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Impact of social distancing measures for preventing coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

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Abstract

Introduction: Social distancing measures (SDMs) protect public health from the outbreak of coronavirus disease 2019 (COVID-19). However, the impact of SDMs has been inconsistent and unclear. This study aims to assess the effects of SDMs (e.g. isolation, quarantine) for reducing the transmission of COVID-19.

Methods and analysis: We will conduct a systematic review meta-analysis research of both randomised controlled trials and non-randomised controlled trials. We will search MEDLINE, EMBASE, Allied & Complementary Medicine, COVID-19 Research and WHO database on COVID-19 for primary studies assessing the enablers and barriers associated with SDMs, and will be reported in accordance with PRISMA statement. The PRISMA-P checklist will be used while preparing this protocol. We will use Joanna Briggs Institute guidelines (JBI Critical Appraisal Checklists) to assess the methodological qualities and synthesised performing thematic analysis. Two reviewers will independently screen the papers and extracted data. If sufficient data are available, the random-effects model for meta-analysis will be performed to measure the effect size of SDMs or the strengths of relationships. To assess the heterogeneity of effects, I^2 together with the observed effects (Q-value, with degrees of freedom) will be used to provide the true effects in the analysis.

Ethics and dissemination: Ethics approval and consent will not be required for this systematic review of the literature as it does not involve human participation. We will be able to disseminate the study findings using the following strategies: we will be publishing at least one paper in peer-reviewed journals, and an abstract will be presented at suitable national/international conferences or workshops. We will also share important information with public health authorities as well as with the World Health Organization. In addition, we may post the submitted manuscript under review to bioRxiv, medRxiv, or other relevant pre-print servers.

Strengths and limitations of this study

- To our knowledge, this study will be the first systematic review to examine the factors impacting SDMs to reduce transmission of COVID-19.
- This study will offer highest level of evidence for informed decisions, drawing a broader framework.
- This protocol reduces the possibility of duplication, provides transparency to the methods and procedures that will be used, minimise potential biases and allows peer-review.
- This research is not externally funded, and therefore time and resource will be constrained.
- If included studies will be variable in sample size, quality and population, which may open to bias, and the heterogeneity of data will preclude a meaningful meta-analysis to measure the impact of specific SDMs

Introduction

Coronavirus disease 2019 (COVID-19; caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), emerged in Wuhan, China in December 2019, has been the biggest challenge for us in our lifetime posing a global public health threat. At the time of writing (1/6/20) WHO COVID-19 Situation Dashboard reported that this virus has already affected 216 countries with approximately 5,939,234 confirmed cases and 367,255 confirmed deaths; a fatality rate of approximately 6.18%, i.e. more than six deaths in every 100 confirmed cases. The highest number of confirmed cases were reported in the Americas (2,743,793) followed by Europe (2,142,547), Eastern Mediterranean (504,001) and South-East Asia (264, 015), whereas Western Pacific and Africa reported relatively low cases i.e. 182, 527 and 100,610 respectively.[1] In Europe, the UK has become the 'epicentre' of the pandemic.

Based on reported cases and deaths, this disease is portrayed as a great equaliser, but 1:10 reported infections were among health professionals, e.g. medical doctors, nurses and other healthcare professionals. Evidence further indicates that in England, Black, Asian and Minority Ethnic (BAME) groups recorded higher mortality, ranging from 1.5 (in Asian) to 7.3 (in Black Caribbean population) times compared to white individuals.[2] Similarly, COVID-19 mortality rate in the US for African Americans was 2.4-2.7 times more than white individuals. However, deaths are not consistent across these groups. Several factors could be

considered, e.g. ethnicity, age, sex, co-morbidities (diabetes, renal conditions), occupation, socioeconomic status, multifamily and multigenerational households.[2–4]

Similarly, it is difficult to predict an exact future, but recent data from Johns Hopkins University reported that global COVID-19 deaths have surpass over 370,000 worldwide [5]. Imperial College London highlights that this outbreak could kill 40 million people this year without public health measures (e.g. case finding, contact tracing and testing, and strict quarantine).[6] Evidence suggests that the number of cases reported would possibly "represent an underestimation of the true burden due to lack of surveillance and diagnostic capacity"[7] as well as pharmaceuticals to manage severe COVID-19.[8]

Several countries, including the UK, USA and other EU countries are adopting SDMs as a form of non-pharmaceutical or physical intervention. Social distancing is defined as a measure to ban large gatherings and advise individuals not to socialize outside their households by closing borders, some public places, schools and universities; isolation/quarantine, physical distancing and room separation to isolate symptomatic individuals and their contacts; and large-scale lockdowns of populations by staying at least 2m apart aiming to minimize mixing of infectious patients with susceptibles.[8] WHO recommends case finding, testing, isolation, contact tracing and quarantine of close contacts.[9]

A preliminary scan of the literature demonstrated some research on COVID-19 from China, South Korea, UK, USA and other countries, but these are very limited systemically reviewed or synthesised. Several rapid reviews and summaries have been covered on COVID-19 epidemiology,[10,11] the effectiveness of real-time PCR for diagnosis,[12] effects of school closure,[13] quarantine,[14,15] social distancing[16] (whose study was primarily based on two previous reviews[17,18] on influenza conducted in 2012 and 2018, respectively), and mathematical modelling studies incorporating the effect of social distancing.[8,19–27] These models would generally help to "predict epidemic curve representing the number of infections caused by the virus over time."[28]

Recently, few systematic review and meta-analysis conducted to investigate the optimum distance for avoiding transmissions and ethnicity and clinical outcomes.[4,29] Cochrane further conducted three studies. First, a rapid review in 2020, involving 29 studies on COVID-19, SARS, MERS plus other viruses from China, UK, South Korea and Japan.[30] Second, a rapid qualitative evidence synthesis conduced in 2020 capturing 36 studies from Asia, Africa, Central and North America and Australia examined healthcare workers' adherence and enablers or challenges associated with infection control guidelines for respiratory infections. Another study examined 67 studies including RCTs and observational

studies exploring the role of physical interventions for reducing the spread of respiratory viruses, and found no evidence regarding screening at entry ports and social distancing.[31]

Lewnard and Lo[7] and Michigan Medicine Projections[32] reported that combined SDMs or interventions using social isolation, quarantine, school closure, and workplace distancing appeared effective in reducing COVID-19 compared to no interventions at all. This approach, however, reported considerable challenges, e.g. societal disruption, social isolation/rejection, mental stress and psychological trauma, lack of tests and testing facilities, poor contact tracing, lack of surveillance. None of these studies examined the SDMs factors in reducing the transmission of COVID-19 systematically. We proposed a systematic review to assess the effects of SDMs (e.g. isolation, quarantine) for reducing the transmission of COVID-19.

Review question

What has been the impact of social distancing measures for preventing coronavirus disease 2019 [COVID-19]?

Methods and designs

This study will utilise a systematic review (SR), which will consider both randomised controlled trials and non-randomised trials (prospective and retrospective observational studies) of good-quality studies. SR is a research method that reviews relevant research literature, using systematic and explicit, accountable methods, to answer a specific research question objective.[33] Meta-analysis includes the statistical analysis for combining the results of a number of individual studies to produce summary results, e.g. pooled research studies.[34] The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist has been used in the preparation of this protocol.[35]

Criteria for considering studies for review

Inclusion criteria

1. Primary research describing SDMs, e.g. social distance, isolation and quarantine across all age groups.
2. Research reporting different factors and SDMs or social distancing interventions, e.g., social distance by avoiding crowds and restricting movement, isolating ill people and quarantine of exposed people (as a secondary outcome) and reducing transmission of

COVID-19 trend (as a primary outcome). Additional outcomes include – anxiety, depressions, physical and psychological distress,

3. Published peer-reviewed article using randomised controlled trials and non-randomised controlled trials
4. Articles published in English language regardless of the location (or settings) of the studies, up to May 2020.
   [We proposed to collect data from July/August until October 2020 for the study]

Exclusion criteria

1. Articles published in narrative reviews, modelling studies, opinion pieces, letters, news, editorials, perspectives, commentaries and any other publications lacking primary data, including grey literatures.
2. Studies deemed to have overall low quality.

Search strategy to identify relevant studies

Five major databases will be searched: MEDLINE, EMBASE, Allied & Complementary Medicine, COVID-19 Research and WHO database on COVID-19. The literature search use the following terms: “social distancing measures”, “social distancing”, “quarantine”, “patient isolation” combined with "COVID-19". Primary search terms are SDMs (all synonyms) and COVID-19 (all synonyms) using ‘Textword searching’ – searching for a word or phrase appearing anywhere in the document, where the document is the citation (article title, journal name, author), not the full text of an article, and ‘Thesaurus (MeSH, EMTREE) searching’, employing Boolean operators and truncations. To maximise sensitivity, a broad search strategy will be designed as shown in table 1. The ‘Related Articles’ feature in PubMed will be consulted. Searches will also be supplemented by reviewing the reference lists (‘references of references’) of selected articles to find any other relevant papers. We will also ask subject experts/information specialists from authors’ Universities to verify the research strategy, ensuring its comprehensiveness.

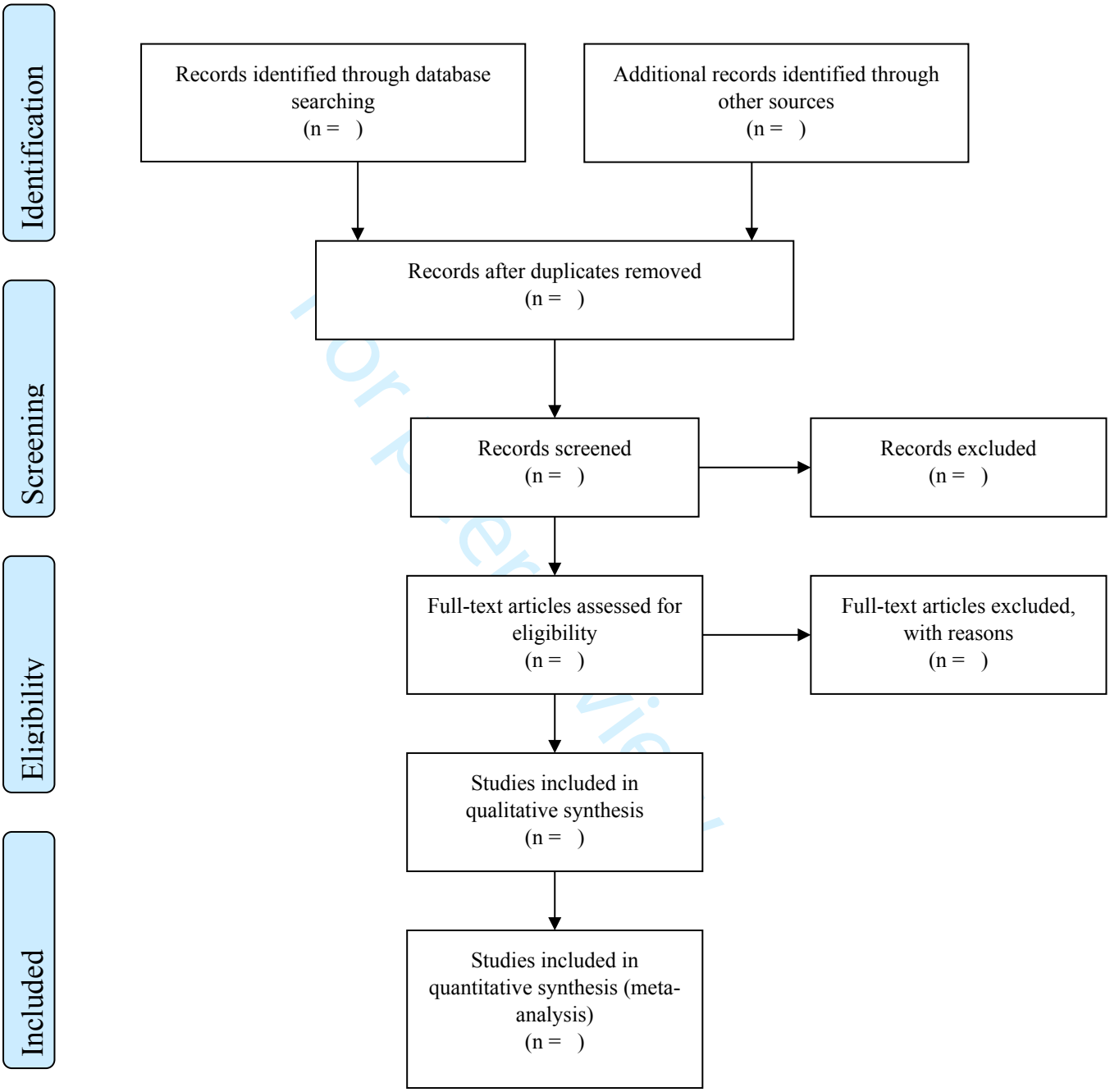
Table 1. Search strategy for the MEDLINE

Search	Search terms will be modified as needed for use in other databases
#1	social distancing
#2	social distance
#3	distancing
#4	isolation
#5	patient isolation
#6	patient isolators
#7	physical contact
#8	physical distancing
#9	quarantine
#10	quarantined
#11	#1 OR #2 OR #3 OR #4 OR#5 OR #6 OR #7 OR #8 OR#9 OR #10
#12	COVID-19
#13	2019 ncov
#14	2019-nCoV
#15	2019 novel coronavirus
#16	betacoronavirus
#17	Wuhan coronavirus
#18	coronavirus infections
#19	covid 19 pandemic
#20	sars cov 2
#21	SARS-CoV-2
#22	sars virus
#23	#12 OR #13 OR #14 OR #15 OR#16 OR #17 OR #18 OR #19 OR#20 OR #21 OR#22
#24	clinical trials
#25	cross-sectional studies
#26	Survey
#27	epidemiologic studies
#28	Quantitative research
#29	#24 OR #25 OR #26 OR #27 OR#28

Selection of studies

The citations identified through the searches will be imported into Mendeley Reference Manager (https://www.mendeley.com/). All studies emerging from the databases will be screened twice: i) screening of screening of titles, abstracts with two reviewer against minimum inclusion criteria, and ii) review of full text. We will use the standard PRISMA flow diagram to provide the process of study selection (figure 2).[36]

Figure 1. PRISMA flow diagram



Quality appraisal of included studies

Joanna Briggs Institute (JBI) critical appraisal checklists for randomised controlled trials and non-randomised controlled trials will use to assess the methodological qualities [37] (Box 1). All included studies will assess by two reviewers (KR, CML) using the standardised questions 4-item checklists i.e. Yes, No, Unclear and Not Applicable and the results will use to inform synthesis and interpretation of the findings. To facilitate comparison of appraisal

processes, all reviewers will record the rationale for inclusion or exclusion, and discrepancies will discuss and resolve by consensus.

