infection (unadjusted n=10170, RR 0.34, 95% CI 0.26 to 0.45; adjusted studies n=2647, aOR 0.15, 95% CI 0.07 to 0.34; AR 3.1% with face mask vs 17.4% with no face mask, RD -14.3%, 95% CI -15.9 to -10.7; low certainty; figure 4; table 2; appendix pp 16, 18) with stronger associations in health-care settings (RR 0.30, 95% CI 0.22 to 0.41) compared with non-health-care settings (RR 0.56, 95% CI 0.40 to 0.79; $p_{\text{interaction}}=0.049$; low-to-moderate credibility for subgroup effect; figure 4; appendix p 19). When differential N95 or similar respirator use, which was more frequent in health-care settings than in non-health-care settings, was adjusted for the possibility that face masks were less effective in non-health-care settings, the subgroup effect was slightly less credible ($p_{\text{interaction}}=0.11$, adjusted for differential respirator use; figure 4). Indeed, the association with protection from infection was more pronounced with N95 or similar respirators (aOR 0.04, 95% CI 0.004 to 0.30) compared with other masks (aOR 0.33, 95% CI 0.17 to 0.61; $p_{\text{interaction}}=0.090$; moderate credibility subgroup effect; figure 5). The interaction was also seen when additionally adjusting for three studies that clearly reported aerosol-generating procedures ($p_{\text{interaction}}=0.048$; figure 5). Supportive evidence for this interaction was also seen in within-study comparisons (eg, N95 had a stronger protective association compared with surgical masks or 12–16-layer cotton masks); both N95 and surgical masks also had a stronger association with protection versus single-layer masks.^{38,39,51,53,54,61,66,67,75}

We did a sensitivity analysis to test the robustness of our findings and to integrate all available information on face mask treatment effects for protection from COVID-19. We reconsidered our findings using random-effects Bayesian meta-analysis. Although non-informative priors showed similar results to frequentist approaches (aOR 0.16, 95% CrI 0.04–0.40), even using informative priors from the most recent meta-analysis on the effectiveness of masks versus no masks to prevent influenza-like illness (RR 0.93, 95% CI 0.83–1.05)³¹ yielded a significant association with protection from COVID-19 (aOR 0.40, 95% CrI 0.16–0.97; posterior probability for RR <1, 98%). Minimally informing (25% influence with or without four-fold smaller mean effect size) the most recent and rigorous meta-analysis of the effectiveness of N95

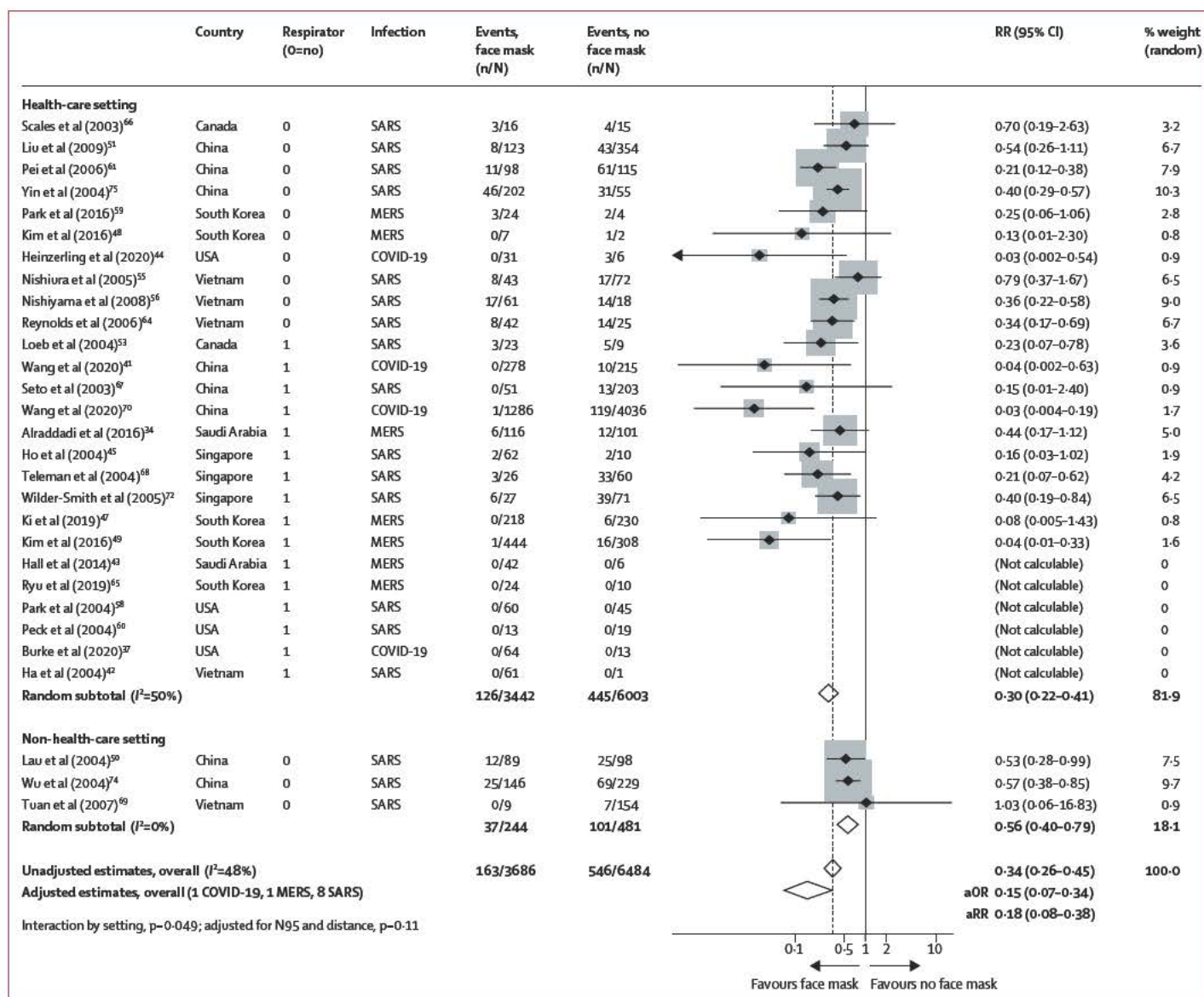


Figure 4: Forest plot showing unadjusted estimates for the association of face mask use with viral infection causing COVID-19, SARS, or MERS. SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. aRR=adjusted relative risk.

respirators versus medical masks in randomised trials (OR 0.76, 95% CI 0.54–1.06)¹³ with the effect-modification seen in this meta-analysis on COVID-19 (ratio of aORs 0.14, 95% CI 0.02–1.05) continued to support a stronger association of protection from COVID-19, SARS, or MERS with N95 or similar respirators versus other face masks (posterior probability for RR <1, 100% and 95%, respectively).

