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Effectiveness of SARS-CoV-2 testing strategies

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effectiveness of different SARS-CoV-2 testing strategies in reducing COVID-19 cases, hospitalisations, and deaths among suspected cases and asymptomatic individuals.

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, was first described in Wuhan, China in December 2019 and subsequently spread rapidly worldwide [1]. The World Health Organization (WHO) declared a global pandemic on 11 March 2020; by the end of March 2020, cases were confirmed in 189 countries. As of May 2024, there have been 775 million confirmed cases of coronavirus disease 2019 (COVID-19) – the disease caused by the SARS-CoV-2 virus – including over seven million reported deaths [2].

The exceptionally rapid spread of the virus caused catastrophic consequences for daily life [3]. Global response to the pandemic varied widely, with some governments imposing 'lockdowns' in attempts at mitigation. These containment strategies included stay-at-home requirements; school, workplace, and public transport closures; and national and international travel restrictions [4, 5]. Although most countries have eased these strict mitigation policies, ongoing non-pharmacological interventions to reduce disease transmission and severity continue to be utilised [6, 7]. These include vaccination 'booster' doses, targeted testing, and selective use of personal protective equipment [8, 9]. Testing remains a critical measure to control SARS-CoV-2 transmission, as identification of a positive case allows individuals to take appropriate measures to prevent further transmission, including isolation, mask-wearing, and seeking medical care [10]. Furthermore, evidence indicates positive cases at risk of severe disease benefit from early antiviral medication. Therefore, timely identification of these high-risk patients helps reduce the risk of progression to severe disease [11, 12]. At the population level, testing plays a critical role by identifying infected individuals who may be asymptomatic or presymptomatic but still capable of spreading the disease. This enables health authorities to track the spread of infection, implement targeted interventions, and allocate resources effectively.

However, testing responses vary across regions and countries due to differences in healthcare infrastructure, resources, and public health priorities. High-income countries have typically implemented widespread testing with advanced tools, while resource-limited settings face challenges like inadequate access to kits and laboratory capacity. These disparities underscore the importance of context-specific strategies to ensure testing efforts are practical and effective.

Description of the condition

The SARS-CoV-2 virus is spread through the respiratory route with a median incubation period of 5.1 days, with most patients developing symptoms within 11.5 days of virus acquisition [13]. The novel coronavirus has a higher affinity for angiotensin-converting enzyme 2 (ACE2) receptors in nasal passages and conjunctiva than previous coronaviruses. This, along with asymptomatic transmission, high viral load, and the stability of the virus in the air, results in a higher R0 and more rapid spread compared to other coronaviruses [14].

Those with symptomatic SARS-CoV-2 infections most commonly present with fever, cough, and shortness of breath. Less common symptoms include sore throat, anosmia (loss of ability to smell), and gastrointestinal symptoms. A proportion of these cases will progress to severe disease requiring hospitalisation for respiratory support [15], or long term sequelae known as post COVID-19 condition, or both. The understanding of the at-risk cohorts has improved significantly through research, with groups identified including individuals who are unvaccinated, immunosuppressed, elderly, or living with certain chronic diseases [16].

There is a notable proportion of asymptomatic COVID-19 cases, estimated at 44.1% [17]. A specific challenge of the SARS-CoV-2 virus is that it is effectively transmitted during the presymptomatic phase and through asymptomatic cases. This asymptomatic transmission supports the argument for widespread screening to prevent the spread to high-risk groups. However, it remains unclear whether this approach can effectively reduce the number of cases or hospitalisations.

Description of the intervention and how it might work

Testing methods for SARS-CoV-2 include nucleic acid amplification tests (NAAT) such as reverse transcription-polymerase chain reaction (RT-PCR), the gold standard with high sensitivity and specificity, and antigen-detecting rapid diagnostic tests (RDTs), which offer faster and more accessible testing despite lower accuracy. Both methods can use specimens such as nasopharyngeal swabs, nasal swabs, sputum, and saliva, addressing different testing needs and contexts. Testing strategies encompass both the choice of test and its implementation, including:

- the target population (symptomatic cases, contacts, screening);
- testing frequency and timing;
- test administration (self versus professional); and
- response protocols for positive results.