Box 1. Critical appraisal checklist

JBI Critical Appraisal Checklists for randomized controlled trials and non-randomized experimental studies to appraise the retrieved studies with respect to the possibility of biases in their designs, conduct and analysis [37]. The results will be provided in Table 2, with number 1-13 (for Randomised control trials and 1-9 (for Non-randomised studies) representing satisfactory fulfilment of the corresponding criteria.

Randomised control trials

1) Was true randomization used for assignment of participants to treatment groups?
2) Was allocation to treatment groups concealed?
3) Were treatment groups similar at the baseline?
4) Were participants blind to treatment assignment?
5) Were those delivering treatment blind to treatment assignment?
6) Were outcomes assessors blind to treatment assignment?
7) Were treatment groups treated identically other than the intervention of interest?
8) Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?
9) Were participants analyzed in the groups to which they were randomized?
10) Were outcomes measured in the same way for treatment groups?
11) Were outcomes measured in a reliable way?
12) Was appropriate statistical analysis used?
13) Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Non-randomised studies

1) Is it clear in the study what is the 'cause' and what is the 'effect' (i.e. there is no confusion about which variable comes first)?
2) Were the participants included in any comparisons similar?
3) Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?
4) Was there a control group?
5) Were there multiple measurements of the outcome both pre and post the intervention/exposure?
6) Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?
7) Were the outcomes of participants included in any comparisons measured in the same way?
8) Were outcomes measured in a reliable way?
9) Was appropriate statistical analysis used?

Assessment of reporting biases

Publication bias, often called reporting bias and dissemination bias, refers to the concern that studies which report relatively large effects are more likely to be published as compared to studies reporting smaller effects.[38] Similarly, published studies that include multiple outcomes would be more likely to report the outcomes than if they showed statistically significant results.[39] One approach to address the publication bias is to follow the Trim and Fill procedures, i.e. assessing asymmetry or symmetry in the Funnel plot if more than 10 eligible studies are identified. This approach would estimate the extent of bias or estimate of the adjusted effect size.[40] We will use this approach while assessing the publication bias in the included studies, but Borenstein[38(p.165)] warns that the presence of bias will not automatically invalidate the results.

Data analysis and synthesis

A narrative synthesis, using thematic analysis, will be conducted for the included studies. We will also provide a descriptive numerical summary. We will use risk ratios (RRs), mean differences (MD), or standardised mean differences (SMD, where applicable, will be used for the dichotomous and continuous outcomes respectively.[38]

If sufficient data are available, i.e. identical on important factors and addressing the same fundamental question, to make an inference to a universe of comparable studies, the random-effects model for meta-analysis will be employed for the analysis to measure the effect size of SDMs or the strengths of relationships using the software Comprehensive Meta-Analysis (CMA, version 3. https://www.meta-analysis.com/pages/new_v3.php?cart=BT2P4569026). The purpose of using a random-effects model in the analysis is "to incorporate the assumption that the different studies are estimating different, yet related, intervention effects".[41] To assess the heterogeneity of effects, I^2 together with the observed effects (Q-value, with degrees of freedom) will be used to provide the true effects in the analysis. Q-value is the sum of the squared deviations of all effect sizes from the mean effect size. Generally, this value is on a standardised scale, so that a large deviation gets more weight if the estimate is precise, and less weight if the estimate is imprecise.[42] In fact, I^2 statistics does not tell us how much heterogeneity there is, but it tells what proportion of the observed variance reflects in true effect sizes rather than the sampling error. As such, it provides some context for understanding the forest plot.[43] If I^2 statistics is low (near zero), then most of the variable in the forest plot is due to sampling error. Conversely, if I^2 statistics is very high (say, more than 75%) then most of the variance in the

forest plot is due to variance in true effects. If we could somehow plot the variance of true effects, most of the variance would remain.[41]

Tabulating the included studies

Data from eligible studies will be extracted independently by two reviewers based on the summary of review studies (Table 2). As Rodgers and colleagues confirm, this would not only improve the process of transparency by better understanding what sorts of data extracted from which studies, but also recognising the contribution made by each study to the overall synthesis.[44] In addition, such tables will demonstrate how the individual study area contributes to the reviewers' final conclusion.

Table 2. Summary of reviewed studies

Study	Aims/study question	Country	Design/ method(s)	Number of subjects (sample size)	Critical appraisal checklists*	Reviewer comments

*Numbers in this column signify the quality criteria from Box 1 that studies were deemed to have met.

Dealing with missing data

In the case of missing data that might be important to summarise/synthesise the findings of the study or details of the studies are unclear, corresponding authors of included studies will be contacted.

Sub-group analysis

An a priori sub-group analysis will be planned, if data available, for:

(a) social distancing;

(b) isolation; and

(c) quarantine.

Risk of bias

Risk of bias will be examined, as it provides the variation, e.g. heterogeneity in the results of the studies included in the study. As Higgins et al.[41] argue, rigorously conducted studies in the systematic review would provide more truthful results, and the results from the studies of variable validity would give either false negative or false positive conclusions. Therefore,

assessing the risk of bias in all studies in any review is important. In assessing risk, we will create a table with a row for every relevant type of potential bias, and then classify each study on each row as having a low, unclear, or high risk of bias. In this study, the issue of bias will be kept separate from the core analysis – meaning analysis will be performed without worrying about the quality/bias. We will then use the risk of bias table to provide the context for the analysis.[38] As Borenstein[38(p.326)] suggests, "if the analysis shows a clinically and/or substantially important effect, we will assess the entirety of the evidence by considering the risk of bias as well." Generally, the bias table provides the type of bias (e.g., selective reporting of outcomes, random sequence generation, allocation of concealment, blinding of participants, personnel and assessors, incomplete outcome data and other potential threats to validity) in each study. If, for example, most rows are unshaded then that it is considered a low risk of bias, whereas if some (or all) rows are either partly shaded or dark (risk of bias will be either unclear or high), this would provide relatively less confidence in the results.[41] We will use both RoB 2 tool [45] for randomised and ROBINS-I tool [46] for non-randomised trials while assessing the risk of bias.

Patient and public involvement

As this is a protocol for a systematic review and meta-analysis, neither patients nor public participation will be directly involved, and ethics approval and consent will not be required either.

Dissemination

We will be able to disseminate the study findings using the following strategies: we will be publishing at least one paper in peer-reviewed journals, and an abstract will be presented at suitable national/international conferences or workshops. We will also share important information with public health authorities as well as with the World Health Organization. In addition, we may post the submitted manuscript under review to bioRxiv, medRxiv, or other relevant pre-print servers.

Discussion

To our knowledge, this study will be the first systematic review to examine the effects of SDMs (e.g. isolation, quarantine) for reducing the transmission of COVID-19.
enablers and barriers impacting SDMs to reduce transmission of COVID-19. Social distancing becomes a highly charged topic creating a lieu of debate among the politicians,

economists, medical and public health professions. The likelihood is that COVID-19 will become endemic, which suggests long-term behavioural adjustments.[47] Similarly, we argued that social distancing is not part of the culture in either developed or developing countries, for different reasons.[48] In developing countries, it is more related to population density, crowding, workplace conditions etc., such as overcrowding in public transport. In developed countries such as Switzerland, people were still following Swiss kiss as late as 20 March, when COVID-19 was already peaking. Similarly, some evidence shows some relationships between social distancing and economic aspects: poverty, living in slums etc. in developing countries; marginalized populations in developed countries. A similar issue has also been reported in the previous study.[49] Therefore, there is a need to completely change the way the economy, businesses, and life are organised to protect the vulnerable groups such as homeless, disabled, undocumented migrant workers and inmates. Similarly, home life should be looked at, as evidence suggests we need to change the way we interact at home, for example, with vulnerable family members – elderly, pregnant, immunocompromised due to chronic disease or protracted illnesses, at least until the pandemic is over, e.g. curbing the possibility of transferring the disease to the elderly. A recent descriptive review of data on disparities in the risk and outcomes from COVID19 in the UK has reported that:

> "The largest disparity found was by age. Among people already diagnosed with COVID19, people who were 80 or older were seventy times more likely to die than those under 40. Risk of dying among those diagnosed with COVID-19 was also higher in males than females; higher in those living in the more deprived areas than those living in the least deprived; and higher in those in Black, Asian and Minority Ethnic (BAME) groups than in White ethnic groups" [3]

Marmot et al.[50(p.13)] also argued that: "There are clear socioeconomic gradients in preventable mortality. The poorest areas have the highest preventable mortality rates and the richest areas have the lowest." We argue that public health has failed to convince politicians to take rapid action on prevention of spread or prepare for necessary treatment arrangements. Several authors reported that the "structure and capacity of our depleted healthcare system are now largely driving the response to this epidemic" and most likely "it will continue to do so until services that support local communicable disease control are rebuilt and reintegrated."[51,52]

The potential limitations of this study would be that if the retrieved studies would be variable in sample size, quality and population, which may open to bias, and the

heterogeneity of data precludes a meaningful meta-analysis to measure the impact of specific SDMs for COVID-19, therefore the findings might warrant generalisation. Second, methodologies might be poorly reported (mostly due to preprints - postings in MedRxiv), lacking comprehensive strategies for sampling and procedures, and lacking detail in data gathering and analysis. Wolkewitz and Puljak[53] warned that: "there are many methodological challenges related to producing, gathering, analysing, reporting and publishing data in condensed timelines required during a pandemic." Third, searching "social distancing" in different databases might be challenging mainly due to rapidly-growing COVID-19 studies in PubMed and other search interfaces, which are not visible in the major search databases (PubMed, EMBASE) due to i) indexing, and ii) often bibliographic databases failed to capture preprint and unpublished studies including registered clinical trials,[54,55] and the majority are commentaries, news, perspectives or opinions.[53] Finally, this research is not externally funded, and therefore time and resource will be constrained.

Nevertheless, this study will add to the literature on highlighting the major enablers and barriers of SDM in controlling COVID-19 in public health policy and interventions: i) given the fact that there is no vaccine or treatment available at the time of writing, and ii) there have been limited robust published studies of SDM success factors, with most studies exploring the process rather than hard or tangible outcomes. In addition, this review will provide a basis for developing the best methods and approaches in terms of developing objective measures and interventions to establish the link between different factors and SDMs (as a secondary outcome) and reducing transmission of COVID-19 trend (as a primary outcome) effectively, efficiently and equitably.

Contributors

KR conceived and designed the research with the advice from CML; KR wrote the first draft; KR and CML reviewed and contributed to drafting, revising and finalising the manuscript. All authors have reviewed and approved the final version of the manuscript and have given their permission for publication.

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Competing interests

The authors declare that they have no competing interests.

Patient consent for publication

Not required

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Impact of non-pharmaceutical interventions for reducing transmission of coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

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Abstract

Introduction: Implementing non-pharmaceutical interventions (NPIs) protect the public from coronavirus disease 2019 (COVID-19). However, the impact of NPIs has been inconsistent and remains unclear. This study, therefore, aims to measure the impact of NPIs (social distancing, social isolation and quarantine) on reducing COVID-19 transmission.

Methods and analysis: We will conduct a systematic review (SR) and meta-analysis (MA) research of both randomised and non-randomised controlled trials. We will undertake a systematic search of: MEDLINE, EMBASE, Allied & Complementary Medicine, COVID-19 Research, WHO database on COVID-19, ClinicalTrails.Gov for clinical trials on COVID-19, Cochrane Resources on Coronavirus (COVID-19), Oxford COVID-19 Evidence Service, Google Scholar for published and unpublished literatures on COVID-19 including pre-print engines such as medRxiv, bioRxiv, Litcovid and SSRN for unpublished studies on COVID-19, and will be reported in accordance with PRISMA. Outcomes of interest for impact analysis will include the reduction of COVID-19 transmission, avoiding crowds and restricting movement, isolating ill and psychological impacts. The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist has been used for this protocol. For quality of included studies, we will use the Cochrane Collaboration's tool for assessing risk of bias for randomised controlled trials and the Newcastle Ottawa scale for observational studies. The GRADE approach will grade the certainty of the evidence for all outcome measures across studies. A narrative synthesis – performing thematic analysis – will be conducted for all included studies. Random-effects model for meta-analysis will measure the effect size of NPIs or the strengths of relationships. To assess the heterogeneity of effects, I^2 together with the observed effects will be evaluated to provide the true effects in the analysis.