In 13 unadjusted studies and two adjusted studies,^{34,37-39,47,49,51,54,58,60,61,65,75} eye protection was associated with lower risk of infection (unadjusted n=3713, RR 0.34, 95% CI 0.22 to 0.52; AR 5.5% with eye protection vs 16.0% with no eye protection, RD -10.6%, 95% CI -12.5 to -7.7; adjusted n=701, aOR 0.22,

95% CI 0.12 to 0.39; low certainty; figure 6; table 2; appendix pp 16–17).

Across 24 studies in health-care and non-health-care settings during the current pandemic of COVID-19, previous epidemics of SARS and MERS, or in general use, looking at contextual factors to consider in recommendations, most stakeholders found physical distancing and use of face masks and eye protection acceptable, feasible, and reassuring (appendix pp 20–22). However, challenges included frequent discomfort, high resource use linked with potentially decreased equity, less clear communication, and perceived reduced empathy of care providers by those they were caring for.

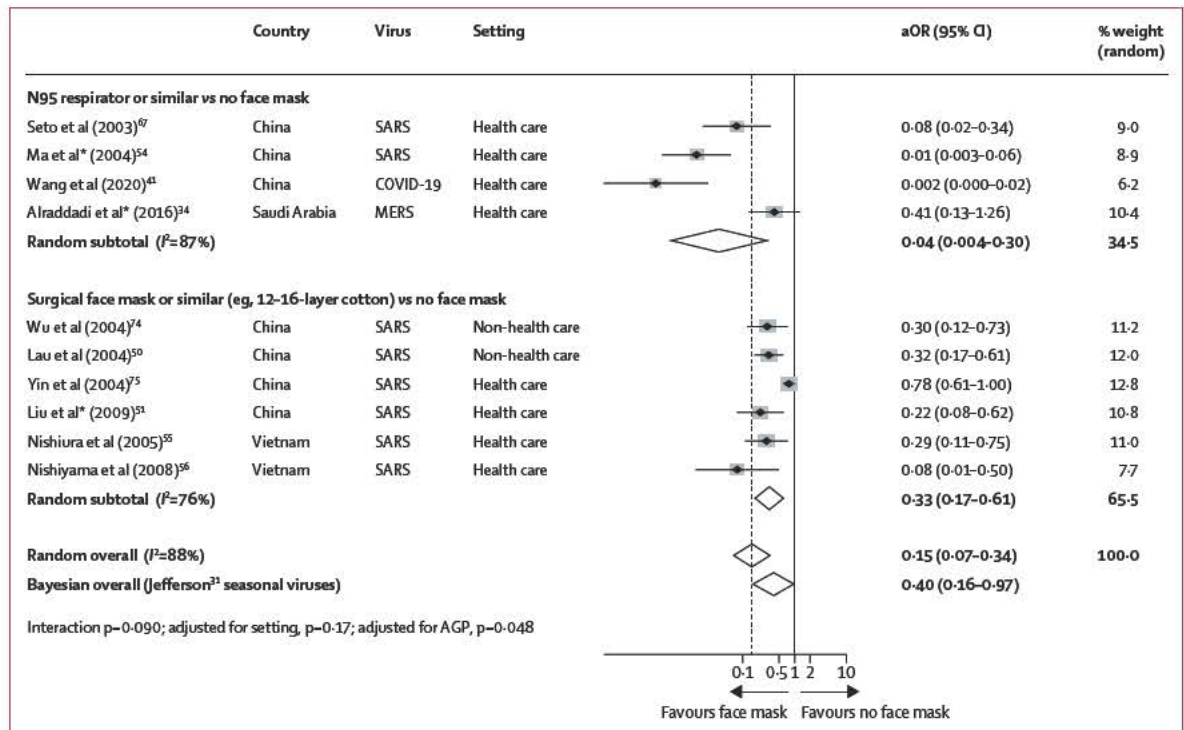


Figure 5: Forest plot showing adjusted estimates for the association of face mask use with viral infection causing COVID-19, SARS, or MERS. SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. AGP=aerosol-generating procedures. *Studies clearly reporting AGP.

Discussion

The findings of this systematic review of 172 studies (44 comparative studies; n=25 697 patients) on COVID-19, SARS, and MERS provide the best available evidence that current policies of at least 1 m physical distancing are associated with a large reduction in infection, and distances of 2 m might be more effective. These data also suggest that wearing face masks protects people (both health-care workers and the general public) against infection by these coronaviruses, and that eye protection could confer additional benefit. However, none of these interventions afforded complete protection from infection, and their optimum role might need risk assessment and several contextual considerations. No randomised trials were identified for these interventions in COVID-19, SARS, or MERS.

Previous reviews are limited in that they either have not provided any evidence from COVID-19 or did not use direct evidence from other related emerging epidemic betacoronaviruses (eg, SARS and MERS) to inform the effects of interventions to curtail the current COVID-19 pandemic.^{13,19,31,78} Previous data from randomised trials are mainly for common respiratory viruses such as seasonal influenza, with a systematic review concluding low certainty of evidence for extrapolating these findings to COVID-19.¹³ Further, previous syntheses of available randomised controlled trials have not accounted for cluster effects in analyses, leading to substantial

imprecision in treatment effect estimates. In between-study and within-study comparisons, we noted a larger effect of N95 or similar respirators compared with other masks. This finding is inconsistent with conclusions of a review of four randomised trials,¹³ in which low certainty of evidence for no larger effect was suggested. However, in that review, the CIs were wide so a meaningful protective effect could not be excluded. We harmonised these findings with Bayesian approaches, using indirect data from randomised trials to inform posterior estimates. Despite this step, our findings continued to support the ideas not only that masks in general are associated with a large reduction in risk of infection from SARS-CoV-2, SARS-CoV, and MERS-CoV but also that N95 or similar respirators might be associated with a larger degree of protection from viral infection than disposable medical masks or reusable multilayer (12-16-layer) cotton masks. Nevertheless, in view of the limitations of these data, we did not rate the certainty of effect as high.²¹ Our findings accord with those of a cluster randomised trial showing a potential benefit of continuous N95 respirator use over medical masks against seasonal viral infections.⁷⁹ Further high-quality research, including randomised trials of the optimum physical distance and the effectiveness of different types of masks in the general population and for health-care workers' protection, is urgently needed. Two trials are registered to better inform the optimum use of face masks for COVID-19 (NCT04296643 [n=576] and