In July 2022, researchers noted that over six billion COVID-19 tests had been performed [18]. Testing strategies have varied across countries and stages of the pandemic, ranging from targeting suspected cases to widespread screening of asymptomatic populations [19, 20].

The WHO declared an end to the public health emergency phase of the COVID-19 pandemic in May 2023 [21]. In the current evolving landscape, sustainable testing practices remain necessary to balance resource-intensive testing efforts and the need to limit health impacts of SARS-CoV-2. Targeted testing can be a cost-effective public health tool in managing future emergencies [22]. A strategic approach could avert further COVID-19 cases and subsequent deaths and hospitalisation.

The unpredictable nature of SARS-CoV-2 and evolving population immunity requires ongoing vigilance. A strategic testing approach can provide early warning signals to public health authorities when cases rise, enabling the enforcement of additional control measures [23].

Why it is important to do this review

The post-emergency phase of the SARS-CoV-2 pandemic requires a shift to long-term, cost-effective strategies that utilise controlled testing methods efficiently to achieve outcome-based targets in reducing morbidity and mortality rates. Therefore, an evidence-based approach to testing recommendations is required. Mitigation strategies can be implemented based on positive test results to prevent severe individual disease and outbreaks. Given this, a

review of current evidence is needed to inform specific testing strategies for both symptomatic and asymptomatic individuals. It is particularly crucial to understand the research base guiding testing strategies in congregate settings such as long-term care facilities, given the vulnerability of these individuals [24].

We conducted a scoping review published in November 2023 [25]. The review examined SARS-CoV-2 testing strategies, and we noted a lack of data comparing testing strategies in congregate settings. However, the review highlighted the need for a synthesis of outcomes of testing strategies to guide future testing, which this systematic review aims to achieve. It is important to note that this is not a review of diagnostic test accuracy (DTA) but a systematic review of the effectiveness of interventions. DTA reviews typically focus on cross-sectional comparison of the result of one or more index tests against a reference standard classification, whereas intervention reviews consider outcomes outside and downstream of the results of a diagnostic test. A number of Cochrane reviews of the accuracy of available tests for SARS-CoV-2 have already been published [26, 27, 28, 29]. This review will assess the effectiveness of different SARS-CoV-2 testing strategies in reducing COVID-19 cases, hospitalisations, and deaths among suspected cases and asymptomatic individuals.

OBJECTIVES

To assess the effectiveness of different SARS-CoV-2 testing strategies in reducing COVID-19 cases, hospitalisations, and deaths among suspected cases and asymptomatic individuals.

METHODS

We will follow the Methodological Expectations for Cochrane Intervention Reviews (MECIR) when conducting the systematic review [30, 31, 32], and PRISMA 2020 for the reporting [33].

Criteria for considering studies for this review

We will adhere to the eligibility criteria set forth in the *Cochrane Handbook for Systematic Reviews of Interventions* [32, 34] and the PRISMA 2020 guidelines [33].

Types of studies

We will consider the following comparative study designs.

- Randomised controlled trials (RCTs) – where participants are randomly assigned to either the testing strategy or a control group (or another testing strategy).
- Non-randomised studies of interventions (NRSIs) – where participants are allocated to different testing strategy groups using a non-random method.
- Controlled before-and-after studies (CBAs) – where the allocation of participants to comparison groups is not determined by the investigators. The outcomes of interest are measured in both the testing strategy group and the control/alternate testing strategy group before and after the testing strategy is implemented. These studies carry a higher risk of bias due to the potential presence of unrecognised differences between the intervention and control groups (such as allocation at the level of cluster), which could influence changes in the outcome measure. For CBAs, we will assess clustering effects and baseline comparability between groups. Studies with single clusters per arm or substantial baseline imbalances will be analysed separately with appropriate caution in interpretation.
- Matched cohort studies of interventions – observational studies in which participants with and without the testing strategy will be matched on key confounding variables relevant to the outcomes, such as age, sex, comorbidities, and exposure risk, and their outcomes will be compared.