Ethics and dissemination: Ethics approval and consent will not be required for this systematic literature review, as it does not involve human participation. We will disseminate the study findings as follows: publishing at least one paper in peer-reviewed journals, and an abstract will be presented at suitable national/international conferences or workshops. We will also share important information with public health authorities as well as with the World

Health Organization (WHO). In addition, we may post the submitted manuscript under review to medRxiv, or other relevant pre-print servers.

Strengths and limitations of this study

- To our knowledge, this study is the first SR to measure the impact of NPIs – social distancing, isolation and quarantine – on reducing COVID-19 transmission.
- This study will offer the highest level of evidence to assist policy-makers and researchers in synthesising a large and complex literature, drawing a broader framework.
- This protocol reduces the possibility of duplication, provides transparency to the methods and procedures used, minimises potential biases and allows peer-review.
- This research is not externally funded, and therefore time and resource will be constrained.
- If included studies vary in sample size, quality and population, they may be open to bias, and the heterogeneity of data will preclude a meaningful meta-analysis to measure the effects of specific NPIs.

Introduction

Coronavirus disease 2019 (COVID-19; caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) emerged in Wuhan, China in December 2019, and has been posing a global public health threat. On March 11, 2020, WHO declared the COVID-19 outbreak a pandemic.[1] At the time of writing (August 10, 2020), the WHO COVID-19 Situation Dashboard reports that this virus has already affected 216 countries, areas or territories with 19,462,112 confirmed cases of COVID-19 and 722,285 deaths; a fatality rate of approximately 4% (3.71%).[2]

Based on reported cases, approximately 1:10 reported infections were among healthcare professionals, e.g. medical doctors, nurses.[3] We have seen disproportionate numbers of black, Asian and minority ethnic (BAME) doctors and other healthcare professionals die from COVID-19 in the UK. A study conducted by Cook and Lennane reported that in the National Health Service (NHS), it is estimated 21% of all staff are BAME, whereas 63% of healthcare professionals who died were BAME. Similarly, 20% of nursing staff are BAME whereas 64% of nurses who died were BAME, and 44% of medical staff are BAME whereas 95% of doctors who died were BAME.[4]

Similarly, the COVID-19 mortality rate in the USA for African-Americans was 2.4-2.7 times more than for White individuals.[3] However, deaths are not consistent across these groups. A recent UK government review[5] highlighted that the highest age-standardised diagnosis rates of COVID-19 per 100,000 population were in people of BAME groups (486 female and 649 male) and the lowest were in White people (220 female and 224 male). Accounting for the effect of sex, age, deprivation and region, Bangladeshi people had about twice the risk of death compared with White British. Similarly, Chinese, Indian, Pakistani, other Asian, Caribbean and other Black ethnicity had between 10 and 50% higher risk of death compared to White British. Death rates from COVID-19 were higher for BAME groups compared to White ethnic groups. In fact, this is the opposite of observations in previous years, when all-cause mortality rates were lower in BAME. Compared to previous years, all-cause mortality was almost four times higher than expected among Black males for this period, almost three times higher in Asian males and almost two times higher in White males. Among females, deaths were almost three times higher in this period in Black, Mixed and Other females, and 2.4 times higher in Asian females compared with 1.6 times in White females.[3,5]

Several factors could be considered, e.g. ethnicity, age, sex, co-morbidities (diabetes, renal conditions), occupation, socio-economic status, multifamily and multigenerational households.[6–8] Likewise, several studies identified physical and psychological impacts of COVID-19. The commonest associated factors reported were: anxiety,[9] increased time in quarantine associated with post-traumatic stress disorder, depression,[9] distance of physical activity,[10] loss of social interaction, and emotional and psychological distress.[11] One cross-sectional survey in Canada reported the psychological effects of quarantine:

> The mandated lack of social and, especially, physical contact with family members were identified as particularly difficult. Confinement at home and work, being unable to see friends, being unable to shop for basic necessities of everyday life, and being unable to purchase thermometers and prescribed medications enhanced their feeling of distance from the outside world.[9(p.10)]

It is difficult to predict an exact future, but recent data from Johns Hopkins University reported that global COVID-19 deaths have surpassed 700,000.[12] Imperial College London highlights that this outbreak could kill 40 million people this year without public health measures (e.g. case finding, contact tracing and testing, and strict quarantine).[7] Evidence suggests that the number of cases reported would possibly "represent an underestimation of

the true burden due to lack of surveillance and diagnostic capacity"[8] as well as pharmaceuticals to manage severe COVID-19.[13]

Several countries, including the United Kingdom (UK), United States of America (USA) and other European Union (EU) countries are adopting social distancing measure (SDM) as a form of non-pharmaceutical or physical interventions to control COVID-19 by slowing down transmission of the virus and preventing associated illness and death.[14] Social distancing (SD) is the new buzzword with the outbreak of coronavirus and COVID-19. In the literature, the term SD can have different meanings; for example, some considered it as strategy,[15] policy,[16] an approach to flatten the curve,[17] mitigation measure to increase physical distance or reduce frequency of congregation in socially dense community settings.[18–20] Flaxman et al.[13] defined SD as a measure to ban large gatherings and advise individuals not to socialise outside their households by closing borders, some public places, schools and universities; isolation/quarantine, physical distancing and room separation to isolate symptomatic individuals and their contacts; and large-scale lockdowns of populations by staying at least 2m apart aiming to minimise mixing of infectious susceptible patients. This definition of SD, in fact, is very vague and includes interventions which are considered different to social distancing, e.g. quarantine including school closure and case findings.

For clarity, in this SR, the definition of SD (also called physical distancing) is considered as a set of NPIs intended to prevent spread of COVID-19 by maintaining physical distance between people and reducing the number of times people come into close contact.[21,22] This review focuses only on COVID-19/SARS-CoV-2 and three major NPIs, namely social distancing, isolation and quarantine. Isolation of cases refers to the separation of ill persons with contagious diseases from non-infected persons, either hospitalised (moderate or severe cases) to provide care, or in dedicated isolation facilities or at home (mild cases),[23] and quarantine is the restriction of persons who are presumed to have been exposed to a contagious disease but are not ill, either because they did not become infected or because they are still in the incubation period.[24] WHO recommends isolation, physical (social) distancing, contact tracing and quarantine of close contacts as the key measures to reduce COVID-19.[25]s

A preliminary scan of the work (book, chapter, report or article) using a quick Google Scholar search and PubMed using variations on the ultimate search terms, e.g. COVID-19 and NPIs, shows some empirical research on COVID-19 from China, South Korea, UK, USA and other countries, but these are not systemically reviewed or synthesised well. Several rapid reviews and summaries have been covered on COVID-19 epidemiology,[26,27] the

effectiveness of real-time PCR for diagnosis,[28] effects of school closure,[29] quarantine,[30,31] social distancing[32] (study primarily based on two previous reviews[33,34] on influenza from 2012 and 2018, respectively), and mathematical modelling studies incorporating the effect of social distancing.[13,23,35–42] These models would generally help to "predict epidemic curve representing the number of infections caused by the virus over time."[43]

Recently, some SRs and MAs have been conducted to investigate the optimum distance for avoiding transmissions and ethnicity and clinical outcomes.[44,45] Cochrane further conducted three studies; First, a rapid review in 2020, involving 29 studies on COVID-19 from China, UK, South Korea and Japan.[46] Second, a rapid qualitative evidence synthesis conduced in 2020 capturing 36 studies from Asia, Africa, Central and North America and Australia examining healthcare workers' adherence and enablers or challenges associated with infection control guidelines for respiratory infections. Another study examined 67 studies including RCTs and observational studies exploring the role of physical interventions for reducing the spread of respiratory viruses, and found no evidence regarding screening at entry ports and social distancing.[47]

Lewnard and Lo[8] and Michigan Medicine Projections[48] reported that combined NPIs using social distancing, isolation and quarantine, including workplace distancing, appeared effective in reducing COVID-19 compared to no interventions. This approach, however, reported considerable challenges, e.g. societal disruption, social isolation/rejection, mental stress and psychological trauma, lack of tests and testing facilities, poor contact tracing and lack of surveillance. No studies examined the effects of NPIs in reducing the transmission of COVID-19. This study, therefore, aims to measure the impact of NPIs on reducing COVID-19 transmission.

Review question

What has been the impact of NPIs – social distancing, quarantine and isolation – on reducing transmission of coronavirus disease 2019 [COVID-19]?

Methods and designs

This study will utilise a SR and MA, which will consider both randomised controlled trials and non-randomised trials (prospective and retrospective observational studies). The PRISMA-P checklist has been used in the preparation of this protocol.[49] In addition, we also completed a 27-item PRISMA checklist (Additional file 1).

Criteria for considering studies for review

Inclusion criteria

1. Study design – we will not add a study design filter. To measure the impact of NPIs, we will follow both randomised controlled trials and non-randomised controlled trials, e.g. cross-sectional, survey, case-control, randomised controlled trials, observational studies (retrospective or prospective).
2. Intervention – we will include research describing major NPIs, e.g. social distance, isolation and quarantine focusing only COVID-19/SARS-CoV-2.
3. Population – we will include all age, gender, ethnic (Black, Asian, White) and healthcare workers (medical doctors, nurses, allied healthcare professions) groups.
4. Research reporting different factors and NPIs, e.g., social distance by avoiding crowds and restricting movement, isolating ill people and quarantine of exposed people and reducing transmission of COVID-19. Where possible, additional outcomes including anxiety, physical and psychological distress and depression will be examined.
5. Articles published in English language, regardless of study location or setting, up to July 2020. [We proposed to collect data from August/September until October/November 2020 for the study]

Exclusion criteria

1. Articles in narrative reviews, modelling studies, opinion pieces, letters, news, editorials, perspectives, commentaries, conference abstracts and other publications lacking primary data and/or poor methodological details.
2. Studies containing duplicate datasets.

Search strategy to identify relevant studies

We aim to undertake a systematic search of the following sources: MEDLINE, EMBASE, Allied & Complementary Medicine, COVID-19 Research, WHO database on COVID-19, ClinicalTrials.Gov for clinical trials on COVID-19, Cochrane Resources on Coronavirus (COVID-19), Oxford COVID-19 Evidence Service, Google Scholar for published and unpublished literatures on COVID-19 including pre-print engines such as medRxiv, bioRxiv, Litcovid and SSRN for unpublished studies on COVID-19 will be searched given the lags in publication. The literature search uses the following terms: “social distancing”, “quarantine”, “isolation”, “non-pharmacological interventions [NPIs]”, “psychological distress”, “anxiety”

combined with "COVID-19". Primary search terms are non-pharmacological interventions or measures (all synonyms) and COVID-19 (all synonyms) using 'Textword searching' – searching for a word or phrase anywhere in the document, where the document is the citation (article title, journal name, author), not the full text of an article, and 'Thesaurus (MeSH, EMTREE) searching', employing Boolean operators and truncations. The 'Related Articles' feature in PubMed will be consulted. Searches will also be supplemented by reviewing the reference lists ('references of references') of selected articles to find any other relevant papers. From the identified studies in the search, forward and backward citations will also be carried out to find potential studies reporting NPIs and reducing transmission of COVID-19 for the full texts. The literature search strategy was developed by KR in collaboration with departmental subject librarians from authors' universities, who were experienced in SRs, and subsequently refined ensuring its comprehensiveness. While piloting the search strategy, we followed these broad steps:

- Tested out keywords and phrases in a MEDLINE database to see the number of hits returned, and assessed the degree of relevance;
- Reviewed some (e.g. five) papers including those marked 'highly cited' on COVID-19/SARS-CoV-2 that meet inclusion/exclusion criteria, where we looked at the terms used in the titles and abstracts for main concepts e.g. NPIs and COVID-19.
- Took notes of keywords supplied by authors and incorporated those into our strategy.
- Experimented with combinations of keywords using 'AND' (limits search) and 'OR' (expands search) operators.
- Looked at subject headings assigned for key papers and used them too.

A broad search strategy has been designed to maximise the level of sensitivity (or comprehensiveness) in searching,[50] and improve both *recall ratio* (number of relevant references retrieved divided by all of the relevant references) and *precision ratio* (number of relevant references retrieved divided by the number of references retrieved).[51(p.34)] Key terms for one MEDLINE are shown in Table 1.