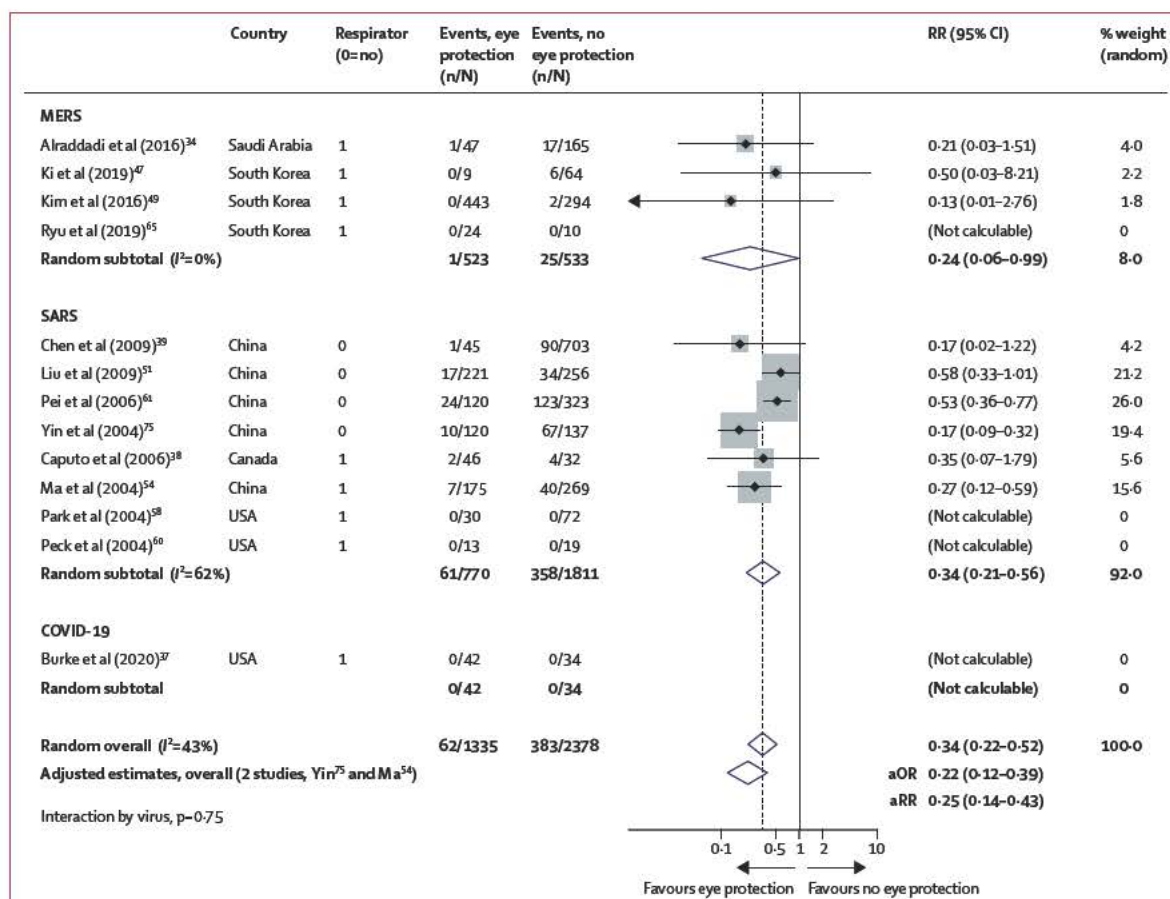


Figure 6: Forest plot showing the association of eye protection with risk of COVID-19, SARS, or MERS transmission

Forest plot shows unadjusted estimates. SARS=severe acute respiratory syndrome. MERS=Middle East respiratory syndrome. RR=relative risk. aOR=adjusted odds ratio. aRR=adjusted relative risk.

NCT04337541 [n=6000]). Until such data are available, our findings represent the current best estimates to inform face mask use to reduce infection from COVID-19. We recognise that there are strong, perhaps opposing, sentiments about policy making during outbreaks. In one viewpoint, the 2007 SARS Commission report stated:

“...recognize, as an aspect of health worker safety, the precautionary principle that reasonable action to reduce risk, such as the use of a fitted N95 respirator, need not await scientific certainty”.⁸⁰

“...if we do not learn from SARS and we do not make the government fix the problems that remain, we will pay a terrible price in the next pandemic”.⁸¹

A counter viewpoint is that the scientific uncertainty and contextual considerations require a more nuanced approach. Although challenging, policy makers must carefully consider these two viewpoints along with our findings.

We found evidence of moderate certainty that current policies of at least 1 m physical distancing are probably

associated with a large reduction in infection, and that distances of 2 m might be more effective, as implemented in some countries. We also provide estimates for 3 m. The main benefit of physical distancing measures is to prevent onward transmission and, thereby, reduce the adverse outcomes of SARS-CoV-2 infection. Hence, the results of our current review support the implementation of a policy of physical distancing of at least 1 m and, if feasible, 2 m or more. Our findings also provide robust estimates to inform models and contact tracing used to plan and strategise for pandemic response efforts at multiple levels.

The use of face masks was protective for both health-care workers and people in the community exposed to infection, with both the frequentist and Bayesian analyses lending support to face mask use irrespective of setting. Our unadjusted analyses might, at first impression, suggest use of face masks in the community setting to be less effective than in the health-care setting, but after accounting for differential N95 respirator use between health-care and non-health-care settings, we did not detect any striking differences in effectiveness of

face mask use between settings. The credibility of effect-modification across settings was, therefore, low. Wearing face masks was also acceptable and feasible. Policy makers at all levels should, therefore, strive to address equity implications for groups with currently limited access to face masks and eye protection. One concern is that face mask use en masse could divert supplies from people at highest risk for infection.¹⁰ Health-care workers are increasingly being asked to ration and reuse PPE,^{82,83} leading to calls for government-directed repurposing of manufacturing capacity to overcome mask shortages⁸⁴ and finding solutions for mask use by the general public.⁸⁴ In this respect, some of the masks studied in our review were reusable 12–16-layer cotton or gauze masks.^{51,54,61,75} At the moment, although there is consensus that SARS-CoV-2 mainly spreads through large droplets and contact, debate continues about the role of aerosol,^{2–8,85,86} but our meta-analysis provides evidence (albeit of low certainty) that respirators might have a stronger protective effect than surgical masks. Biological plausibility would be supported by data for aerosolised SARS-CoV-2^{5–8} and preclinical data showing seasonal coronavirus RNA detection in fine aerosols during tidal breathing,⁸⁷ albeit, RNA detection does not necessarily imply replication and infection-competent virus. Nevertheless, our findings suggest it plausible that even in the absence of aerosolisation, respirators might be simply more effective than masks at preventing infection. At present, there is no data to support viable virus in the air outside of aerosol generating procedures from available hospital studies. Other factors such as super-spreading events, the subtype of health-care setting (eg, emergency room, intensive care unit, medical wards, dialysis centre), if aerosolising procedures are done, and environmental factors such as ventilation, might all affect the degree of protection afforded by personal protection strategies, but we did not identify robust data to inform these aspects.