Studies of the designs mentioned above must meet at least one of the following criteria.

- Collected quantitative data on at least one outcome relevant to this review at least once after the intervention
- Estimated the effects of the intervention on the same or different individuals by comparing outcomes at multiple timepoints before and after the intervention
- Estimated the differences between groups receiving the intervention of interest and a comparator

We have considered this wide range of study designs because randomised trials are often not suitable for addressing questions about the effectiveness of health system interventions and implementation strategies. Specifically, testing strategies are often implemented at the system level, and randomisation may not be feasible or ethical.

We will include all settings.

Exclusion criteria

- Single-arm studies, including case reports and case series
- Review articles
- Theses, editorials, letters, and commentaries
- Results reported only in abstract form (due to limited information on study methods)
- Laboratory and animal studies
- Mathematical modelling studies
- Diagnostic test accuracy studies

Types of participants

We will include participants from the general population who either:

- meet the WHO suspected case definition of SARS-CoV-2 infection, described as “a person who meets clinical or epidemiological criteria, a patient with severe acute respiratory illness, or an asymptomatic person who meets epidemiological criteria and tests positive on a professional-use or self-test SARS-CoV-2 antigen-detecting RDT” [35]; or
- are asymptomatic but may or may not have been exposed to SARS-CoV-2, such as those who have been in close contact with confirmed cases.

We will include participants regardless of age, sex, gender, sexual identity, race, ethnicity, socioeconomic status, level of education, disability, location, and other relevant factors pertinent to equity considerations.

We will consider both community-dwelling individuals and those in congregate settings, such as schools, workplaces, and long-term care facilities.

Types of interventions

We will include studies of test-based screening strategies for SARS-CoV-2, including both one-off and regular repeated testing, using antigen-detecting RDT or NAAT, including RT-PCR tests. This review will not focus on the diagnostic accuracy of the various tests. We will not consider co-interventions, i.e. we will exclude studies with co-interventions unless we can isolate the effects of the testing strategy.

Comparator(s)

- Testing strategy versus no testing or standard care or usual practice (i.e. the typical testing practices in the specific setting without additional interventions)
- Comparing one testing strategy to another, such as:
  - antigen-detecting RDT versus NAAT testing;
  - home-based versus health professional-based testing;
  - one-time testing versus different testing frequencies, e.g. weekly or bi-weekly testing;
  - targeted testing versus widespread testing; and
  - a different testing strategy from the intervention using any combination of the components above.

Outcome measures

We will not exclude studies that do not report the critical and important outcomes listed below. We will:

- contact authors to determine if relevant outcomes were measured but not reported;
- document which outcomes were not measured versus not reported; and
- consider the potential impact of missing outcome data in our certainty assessment.

If a study reports multiple measures of an outcome, we will consider them all. If multiple time points are reported, we will consider the latest time point.

Critical outcomes

- COVID-19 cases avoided (reduction in new cases)
- COVID-19-related hospitalisations avoided (reduction in hospital admissions)
- COVID-19-related deaths avoided (reduction in mortality)
- Serious adverse events related to testing, including unnecessary interventions, employment impacts, isolation effects, and psychological harms

Important outcomes

- Time interval to initiation of treatment for COVID-19
- Proportion of treatment initiated for COVID-19 (the number of people for whom treatment is initiated)
- Acceptability of the testing strategy (provider perspective)
- Feasibility of the testing strategy (program perspective)
- Value/preference (participant perspective)
- Cost of the test
- Harms related to false positive results:
  - economic burden from unnecessary isolation
  - employment disruption
  - reduced access to necessary medical care

Search methods for identification of studies

We will employ the same search strategy used in the scoping review [25]. An experienced information specialist constructed and executed a comprehensive search strategy for relevant studies following the Peer Review of Electronic Search Strategies (PRESS) guidelines [33, 36, 37, 38]. A second information specialist peer-reviewed the complete electronic search strategy and validated it by ensuring it identified already known studies.