Table 1. Search strategy for MEDLINE

Concepts	Search terms in each concepts will be modified as needed for use in other databases
Concept #1	***P**roblem: COVID-19/*
	"covid 19 pandemic"[All Fields] OR "COVID19"[All Fields] OR "COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "2019-nCoV"[All Fields] OR "2019nCoV"[All Fields] OR "coronavirus infections"[All Fields] OR "coronavirus infections"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronavirus"[All Fields] OR "coronavirus"[MeSH Terms] OR "coronavirus"[MeSH Terms] OR "Betacoronavirus"[MAJR] "SARS coronavirus2"[All Fields] "sars cov"[All Fields] OR "sars virus"[All Fields] OR "sars virus"[MeSH Terms] OR "SARS"[All Fields] OR "SARS2"[All Fields] OR "SARS-2"[All Fields] OR "SARScoronavirus 2"[All Fields] OR "SARScoronavirus2"[All Fields] OR "SARS-coronavirus-2"[All Fields] OR"SARS-CoV-2"[All Fields] OR "SARSCov2019*"[All Fields] OR "SARS-Cov2019*"[All Fields] OR "SARS-Cov-2019*"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "Wuhan coronavirus"[All Fields] OR "Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "COVID-19"[nm]
Concept #2	***I**ntervention: Non-Pharmaceutical Intervention*
	“social distancing"[TIAB] OR "cohorting"[All Fields] OR "community containment"[All Fields] OR "isolation strategy"[All Fields] OR "isolation"[All Fields] OR "patient isolation"[All Fields] OR "patient isolation"[MeSH Terms] OR "patient isolators"[All Fields] OR "patient isolators"[MeSH Terms] OR "physical contact"[All Fields] OR "physical distancing"[All Fields] OR "quarantine"[All Fields] OR "quarantines"[All Fields] OR "quarantine"[MeSH Terms] OR "social distance"[All Fields] OR “quarantines”[All Fields] OR “quarantined”[All Fields] OR “quarantining”[All Fields] OR "social distance"[MeSH Terms] OR "Social distancing"[All Fields] OR "Banning"[All Fields] OR "distancing"[All Fields]
Concept #3	***O**utcome: (a) Reduce transmission*
	"reduce"[All Fields] OR "reduced"[All Fields] OR "reduces"[All Fields] OR "transmission"[MeSH Subheading] OR "transmission"[All Fields] OR "transmissions"[All Fields] OR "prevention and control"[Subheading] OR prevention[Text Word] OR "reduce infection"[All Fields] OR infect"[All Fields] OR "infectability"[All Fields] OR "infectable"[All Fields] OR "infectant"[All Fields] OR "infectants"[All Fields] OR "infected"[All Fields] OR "infecteds"[All Fields] OR "infectibility"[All Fields] OR "infectible"[All Fields] OR "infecting"[All Fields] OR "infection s"[All Fields] OR "infections"[MeSH Terms] OR "infections"[All Fields] OR "infection"[All Fields] OR "infective"[All Fields] OR "infectiveness"[All Fields] OR "infectives"[All Fields] OR "infectivities"[All Fields] OR "infects"[All Fields] OR "pathogenicity"[MeSH Subheading] OR

	"pathogenicity"[All Fields] OR "infectivity"[All Fields] OR "Coronavirus Infections/prevention and control"[MAJR] OR "Pandemics/prevention and control"[MAJR]
Concept #4	***O**utcome: (b) Psychological impact*
	"psychological distress"[MeSH Terms] OR psychological distress[Text Word] "emotional disturbance"[All Fields] OR "depressed"[All Fields] OR "depression"[MeSH Terms] OR "depression"[All Fields] OR "depressions"[All Fields] OR "depression s"[All Fields] OR "depressive disorder"[MeSH Terms] OR "depressive"[All Fields] OR "depressives"[All Fields] OR depression[Text Word] OR "stress"[All Fields] OR "stressed"[All Fields] OR "stresses"[All Fields] OR "stressful"[All Fields] OR "stressfulness"[All Fields] OR "stressing"[All Fields] OR "low mood"[All Fields] OR "insomnia"[All Fields] OR "insomnias"[All Fields] OR insomnia[Text Word] OR "insomnia's"[All Fields] OR "sleep initiation and maintenance disorders"[MeSH Terms] OR "sleep initiation and maintenance disorders"[All Fields]

We combined these concepts (using AND), so all concepts are in the same references.

Selection of studies

The citations identified will be imported into Mendeley Reference Manager (https://www.mendeley.com/). All studies emerging from the databases will be screened twice: (i) screening of titles, abstracts with two reviewers against minimum inclusion criteria, and (ii) review of full text. We will use the standard PRISMA flow diagram to provide the study selection process.[52]

Quality assessment and risk of bias

Quality of the included studies will be assessed using Cochrane Collaboration's tool for assessing risk of bias for randomised controlled trials and the Newcastle Ottawa scale (NOS) for non-randomised studies.[53] Where possible, we will analyse randomised (according to effectiveness of randomisation method, generation of allocation sequence, allocation concealment, blinding, and follow-up) and non-randomised studies (for presence of potential confounders for case-control and cohort studies), and a three-point checklist will be used for controlled before and after studies[54] separately. In NOS, "a 'star system' has been developed in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively".[53] Some items or questions in these quality assessments e.g. blinded study, are irrelevant to social distancing studies; we therefore consider removing them. Risk of bias will be examined, as it provides variation,

e.g. heterogeneity in results of studies included in the study. As Higgins et al.[50] argue, rigorously conducted studies in the SR would provide more truthful results, and the results from the studies of variable validity would give either false negative or false positive conclusions. In this study, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach will be used to assess the certainty of the evidence – risk of bias across studies.[55]

Generally, the bias table provides the type of bias (e.g., selective reporting of outcomes, random sequence generation, allocation of concealment, blinding of participants, personnel and assessors, incomplete outcome data and other potential threats to validity) in each study. If, for example, most rows are unshaded then that is considered a low risk of bias, whereas if some rows are either partly-shaded or dark (risk of bias either unclear or high), this would provide relatively less confidence in the results.[50] A narrative synthesis – performing thematic analysis – will be conducted for all included studies. Included studies will be assessed by two authors (KR, CML) and the results will inform synthesis and interpretation of the findings. To facilitate comparison of appraisal processes, all reviewers will record the rationale for inclusion or exclusion, and discrepancies will be discussed and resolved by consensus.

Assessment of reporting biases

Publication bias, often called reporting bias and dissemination bias, is the concern that studies reporting relatively large effects are more likely to be published than studies reporting smaller effects.[56] Similarly, published studies including multiple outcomes would be more likely to report the outcomes than if they showed statistically significant results.[57] We will use funnel plot to estimate the publication bias.[58] If meta-analysis had captured all relevant studies we would expect the funnel plot to be symmetric, i.e. we would expect studies to be dispersed equally on either side of the overall effect.[56] One approach to address publication bias is to follow the trim and fill procedures, i.e. assessing asymmetry or symmetry in the funnel plot if more than 10 eligible studies are identified.[56(p.175)] Trim and fill is a method which allows us to impute these studies, i.e. we determine where missing studies are likely to fall, add them to the analysis, and then recompute the combined effect. There are two parts to this method: first we impute the missing data, then re-run the analysis with the original studies plus the imputed ones, using either a fixed-effect or random-effects model. Though several studies have shown the trim and fill method may not perform well in the presence of

very high heterogeneity,[59–62] this method is equally useful for sensitivity analysis and gives less biased estimates when there is both heterogeneity and publication bias.[61] In fact, high heterogeneity may impact the many publication bias methods based on the funnel plot, not limited to the trim and fill method.[60,62]

Data analysis and synthesis

A narrative synthesis, performing thematic analysis, will be conducted for the included studies. We will also provide a descriptive numerical summary. We will use risk ratios (RRs), mean differences (MD), or standardised mean differences (SMD) where applicable, for the dichotomous and continuous outcomes, respectively.[56]

All data analyses will be carried out using Comprehensive Meta-Analysis (CMA, version 3. https://www.meta-analysis.com/pages/new_v3.php?cart=BT2P4569026) to measure the effect size of NPIs or the strengths of relationships employing random-effects method for meta-analysis. The purpose of using a random-effects model in the analysis is "to incorporate the assumption that the different studies are estimating different, yet related, intervention effects".[50] To test the heterogeneity of effects in the included studies, we will use Higgins et al.'s I^2 together with the observed effects to measure the true effects in the analysis.[50] The I^2 test for heterogeneity is meant to evaluate whether there is variability across publications. This will be computed as follows:

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

Q-value (Cochran's heterogeneity statistic) is the sum of the squared deviations of all effect sizes from the mean effect size and *df* indicates the degrees of freedom. Generally, this value is on a standardised scale between 0% (not heterogeneity) and 100% (maximum heterogeneity), where a large deviation gets more weight if the estimate is precise, and less weight if the estimate is imprecise.[63] A rough guide, it is interpreted that: 0%-40% might not be important, 30%-60% may represent moderate heterogeneity, 50%-90% may represent substantial heterogeneity, and 75%-100% may represent considerably heterogeneity.[50] Generally, the importance of observed value of I^2 on moderate and substantial heterogeneity depends on the magnitude and direction of effects as well as the strength of heterogeneity.[50,63]

Tabulating included studies

Data from eligible studies will be extracted independently by two authors using a data extraction form to record demographic data (including age, gender, ethnicity, professions), study details (aims/study question, country of origin, methods/study designs, NPI(s)), and study outcomes. As Rodgers and colleagues confirm, this would not only improve the process of transparency by better understanding the sorts of data extracted from which studies, but also recognising the contribution made by each study to the overall synthesis.[64] In addition, such tables will demonstrate how the individual study area contributes to the reviewers' final conclusion.

Dealing with missing data

In the case of missing data that might be important to summarise/synthesise study findings, or details of the studies are unclear, we will contact all corresponding authors of included studies to give the opportunity to provide missing data. If authors do not respond, we will record the fact that we tried to contact them, and the number of non-respondents. In such cases, we can either use imputation or risk of bias tools to reduce the likelihood of this being problematic. Generally it is considered that non-responding authors are equivalent to non-responders to interviews in observational/experimental studies. The impact of this will be reported in the discussion section of the SR.

Subgroup analysis

We anticipate much variation on the type and nature of NPIs or settings in relation to COVID-19. Based on the scoping search, it is difficult to disentangle the individual effect of each NPI on reducing or preventing COVID-19 transmission, as the role of combined NPIs have been often reported in different literatures, therefore we do not consider a subgroup analysis to measure which NPIs would be more effective than others. However, some emerging data confirmed cases of COVID-19 and deaths amongst (i) different healthcare professionals (medical doctors, nurses, allied healthcare professionals) and (ii) socio-economic groups (Black, Asian, White) therefore we will be doing a subgroup analysis examining the association between NPIs and cases/deaths from COVID-19/SARS-CoV-2 on those specific groups when applicable. As Higgins et al. argue, "subgroup analyses are observational by nature and are not based on randomised comparisons" so results from such multiple subgroup analyses may be misleading. [50]

Patient and public involvement

As this is a protocol for a SR and MA, neither patients nor public will be directly involved, and ethics approval and consent will not be required.

Dissemination

We will be able to disseminate the study findings as follows: publishing at least one paper in peer-reviewed journals, and abstract presented at suitable national/international conferences or workshops. We will also share important information with public health authorities as well as with the WHO. In addition, we may post the submitted manuscript under review to bioRxiv, medRxiv, or other relevant pre-print servers.

Discussion

Impact of NPIs on preventing COVID-19 is a highly charged topic creating much debate among politicians, economists, and medical and public health professions. Given the rapidly-growing field, it is imperative to generate a substantial conclusion regarding the prevention, control and management of COVID-19 in public health practice. The proposed SR will therefore measure the impact of NPIs on reducing transmission of COVID-19. As such, significant outcomes from this review will guide patients and clinicians in their treatment arrangements given that there is no vaccine or treatment available at the time of writing. Furthermore, these significant findings will be vital to assist policy-makers and researchers in synthesising a large and complex literature. Similarly, this review will provide a basis for developing the best methods and approaches for developing objective measures and interventions to establish the link between different factors and NPIs and reducing transmission of COVID-19 effectively, efficiently and equitably. It is equally important that the "structure and capacity of our depleted healthcare system are now largely driving the response to this epidemic"[65] and most likely it will continue to do so until services that support local communicable disease control are rebuilt and reintegrated.[66] It is, therefore, important to make appropriate efforts now that would address COVID-19, through strengthening the primary healthcare system, to reduce the chances of future pandemics.

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Contributors

KR conceived and designed the research with the advice from CML; KR wrote the first draft; KR and CML reviewed and contributed to drafting, revising and finalising the manuscript. All authors have reviewed and approved the final version of the manuscript and have given their permission for publication.

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Competing interests

None declared.

Patient consent for publication

Not required.

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Additional file

Additional file 1: PRISMA checklist.

Additional file 1. PRISMA 2009 Checklist

Impact of non-pharmaceutical interventions for reducing transmission of coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

Section/topic	#	Checklist item	Reported on page #	Notes
TITLE				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2	Title page
ABSTRACT				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2	
INTRODUCTION				
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-6	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6	
METHODS				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not registered	Refer to the recently published preprint study protocol: https://www.medrxiv.org/content/10.1101/2020.06.13.20130294v1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9-10	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	11	

Additional file 1. PRISMA 2009 Checklist

Impact of non-pharmaceutical interventions for reducing transmission of coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	13	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	12	

Section/topic	#	Checklist item	Reported on page #	Notes
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	13	
RESULTS				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	NA	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA	

Additional file 1. PRISMA 2009 Checklist

Impact of non-pharmaceutical interventions for reducing transmission of coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA	
DISCUSSION				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	NA	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14	
FUNDING				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Impact of non-pharmaceutical interventions for reducing transmission of coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

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Impact of non-pharmaceutical interventions for reducing transmission of coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

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Abstract

Introduction: Implementing non-pharmaceutical interventions (NPIs) protect the public from coronavirus disease 2019 (COVID-19). However, the impact of NPIs has been inconsistent and remains unclear. This study, therefore, aims to measure the impact of major NPIs (social distancing, social isolation and quarantine) on reducing COVID-19 transmission.