Strengths of our review include adherence to full systematic review methods, which included artificial intelligence-supported dual screening of titles and abstracts, full-text evaluation, assessment of risk of bias, and no limitation by language. We included patients infected with SARS-CoV-2, SARS-CoV, or MERS-CoV and searched relevant data up to May 3, 2020. We followed the GRADE approach¹⁶ to rate the certainty of evidence. Finally, we identified and appraise a large body of published work from China, from which much evidence emerged before the pandemic spread to other global regions.

The primary limitation of our study is that all studies were non-randomised, not always fully adjusted, and might suffer from recall and measurement bias (eg, direct contact in some studies might not be measuring near distance). However, unadjusted, adjusted, frequentist, and Bayesian meta-analyses all supported the main findings, and large or very large effects were recorded. Nevertheless, we are cautious not to be overly certain in the precise

quantitative estimates of effects, although the qualitative effect and direction is probably of high certainty. Many studies did not provide information on precise distances, and direct contact was equated to 0 m distance; none of the eligible studies quantitatively evaluated whether distances of more than 2 m were more effective, although our meta-regression provides potential predictions for estimates of risk. Few studies assessed the effect of interventions in non-health-care settings, and they primarily evaluated mask use in households or contacts of cases, although beneficial associations were seen across settings. Furthermore, most evidence was from studies that reported on SARS and MERS (n=6674 patients with COVID-19, of 25 697 total), but data from these previous epidemics provide the most direct information for COVID-19 currently. We did not specifically assess the effect of duration of exposure on risk for transmission, although whether or not this variable was judged a risk factor considerably varied across studies, from any duration to a minimum of 1 h. Because of inconsistent reporting, information is limited about whether aerosol-generating procedures were in place in studies using respirators, and whether masks worn by infected patients might alter the effectiveness of each intervention, although the stronger association with N95 or similar respirators over other masks persisted when adjusting for studies reporting aerosol-generating medical procedures. These factors might account for some of the residual statistical heterogeneity seen for some outcomes, albeit *I*² is commonly inflated in meta-analyses of observational data,^{21,22} and nevertheless the effects seen were large and probably clinically important in all adjusted studies.

Our comprehensive systematic review provides the best available information on three simple and common interventions to combat the immediate threat of COVID-19, while new evidence on pharmacological treatments, vaccines, and other personal protective strategies is being generated. Physical distancing of at least 1 m is strongly associated with protection, but distances of up to 2 m might be more effective. Although direct evidence is limited, the optimum use of face masks, in particular N95 or similar respirators in health-care settings and 12–16-layer cotton or surgical masks in the community, could depend on contextual factors; action is needed at all levels to address the paucity of better evidence. Eye protection might provide additional benefits. Globally collaborative and well conducted studies, including randomised trials, of different personal protective strategies are needed regardless of the challenges, but this systematic appraisal of currently best available evidence could be considered to inform interim guidance.

Contributors

DKC, EAA, SD, KS, SY, and HJS designed the study. SY, SD, KS, and HJS coordinated the study. SY and LH designed and ran the literature search. All authors acquired data, screened records, extracted data, and assessed risk of bias. DKC did statistical analyses. DKC and HJS wrote the report. All authors provided critical conceptual input, analysed and interpreted data, and critically revised the report.

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Declaration of interests

ML is an investigator of an ongoing clinical trial on medical masks versus N95 respirators for COVID-19 (NCT04296643). All other authors declare no competing interests.

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Physical distancing, face masks, and eye protection for prevention of COVID-19



The choice of various respiratory protection mechanisms, including face masks and respirators, has been a vexed issue, from the 2009 H1N1 pandemic to the west African Ebola epidemic of 2014,¹ to the current COVID-19 pandemic. COVID-19 guidelines issued by WHO, the US Centers for Disease Control and Prevention, and other agencies have been consistent about the need for physical distancing of 1–2 m but conflicting on the issue of respiratory protection with a face mask or a respirator.² This discrepancy reflects uncertain evidence and no consensus about the transmission mode of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For eye protection, data are even less certain. Therefore, the systematic review and meta-analysis by Derek Chu and colleagues in *The Lancet*³ is an important milestone in our understanding of the use of personal protective equipment (PPE) and physical distancing for COVID-19. No randomised controlled trials were available for the analysis, but Chu and colleagues systematically reviewed 172 observational studies and rigorously synthesised available evidence from 44 comparative studies on SARS, Middle East respiratory syndrome (MERS), COVID-19, and the betacoronaviruses that cause these diseases.

The findings showed a reduction in risk of 82% with a physical distance of 1 m in both health-care and community settings (adjusted odds ratio [aOR] 0.18, 95% CI 0.09–0.38). Every additional 1 m of separation more than doubled the relative protection, with data available up to 3 m (change in relative risk [RR] 2.02 per m; $p_{\text{interaction}}=0.041$). This evidence is important to support community physical distancing guidelines and shows risk reduction is feasible by physical distancing. Moreover, this finding can inform lifting of societal restrictions and safer ways of gathering in the community.