We will include studies regardless of language of publication that are available in full text and published or available as a pre-print in peer-reviewed journals. We will make efforts to translate non-English studies and assess their eligibility. To capture evidence on SARS-CoV-2 variants of concern, we will consider studies published from January 2020 onwards.

Electronic searches

The search strategy has been previously developed and implemented by an information specialist (KK) with input from topic and methods experts on the team for our related scoping review [25]. The initial search, conducted in January 2023, covered the period from January 2020 to January 2023 and included MEDLINE (OVID), Embase (Elsevier), and Europe PMC. This comprehensive search strategy will be used for the current systematic review to maintain methodological consistency with our scoping review. In addition to the databases previously mentioned, we will search the Cochrane Central Register of Controlled Trials (CENTRAL) and trial registries, including ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP), to identify relevant studies. We updated the search in October 2024 to include the period from February 2023 to August 2024. The detailed search strategy for all databases is available in Supplementary material 1.

Searching other resources

We will review relevant studies and related systematic reviews to find additional references through forward citation tracking; we will also examine their reference lists. We will search for amendments, errata, or retractions related to the included studies on PubMed. Before publication, we will also check MEDLINE, Embase, and Retraction Watch (retractionwatch.com) to confirm that none of the included studies has been withdrawn due to errors or fraud. We will review the amendments made and assess their implications for the data already extracted.

Data collection and analysis

We will screen the studies using the specific inclusion and exclusion criteria mentioned above, following the guidelines of the *Cochrane Handbook* [31, 32, 33, 37].

Selection of studies

We will use Covidence [39], a web-based collaboration software designed to streamline systematic reviews and evidence synthesis, to remove duplicates and screen citations. We will conduct the screening process in two phases, following pilot testing for each. After removing duplicates, two review authors will independently screen the titles and abstracts for eligibility. We will resolve any disagreements through discussion with a third review author.

Two independent authors will also screen full-text articles, with discrepancies addressed through consultation with a third review author. We will record reasons for exclusions during the full-text screening phase.

Data extraction and management

Two review authors will independently extract data from the included studies. We will resolve any discrepancies through discussion with a third reviewer where necessary. We will extract the following data.

- Study characteristics
  - Author and year of publication
  - Study type
  - Start and end dates of study
  - Sample size (total and for each study arm)
  - Recruitment method
  - Funding sources
  - Conflict of interest
- Setting
  - Geographical setting
  - Institutional setting (outpatients, inpatients, school, long-term care facilities, etc.)
- Characteristics of the participants
  - Age
  - Socioeconomic status
  - Ethnicity
  - Education – in case of children, we will collect parent's educational status (if available)
  - Occupation
  - Comorbidities
  - SARS-CoV-2 vaccination status
  - Prior infection with SARS-CoV-2
  - Symptom status
  - Ascertainment of exposure to confirmed case
  - Ascertainment of vaccination status
    - Self-report
    - Medical chart review
    - Immunisation registry
- Characteristics of the intervention
  - Testing frequency (one-off or regular repeated testing)
  - Testing approach (mandatory or voluntary)
  - Using antigen-detecting RDT or NAAT including RT-PCR tests (including the name of the test)
  - Testing context (in any healthcare, community, or workplace setting)
  - Self-testing or testing done by a healthcare professional
  - Action recommended if positive
  - Test uptake
  - Adherence to testing schedules
  - Validation of the testing methods
- Characteristics of the comparator
  - No testing or standard care or usual practice
  - Alternative testing strategy
- Outcome measures
  - Outcome description (including the follow-up time)
  - Unit of measurement
- Specimen characteristics
  - Type (saliva, sputum, oropharyngeal swab, nasopharyngeal swab, mid-turbinate, anterior nasal swab, etc.)
  - Collection methods
  - Processing time

We will create a prespecified data extraction template using an Excel spreadsheet, and pilot test this on two included studies.