Methods and analysis: We will conduct a systematic review (SR) and meta-analysis (MA) research of both randomised and non-randomised controlled trials. We will undertake a systematic search of: MEDLINE, EMBASE, Allied & Complementary Medicine, COVID-19 Research, WHO database on COVID-19, ClinicalTrails.Gov for clinical trials on COVID-19, Cochrane Resources on Coronavirus (COVID-19), Oxford COVID-19 Evidence Service, Google Scholar for published and unpublished literatures on COVID-19 including pre-print engines such as medRxiv, bioRxiv, Litcovid and SSRN for unpublished studies on COVID-19, and will be reported in accordance with PRISMA. Outcomes of interest for impact analysis will include the reduction of COVID-19 transmission, avoiding crowds and restricting movement, isolating ill and psychological impacts. The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist has been used for this protocol. For quality of included studies, we will use the Cochrane Collaboration's tool for assessing risk of bias for randomised controlled trials and the Newcastle Ottawa scale for observational studies. The GRADE approach will grade the certainty of the evidence for all outcome measures across studies. Random-effects model for meta-analysis will measure the effect size of NPIs or the strengths of relationships. For quantitative data, risk ratio or odds ratio, absolute risk difference (for dichotomous outcome data), or mean difference or standardised mean difference (for continuous data) and their 95% confidence intervals we will be calculated. Where statistical pooling is not possible, a narrative synthesis, will be conducted for the included studies. To assess the heterogeneity of effects, I^2 together with the observed effects will be evaluated to provide the true effects in the analysis.

Ethics and dissemination: Ethics approval and consent will not be required for this systematic literature review, as it does not involve human participation. We will disseminate the study findings as follows: publishing at least one paper in peer-reviewed journals, and an

abstract will be presented at suitable national/international conferences or workshops. We will also share important information with public health authorities as well as with the World Health Organization (WHO). In addition, we may post the submitted manuscript under review to medRxiv, or other relevant pre-print servers.

Registration: International Prospective Register of Systematic Reviews (PROSPERO) registration number CRD42020207338.

Strengths and limitations of this study

- To the best of our knowledge, this study is the first SR to measure the impact of NPIs – social distancing, isolation and quarantine – on reducing COVID-19 transmission.
- This study will offer the highest level of evidence to assist policy-makers and researchers in synthesising a large and complex literature, drawing a broader framework.
- This protocol reduces the possibility of duplication, provides transparency to the methods and procedures used, minimises potential biases and allows peer-review.
- This research is not externally funded, and therefore time and resource will be constrained.
- If included studies vary in sample size, quality and population, they may be open to bias, and the heterogeneity of data will preclude a meaningful meta-analysis to measure the effects of specific NPIs.

Introduction

Coronavirus disease 2019 (COVID-19; caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) emerged in Wuhan, China in December 2019, and has been posing a global public health threat. On March 11, 2020, WHO declared the COVID-19 outbreak a pandemic.[1] At the time of writing (September 12, 2020), the WHO COVID-19 Situation Dashboard reports that this virus has already affected 216 countries, areas or territories with 28,040,853 confirmed cases of COVID-19 and 906,092 deaths; a fatality rate of approximately 4% (3.23%).[2]

Based on reported cases, approximately 1:10 reported infections were among healthcare professionals, e.g. medical doctors, nurses.[3] We have seen disproportionate numbers of black, Asian and minority ethnic (BAME) doctors and other healthcare professionals die from COVID-19. A study conducted by Cook and Lennane reported

that in the UK National Health Service (NHS), it is estimated 21% of all staff are BAME, whereas 63% of healthcare professionals who died were BAME.[4] A recent UK government review[5] highlighted that the highest age-standardised diagnosis rates of COVID-19 per 100,000 population were in people of BAME groups (486 female and 649 male) and the lowest were in White people (220 female and 224 male). Accounting for the effect of sex, age, deprivation and region, Bangladeshi people had about twice the risk of death compared with White British. Similarly, Chinese, Indian, Pakistani, other Asian, Caribbean and other Black ethnicity had between 10 and 50% higher risk of death compared to White British. In fact, this is the opposite of observations in previous years, when all-cause mortality rates were lower in BAME.[3,5]

Similarly, the COVID-19 mortality rate in the USA for African-Americans was 2.4-2.7 times more than for White individuals.[3] However, death rates are not consistent across these groups. Inequalities in COVID-19 mortalities are rife, which is most recently shown by Public Health England.[6] Several factors were identified as risks for COVID-19, e.g. ethnicity, age, sex, co-morbidities (diabetes, renal conditions), occupation, socio-economic status, and multifamily and multigenerational households.[6–8]

Recent data from Johns Hopkins University reported that global COVID-19 deaths have surpassed 890,000.[9] Imperial College London highlights that this outbreak could kill 40 million people this year without public health measures (e.g. case finding, contact tracing and testing, and strict quarantine).[7] Evidence suggests that the number of cases reported would possibly "represent an underestimation of the true burden due to lack of surveillance and diagnostic capacity"[8] as well as pharmaceuticals to manage severe COVID-19.[10]

Several countries, including the United Kingdom (UK), United States of America (USA) and other European Union (EU) countries are adopting social distancing (SD) measure as a form of non-pharmaceutical or physical interventions to control COVID-19 by slowing down transmission of the virus and preventing associated illness and death.[11] SD is the new buzzword with the outbreak of coronavirus and COVID-19. In the literature, the term SD can have different meanings; for example, some considered it as strategy,[12] policy,[13] an approach to flatten the curve,[14] mitigation measure to increase physical distance or reduce frequency of congregation in socially dense community settings.[15–17] Flaxman et al.[10] defined SD as a measure to ban large gatherings and advise individuals not to socialise outside their households by closing borders, some public places, schools and universities; isolation/quarantine, physical distancing and room separation to isolate symptomatic individuals and their contacts; and large-scale lockdowns of populations by staying at least

2m apart aiming to minimise mixing of infectious susceptible patients. This definition of SD, in fact, is very vague and includes interventions which are considered different to SD, e.g. quarantine including school closure and case findings.

For clarity, in this SR, the definition of SD (also called physical distancing) is considered as a set of NPIs intended to prevent spread of COVID-19 by maintaining physical distance between people and reducing the number of times people come into close contact.[18,19] This review focuses only on COVID-19/SARS-CoV-2 and three major NPIs, namely SD, isolation and quarantine. Isolation of cases refers to the separation of ill persons with contagious diseases from non-infected persons, either hospitalised (moderate or severe cases) to provide care, or in dedicated isolation facilities or at home (mild cases),[20] and quarantine is the restriction of persons who are presumed to have been exposed to a contagious disease but are not ill, either because they did not become infected or because they are still in the incubation period.[21] WHO recommends isolation, physical (social) distancing, contact tracing and quarantine of close contacts as the key measures to reduce COVID-19.[22]

A scoping search of MEDLINE was done on 9 September 2020 for publications entered by the end of August 2020 with the following terms: ((“COVID-19” OR “SARS-CoV-2”) AND (“systematic review” OR “literature search” OR “meta-analysis” OR “evidence synthesis”) AND (“social distancing” OR “isolation” OR “quarantine”)). It revealed some empirical research on COVID-19 from China, South Korea, the UK, the USA and other countries, but these are not systemically reviewed or synthesised well. Several rapid reviews and summaries have been covered on COVID-19 epidemiology,[23,24] the effectiveness of real-time PCR for diagnosis,[25] effects of school closure,[26] quarantine,[27,28] SD[29] (study primarily based on two previous reviews[30,31] on influenza from 2012 and 2018, respectively), and mathematical modelling studies incorporating the effect of SD.[10,20,32–39] These models would generally help to “predict epidemic curve representing the number of infections caused by the virus over time.”[40]

Recently, some SRs and MAs have been conducted to investigate ethnicity and clinical outcomes.[41] Chu and colleagues[42] published a systematic review including physical distancing to investigate the optimum distance for avoiding person-to-person transmissions, focusing more on face masks and eye protection. Though their study was, perhaps, the first rapidly synthesised review, and identified 172 studies across 16 countries and six continents, none of the included studies were randomised controlled trials, therefore their findings might suffer from both recall and measurement biases. Cochrane further conducted three studies; First, a rapid review in 2020, involving 29 studies on COVID-19 from China, UK, South

Korea and Japan.[43] Second, a rapid qualitative evidence synthesis conduced in 2020 capturing 36 studies from Asia, Africa, Central and North America and Australia examining healthcare workers' adherence and enablers or challenges associated with infection control guidelines for respiratory infections. Another study examined 67 studies including RCTs and observational studies exploring the role of physical interventions for reducing the spread of respiratory viruses, and found no evidence regarding screening at entry ports and SD.[44]

Lewnard and Lo[8] and Michigan Medicine Projections[45] reported that combined NPIs using SD, isolation and quarantine, including workplace distancing, appeared effective in reducing COVID-19 compared to no interventions. This approach, however, reported considerable challenges, e.g. societal disruption, social isolation/rejection, mental stress and psychological trauma, lack of tests and testing facilities, poor contact tracing and lack of surveillance. No studies examined the combined effects of NPIs in reducing the transmission of COVID-19. This study, therefore, aims to measure the impact of NPIs on reducing COVID-19 transmission.

Review question

What has been the impact of NPIs – social distancing, quarantine and isolation – on reducing transmission of coronavirus disease 2019 [COVID-19]?

Methods and designs

This study will utilise a SR and MA, which will consider both randomised controlled trials and non-randomised trials (prospective and retrospective observational studies). The PRISMA-P checklist has been used in the preparation of this protocol.[46] In addition, we also completed a 27-item PRISMA checklist, which is included in the online supplementary file (Additional file 1).

Criteria for considering studies for review

Inclusion criteria

1. Types of participants – this review will consider all studies that involve human subjects of any age-gender, including ethnic (Black, Asian, White) and healthcare workers (medical doctors, nurses, allied healthcare professions) groups.
2. Types of intervention – we will include research describing three major NPIs, e.g. social distance, isolation and quarantine focusing only COVID-19/SARS-CoV-2.

3. Types of outcome measure. Primary outcomes include: COVID-19; reducing the risk of transmission/infection of COVID-19; hospitalisation, ICU admissions, COVID-19 related complications, quality of life; and mortality and morbidity. Secondary outcomes include changes in social behaviour, e.g. social distancing by avoiding crowds, restricting movements, isolating ill patients and quarantine of exposed people.
4. Types of studies. No study design filter is added, and there is no limit on our search by language. To measure the impact of NPIs, this review considers all studies evaluating the effectiveness of NPIs relating to reducing the risk of transmission/infection of COVID-19. We include both randomised controlled trials and non-randomised controlled trials, e.g. cross-sectional, survey, case-control, randomised controlled trials, and observational studies (retrospective or prospective).

Exclusion criteria

1. Articles in narrative reviews, modelling studies, opinion pieces, letters, news, editorials, perspectives, commentaries, conference abstracts and other publications lacking primary data and/or poor methodological details.
2. Studies containing duplicate datasets.

Search strategy to identify relevant studies

We aim to undertake a systematic search of the following sources: MEDLINE, EMBASE, Allied & Complementary Medicine, COVID-19 Research, WHO database on COVID-19, ClinicalTrials.Gov for clinical trials on COVID-19, Cochrane Resources on Coronavirus (COVID-19), Oxford COVID-19 Evidence Service, Google Scholar for published and unpublished literatures on COVID-19 including pre-print engines such as medRxiv, bioRxiv, Litcovid and SSRN for unpublished studies on COVID-19 will be searched given the lags in publication. The literature search uses the following terms: “social distancing”, “quarantine”, “isolation”, “non-pharmacological interventions” combined with “COVID-19”. Primary search terms are non-pharmacological interventions or measures (all synonyms) and COVID-19 (all synonyms) using ‘Textword searching’ – searching for a word or phrase anywhere in the document, where the document is the citation (article title, journal name, author), not the full text of an article, and ‘Thesaurus (MeSH, EMTREE) searching’, employing Boolean operators and truncations. The ‘Related Articles’ feature in PubMed will be consulted. Searches will also be supplemented by reviewing the reference lists (‘references of

references') of selected articles to find any other relevant papers. From the identified studies in the search, forward and backward citations will also be carried out to find potential studies reporting NPIs and reducing transmission of COVID-19 for the full texts. The literature search strategy was developed by KR in collaboration with departmental subject librarians from authors' universities, who were experienced in SRs, and subsequently refined ensuring its comprehensiveness. While piloting the search strategy, we followed these broad steps:

- Tested out keywords and phrases in a MEDLINE database to see the number of hits returned, and assessed the degree of relevance;
- Reviewed some (e.g. five) papers including those marked 'highly cited' on COVID-19/SARS-CoV-2 that meet inclusion/exclusion criteria, where we looked at the terms used in the titles and abstracts for main concepts e.g. NPIs and COVID-19.
- Took notes of keywords supplied by authors and incorporated those into our strategy.
- Experimented with combinations of keywords using 'AND' (limits search) and 'OR' (expands search) operators.
- Looked at subject headings assigned for key papers and used them too.

A broad search strategy has been designed to maximise the level of sensitivity (or comprehensiveness) in searching,[47] and improve both *recall ratio* (number of relevant references retrieved divided by all of the relevant references) and *precision ratio* (number of relevant references retrieved divided by the number of references retrieved).[48(p.34)] Key terms for one MEDLINE are shown in Table 1.