The 1–2 m distance rule in most hospital guidelines is based on out-of-date findings from the 1940s, with studies from 2020 showing that large droplets can travel as far as 8 m.⁴ To separate droplet and airborne transmission is probably somewhat artificial, with both routes most likely part of a continuum for respiratory transmissible infections.⁴ Protection against presumed droplet infections by use of respirators, but not masks,⁵

supports a continuum rather than discrete states of droplet or airborne transmission. Both experimental and hospital studies have shown evidence of aerosol transmission of SARS-CoV-2.^{6–8} One study found viable virus in the air 16 h after aerosolisation and showed greater airborne propensity for SARS-CoV-2 compared with SARS-CoV and MERS-CoV.⁶

Chu and colleagues reported that masks and respirators reduced the risk of infection by 85% (aOR 0.15, 95% CI 0.07–0.34), with greater effectiveness in health-care settings (RR 0.30, 95% CI 0.22–0.41) than in the community (0.56, 0.40–0.79; $p_{\text{interaction}}=0.049$). They attribute this difference to the predominant use of N95 respirators in health-care settings; in a sub-analysis, respirators were 96% effective (aOR 0.04, 95% CI 0.004–0.30) compared with other masks, which were 77% effective (aOR 0.33, 95% CI 0.17–0.61; $p_{\text{interaction}}=0.090$). The other important finding for health workers by Chu and colleagues was that eye protection resulted in a 78% reduction in infection (aOR 0.22, 95% CI 0.12–0.39); infection via the ocular route might occur by aerosol transmission or self-inoculation.⁹

For health-care workers on COVID-19 wards, a respirator should be the minimum standard of care. This study by Chu and colleagues should prompt a review of all guidelines that recommend a medical mask for health workers caring for COVID-19 patients. Although medical masks do protect, the occupational health and safety of health workers should be the highest priority and the precautionary principle should be applied. Preventable infections in health workers can result not only in deaths but also in large numbers of health workers being quarantined and nosocomial outbreaks. In the National Health Service trusts in the UK, up to one in five health workers have been infected with COVID-19,¹⁰ which is an unacceptable risk for front-line workers. To address global shortages of PPE, countries should take responsibility for scaling up production rather than expecting health workers to work in suboptimum PPE.¹¹

Chu and colleagues also report that respirators and multilayer masks are more protective than are single layer masks. This finding is vital to inform the proliferation of home-made cloth mask designs, many



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of which are single-layered. A well designed cloth mask should have water-resistant fabric, multiple layers, and good facial fit.¹² This study supports universal face mask use, because masks were equally effective in both health-care and community settings when adjusted for type of mask use. Growing evidence for presymptomatic and asymptomatic transmission of SARS-CoV-2¹³ further supports universal face mask use and distancing. In regions with a high incidence of COVID-19, universal face mask use combined with physical distancing could reduce the rate of infection (flatten the curve), even with modestly effective masks.¹⁴ Universal face mask use might enable safe lifting of restrictions in communities seeking to resume normal activities and could protect people in crowded public settings and within households. Masks worn within households in Beijing, China, prevented secondary transmission of SARS-CoV-2 if worn before symptom onset of the index case.¹⁵ Finally, Chu and colleagues reiterate that no one intervention is completely protective and that combinations of physical distancing, face mask use, and other interventions are needed to mitigate the COVID-19 pandemic until we have an effective vaccine. Until randomised controlled trial data are available, this study provides the best specific evidence for COVID-19 prevention.

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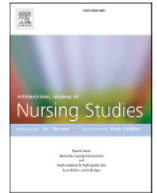
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Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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A rapid systematic review of the efficacy of face masks and respirators against coronaviruses and other respiratory transmissible viruses for the community, healthcare workers and sick patients



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ABSTRACT

Background: The pandemic of COVID-19 is growing, and a shortage of masks and respirators has been reported globally. Policies of health organizations for healthcare workers are inconsistent, with a change in policy in the US for universal face mask use. The aim of this study was to review the evidence around the efficacy of masks and respirators for healthcare workers, sick patients and the general public.

Methods: A systematic review of randomized controlled clinical trials on use of respiratory protection by healthcare workers, sick patients and community members was conducted. Articles were searched on Medline and Embase using key search terms.

Results: A total of 19 randomised controlled trials were included in this study – 8 in community settings, 6 in healthcare settings and 5 as source control. Most of these randomised controlled trials used different interventions and outcome measures. In the community, masks appeared to be effective with and without hand hygiene, and both together are more protective. Randomised controlled trials in health care workers showed that respirators, if worn continually during a shift, were effective but not if worn intermittently. Medical masks were not effective, and cloth masks even less effective. When used by sick patients randomised controlled trials suggested protection of well contacts.

Conclusion: The study suggests that community mask use by well people could be beneficial, particularly for COVID-19, where transmission may be pre-symptomatic. The studies of masks as source control also suggest a benefit, and may be important during the COVID-19 pandemic in universal community face mask use as well as in health care settings. Trials in healthcare workers support the use of respirators continuously during a shift. This may prevent health worker infections and deaths from COVID-19, as aerosolisation in the hospital setting has been documented.

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What is already known about the topic?

- Masks and respirators are commonly used to protect from respiratory infections in three different indications – for healthcare workers, sick patients and well community members.
- Currently there is debate and conflicting guidelines around the use of masks and respirators in healthcare and community settings.

What this paper adds

- In the community, masks may be more protective for well people.
- In healthcare settings continuous use of respirators, is more protective compared to the medical masks, and medical masks are more protective than cloth masks. Depending on the fabric and design, some cloth masks may not be safe for healthcare workers.
- The use of masks by sick patients is likely protective, and coronaviruses can be emitted in normal breathing, in fine airborne particles.

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1. Introduction

The use of personal protective equipment for coronavirus disease (COVID-19) has been controversial, with differing guidelines issued by different agencies (Chen et al., 2020). COVID-19 is caused by severe acute respiratory syndrome coronavirus2 (SARS-CoV-2), a beta-coronavirus, similar to severe acute respiratory syndrome coronavirus (SARS CoV) (Chen et al., 2020). Seasonal alpha and beta coronaviruses cause common colds, croup and bronchitis. The transmission mode of coronaviruses in humans is similar, thought to be by droplet, contact and sometimes airborne routes (Ong et al., 2020; Zhang et al., 2020; Zou et al., 2020). The World Health Organization recommends surgical mask for health workers providing routine care to a coronavirus disease patient (World Health Organisation (WHO) 2020), whilst the US Centers for Disease Control and Prevention recommended a respirator (Center for Disease Control and Prevention CDC, 2020). Most authorities, except the US CDC, are recommending that community members not wear a mask, and that a mask should only be worn by a sick patient (also referred to as *source control*) (Chughtai et al., 2020). There are more randomised controlled trials of community use of masks in well people than studies of the use by sick people (*source control*). The aim of this study was to review the randomised controlled trials evidence for use of masks and respirators by the community, health care workers and sick patients for prevention of infection.

2. Methods

We searched Medline and EmBase for clinical trials on masks and respirators using the key words “mask”, “respirator”, and “personal protective equipment”. The search was conducted between 1 March to April 17 2020, and all randomised controlled trials published before the search date were included. Two authors (CRM and AAC) reviewed the title and abstracts to identify randomised controlled trials on masks and respirators. We also searched relevant papers from the reference lists of previous clinical trials and systematic reviews. Studies that were not randomised controlled trials, were about anesthesia, or not about prevention of infection were excluded. Animal studies, experimental and observational epidemiologic studies were also excluded. Studies published in English language were included.