We will extract both adjusted and unadjusted effect measures of outcomes from the NRSIs; however, we will consider only the unadjusted measures in our analyses.

Risk of bias assessment in included studies

Two authors will independently evaluate the risk of bias for each critical outcome in the included studies. We will present risk of bias judgments alongside forest plots which will inform our certainty of evidence assessments for each outcome. We will resolve any disagreements through consensus, with a third reviewer stepping in if needed. We will document these consensus assessments in risk of bias tables. We will pilot the risk of bias assessment on two studies using the tools listed below. The pilot will:

- ensure consistent application between reviewers;
- refine our approach to handling challenging assessments; and
- document decision rules for similar situations.

We will evaluate bias in randomised controlled trials (RCTs) using version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2), which includes five domains [40].

- Bias from the randomisation process
- Bias due to deviations from intended interventions
- Bias from missing outcome data
- Bias in outcome measurement
- Bias in selecting the reported result

We will categorise the study outcomes as 'low risk of bias,' 'some concerns,' or 'high risk of bias' for each domain. We will assess the overall risk of bias as follows.

- Low risk of bias – if we assess the trial as low risk of bias across all domains for the outcome.
- Some concerns – if we assess the trial as some concerns in at least one domain for the outcome, but none at high risk of bias.
- High risk of bias – if we assess the trial as high risk of bias in at least one domain for the outcome, or if there are some concerns across multiple domains.

We will use the RoB 2 tool [40], in Microsoft Excel [41], to assist with RoB 2 assessments.

We will assess the critical outcomes regarding the effectiveness of testing strategies for risk of bias. We will consider the intention-to-treat effect. We will include all eligible studies in the primary analysis, regardless of the risk of bias assessment. We will not conduct a sensitivity analysis based on the risk of bias. However, we will exclude RCTs with some concerns or a high risk of bias in any of

the five RoB 2 domains and compare these results with the primary analysis that includes all studies.

For cluster RCTs, we will use the specific variant of the ROB 2 tool [40] designed for cluster-randomised trials. We will address issues unique to cluster RCTs, including domains specific to these trials, such as bias arising from the timing of participant identification and recruitment.

For the non-randomised studies of interventions (NRSIs), we will assess the risk of bias using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool [42], which examines eight domains.

- Bias due to confounding – we will consider the following key confounders and will assess whether these confounders were appropriately measured and controlled for through study design or statistical analysis: age, sex, comorbidities, vaccination status, COVID-19 prevalence levels, presence of public health measures, testing approach (mandatory/voluntary), socioeconomic status, and healthcare system capacity
- Bias in selecting participants into the study (e.g. inception bias)
- Bias in measuring the intervention
- Bias due to deviations from intended interventions
- Bias from missing data
- Bias in measuring outcomes
- Bias in selecting the reported result
- Overall bias

We will categorise these domains as having a 'low,' 'moderate,' 'serious,' 'critical,' or 'unclear' risk of bias. For the confounding domain specifically, we will consider a study at low risk of bias if all key confounders were appropriately measured and controlled for, moderate risk if most key confounders were addressed but some minor limitations exist, serious risk if one or more key confounders were not adequately controlled for, and critical risk if multiple key confounders were uncontrolled with clear evidence of confounding. We will assess the critical outcomes regarding the effectiveness of testing strategies for risk of bias. We will consider the intention-to-treat effect. The potential confounders for the critical outcomes would be age, sex, COVID-19 prevalence levels, the presence of public health measures, and testing approach (mandatory or voluntary). We will consider a study to be at overall low risk of bias if we assess it as having low risk of bias across all domains for the outcome. We will consider studies with moderate risk of bias in any domain as having moderate overall risk of bias, while serious or critical risk of bias in any domain will result in corresponding overall risk of bias judgments.