Table 1. Search strategy for MEDLINE

Concepts	Search terms in each concepts will be modified as needed for use in other databases
Concept #1	*COVID-19*
	"covid 19 pandemic"[All Fields] OR "COVID19"[All Fields] OR "COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "2019-nCoV"[All Fields] OR "2019nCoV"[All Fields] OR "coronavirus infections"[All Fields] OR "coronavirus infections"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronavirus"[All Fields] OR "coronavirus"[MeSH Terms] OR "coronavirus"[MeSH Terms] OR "Betacoronavirus"[MAJR] "SARS coronavirus2"[All Fields] "sars cov"[All Fields] OR "sars virus"[All Fields] OR "sars virus"[MeSH Terms] OR "SARS"[All Fields] OR "SARS2"[All Fields] OR "SARS-2"[All Fields] OR "SARScoronavirus 2"[All Fields] OR "SARScoronavirus2"[All Fields] OR "SARS-coronavirus-2"[All Fields] OR"SARS-CoV-2"[All Fields] OR "SARSCov2019*"[All Fields] OR "SARS-Cov2019*"[All Fields] OR "SARS-Cov-2019*"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "Wuhan coronavirus"[All Fields] OR "Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "COVID-19"[nm]
Concept #2	*Non-Pharmaceutical Interventions*
	“social distancing"[TIAB] OR "cohorting"[All Fields] OR "community containment"[All Fields] OR "isolation strategy"[All Fields] OR "isolation"[All Fields] OR "patient isolation"[All Fields] OR "patient isolation"[MeSH Terms] OR "patient isolators"[All Fields] OR "patient isolators"[MeSH Terms] OR "physical contact"[All Fields] OR "physical distancing"[All Fields] OR "quarantine"[All Fields] OR "quarantines"[All Fields] OR "quarantine"[MeSH Terms] OR "social distance"[All Fields] OR “quarantines”[All Fields] OR “quarantined”[All Fields] OR “quarantining”[All Fields] OR "social distance"[MeSH Terms] OR "Social distancing"[All Fields] OR "Banning"[All Fields] OR "distancing"[All Fields]
Concept #3	*Reduce transmission*

	"reduce"[All Fields] OR "reduced"[All Fields] OR "reduces"[All Fields] OR "transmission"[MeSH Subheading] OR "transmission"[All Fields] OR "transmissions"[All Fields] OR "prevention and control"[Subheading] OR prevention[Text Word] OR "reduce infection"[All Fields] OR infect"[All Fields] OR "infectability"[All Fields] OR "infectable"[All Fields] OR "infectant"[All Fields] OR "infectants"[All Fields] OR "infected"[All Fields] OR "infecteds"[All Fields] OR "infectibility"[All Fields] OR "infectible"[All Fields] OR "infecting"[All Fields] OR "infection s"[All Fields] OR "infections"[MeSH Terms] OR "infections"[All Fields] OR "infection"[All Fields] OR "infective"[All Fields] OR "infectiveness"[All Fields] OR "infectives"[All Fields] OR "infectivities"[All Fields] OR "infects"[All Fields] OR "pathogenicity"[MeSH Subheading] OR "pathogenicity"[All Fields] OR "infectivity"[All Fields] OR "Coronavirus Infections/prevention and control"[MAJR] OR "Pandemics/prevention and control"[MAJR]

We combined these concepts (using AND), so all concepts are in the same references.

Selection of studies

The citations identified will be imported into Mendeley Reference Manager (https://www.mendeley.com/). All studies emerging from the databases are screened in two stages: (i) screening of titles and abstracts by two reviewers against minimum inclusion criteria, and (ii) review of full text. We will use the standard PRISMA flow diagram to provide the study selection process.[49]

Quality assessment and risk of bias

Quality of the included studies will be assessed using Cochrane Collaboration's tool for assessing risk of bias for randomised controlled trials and the Newcastle Ottawa scale (NOS) for non-randomised studies.[50] Where possible, we will analyse randomised (according to effectiveness of randomisation method, generation of allocation sequence, allocation concealment, blinding, and follow-up) and non-randomised studies (for presence of potential confounders for case-control and cohort studies), and a three-point checklist will be used for controlled before and after studies[51] separately. In NOS, "a 'star system' has been developed in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively".[50] Some items or questions in these

quality assessments e.g. blinded study, are irrelevant to social distancing studies; we therefore consider removing them. Risk of bias will be examined, as it provides variation, e.g. heterogeneity in results of studies included in the study. As Higgins et al.[47] argue, rigorously conducted studies in the SR would provide more truthful results, and the results from the studies of variable validity would give either false negative or false positive conclusions. In this study, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach will be used to assess the certainty of the evidence – risk of bias across studies.[52]

Generally, the bias table provides the type of bias (e.g., selective reporting of outcomes, random sequence generation, allocation of concealment, blinding of participants, personnel and assessors, incomplete outcome data and other potential threats to validity) in each study. If, for example, most rows are unshaded then that is considered a low risk of bias, whereas if some rows are either partly-shaded or dark (risk of bias either unclear or high), this would provide relatively less confidence in the results.[47] A narrative synthesis will be conducted for all included studies. Included studies will be assessed by two authors (KR, CML) and the results will inform synthesis and interpretation of the findings. To facilitate comparison of appraisal processes, all reviewers will record the rationale for inclusion or exclusion, and discrepancies will be discussed and resolved by consensus.

Assessment of reporting biases

Publication bias, often called reporting bias and dissemination bias, is the concern that studies reporting relatively large effects are more likely to be published than studies reporting smaller effects.[53] Similarly, published studies including multiple outcomes would be more likely to report the outcomes than if they showed statistically significant results.[54] We will use funnel plot to estimate the publication bias.[55] If meta-analysis had captured all relevant studies we would expect the funnel plot to be symmetric, i.e. we would expect studies to be dispersed equally on either side of the overall effect.[53] One approach to address publication bias is to follow the trim and fill procedures, i.e. assessing asymmetry or symmetry in the funnel plot if more than 10 eligible studies are identified.[53(p.175)] Trim and fill is a method which allows us to impute these studies, i.e. we determine where missing studies are likely to fall, add them to the analysis, and then recompute the combined effect. In any meta-analysis where the studies are pulled from journals or unpublished data in preprint servers, such as medRxiv, we need to be concerned about the potential impact of publication bias.[56–59] If the

funnel plot is still asymmetric and implies potential bias after including these unpublished data, we use the Trim and Fill method to quantitatively assess the bias. The Trim and Fill method serves as a sensitivity analysis.[58] Specifically, if the smaller studies tend to have larger effects, and if this is actually due to publication bias, this method tells us what the effect size would be in the absence of bias.[57,59]

Data analysis and synthesis

For quantitative data, where possible, we will measure a risk ratio (RR) or odds ratio (OR), absolute risk difference (ARD) for dichotomous/categorical outcome data, and mean difference (MD) or standardised mean difference (SMD) will be calculated for continuous data, with their 95% confidence intervals (CIs) from the data generated by each included study.[53]

If sufficient data are available to make an inference to a universe of comparable studies, results from the comparable groups of studies will be pooled into the statistical random-effects model for meta-analysis to measure the effect size of NPIs on reducing transmission of COVID-19 or the strengths of relationships using the software Comprehensive Meta-Analysis (CMA, version 3. https://www.meta-analysis.com/pages/new_v3.php?cart=BT2P4569026). The purpose of using a random-effects model in the analysis is "to incorporate the assumption that the different studies are estimating different, yet related, intervention effects".[47] To test the heterogeneity of effects in the included studies, we will use Higgins et al.'s I^2 together with the observed effects to measure the true effects in the analysis.[47] The I^2 test for heterogeneity is meant to evaluate whether there is variability across publications.

This will be computed as follows:

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

Q-value (Cochran's heterogeneity statistic) is the sum of the squared deviations of all effect sizes from the mean effect size and *df* indicates the degrees of freedom. We report the prediction interval. This speaks directly to the actual utility of the interventions, but provides the smallest and largest effect sizes associated with this intervention.[60] A rough guide, it is interpreted that: 0%-40% might not be important, 30%-60% may represent moderate heterogeneity, 50%-90% may represent substantial heterogeneity, and 75%-100%

considerable heterogeneity.[47] Generally, the importance of observed value of I^2 on moderate and substantial heterogeneity depends on the magnitude and direction of effects as well as the strength of heterogeneity.[47,60] Where statistical pooling is not possible, a narrative synthesis is conducted for the included studies. For qualitative data, where meta-synthesis is possible, textual data is pooled using the JBI Qualitative Assessment and Review Instrument (JBI-QARI) and Narrative, Opinion and Text Assessment and Review Instrument (JBI-NOTARI).[61]

Data extraction and data items

Two reviewers independently extract descriptive data and data relevant to the quality of each study using the data extraction form. Data items i.e. source of study, eligibility, reasons for exclusion, methods (study design, duration), participants (number, setting, age-gender), intervention and comparator characteristics, results (number of participants, sample size, data for each intervention group, quantitative outcomes – mean, SDs, estimate effect), source of funding, ethics approval and study limitation will be extracted, based on the checklist provided by Higgins and Deeks[62] with appropriate modifications for the review. The data for analysis also include either verbatim quotes directly from participants or the authors' findings. As Rodgers and colleagues confirm, this would not only improve the process of transparency by better understanding the sorts of data extracted from which studies, but also recognising the contribution made by each study to the overall synthesis.[63] In addition, such tables will demonstrate how the individual study area contributes to the reviewers' final conclusion.

Dealing with missing data

In the case of missing data that might be important to summarise/synthesise study findings, or details of the studies are unclear, we will contact all corresponding authors of included studies to give the opportunity to provide missing data. If authors do not respond, we will record the fact that we tried to contact them, and the number of non-respondents. In such cases, we can either use imputation or risk of bias tools to reduce the likelihood of this being problematic. Generally it is considered that non-responding authors are equivalent to non-responders to interviews in observational/experimental studies. The impact of this will be reported in the discussion section of the SR.

Subgroup analysis

We anticipate much variation on the type and nature of NPIs or settings in relation to COVID-19. Based on the scoping search, it is difficult to disentangle the individual effect of each NPI on reducing or preventing COVID-19 transmission, as the role of combined NPIs have been often reported in different literatures, therefore we do not consider a subgroup analysis to measure which NPIs would be more effective than others. However, some emerging data confirmed cases of COVID-19 and deaths amongst (i) different healthcare professionals (medical doctors, nurses, allied healthcare professionals) and (ii) socio-economic groups (Black, Asian, White) therefore we will be doing a subgroup analysis examining the association between NPIs and cases/deaths from COVID-19/SARS-CoV-2 on those specific groups when applicable. As Higgins et al. argue, "subgroup analyses may be done as a means of investigating heterogeneous results, or to answer specific questions about particular patient groups, types of intervention or type of study." [47(p.283)]

Patient and public involvement

As this is a protocol for a SR and MA, neither patients nor public will be directly involved, and ethics approval and consent will not be required.

Dissemination

We will be able to disseminate the study findings as follows: publishing at least one paper in peer-reviewed journals, and abstract presented at suitable national/international conferences or workshops. We will also share important information with public health authorities as well as with the WHO. In addition, we may post the submitted manuscript under review to bioRxiv, medRxiv, or other relevant pre-print servers.

Discussion

Impact of NPIs on preventing COVID-19 is a highly charged topic creating much debate among politicians, economists, and medical and public health professions. Given the rapidly-growing field, it is imperative to generate a substantial conclusion regarding the prevention, control and management of COVID-19 in public health practice. The proposed SR will therefore measure the impact of NPIs on reducing transmission of COVID-19. As such, significant outcomes from this review will guide patients and clinicians in their treatment arrangements given that there is no vaccine or treatment available at the time of writing. Furthermore, these significant findings will be vital to assist policy-makers and researchers in

synthesising a large and complex literature. Similarly, this review will provide a basis for developing the best methods and approaches for developing objective measures and interventions to establish the link between different factors and NPIs and reducing transmission of COVID-19 effectively, efficiently and equitably. It is equally important that the "structure and capacity of our depleted healthcare system are now largely driving the response to this epidemic"[64] and most likely it will continue to do so until services that support local communicable disease control are rebuilt and reintegrated.[65] It is, therefore, important to make appropriate efforts now that would address COVID-19, through strengthening the primary healthcare system, to reduce the chances of future pandemics.

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Contributors

KR conceived and designed the research with the advice from CML; KR wrote the first draft; KR and CML reviewed and contributed to drafting, revising and finalising the manuscript. All authors have reviewed and approved the final version of the manuscript and have given their permission for publication.

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Competing interests

None declared.

Patient consent for publication

Not required.

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Additional file 1. PRISMA 2009 Checklist

Impact of non-pharmaceutical interventions for reducing transmission of coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

Section/topic	#	Checklist item	Reported on page #	Notes
TITLE				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1	Title page
ABSTRACT				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2	
INTRODUCTION				
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-6	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6	
METHODS				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	CRD42020207338 (see p.3)	We recently published preprint study protocol: https://www.medrxiv.org/content/10.1101/2020.06.13.20130294v1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	10	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	12	

Additional file 1. PRISMA 2009 Checklist

Impact of non-pharmaceutical interventions for reducing transmission of coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	13	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	12	

Section/topic	#	Checklist item	Reported on page #	Notes
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10-11	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	14	
RESULTS				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	NA	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	NA	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA	

Additional file 1. PRISMA 2009 Checklist

Impact of non-pharmaceutical interventions for reducing transmission of coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

DISCUSSION				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-15	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	NA	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15	
FUNDING				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Impact of non-pharmaceutical interventions for reducing transmission of coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

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Impact of non-pharmaceutical interventions for reducing transmission of coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

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Keywords: Non-pharmaceutical interventions, Social distancing, COVID-19, Prevention, Control, Systematic review

Impact of non-pharmaceutical interventions for reducing transmission of coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

Abstract

Introduction: Implementing non-pharmaceutical interventions (NPIs) protect the public from coronavirus disease 2019 (COVID-19). However, the impact of NPIs has been inconsistent and remains unclear. This study, therefore, aims to measure the impact of major NPIs (social distancing, social isolation and quarantine) on reducing COVID-19 transmission.