We found 602 papers on Medline and 250 on Embase. 820 papers were excluded by title and abstract review. Full texts were reviewed for 32 papers and 19 were selected in this review. Results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria (Moher et al., 2015).

3. Results

In general, the results show protection for healthcare workers and community members, and likely benefit of masks used as source control. We found eight clinical trials (Aiello et al., 2012; Simmerman et al., 2011; Larson et al., 2010; Aiello et al., 2010; MacIntyre et al., 2009; Cowling et al., 2008, Suess et al., 2012; Cowling et al., 2009) on the use of masks in the community (Table 1). In the community, masks appear to be effective with and without hand hygiene, and both together are more protective (Aiello et al., 2012; Aiello et al., 2010; MacIntyre et al., 2009). However, some randomised controlled trials which measured both hand hygiene and masks measured the effect of hand hygiene alone, but not of masks alone (Simmerman et al., 2011, Cowling et al., 2009). In more than one trial, interventions had to be used within 36 hours of exposure to be effective (Cowling et al., 2009; Suess et al., 2012).

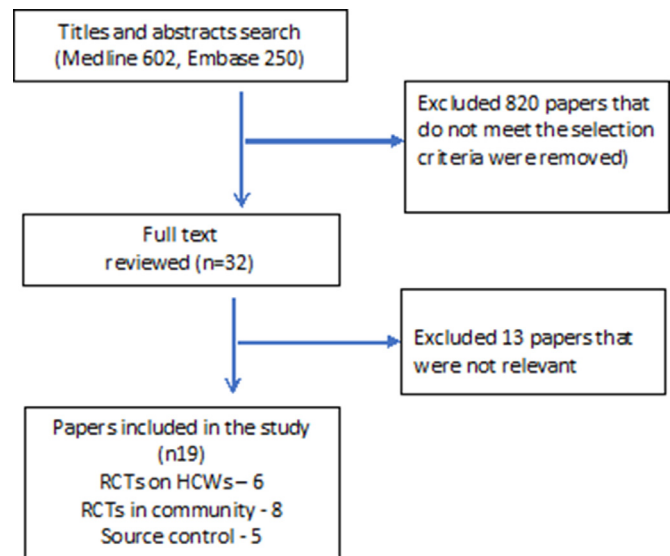


Fig. 1. Search strategy and selection of papers.

To date, six randomised controlled trials (Radonovich et al., 2019; Jacobs et al., 2009, Loeb et al., 2009; MacIntyre et al., 2011, 2013, 2015) have been conducted on the use of masks and/or respirators by healthcare workers in health care settings (Table 2). The healthcare worker trials (Table 2) used different interventions and different outcome measures, and one was in the outpatient setting. A Japanese study had only 32 subjects, and likely was underpowered to find any difference between masks and control (Jacobs et al., 2009). Two North American trials of masks and respirators against influenza infection found no difference between the arms, but neither had a control arm to differentiate equal efficacy from equal inefficacy (Radonovich et al., 2019, Loeb et al., 2009). Neither trial can prove equivalence, as this requires one intervention to be already proven efficacious against placebo. Without a control group to determine rates of influenza in unprotected healthcare workers, neither study is able to determine efficacy if no difference was observed between the two interventions. A serologic study showed that up to 23% of unprotected healthcare workers (a rate identical to that observed in Loeb the trial, which also used serology) contract influenza during outbreaks (Elder et al., 1996), which suggests lack of efficacy. Studies of nosocomial influenza generally find lower influenza attack rates in unprotected healthcare workers than observed in the Loeb trial (Salgado et al., 2002).

Further problems with this study are that the majority of subjects were defined as having influenza on the basis of serological positivity (Loeb et al., 2009). The 10% seroconversion to pandemic H1N109 (with no pandemic virus isolation or positive PCR) observed in the trial, suggests that pandemic H1N109 was circulating in Ontario before April 2009, which is unlikely.

A serological definition of influenza can be affected by vaccination. The authors claim they excluded influenza vaccinated subjects in the outcome, but according to figure 1 in the Loeb trial, (Loeb et al., 2009) these subjects (130 in total) are included in the analysis. If they had been excluded and even if no other subjects were excluded, the total analysed would be 348, which is lower than the 422 subjects analysed (Loeb et al., 2009). These 130 vaccinated subjects should have been excluded entirely from the analysis. The vaccination status of subjects with seropositivity is not provided in the paper, but it appears people with positive serology due to vaccination may have been misclassified as influenza cases (Loeb et al., 2009).

Table 1
Community mask trials.

Author, year	N, country	Interventions	Results
Cowling et al. (2008)	198 Households Hong Kong	Medical masks Hand washing Control	NS – this was a preliminary report of the 2009 trial.
MacIntyre et al. (2009)	143 Households Australia	Medical masks P2 masks Control	Intention to treat non-significant. Adherence with mask wearing low (25–30% by day 5). In sub-analysis, masks/P2 protective if adherent.
Cowling et al., 2009)	407 households Hong Kong	Hand hygiene Masks + hand hygiene Control	Intention to treat not significant. Masks plus hand hygiene protective against lab confirmed influenza if used within 36 hours. Hand hygiene alone not significant.
Aiello et al. (2010)	1437 college students, United States of America	Masks Masks + hand washing Control	Intention to treat non-significant. Masks + handwashing protective in week 4–6 of observation and beyond.
Aiello et al. (2012)	1178 college students, United States of America	Masks Masks + hand hygiene Control	Intention to treat non-significant. Masks + hand hygiene protective in week 3 of observation and beyond. Masks alone not protective.
Larson et al. (2010)	617 households, United States of America	Health education (HE) Hand hygiene + HE Masks + hand hygiene + HE	Masks + hand hygiene + HE protective against secondary transmission measured by confirmed influenza and ILI. Mean secondary attack rates for HE, HE + HH, HE+HH+M groups were 0.023, 0.020, and 0.018, respectively
Simmernan et al. (2011)	465 index patients and their families, Thailand	Hand hygiene Masks + hand hygiene Control	No significant difference in confirmed influenza infection
Suess et al. (2012)	84 index cases and 218 household contacts, Germany	Masks Masks + hand hygiene Control	Intention to treat analysis was non-significant. Where used within 36 h, secondary infection in the pooled M and MH groups was significantly lower compared to the control group. In multivariable analysis for predictors of qRT-PCR confirmed influenza infection and clinical influenza among included households in separate models allowing for within household correlation, M and MH were protective against Influenza A/H1N1pdm09.