Measures of treatment effect

Effect estimates for the testing strategy will be derived from the primary studies. We will calculate the testing strategy effect ratio, represented as a risk ratio (RR). This ratio indicates the relative likelihood of an event, such as avoiding COVID-19, in the intervention group compared to the control group. We will present the effect estimates with their respective 95% confidence intervals (CI), which measure the precision of the testing strategy effect estimate. If studies report odds ratios (ORs) and conversion to RRs is not feasible, we will include ORs in our analysis and interpret them accordingly. For continuous outcomes, e.g. time interval to initiation of treatment for COVID-19; proportion of treatment initiated for COVID-19; or cost of the test, we will use the inverse variance method to estimate the pooled effect size.

Unit of analysis issues

The unit of analysis will be the individual study participant. Since the outcomes are binary (e.g. whether COVID-19 cases are avoided), we will count the number of participants who experienced the outcome rather than the number of occurrences of the outcome per participant [43]. For cluster-randomised studies, we will adjust for clustering as recommended by the *Cochrane Handbook* [44].

In studies with multiple treatment groups for the same intervention, such as different frequencies of testing strategies, we will assess whether these groups are sufficiently similar to combine. If they are, we will merge these groups into a single "intervention" category. We will apply this approach to studies comparing various testing strategy groups against a control group. If pooling multiple treatment arms is not feasible, we will compare each arm independently to the control group. In such cases, for pairwise meta-analysis involving a shared control group, we will divide the control group proportionally to maintain the independence of each comparison. We will apply this allocation to both the number of events and the sample sizes for dichotomous outcomes. This strategy ensures that each participant is counted only once in the meta-analysis, thereby preserving the validity of the pooled effect estimates [30].

Dealing with missing data

We will analyse data on an intention-to-treat basis, following the latest recommendations for systematic reviewers on handling missing data in clinical trials [44]. We will contact study authors (with up to two attempts) for missing information. For non-responses, we will document the nature and extent of missing data, consider its impact in our risk of bias assessment, and address implications in our certainty of evidence evaluation. We will not impute missing data.

Reporting bias assessment

We will minimise the risk of reporting bias by comprehensively searching for eligible studies (see Search methods for identification of studies). If more than ten studies addressing the same outcome are available, we will perform a funnel plot and Egger's test to detect small study effects [45]. We will also apply the Risk Of Bias due to Missing Evidence (ROB-ME) tool [46], which is intended to evaluate the risk of bias caused by missing evidence in a meta-analysis comparing two interventions. It applies regardless of the number or types of studies included, even when results are available from only a single identified study.

Synthesis methods

We will conduct separate meta-analyses for RCTs and NRSIs.

We will consider separate comparisons where applicable, such as testing strategy versus no testing or standard care or usual practice, antigen-detecting RDT versus NAAT testing, home-based versus health professional-based testing, and one-time testing versus different testing frequencies (e.g. weekly versus bi-weekly testing). Each comparison type will require:

- similar implementation contexts;

- comparable outcome measures and time points; and
- sufficient methodological homogeneity.

Where pooling is appropriate, we will use Review Manager [47] to pool the data in a meta-analysis following the *Cochrane Handbook*'s guidelines [30]. If there is variation amongst the studies but pooling the data still seems reasonable, we will use a random-effects model. This model accounts for the possibility that the true effect size may vary across studies due to differences in factors such as study populations, interventions, or methodologies. It provides a more conservative estimate of the effect size and its uncertainty, which is more suitable when there is potential heterogeneity amongst the included studies.

For binary outcomes, we will calculate the testing strategy effect ratio, represented as a risk ratio, using the Cochran-Mantel-Haenszel method. This method will estimate the between-study variance and the pooled effect size across strata.

We will conduct a meta-analysis of NRSI data following the guidelines in Chapter 24 of the *Cochrane Handbook* [48], provided the studies are suitably homogeneous, offer sufficient data, and are categorised as having an overall 'low' or 'moderate' risk of bias. We will exclude data from studies with 'serious,' 'critical,' or 'unclear' risk of bias.

