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EFFECTIVENESS OF MASS TESTING FOR CONTROL OF COVID-19: A SYSTEMATIC REVIEW PROTOCOL

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Title Page – BMJ Open

EFFECTIVENESS OF MASS TESTING FOR CONTROL OF COVID-19: A SYSTEMATIC REVIEW PROTOCOL

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None do declare.

Author Contributions: LCLJ conceptualized and designed the protocol, drafted the initial manuscript and reviewed the manuscript. EB, RMP, SISPCS, RAGL and LCLJ defined the concepts and search items, data extraction process as well as methodological appraisal of the studies. EB, RMP, SISPCS, and LCLJ planned the data extraction and statistical analysis. RAGL, EB and LCLJ provided critical insights. All authors have approved and contributed to the final written manuscript.

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ABSTRACT

Introduction: Since the World Health Organization declared COVID-19 as a pandemic, the exponential spreading of the new coronavirus has been the focus of attention for scientists, governments and populations. One of the great concerns and challenges in several countries, mainly for low and middle-income ones, refers to the notification and monitoring of COVID-19's cases. The wide availability of antibody tests would be an important advance in the control of COVID-19, but there is still no systematic review and meta-analysis to confirm it, and currently, this is the biggest challenge faced by many countries worldwide. We aim to synthesize and critically evaluate the scientific evidence on the effectiveness of testing capacity for symptomatic individuals for the control of COVID-19.

Methods and analysis: A systematic review will be held in eight databases: MEDLINE, ISI of Knowledge, CENTRAL, EMBASE, SCOPUS, LILACS, PsycINFO and CNKI, with no restriction regarding the publication date or languages. Primary outcomes will include the better notification, control and timely monitoring of COVID-19 cases. Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. Methodological appraisal of the studies will be assessed by the Cochrane Risk-of-Bias Tool for Randomized Controlled Trials, besides MINORS for assessing the risk-of-bias for Non-Randomized Studies. A narrative synthesis of the findings will be structured around the type of intervention, target population characteristics, focused on the primary outcome and intervention/exposure follow-up. Additionally, if sufficient data are available, a meta-analysis will be conducted using Hedges' g score for both fixed and random effect models. I^2 statistics will be used to assess heterogeneity.

Ethics and dissemination: Ethical approval is not required once primary data will not be collected. Findings will be disseminated widely via peer-reviewed publication as well as in different media, such as, symposia, congresses.

PROSPERO registration number: CRD42020182724.

Keywords: COVID-19; Coronavirus; Coronavirus Infections; Testing; Effectiveness; Public Health; Health Surveillance.

Strengths and limitations of this study:

- This systematic review protocol reduces the possibility of duplication, gives transparency to the methods and processes that will be used, reduces possible biases and also will be allows peer review.
- We will offer highest level of evidence for Health Surveillance support for shared decision making from the healthcare providers, stakeholders and governments from this systematic review for control of COVID-19.
- This systematic review will be the first to evaluate critically the scientific evidences on the effectiveness of testing capacity for symptomatic individuals for the control of COVID-19. This study will be relevant to address this gap in the literature with regards to achieving better notification, control and timely monitoring of COVID-19 cases as well as guiding strategies and health policies decision-making to the several countries.
- The scarcity of randomized controlled trials as well as observational studies undertaken on this particular topic, the publication bias of the original researches and the methodological quality of the grey literature found may be the main limitations of the study.

INTRODUCTION

Recent cases of pneumonia in Wuhan, China, have led to the discovery of a new type of zoonotic Coronavirus - an enveloped RNA virus, commonly found also in humans capable of causing respiratory, enteric, liver and neurological disorders. ¹ Despite COVID-19 has a low lethality of around 3%, transmissibility is high, ¹ with respiratory secretions being the main means of spreading SARS-CoV-2. ² Since the World Health Organization declared COVID-19 a pandemic on March 11, 2020, ³ the SARS-CoV-2 spreading has been the focus of attention for scientists, government officials, and populations. ⁴

A study on observations of SARS-CoV-2 infections in China, using a networked metapopulation dynamics and Bayesian inference models to infer epidemiological characteristics associated with COVID-19, estimated that the rate of transmission of undocumented infections per person was 55% of documented infections. However, due to their greater number, undocumented infections were the source of infection for 79% of documented cases. ⁵ SARS-CoV2 is already circulating in 212 countries and territories worldwide, with 4,241,956 infected and 286,492 deaths recorded on May 11, 2020, ⁶ being the Brazil the new epicenter of the pandemic ⁷ with 165,475 confirmed cases and 11,309 deaths so far. ⁶

One of the great concerns and challenges of COVID-19 in several countries, especially for low and middle income, refers to the notification of cases. ⁸ The definitions of suspected cases, as expected, were changed as the transmission situation changed over time. Notification platforms have also undergone modifications over the months. It is worrying the volume of changes that occurred in such a short time, especially in relation to notification platforms. It is not possible to know whether these changes arrive in a timely manner, especially in populous, middle and low-income countries. ⁹ The coexistence of several criteria and platforms can generate serious failures in the Health Surveillance system, resulting in underreporting, the magnitude of which is difficult to be estimated. Indeed, the main reason for criticism of the Health Surveillance process in several countries there has been a low capacity for mass testing. ^{8 10}

One of the crucial issues that the World Health Organization (WHO) has pointed out, is that testing all suspected cases is essential for controlling the pandemic. ¹¹ However, inadequate access to diagnostic tests still exists globally and the confusion among health professionals and the public about prioritizing tests and interpreting results is still a reality. ¹⁰ ¹² The lack of diagnostic tests and laboratory capacity for the detection of COVID-19 in many

