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Masks and respirators for the prevention of respiratory infections: a mechanism-informed systematic review.

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Greenhalgh, T; Williamson, J; Ratnayake, S; Poliseli, L; Helm, R; Trofimov, A; Ungrin, M.

Corresponding author:
Trisha Greenhalgh

trish.greenhalgh@phc.ox.ac.uk

Author Affiliation:
University of Oxford.

ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - JW developed the Evidential Pluralism methodology that is the basis for the proposed Systematic Review+ approach. TG led a previous narrative review on masks (on which MU was a coauthor) and is a member of Independent SAGE. MU has written critiques of mask RCTs. All other authors declare no conflicts of interest.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 May 2025 and was last updated on 11 May 2025.

INTRODUCTION

Review question / Objective Empirical objectives (this protocol):
1. To determine the efficacy of face coverings (masks and respirators) in reducing the spread of respiratory infections.
2. To identify the mechanisms through which this effect is achieved (or the mechanisms which explain why it is not achieved).

Methodological objective (described in detail in a separate protocol paper). Using this mask mandate review as a worked example:
1. To produce a potentially generalisable methodology (both qualitative and quantitative) for combining associative and mechanistic evidence in systematic review (known as 'mechanism-informed systematic review', Systematic Review + or SR+).
2. To examine the extent to which SR+ mitigates key criticisms of orthodox systematic reviews, both epistemological and ethical.

Rationale The question of whether face masks and face mask mandates are effective in reducing transmission of respiratory diseases generated much controversy during the COVID-19 pandemic. An orthodox systematic review, analysing only randomised controlled trials (RCTs) and published in the Cochrane Library, concluded that the existing evidence on face mask efficacy was not definitive (i.e. the authors decided that they could not firmly conclude either that masks were effective or that they were ineffective).1 One review which included non-RCT evidence, especially evidence of mechanism ('mechanistic evidence'), concluded that there was evidence of efficacy; it proposed explanations for why some RCTs demonstrated efficacy while others did not.2 One key area of contestation is whether trials were testing masking itself or ‘advice to mask’.

Accordingly, we are currently exploring both the efficacy of masks and the efficacy of mask mandates in separate reviews. This review addresses the former.

One contentious issue is whether (and if so, why) respirators are superior to medical masks or cloth masks. Another contentious issue is whether masks or respirators should be worn by healthcare workers a) only when in close vicinity of a patient with known or suspected respiratory infection, b) only when doing a so-called aerosol-generating medical procedure, or c) continuously when at work. To design optimal association studies that could answer these questions, we need to know how masks and respirators achieve any effect they may have. In other words, we need evidence of mechanism.

To demonstrate causality, we typically need two kinds of evidence: associative (to show that a change in one phenomenon is associated with a change in another) and mechanistic (to be confident that any observed association is genuinely causal). In biomedicine, the former is, ideally, obtained from RCTs but the latter may come from a wide range of study designs. Orthodox methods of evidence synthesis, such as those used for Cochrane reviews and informed by the GRADE criteria, classify mechanistic evidence as inherently lower quality than RCT evidence. But this position can be challenged on both epistemological grounds (since mechanistic evidence can raise or lower confidence in a causal claim) and on ethical grounds (since dismissing certain forms of evidence may be a form of epistemic injustice). Furthermore, a poorly designed RCT, which tests an intervention but takes no account of mechanism and is hence sub-optimally designed, may mislead. This study, which seeks to extend the emerging scholarly tradition of ‘EBM+’ with ‘SR+’, will formally and systematically evaluate mechanistic evidence and use that evidence to complement and challenge findings from RCTs and other associative evidence.

The evidence pertaining to whether and how mask and respirators work is heterogeneous and comes from multiple disciplines. The associative evidence comprises RCTs and observational (non-randomised comparative) studies, but many are difficult to interpret because a) different studies tested different products; b) people received variable instruction on when and how to wear their face covering; c) compliance with these instructions varied (and was sometimes unmeasured); d) many of the associative studies did not engage adequate specialist expertise; and e) reviews of associative studies have tended to overlook the extensive body of work by topic experts in the field (e.g. of occupational health). Mechanistic evidence (e.g. on the behaviour of droplets and aerosols in indoor air, the physical and material properties of masks and respirators, the process by which particles are filtered, the impact of masking on physiological biomarkers, and the impact of different communication strategies in advice to mask) comes from a wide range of disciplines and study designs including aerosol science, engineering, and physiology.

Condition being studied Face masks and respirators in reducing transmission in the context of respiratory infection outbreaks. (See also separate protocol, INPLASY 7685, on mask mandates).