We will use unadjusted data for RCTs and adjusted data for NRSIs if available (and track which variables were adjusted for); otherwise, we will use the unadjusted data reported in the study.

Where meta-analysis is not possible but data synthesis is appropriate, we will conduct a structured synthesis informed by the Synthesis Without Meta-analysis (SWiM) guidelines [49]. This will include presenting findings in summary tables alongside study and clinical characteristics that may contribute to heterogeneity. Additionally, we will include forest plots without pooling to visualise the data. We will attempt a description of the direction and size of any observed effects across studies without conducting a meta-analysis if this is the case.

When synthesis is not appropriate, we will present individual study results and clearly document reasons preventing synthesis, avoiding vote counting approaches.

For acceptability, feasibility, and values/preferences outcomes, we will extract available quantitative data from intervention studies, such as validated scales and survey results. Where appropriate, we will synthesise findings descriptively following SWiM guidelines; otherwise, we will present results narratively. We acknowledge that these outcomes are typically addressed through qualitative research, which is beyond this review's scope.

We will report costs by presenting original values and currency as reported in each study, documenting the healthcare system context and cost components included, and addressing limitations in cross-study cost comparisons in our discussion.

If synthesis is not feasible due to missing data, we will report the results using a descriptive approach without attempting synthesis.

Investigation of heterogeneity and subgroup analysis

We will evaluate and statistically quantify different types of heterogeneity (due to different clinical characteristics, methodological diversity, or small study effects) using the I^2 statistic and Chi^2 test. The following thresholds will be used to interpret I^2 [44].

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- ≥ 75%: will be considered considerable heterogeneity

Using the random-effects model, we will calculate 95% prediction intervals for meta-analyses. These intervals will indicate the range of values likely to contain the true effect in a new study with characteristics similar to those included in the meta-analysis. This approach will help us assess the extent and implications of heterogeneity amongst the studies [44].

We will perform subgroup analyses if there are a sufficient number of studies (at least 10) in each comparison for meaningful analysis.

If possible, we will conduct subgroup analyses using age and geographic location as stratifying variables. We will stratify each outcome by age group (adults, older adults, infants); settings (hospitals, schools); qualification of tests by the WHO and other regulatory bodies; and geographic location (low- and middle-income countries and high-income countries as defined by the World Bank [50]). Where data permit, we will perform subgroup analyses based on COVID-19 prevalence levels and the presence of public health measures.

Subgroup analyses will provide insights into how age, settings, test qualifications, and geographic location influence outcomes. Age affects susceptibility and immune response, with infants and older adults often experiencing more severe disease, while settings like hospitals and schools present different exposure risks and testing scenarios. We expect that tests approved by regulatory bodies, such as the WHO, will yield more reliable outcomes, highlighting the importance of test qualifications. Geographic disparities, particularly between low- and middle-income and high-income countries, can impact resource availability and healthcare access, influencing the effectiveness of interventions.

Equity-related assessment

We will consider the PRO-EDI criteria (tools to help reviewers make equity, diversity, and inclusion assessments) to address equity issues [51]. The PRO-EDI participant characteristics table includes factors such as age, sex, gender, sexual identity, race, ethnicity, ancestry, socioeconomic status, level of education, disability, location, and other relevant factors relevant to the review's focus on equity. It offers a framework for detailing the study populations included in a review, aiding in equity-related judgments when interpreting the results. This structure helps identify who should ideally be represented in the evidence based on the disease or condition and highlights who is actually represented in the studies.

Sensitivity analysis

We will conduct sensitivity analyses based on the following criteria.

- Impact of risk of bias on meta-analysis: we will exclude RCTs rated as having some concerns or a high risk of bias in any of the five domains of ROB 2 and compare these results with those of the primary analysis that includes all studies.

- Impact of risk of bias due to confounding on meta-analysis: we will exclude NRSIs rated as not having an overall low risk of bias in ROBINS-I and compare these results with those of the main analysis that includes all studies.