Methods and analysis: We will conduct a systematic review (SR) and meta-analysis (MA) research of both randomised and non-randomised controlled trials. We will undertake a systematic search of: MEDLINE, EMBASE, Allied & Complementary Medicine, COVID-19 Research, WHO database on COVID-19, ClinicalTrails.Gov for clinical trials on COVID-19, Cochrane Resources on Coronavirus (COVID-19), Oxford COVID-19 Evidence Service, Google Scholar for published and unpublished literatures on COVID-19 including pre-print engines such as medRxiv, bioRxiv, Litcovid and SSRN for unpublished studies on COVID-19, and will be reported in accordance with PRISMA. Outcomes of interest for impact analysis will include the reduction of COVID-19 transmission, avoiding crowds and restricting movement, isolating ill and psychological impacts. The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist has been used for this protocol. For quality of included studies, we will use the Cochrane Collaboration's tool for assessing risk of bias for randomised controlled trials and the Newcastle Ottawa scale for observational studies. The GRADE approach will grade the certainty of the evidence for all outcome measures across studies. Random-effects model for meta-analysis will measure the effect size of NPIs or the strengths of relationships. For quantitative data, risk ratio or odds ratio, absolute risk difference (for dichotomous outcome data), or mean difference or standardised mean difference (for continuous data) and their 95% confidence intervals we will be calculated. Where statistical pooling is not possible, a narrative synthesis, will be conducted for the included studies. To assess the heterogeneity of effects, I^2 together with the observed effects will be evaluated to provide the true effects in the analysis.

Ethics and dissemination: Formal ethical approval from an institutional review board or research ethics committee is not required as primary data will not be collected. The final results of this study will be published in an open-access peer-reviewed journal, and abstract

will be presented at suitable national/international conferences or workshops. We will also share important information with public health authorities as well as with the World Health Organization (WHO). In addition, we may post the submitted manuscript under review to medRxiv, or other relevant pre-print servers.

Registration: International Prospective Register of Systematic Reviews (PROSPERO) registration number CRD42020207338.

Strengths and limitations of this study

- To the best of our knowledge, this study is the first SR to measure the impact of NPIs – social distancing, isolation and quarantine – on reducing COVID-19 transmission.
- This study will offer the highest level of evidence to assist policy-makers and researchers in synthesising a large and complex literature, drawing a broader framework.
- This protocol reduces the possibility of duplication, provides transparency to the methods and procedures used, minimises potential biases and allows peer-review.
- This research is not externally funded, and therefore time and resource will be constrained.
- If included studies vary in sample size, quality and population, they may be open to bias, and the heterogeneity of data will preclude a meaningful meta-analysis to measure the effects of specific NPIs.

Introduction

Coronavirus disease 2019 (COVID-19; caused by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) emerged in Wuhan, China in December 2019, and has been posing a global public health threat. On March 11, 2020, WHO declared the COVID-19 outbreak a pandemic.[1] At the time of writing (September 24, 2020), the WHO COVID-19 Situation Dashboard reports that this virus has already affected 216 countries, areas or territories with 31,664,104 confirmed cases of COVID-19 and 972,221 deaths; a fatality rate of approximately over 3% (3.07%).[2]

Based on reported cases, approximately 1:10 reported infections were among healthcare professionals, e.g. medical doctors, nurses.[3] We have seen disproportionate numbers of black, Asian and minority ethnic (BAME) doctors and other healthcare professionals die from COVID-19. A study conducted by Cook and Lennane reported

that in the UK National Health Service (NHS), it is estimated 21% of all staff are BAME, whereas 63% of healthcare professionals who died were BAME.[4] A recent UK government review[5] highlighted that the highest age-standardised diagnosis rates of COVID-19 per 100,000 population were in people of BAME groups (486 female and 649 male) and the lowest were in White people (220 female and 224 male). Accounting for the effect of sex, age, deprivation and region, Bangladeshi people had about twice the risk of death compared with White British. Similarly, Chinese, Indian, Pakistani, other Asian, Caribbean and other Black ethnicity had between 10 and 50% higher risk of death compared to White British. In fact, this is the opposite of observations in previous years, when all-cause mortality rates were lower in BAME.[3,5]

Similarly, the COVID-19 mortality rate in the USA for African-Americans was 2.4-2.7 times more than for White individuals.[3] However, death rates are not consistent across these groups. Inequalities in COVID-19 mortalities are rife, which is most recently shown by Public Health England.[6] Several factors were identified as risks for COVID-19, e.g. ethnicity, age, sex, co-morbidities (diabetes, renal conditions), occupation, socio-economic status, and multifamily and multigenerational households.[6–8]

Recent data from Johns Hopkins University reported that global COVID-19 deaths have surpassed 890,000.[9] Imperial College London highlights that this outbreak could kill 40 million people this year without public health measures (e.g. case finding, contact tracing and testing, and strict quarantine).[7] Evidence suggests that the number of cases reported would possibly "represent an underestimation of the true burden due to lack of surveillance and diagnostic capacity"[8] as well as pharmaceuticals to manage severe COVID-19.[10]

Several countries, including the United Kingdom (UK), United States of America (USA) and other European Union (EU) countries are adopting social distancing (SD) measure as a form of non-pharmaceutical or physical interventions to control COVID-19 by slowing down transmission of the virus and preventing associated illness and death.[11] SD is the new buzzword with the outbreak of coronavirus and COVID-19. In the literature, the term SD can have different meanings; for example, some considered it as strategy,[12] policy,[13] an approach to flatten the curve,[14] mitigation measure to increase physical distance or reduce frequency of congregation in socially dense community settings.[15–17] Flaxman et al.[10] defined SD as a measure to ban large gatherings and advise individuals not to socialise outside their households by closing borders, some public places, schools and universities; isolation/quarantine, physical distancing and room separation to isolate symptomatic individuals and their contacts; and large-scale lockdowns of populations by staying at least

2m apart aiming to minimise mixing of infectious susceptible patients. This definition of SD, in fact, is very vague and includes interventions which are considered different to SD, e.g. quarantine including school closure and case findings.

For clarity, in this SR, the definition of SD (also called physical distancing) is considered as a set of NPIs intended to prevent spread of COVID-19 by maintaining physical distance between people and reducing the number of times people come into close contact.[18,19] This review focuses only on COVID-19/SARS-CoV-2 and three major NPIs, namely SD, isolation and quarantine. Isolation of cases refers to the separation of ill persons with contagious diseases from non-infected persons, either hospitalised (moderate or severe cases) to provide care, or in dedicated isolation facilities or at home (mild cases),[20] and quarantine is the restriction of persons who are presumed to have been exposed to a contagious disease but are not ill, either because they did not become infected or because they are still in the incubation period.[21] WHO recommends isolation, physical (social) distancing, contact tracing and quarantine of close contacts as the key measures to reduce COVID-19.[22]

A scoping search of MEDLINE was done on 9 September 2020 for publications entered by the end of August 2020 with the following terms: ((“COVID-19” OR “SARS-CoV-2”) AND (“systematic review” OR “literature search” OR “meta-analysis” OR “evidence synthesis”) AND (“social distancing” OR “isolation” OR “quarantine”)). It revealed some empirical research on COVID-19 from China, South Korea, the UK, the USA and other countries, but these are not systemically reviewed or synthesised well. Several rapid reviews and summaries have been covered on COVID-19 epidemiology,[23,24] the effectiveness of real-time PCR for diagnosis,[25] effects of school closure,[26] quarantine,[27,28] SD[29] (study primarily based on two previous reviews[30,31] on influenza from 2012 and 2018, respectively), and mathematical modelling studies incorporating the effect of SD.[10,20,32–39] These models would generally help to “predict epidemic curve representing the number of infections caused by the virus over time.”[40]

Recently, some SRs and MAs have been conducted to investigate ethnicity and clinical outcomes.[41] Chu and colleagues[42] published a systematic review including physical distancing to investigate the optimum distance for avoiding person-to-person transmissions, focusing more on face masks and eye protection. Though their study was, perhaps, the first rapidly synthesised review, and identified 172 studies across 16 countries and six continents, none of the included studies were randomised controlled trials, therefore their findings might suffer from both recall and measurement biases. Cochrane further conducted three studies; First, a rapid review in 2020, involving 29 studies on COVID-19 from China, UK, South

Korea and Japan.[43] Second, a rapid qualitative evidence synthesis conduced in 2020 capturing 36 studies from Asia, Africa, Central and North America and Australia examining healthcare workers' adherence and enablers or challenges associated with infection control guidelines for respiratory infections. Another study examined 67 studies including RCTs and observational studies exploring the role of physical interventions for reducing the spread of respiratory viruses, and found no evidence regarding screening at entry ports and SD.[44]

Lewnard and Lo[8] and Michigan Medicine Projections[45] reported that combined NPIs using SD, isolation and quarantine, including workplace distancing, appeared effective in reducing COVID-19 compared to no interventions. This approach, however, reported considerable challenges, e.g. societal disruption, social isolation/rejection, mental stress and psychological trauma, lack of tests and testing facilities, poor contact tracing and lack of surveillance. No studies examined the combined effects of NPIs in reducing the transmission of COVID-19. This study, therefore, aims to measure the impact of NPIs on reducing COVID-19 transmission.

Review question

What has been the impact of NPIs – social distancing, quarantine and isolation – on reducing transmission of coronavirus disease 2019 [COVID-19]?

Methods and designs

This study will utilise a SR and MA, which will consider both randomised controlled trials and non-randomised trials (prospective and retrospective observational studies). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement has been used in the preparation of this protocol (see online supplementary file 1).[46] Final results will be reported according to the PRISMA statement.

Criteria for considering studies for review

Inclusion criteria

1. Types of participants – this review will consider all studies that involve human subjects of any age-gender, including ethnic (Black, Asian, White) and healthcare workers (medical doctors, nurses, allied healthcare professions) groups.
2. Types of intervention – we will include research describing three major NPIs, e.g. social distance, isolation and quarantine focusing only COVID-19/SARS-CoV-2.

3. Types of outcome measure. Primary outcomes include: COVID-19; reducing the risk of transmission/infection of COVID-19; hospitalisation, ICU admissions, COVID-19 related complications, quality of life; and mortality and morbidity. Secondary outcomes include changes in social behaviour, e.g. social distancing by avoiding crowds, restricting movements, isolating ill patients and quarantine of exposed people.
4. Types of studies. No study design filter is added, and there is no limit on our search by language. To measure the impact of NPIs, this review considers all studies evaluating the effectiveness of NPIs relating to reducing the risk of transmission/infection of COVID-19. We include both randomised controlled trials and non-randomised controlled trials, e.g. cross-sectional, survey, case-control, randomised controlled trials, and observational studies (retrospective or prospective). [We proposed to collect data from October 2020 until February 2021 for the study]

Exclusion criteria

1. Articles in narrative reviews, modelling studies, opinion pieces, letters, news, editorials, perspectives, commentaries, conference abstracts and other publications lacking primary data and/or poor methodological details.
2. Studies containing duplicate datasets.

Search strategy to identify relevant studies

We aim to undertake a systematic search of the following sources: MEDLINE, EMBASE, Allied & Complementary Medicine, COVID-19 Research, WHO database on COVID-19, ClinicalTrials.Gov for clinical trials on COVID-19, Cochrane Resources on Coronavirus (COVID-19), Oxford COVID-19 Evidence Service, Google Scholar for published and unpublished literatures on COVID-19 including pre-print engines such as medRxiv, bioRxiv, Litcovid and SSRN for unpublished studies on COVID-19 will be searched given the lags in publication. The literature search uses the following terms: “social distancing”, “quarantine”, “isolation”, “non-pharmacological interventions” combined with “COVID-19”. Primary search terms are non-pharmacological interventions or measures (all synonyms) and COVID-19 (all synonyms) using ‘Textword searching’ – searching for a word or phrase anywhere in the document, where the document is the citation (article title, journal name, author), not the full text of an article, and ‘Thesaurus (MeSH, EMTREE) searching’, employing Boolean operators and truncations. The ‘Related Articles’ feature in PubMed will be consulted.

Searches will also be supplemented by reviewing the reference lists ('references of references') of selected articles to find any other relevant papers. From the identified studies in the search, forward and backward citations will also be carried out to find potential studies reporting NPIs and reducing transmission of COVID-19 for the full texts. The literature search strategy was developed by KR in collaboration with departmental subject librarians from authors' universities, who were experienced in SRs, and subsequently refined ensuring its comprehensiveness. While piloting the search strategy, we followed these broad steps:

- Tested out keywords and phrases in a MEDLINE database to see the number of hits returned, and assessed the degree of relevance;
- Reviewed some (e.g. five) papers including those marked 'highly cited' on COVID-19/SARS-CoV-2 that meet inclusion/exclusion criteria, where we looked at the terms used in the titles and abstracts for main concepts e.g. NPIs and COVID-19.
- Took notes of keywords supplied by authors and incorporated those into our strategy.
- Experimented with combinations of keywords using 'AND' (limits search) and 'OR' (expands search) operators.
- Looked at subject headings assigned for key papers and used them too.