Examining the relationship between mask wearing and incidence of respiratory infections requires integration of both associative evidence (i.e. whether and to what extent masking can be determined to affect incidence of new cases in particular disease outbreaks and settings) and mechanistic evidence (i.e. whether and how masks and respirators interfere with essential steps in respiratory disease transmission). Successful pathogen transmission involves multiple steps, namely

- production of potentially infectious particles (PIPs) by an infected host;
- release of PIPs (e.g. in mucus, saliva, nasal secretions and exhaled air) through breathing, speaking, sneezing, coughing etc;
- evolution of PIPs (e.g. by evaporation) into smaller particles, a process which depends on the initial size of the released particle and on environmental conditions (temperature, humidity);
- survival (or not) of PIPs in particular environments (e.g. settling rates for different particles in relation to ventilation rates, filtration, UV disinfection, convection, etc);
- entry of PIPs into the body (e.g. via respiratory tract, alimentary tract or other e.g. eyeball), and how this process depends on particle size (e.g. larger particles will be unable to reach the alveoli);
- blockage of transmission of PIPs of different sizes by masks and respirators (e.g. by filtration);
- impact of any leakage around the edges of the mask or respirator, including concepts such as Net Protection (= net reduction in level of PIPs from outside the device to inside it), Workplace Protection Factor, Fit Factor.

To achieve these steps, various causal mechanisms operate at different levels (and whose interactions with masks and respirators must be understood). We list some below.

1. Mechanisms by which an individual who is infected with a pathogen generates aerosols—for example, through
- activities such as speaking or singing;
- so-called 'aerosol-generating medical procedures' (e.g. intubation, bronchoscopy).

2. Mechanisms of aerosol formation, evolution, transportation and survival. These include
- mechanisms by which small particles become aerosolised;
- size distribution of different droplets produced during respiratory events (coughing, sneezing, speaking, breathing);
- mechanisms by which aerosolised particles are transported in air currents;
- mechanisms affecting airborne pathogens' viability (e.g. humidity).

3. Mechanisms by which mask materials interact with suspended particles (e.g. filtration, deposition, adsorption, absorption, electrostatic interference).

4. Mechanisms by which mask materials affect pathogens (e.g. killing, trapping).

5. Mechanisms of respiratory airflow and aerosol deposition, including how air flows within the respiratory tract, how particles of different sizes are deposited at different locations, how breathing patterns (tidal volume, breathing rate) influence airflow and deposition and how mask leakage (e.g. due to poor mask fit) can alter airflow patterns.

6. Mechanisms of mask performance in standardised conditions, including fit factor testing, breathability, aerosol-blocking ability and filtration efficacy under ideal laboratory conditions.

7. Mechanisms by which mask wearing affects physiological (e.g. blood oxygen) and psychological (e.g. perception of breathlessness, claustrophobia) factors.

METHODS

Search strategy Searching will be iterative and use multiple methods. These will include
- key word search of at least 8 databases (Medline, Cinahl, Cochrane, Psychinfo, SSCI, SCOPUS, JSTOR, Annals of Work Exposure and Health);
- author search (authors of seminal papers will be name-searched in relevant databases to identify additional papers by them);
- citation-tracking (via Google Scholar);
- mining previous systematic reviews;
- relevant engineering standards and the references on which they are based, including British/European (e.g. EN14683, EN149), American (e.g. National Institute for Occupational Safety and Health, NIOSH), and Canadian (e.g. Canadian Standards Association, CSA);
- asking experts in relevant fields e.g. occupational health and safety.

Key words and database search strings:
Related to masks: masks, respirators, face coverings, non-pharmaceutical interventions (NPIs), respiratory protective devices.
Related to respiratory outbreaks: respiratory outbreak, respiratory pandemic, epidemic control, public health intervention,
Specific respiratory illness keywords: COVID-19, SARS-CoV-2, influenza, SARS (Severe Acute Respiratory Syndrome), MERS (Middle East Respiratory Syndrome).
Outcome and Effect Keywords: transmission rate, infection rate, disease spread, hospitalization rate, mortality rate, community transmission, effectiveness, impact, efficacy.
Mechanism keywords: aerosols, air filtration, filtration efficiency, adsorption, absorption, breathability, fit factor, mask efficiency, mask coatings, antibacterial
Database Search Strategies:
Combine keywords using Boolean operators (AND, OR, NOT).
Example: (mask*) AND (COVID-19 OR influenza) AND transmission rate
Use truncation (*) to capture variations of words.
Example: mask* will find masks, masking, etc.
Use phrase searching (quotation marks) to find exact phrases.
Example: public health intervention
Use MeSH terms (Medical Subject Headings) in PubMed/MEDLINE for more precise results.
Example Search Strings:
PubMed: (mask*[Title/Abstract] OR face covering[Title/Abstract]) AND (COVID-19[MeSH Terms] OR influenza[MeSH Terms]) AND (transmission[Title/Abstract] OR infection[Title/Abstract])
Google Scholar: mask* AND (respiratory outbreak OR pandemic) AND (transmission OR effectiveness)

These keywords and search strategies will be piloted in the specific databases and modified in response to emerging findings.

Participant or population Any setting where masks or respirators are tested.

Intervention Mask (cloth, medical, surgical) or respirator.

Comparator For associative studies, either no mask/respirator or a different kind of mask/respirator.

Study designs to be included No restriction in study design. We anticipate that a wide range of designs including a preponderance of laboratory and occupational health studies for the mechanistic component.