Where data permit, we will perform sensitivity analyses based on COVID-19 prevalence levels and the presence of public health measures, to assess their impact on the effectiveness of the testing strategies.

Certainty of the evidence assessment

We will assess the certainty of evidence for selected patient-relevant outcomes using the GRADE approach [52]. We will prioritise the following comparisons for the summary of findings tables [53].

- Testing strategy versus no testing or standard care or usual practice
- Antigen-detecting RDT versus NAAT testing

For each comparison, we will include critical outcomes at the latest follow-up time point. The critical outcomes are:

- COVID-19 cases avoided (reduction in new cases);
- COVID-19-related hospitalisations avoided (reduction in hospital admissions);
- COVID-19-related deaths avoided (reduction in mortality); and
- serious adverse events related to testing, including unnecessary interventions, employment impacts, isolation effects, and psychological harms.

The GRADE assessment considers five domains.

- Study limitations (risk of bias): evaluates the risk of bias in the included studies
- Imprecision: considers when 95% confidence intervals are wide and/or close to null effect around the point estimate, or when evidence is derived from only a few studies with a small number of participants
- Inconsistency: assesses differences in effect estimates across studies that assessed the same comparison
- Indirectness: evaluates differences in patient characteristics, co-interventions, the extent to which the intervention of interest is optimally conducted, differing comparators, and differences in measurement of outcomes
- Publication bias: considers the potential for publication bias affecting the results

These domains, in addition to the underlying study design, are used to rate the certainty of evidence for each outcome. For each assessed domain, we will downgrade our certainty by one level for serious concerns or by two levels for very serious concerns, resulting in overall ratings of high, moderate, low, or very low certainty for each evaluated outcome. In line with recent GRADE guidance, we will prespecify thresholds for rating the certainty of evidence [54]. For each outcome, we will define what constitutes an important effect size. For example, for the outcomes of new cases, hospitalisations, and mortality, we will consult with the guideline development group or expert opinion to determine what absolute risk reduction would be considered clinically important. We will then rate our certainty in the evidence reaching or exceeding these thresholds. We will establish clinically important effect thresholds through consultation with the guideline development group and content experts prior to analysis. We will use these thresholds to rate our certainty in the evidence for each critical outcome. We will document the process for determining thresholds in the review.

For NRSIs, in accordance with the GRADE guidelines for NRSIs assessed with ROBINS-I, we will start with a high certainty of evidence.

The GRADE assessment will be conducted by one review author using GRADEpro and cross-checked by another author [55]. We will resolve any disagreements through discussion and consensus, involving a third person if needed.

Consumer involvement

Due to the nature of this review, which builds directly on a previous scoping review and informing time-sensitive WHO guidelines, we were unable to incorporate formal patient and public involvement (PPI) in the review process. We acknowledge this as a limitation. We will share the review protocol and findings with the WHO guideline development group, which includes a range of stakeholders. For future related work, we recommend incorporating PPI from the inception stage to ensure consumer perspectives are fully integrated.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016192.

Supplementary material 1 Search strategies

ADDITIONAL INFORMATION

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Editorial and peer-reviewer contributions

The following people conducted the editorial process for this article.

Sign-off Editor (final editorial decision): Toby Lasserson, Deputy Editor in Chief, The Cochrane Library

Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Liz Bickerdike, Cochrane Central Editorial Service

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KM Saif-Ur-Rahman: Conceptualisation; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; supervision; validation; visualisation; writing – original draft; writing – review and editing.

Nadra Nurdin: Data curation; investigation; writing – original draft; writing – review and editing.

Ani Movsisyan: Conceptualisation; formal analysis; investigation; methodology; validation; writing – review and editing.

Kavita Kothari: Data curation; methodology; resources; software; writing – review and editing.

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Registration and protocol

Cochrane approved the proposal for this review in June 2024.

Data, code and other materials

Data sharing is not applicable to this article as it is a protocol, so no datasets were generated or analysed.

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