A broad search strategy has been designed to maximise the level of sensitivity (or comprehensiveness) in searching,[47] and improve both *recall ratio* (number of relevant references retrieved divided by all of the relevant references) and *precision ratio* (number of relevant references retrieved divided by the number of references retrieved).[48(p.34)] Key terms for one MEDLINE are shown in Table 1.

Table 1. Search strategy for MEDLINE

Concepts	Search terms in each concepts will be modified as needed for use in other databases
Concept #1	*COVID-19*
	"covid 19 pandemic"[All Fields] OR "COVID19"[All Fields] OR "COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "2019-nCoV"[All Fields] OR "2019nCoV"[All Fields] OR "coronavirus infections"[All Fields] OR "coronavirus infections"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronavirus"[All Fields] OR "coronavirus"[MeSH Terms] OR "coronavirus"[MeSH Terms] OR "Betacoronavirus"[MAJR] "SARS coronavirus2"[All Fields] "sars cov"[All Fields] OR "sars virus"[All Fields] OR "sars virus"[MeSH Terms] OR "SARS"[All Fields] OR "SARS2"[All Fields] OR "SARS-2"[All Fields] OR "SARScoronavirus 2"[All Fields] OR "SARScoronavirus2"[All Fields] OR "SARS-coronavirus-2"[All Fields] OR"SARS-CoV-2"[All Fields] OR "SARSCov2019*"[All Fields] OR "SARS-Cov2019*"[All Fields] OR "SARS-Cov-2019*"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "Wuhan coronavirus"[All Fields] OR "Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "COVID-19"[nm]
Concept #2	*Non-Pharmaceutical Interventions*
	“social distancing"[TIAB] OR "cohorting"[All Fields] OR "community containment"[All Fields] OR "isolation strategy"[All Fields] OR "isolation"[All Fields] OR "patient isolation"[All Fields] OR "patient isolation"[MeSH Terms] OR "patient isolators"[All Fields] OR "patient isolators"[MeSH Terms] OR "physical contact"[All Fields] OR "physical distancing"[All Fields] OR "quarantine"[All Fields] OR "quarantines"[All Fields] OR "quarantine"[MeSH Terms] OR "social distance"[All Fields] OR “quarantines”[All Fields] OR “quarantined”[All Fields] OR “quarantining”[All Fields] OR "social distance"[MeSH Terms] OR "Social distancing"[All Fields] OR "Banning"[All Fields] OR "distancing"[All Fields]
Concept #3	*Reduce transmission*

	"reduce"[All Fields] OR "reduced"[All Fields] OR "reduces"[All Fields] OR "transmission"[MeSH Subheading] OR "transmission"[All Fields] OR "transmissions"[All Fields] OR "prevention and control"[Subheading] OR prevention[Text Word] OR "reduce infection"[All Fields] OR infect"[All Fields] OR "infectability"[All Fields] OR "infectable"[All Fields] OR "infectant"[All Fields] OR "infectants"[All Fields] OR "infected"[All Fields] OR "infecteds"[All Fields] OR "infectibility"[All Fields] OR "infectible"[All Fields] OR "infecting"[All Fields] OR "infection s"[All Fields] OR "infections"[MeSH Terms] OR "infections"[All Fields] OR "infection"[All Fields] OR "infective"[All Fields] OR "infectiveness"[All Fields] OR "infectives"[All Fields] OR "infectivities"[All Fields] OR "infects"[All Fields] OR "pathogenicity"[MeSH Subheading] OR "pathogenicity"[All Fields] OR "infectivity"[All Fields] OR "Coronavirus Infections/prevention and control"[MAJR] OR "Pandemics/prevention and control"[MAJR]

We combined these concepts (using AND), so all concepts are in the same references.

Selection of studies

The citations identified will be imported into Mendeley Reference Manager (https://www.mendeley.com/). All studies emerging from the databases are screened in two stages: (i) screening of titles and abstracts by two reviewers against minimum inclusion criteria, and (ii) review of full text. We will use the standard PRISMA flow diagram to provide the study selection process.[49]

Quality assessment and risk of bias

Quality of the included studies will be assessed using Cochrane Collaboration's tool for assessing risk of bias for randomised controlled trials and the Newcastle Ottawa scale (NOS) for non-randomised studies.[50] Where possible, we will analyse randomised (according to effectiveness of randomisation method, generation of allocation sequence, allocation concealment, blinding, and follow-up) and non-randomised studies (for presence of potential confounders for case-control and cohort studies), and a three-point checklist will be used for controlled before and after studies[51] separately. In NOS, "a 'star system' has been developed in which a study is judged on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively".[50] Some items or questions in these

quality assessments e.g. blinded study, are irrelevant to social distancing studies; we therefore consider removing them. Risk of bias will be examined, as it provides variation, e.g. heterogeneity in results of studies included in the study. As Higgins et al.[47] argue, rigorously conducted studies in the SR would provide more truthful results, and the results from the studies of variable validity would give either false negative or false positive conclusions. In this study, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach will be used to assess the certainty of the evidence – risk of bias across studies.[52]

Generally, the bias table provides the type of bias (e.g., selective reporting of outcomes, random sequence generation, allocation of concealment, blinding of participants, personnel and assessors, incomplete outcome data and other potential threats to validity) in each study. If, for example, most rows are unshaded then that is considered a low risk of bias, whereas if some rows are either partly-shaded or dark (risk of bias either unclear or high), this would provide relatively less confidence in the results.[47] A narrative synthesis will be conducted for all included studies. Included studies will be assessed by two authors (KR, CML) and the results will inform synthesis and interpretation of the findings. To facilitate comparison of appraisal processes, all reviewers will record the rationale for inclusion or exclusion, and discrepancies will be discussed and resolved by consensus.

Assessment of reporting biases

Publication bias, often called reporting bias and dissemination bias, is the concern that studies reporting relatively large effects are more likely to be published than studies reporting smaller effects.[53] Similarly, published studies including multiple outcomes would be more likely to report the outcomes than if they showed statistically significant results.[54] We will use funnel plot to estimate the publication bias.[55] If meta-analysis had captured all relevant studies we would expect the funnel plot to be symmetric, i.e. we would expect studies to be dispersed equally on either side of the overall effect.[53] One approach to address publication bias is to follow the trim and fill procedures, i.e. assessing asymmetry or symmetry in the funnel plot if more than 10 eligible studies are identified.[53(p.175)] Trim and fill is a method which allows us to impute these studies, i.e. we determine where missing studies are likely to fall, add them to the analysis, and then recompute the combined effect. In any meta-analysis where the studies are pulled from journals or unpublished data in preprint servers, such as medRxiv, we need to be concerned about the potential impact of publication bias.[56–59] If the

funnel plot is still asymmetric and implies potential bias after including these unpublished data, we use the Trim and Fill method to quantitatively assess the bias. The Trim and Fill method serves as a sensitivity analysis.[58] Specifically, if the smaller studies tend to have larger effects, and if this is actually due to publication bias, this method tells us what the effect size would be in the absence of bias.[57,59]

Data analysis and synthesis

For quantitative data, where possible, we will measure a risk ratio (RR) or odds ratio (OR), absolute risk difference (ARD) for dichotomous/categorical outcome data, and mean difference (MD) or standardised mean difference (SMD) will be calculated for continuous data, with their 95% confidence intervals (CIs) from the data generated by each included study.[53]

If sufficient data are available to make an inference to a universe of comparable studies, results from the comparable groups of studies will be pooled into the statistical random-effects model for meta-analysis to measure the effect size of NPIs on reducing transmission of COVID-19 or the strengths of relationships using the software Comprehensive Meta-Analysis (CMA, version 3. https://www.meta-analysis.com/pages/new_v3.php?cart=BT2P4569026). The purpose of using a random-effects model in the analysis is "to incorporate the assumption that the different studies are estimating different, yet related, intervention effects".[47] To test the heterogeneity of effects in the included studies, we will use Higgins et al.'s I^2 together with the observed effects to measure the true effects in the analysis.[47] The I^2 test for heterogeneity is meant to evaluate whether there is variability across publications.

This will be computed as follows:

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

Q-value (Cochran's heterogeneity statistic) is the sum of the squared deviations of all effect sizes from the mean effect size and *df* indicates the degrees of freedom. We report the prediction interval. This speaks directly to the actual utility of the interventions, but provides the smallest and largest effect sizes associated with this intervention.[60] A rough guide, it is interpreted that: 0%-40% might not be important, 30%-60% may represent moderate heterogeneity, 50%-90% may represent substantial heterogeneity, and 75%-100%

considerable heterogeneity.[47] Generally, the importance of observed value of I^2 on moderate and substantial heterogeneity depends on the magnitude and direction of effects as well as the strength of heterogeneity.[47,60] Where statistical pooling is not possible, a narrative synthesis is conducted for the included studies. For qualitative data, where meta-synthesis is possible, textual data is pooled using the JBI Qualitative Assessment and Review Instrument (JBI-QARI) and Narrative, Opinion and Text Assessment and Review Instrument (JBI-NOTARI).[61]

Data extraction and data items

Two reviewers independently extract descriptive data and data relevant to the quality of each study using the data extraction form. Data items i.e. source of study, eligibility, reasons for exclusion, methods (study design, duration), participants (number, setting, age-gender), intervention and comparator characteristics, results (number of participants, sample size, data for each intervention group, quantitative outcomes – mean, SDs, estimate effect), source of funding, ethics approval and study limitation will be extracted, based on the checklist provided by Higgins and Deeks[62] with appropriate modifications for the review. The data for analysis also include either verbatim quotes directly from participants or the authors' findings. As Rodgers and colleagues confirm, this would not only improve the process of transparency by better understanding the sorts of data extracted from which studies, but also recognising the contribution made by each study to the overall synthesis.[63] In addition, such tables will demonstrate how the individual study area contributes to the reviewers' final conclusion.

Dealing with missing data

In the case of missing data that might be important to summarise/synthesise study findings, or details of the studies are unclear, we will contact all corresponding authors of included studies to give the opportunity to provide missing data. If authors do not respond, we will record the fact that we tried to contact them, and the number of non-respondents. In such cases, we can either use imputation or risk of bias tools to reduce the likelihood of this being problematic. Generally it is considered that non-responding authors are equivalent to non-responders to interviews in observational/experimental studies. The impact of this will be reported in the discussion section of the SR.

Subgroup analysis

We anticipate much variation on the type and nature of NPIs or settings in relation to COVID-19. Based on the scoping search, it is difficult to disentangle the individual effect of each NPI on reducing or preventing COVID-19 transmission, as the role of combined NPIs have been often reported in different literatures, therefore we do not consider a subgroup analysis to measure which NPIs would be more effective than others. However, some emerging data confirmed cases of COVID-19 and deaths amongst (i) different healthcare professionals (medical doctors, nurses, allied healthcare professionals) and (ii) socio-economic groups (Black, Asian, White) therefore we will be doing a subgroup analysis examining the association between NPIs and cases/deaths from COVID-19/SARS-CoV-2 on those specific groups when applicable. As Higgins et al. argue, "subgroup analyses may be done as a means of investigating heterogeneous results, or to answer specific questions about particular patient groups, types of intervention or type of study." [47(p.283)]

Patient and public involvement

Patients or the public were not directly involved in the design of this study. As this is a protocol for a systematic review and no participant recruitment will take place, their involvement on the recruitment and dissemination of findings to participants was not applicable.

Ethics and dissemination

Formal ethical approval is not required as primary data will not be collected in this study. The final results of this study will be published in an open-access peer-reviewed journal, and abstract will be presented at suitable national/international conferences or workshops.
This systematic review and meta-analysis will report the impact of major NPIs (social distancing, social isolation and quarantine) on reducing COVID-19 transmission. We will also share important information with public health authorities as well as with the WHO. In addition, we may post the submitted manuscript under review to bioRxiv, medRxiv, or other relevant pre-print servers.

Discussion

Impact of NPIs on preventing COVID-19 is a highly charged topic creating much debate among politicians, economists, and medical and public health professions. Given the rapidly-growing field, it is imperative to generate a substantial conclusion regarding the prevention,

control and management of COVID-19 in public health practice. The proposed SR will therefore measure the impact of NPIs on reducing transmission of COVID-19. As such, significant outcomes from this review will guide patients and clinicians in their treatment arrangements given that there is no vaccine or treatment available at the time of writing. Furthermore, these significant findings will be vital to assist policy-makers and researchers in synthesising a large and complex literature. Similarly, this review will provide a basis for developing the best methods and approaches for developing objective measures and interventions to establish the link between different factors and NPIs and reducing transmission of COVID-19 effectively, efficiently and equitably. It is equally important that the "structure and capacity of our depleted healthcare system are now largely driving the response to this epidemic"[64] and most likely it will continue to do so until services that support local communicable disease control are rebuilt and reintegrated.[65] It is, therefore, important to make appropriate efforts now that would address COVID-19, through strengthening the primary healthcare system, to reduce the chances of future pandemics.

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Contributors

KR conceived and designed the research with the advice from CML; KR wrote the first draft; KR and CML reviewed and contributed to drafting, revising and finalising the manuscript. All authors have reviewed and approved the final version of the manuscript and have given their permission for publication.

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Competing interests

None declared.

Patient consent for publication

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Supplementary file 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Impact of non-pharmaceutical interventions for reducing transmission of coronavirus disease 2019 [COVID-19]: A systematic review and meta-analysis protocol

Section and topic	Item No	Checklist item	Page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	15
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	15
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6-7
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	9
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	10
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12-13
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	12
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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