Eligibility criteria Empirical research studies (including evidence syntheses as a source of such studies) which contribute to establishing both the association between masking and reduction of respiratory disease transmission, and examining specific mechanism hypotheses underlying this association. Peer reviewed literature will be prioritised but if there is insufficient evidence on important aspects of the review question, publicly available preprints will be considered. Inconsistencies between study outcomes will be elucidated by exploring the cause of the inconsistency.

Information sources Electronic databases, sources known to the authors, topic experts in the field.

Main outcome(s) Whether, to what extent and why the introduction of mask wearing affects the incidence of respiratory infections. Whether existing studies—both associative and mechanistic—are adequate to answer these questions.

Additional outcome(s) These will be added as appropriate as the review unfolds.

Data management Data will be stored on University of Manchester, University of Oxford and University of Exeter computers. Eligible papers will be stored, organised and coded on an Endnote database. Data extraction will occur using summaries on Microsoft Office packages (e.g. Word, Excel). Specialist data management packages compliant with university data policies will be used if needed.

Quality assessment / Risk of bias analysis The study seeks to draw upon, challenge and extend the GRADE criteria and methodology for ranking and evaluating empirical evidence. With that in mind, we will use the GRADE checklists reflexively and critically rather than as a source of settled truth. Using appropriate GRADE checklists, primary studies will be critically appraised for trustworthiness (internal validity) e.g. risk of bias. As the GRADE process involves subjective judgments and is dependent on the expertise of the reviewers, input of topic experts will be sought as appropriate (e.g. from clinicians, occupational health and safety, engineers, aerosol scientists, statisticians etc).

Strategy of data synthesis Tables will be prepared of key studies, including author/year, study design, methods, sample, findings, strengths/limitations and comments.

Where appropriate, formal meta-analysis techniques will be applied to quantitative data to gain an estimate of effect size and confidence interval. Pooling will be limited to data collected from substantially identical studies, or those where there is a clear mechanistic justification for considering the conditions to be functionally equivalent. Where studies are too heterogeneous to justify meta-analysis, disaggregated data will be presented and an attempt will be made to understand how differences in study protocol and conditions explain the differing outcomes.

Qualitative evidence will be analysed thematically and with attention to key theories (e.g. of motivation, social influence and so on), and combined using the hermeneutic cycle in which each new data source is used to refine and enrich the understanding of the whole. In this way, rich explanations will be generated of how an effect may be obtained, should one exist, or why such an effect is not obtained.

Mechanistic evidence will be combined with associative evidence to produce an emerging synthesis of causality in mask mandates, thereby contributing further insights into the overall strength of evidence and to estimates of the generalisability (external validity) of particular empirical findings.

The findings from the mask mandate review will be used to inform the methodological objective of developing SR+ as a generalisable method for combining associative and mechanistic evidence; this aspect of the study will be described in a separate protocol.

Subgroup analysis Hypotheses about subgroup effects will be tested as appropriate if and when they emerge as the review unfolds.

Sensitivity analysis Sensitivity analyses will be undertaken as appropriate if and when they become necessary as the review unfolds.

Language restriction No restriction. Studies published in languages not spoken by the review authors will be translated.

Country(ies) involved United Kingdom (University of Oxford).

Keywords See search strategy above.

Dissemination plans Dissemination plans include preparation of academic papers, including methods and publication guidance for SR+ to be submitted to the EQUATOR network. In addition, we will produce training materials, build links with policymakers and advocacy groups, and hold a series of workshops for academic reviewers, evaluators and lay (e.g. advocacy) groups.

Contributions of each author

Author 1 - Trisha Greenhalgh - TG conceptualised the study along with JW and RH. She will be involved in all aspects of the review including searching, data extraction, data synthesis and writing up.
Email: trish.greenhalgh@phc.ox.ac.uk

Author 2 - Jon Williamson - JW is a philosopher who has worked on Evidential Pluralism. He conceptualised this study along with TG and RH. He will lead the methodological work package on the methodology of SR+, with input from all other authors.
Email: jon.williamson@manchester.ac.uk

Author 3 - Sahanika Ratnayake - SR has a background in philosophy and systematic review. She will undertake searching, data extraction, data synthesis and writing up.
Email: sahanika.ratnayake@manchester.ac.uk

Author 4 - Luana Poliseli - LP has a background in philosophy and science and technology studies. She will support other authors as needed in searching, data extraction, data synthesis and writing up.
Email: luana.poliseli@manchester.ac.uk

Author 5 - Rebecca Helm - RH has a background in law and policy relating to mask mandates. She will support other authors in appropriate aspects of the review.
Email: r.k.helm@exeter.ac.uk

Author 6 - Alexandra Trofimov - AT has a background in philosophy and law. She will support other authors as appropriate in this review.
Email: alexandra.trofimov@manchester.ac.uk

Author 7 - Mark Ungrin - MU brings expertise in associative and mechanistic evidence in mask research. He will support other authors as appropriate.
Email: mark.ungrin@gmail.com