Table 2
Trials of mask and respirator use by health care workers.

Author, year	N healthcare workers, Country	Interventions	Results
Jacobs et al. (2009)	32 Japan	Medical masks Control	NS
Loeb et al. (2009)	446 Canada	Medical masks, targeted N95	No significant difference between Masks and targeted N95
MacIntyre et al. (2011)	1441 China	Masks N95 respirators, fit tested N95 respirators, non-fit tested Control	Continuous N95 protective against clinical, viral and bacterial endpoints
MacIntyre et al. (2013)	1669 China	Medical Mask N95 (continuous) N95 (targeted)	Continuous N95 protective No difference between targeted N95 and medical masks
MacIntyre et al. (2015)	1607 Vietnam	Medical masks, cloth masks, control	Medical masks protective or Cloth masks increase risk of infection
Radonovich et al. (2019)	2862 United States of America	Medical masks, targeted N95 (when 2 m from confirmed respiratory infection) in Outpatient setting.	No significant difference between Masks and targeted N95

In both the North American trials, the intervention comprised wearing the mask or respirator when in contact with recognized ILI or when doing a high risk procedure, which is a targeted strategy ([Radonovich et al., 2019](#), [Loeb et al., 2009](#)). One was in an outpatient setting. ([Radonovich et al., 2019](#)) We conducted a randomised controlled trial comparing the targeted strategy tested in the two North American studies, with the wearing of respiratory protection during an entire shift, and showed efficacy for continual (but not targeted) use of a respirator ([MacIntyre et al., 2013](#)). The study also did not show efficacy for a surgical mask worn continually, and therefore no difference between a surgical mask and targeted use of a respirator ([MacIntyre et al., 2013](#)), which is consistent with the findings of the North American trials ([Radonovich et al., 2019](#), [Loeb et al., 2009](#)). In summary, the evidence is consistent that a respirator must be worn throughout the shift to be

protective. Targeted use of respirators only when doing high risk procedures and medical mask use is not protective. Another randomised controlled trial we conducted in China showed efficacy for continual use of a respirator, but not for a mask, and also found fit-testing of the respirator did not affect efficacy ([MacIntyre et al., 2011](#)). However, this may be specific to the quality of the tested product, and is not generalisable to other respirators – fit testing is a necessary part of respirator use ([Chughtai et al., 2015](#)).

For healthcare workers, there is evidence of efficacy of respirators if worn continually during a shift, but no evidence of efficacy of a mask ([MacIntyre et al., 2011, 2013](#)). For hospitals where COVID-19 patients are being treated, there is growing evidence of widespread contamination of the ward environment, well beyond 2 m from the patient, as well as aerosol transmission ([Ong et al., 2020](#); [Santarpia et al., n.d.](#); [Guo et al., 2020](#)). Several studies have

Table 3
Trials of Masks used by a sick patient as source control.

Author, year	N, country	Interventions	Results
Johnson et al. (2009)	9 subjects with confirmed influenza, Australia	Medical mask N95 (participants coughed 5 times onto a Petri dish wearing each device)	NS - Surgical and N95 masks were equally effective in preventing the spread of PCR-detectable influenza
Canini et al. (2010)	105 index cases and 306 household contacts, France	Medical mask Control	No significant difference, but trial terminated early
MacIntyre et al. (2016)	245 index cases and 597 household contacts,	Medical mask worn by sick case Control (no mask) Household contacts Followed for infection.	Intention to treat analysis not significant. Mask protective if worn
Barasheed et al. (2014)	Hajj Setting. 22 tents were randomised to 'mask' (n = 12) or 'control' (n = 10) 75 pilgrims in 'mask' and 89 in 'control' group Saudi Arabia	Mask and control	Less - Ill among the contacts of mask users compared to the control tents (31% versus 53%, p = 0.04). Laboratory results did not show any difference between the two groups
Leung et al. (2020)	Experimental study of 246 subjects randomised to surgical mask and no mask	Mask and control	111 were infected by human (seasonal) coronavirus. Coronavirus found in exhaled breath of no-mask subjects but not in mask wearers. More virus was found in fine aerosols than large droplets

found SARS-CoV-2 on air vents and in air samples in intensive care units and COVID-19 wards (Santarpia et al., n.d.; Chia et al., 2020; Liu et al., 2020), and an experimental study showed the virus in air samples three hours after aerosolization (van Doremalen et al., 2020). The weight of this evidence and the precautionary principle (MacIntyre et al., 2014a; 2014b), favors respirators for healthcare workers. We showed lower rates of infection outcomes in the medical mask arm compared to control, but the difference was not significant (MacIntyre et al., 2011). It could be that larger trials are needed to demonstrate efficacy of a mask, but any protection is far less than from a respirator. A trial we conducted in Vietnam of 2-layered cotton cloth masks compared to medical masks showed a lower rate of infection in the medical mask group, and a 13 times higher risk of infection in the cloth mask arm (MacIntyre et al., 2015). The study suggests cloth masks may increase the risk of infection (MacIntyre et al., 2015), but may not be generalizable to all homemade masks. The material, design and adequacy of washing of cloth masks may have been a factor (MacIntyre et al., 2020). There are no other randomised controlled trial of cloth masks published at this time, but if any protection is offered by these it would be less than even a medical mask.

Table 3 shows the trials of source control. There were five randomised controlled trials identified of masks used by sick patients (Johnson et al., 2009; Barasheed et al., 2014; Leung et al., 2020; MacIntyre et al., 2016; Canini et al., 2010). One was an experimental study of 9 influenza patients, which did not measure clinical endpoints (Johnson et al., 2009). Participants with confirmed influenza coughed onto culture medium wearing a N95 respirator or a mask. No influenza grew on the medium. A trial of 105 sick patients wearing a mask (or no mask) in the household found no significant difference between arms (Canini et al., 2010). However, the trial was terminated prematurely and did not meet recruitment targets, so was probably underpowered. One randomised controlled trial was conducted among Hajj pilgrims, with both well and sick pilgrims wearing masks, and low rates of Ill were reported among contact of mask pilgrims (Barasheed et al., 2014). Our randomised controlled trial is the largest available with clinical endpoints, and studied 245 patients randomised to mask or control (MacIntyre et al., 2016). Compliance was suboptimal in the mask group and some controls wore masks. The intention to treat analysis showed no difference, but when analysed by actual mask use, the rate of infection in household contacts was lower in those who wore masks (MacIntyre et al., 2016). A trial with an experimental design was published in April 2020, examining a range of viruses including seasonal human coronaviruses (Leung et al., 2020). This

showed that coronaviruses are preferentially found in aerosolized particles compared to large droplets, and could be expelled by normal tidal breathing. Wearing a surgical mask prevented virus from being exhaled.

4. Discussion

There are more randomised controlled trials of community use of masks in well people (Aiello et al., 2012; Simmerman et al., 2011; Larson et al., 2010; Aiello et al., 2010; MacIntyre et al., 2009; Cowling et al., 2008, Suess et al., 2012, Cowling et al., 2009) than studies of the use by sick people (also referred to as "source control"), and these trials are larger than the few on source control (Johnson et al., 2009, Leung et al., 2020; MacIntyre et al., 2016). The evidence suggests protection by masks in high transmission settings such as household and college settings, especially if used early, in some trials if combined with hand hygiene and if wearers are compliant (Aiello et al., 2012; Aiello et al., 2010; MacIntyre et al., 2009; Cowling et al., 2008, 2009; Suess et al., 2012). If masks protect in high transmission settings, they should also protect in crowded public spaces, including workplaces, buses, trains, planes and other closed settings. The trial which did not show efficacy used influenza as the outcome measure (Simmerman et al., 2011), which is a rare outcome, so requires a larger sample size for adequate power and may have been underpowered.

For healthcare workers, the only trials to show a difference between respirators and masks demonstrated efficacy for continuous use of a respirator through a clinical shift, but not masks (MacIntyre et al., 2011, 2013). The two trials which showed no difference are widely cited as evidence that masks provide equal protection as respirators (Radonovich et al., 2019, Loeb et al., 2009). However, without a control arm, the absence of difference between arms could reflect equal efficacy or inefficacy, and it is not possible to draw any conclusions about efficacy. The outpatient setting in the US trial may have had lower exposure risk than the inpatient setting of other trials. (Radonovich et al., 2019) In both the North American trials, the intervention comprised wearing the mask or respirator intermittently when in contact with recognized Ill or when doing a high risk procedure (Radonovich et al., 2019, Loeb et al., 2009). The underlying assumption that the majority of infections in healthcare workers occur during self-identified high-risk exposures is not supported by any evidence. It assumes healthcare workers can accurately identify when they are risk in a busy, clinical setting, when the majority of infections may occur when healthcare workers are unaware of the risk (such as when walking

through a busy emergency room or ward where aerosolized virus may be present). Conversely, infections could occur outside the workplace. This could explain the lack of difference if there was no actual efficacy of either arm and if much of the infection occurs in unrecognized situations of risk either within or outside the workplace.

In practice, hospital infection control divides infections into droplet or airborne spread, and recommends droplet (mask) or airborne (respirator) precautions accordingly (MacIntyre et al., 2017). In a pooled analysis of both healthcare worker trials, we showed that continual use of a respirator is more efficacious in protecting healthcare workers even against infections assumed to be spread by the droplet route (MacIntyre et al., 2017). Medical masks did not significantly protect against viral, bacterial, droplet or other infection outcomes. However, the summary odds ratio for masks was less than one, which suggests a low level of protection. Targeted use of respirator protected against bacterial and droplet infections, but not against viral infections, suggesting viral infections may be more likely to be airborne in the hospital setting (MacIntyre et al., 2017).

The five available studies of mask use by sick patients suggest a benefit, but are much smaller trials than the community trials, two without clinical endpoints, and with less certainty around the findings (Johnson et al., 2009; Barasheed et al., 2014; Leung et al., 2020; MacIntyre et al., 2016; Canini et al., 2010). Only 3/5 trials examined clinical outcomes in close contacts (Barasheed et al., 2014; MacIntyre et al., 2016; Canini et al., 2010) and suggest a benefit.

Many systematic reviews have been conducted on masks, respirators and other PPE in past (Cowling et al., 2010; Bin-Reza et al., 2012; Gralton and McLaws, 2010; Gamage et al., 2005; Jefferson et al., 2009; Jefferson et al., 2011; Jefferson et al., 2008; Aledort et al., 2007; Lee et al., 2011; Verbeek et al., 2020). These reviews generally examined multiple interventions (e.g. masks and hand hygiene etc.), often combined different outcome measures that were not directly comparable and were inconclusive. Moreover, most of these reviews did not include more recent randomised controlled trials (Radonovich et al., 2019; MacIntyre et al., 2015). This systematic review only focuses on masks and respirators and contains all new studies.

In summary, there is a growing body of evidence supporting all three indications for respiratory protection – community, healthcare workers and sick patients (source control). The largest number of randomised controlled trials have been done for community use of masks by well people in high-transmission settings such as household or college settings. There is benefit in the community if used early, with hand hygiene and if compliant.

Respirators protect healthcare workers if worn continually, but not if worn intermittently in self-identified situations of risk. This supports the suggestion that the health care environment is a risk to healthcare workers even when not doing aerosol generating procedures or caring for a known infectious patient. For COVID-19 specifically, the growing body of evidence showing aerosolisation of the virus in the hospital ward highlights the risk of inadvertent exposure for healthcare workers and supports the use of airborne precautions at all times on the ward (Santarpia et al., n.d.; Chia et al., 2020; Liu et al., 2020). Further, the rule of 1–2 m of spatial separation is not based on good evidence, with most research showing that droplets can travel further than 2 m, and that infections cannot be neatly separated into droplet and airborne (MacIntyre et al., 2017; Bahl et al., 2020). In the UK, one healthcare trust found almost one in five healthcare workers to be infected with COVID-19 (Keeley et al., 2020). The deaths of healthcare workers from COVID-19 reflect this risk (Zhan et al., 2020). The use of masks by sick people, despite being the WHO's only recommendation for mask use by community members during COVID-19 pandemic, is supported by the smallest body of evidence. Source control is prob-

ably a sensible recommendation given the suggestion of protection and given specific data on coronaviruses showing protection (Leung et al., 2020). It may help if visitors and febrile patients wear a mask in the healthcare setting, whether in primary care or hospitals. Universal face mask use is likely to have the most impact on epidemic growth in the community, given the high risk of asymptomatic and pre-symptomatic transmission (He et al., 2020).

Conflict of Interest

C Raina MacIntyre receives funding from NHMRC (centre for Research Excellence and Principal Research Fellowship) and Sanofi currently. She has received funding from 3M more than 10 years ago for face mask research.

Abbar Ahmad Chughtai had testing of filtration of masks by 3M for his Ph.D. more than 10 years ago. 3M products were not used in his research. He also has worked with CleanSpace Technology on research on fit testing of respirators (no funding was involved).

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