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3 countries, for example in Brazil, it had led the Ministry of Health to limit testing only to
4 severe cases, with the justification that testing does not change the treatment to be offered.¹³
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6 It should be noted that the incubation period from infection to the first symptom of
7 COVID-19 is typically 5 to 7 days, with an interval of 4-14 days. The diagnosis of the current
8 infection depends on tests to detect viruses in various body fluids.^{10 12} Nasopharyngeal
9 smears (swab) are more sensitive than oropharyngeal smears and are better when the first
10 symptoms appear.^{14 15 16 17 18} However, the gold standard for diagnostic testing is the
11 detection of viral RNA by molecular methods, mainly by reverse-transcriptase polymerase
12 chain reaction (RT-PCR).
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19 New systems are being evaluated for faster detection of major viral sequences^{16 19 20}
20 and a variety of antigen detection devices have been developed, however, their performance
21 varies widely. In countries such as Korea South, mass testing programs, contact tracking and
22 isolation contributed to early infection control.²¹ As the epidemic progresses, the focus is on
23 symptomatic patients and health professionals who are at the forefront of COVID-19 and their
24 families. Testing symptomatic patients for their current infection when they attend health
25 services can inform the tracking and prevention and control of infections, particularly in the
26 screening of patients for COVID-19 referral centers / hospitals.^{10 12}
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33 The World Meters Network, based on consolidated official data, raises some questions
34 that are quite relevant in terms of differences in testing.⁶ Comparing countries by the capacity
35 of testing per million inhabitants from official data, there are expressive differences. For
36 example, on one hand, the United States has already tested 9,700,658 individuals on May 11,
37 2020, i.e., 29,307 per 1,000,000,000 inhabitants. Brazil, on the other hand, tested 339,552
38 individuals to date, representing 1,597 per 1,000,000,000 inhabitants, placing Brazil in a very
39 unfavorable situation in terms of the control of COVID-19 comparing the testing capacity of
40 other countries.⁶
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46 Without symptomatic testing, it will be difficult to isolate patients and quarantine
47 communicants. Thus, the production of diagnostic kits for COVID-19 and the laboratory
48 capacity to perform the testing of symptomatic patients urgently need to be expanded.^{10 12} It
49 is hypothesized that the wide availability of antibody tests would be an important advance in
50 the control of COVID-19, but there is still no systematic review and meta-analysis to confirm
51 it, and currently, this is the biggest challenge faced by many countries. Hence, following the
52 Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)
53 checklist as guidance,²² we propose a systematic and a reproducible strategy to query the
54 literature about the effectiveness of mass testing for control of COVID-19 worldwide.
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RESEARCH AIMS

The purpose of this systematic review was to synthesize and critically evaluate the scientific evidence on the effectiveness of testing capacity for symptomatic individuals for the control of COVID-19.

METHODS AND ANALYSIS

Search Strategy

Search strategy will be undertaken using resources for enhance methodological transparency and improve the reproducibility of the findings as well as evidence synthesis, following the PRISMA-P checklist.²² Additionally, using the PICO (Population/Intervention/Comparison/Outcomes) acronym²³ we elaborated the research question for this review, for ensuring the systematic search of the literature: *"What is the scientific evidence from studies about the effectiveness of the capacity to testing symptomatic patients for the control of the COVID-19 pandemic?"* Approval of this systematic review protocol was obtained by The PROSPERO – International Prospective Register of Systematic Reviews, under Registration Number CRD42020182724.

Studies will be searched using eight databases: Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed, ISI of Knowledge via Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Excerpta Medica database (EMBASE), SCOPUS, Latin American and Caribbean Health Sciences Literature (LILACS), Psychology Information (PsycINFO) and Chinese National Knowledge Infrastructure (CNKI). There will be no restriction regarding the publication dates or languages for this systematic review. Additionally, secondary searches in other sources, such as, into the registration site of clinical trials (e.g. ClinicalTrials.gov), The British Library and Google Scholar. The reference section of the included studies will be hand searched for additional relevant studies. The search strategy will comprise for only key terms according to a pre-established PICO acronym. It is stand out that two researchers (LCLJ and EB) will carry out the search strategy in all databases independently. Also, the bibliographic software EndNote (<https://www.myendnoteweb.com/>) as well as Rayyan™ app (*Qatar Computing Research Institute*)²⁴ will be used to store, organize, and manage all the references and ensure a systematic and comprehensive search.

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3 Firstly, we will identify the existence of specific subject headings index in each
4 database (such as MeSH terms, Emtree terms, PsycINFO Thesaurus and DeCS-Health
5 Science Descriptors) and their synonyms (keywords). The search terms were combined using
6 the Boolean operators “AND” and “OR”.²⁵ Subsequently, the search strategy combining
7 MeSH terms and keywords that will be used in MEDLINE (via PubMed) and adjusted to the
8 other databases will be as depicted in Table 1.
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15 **Table 1** Concepts and search items

Databases	Search strategy
MEDLINE	#1 ((“Infant” [MeSH Terms] OR “Child, Preschool” [MeSH Terms] OR “Adolescent” [MeSH Terms] OR “Young Adult” [MeSH Terms] OR “Adult” [MeSH Terms] OR “Aged” [MeSH Terms] OR “Aged, 80 and over” [MeSH Terms]))
ISI of Knowledge	
CENTRAL	
EMBASE	#2 (“Coronavirus”[MeSH Terms] OR "Coronavirus"[All Fields]) OR ("COVID-19"[All Fields] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[Supplementary Concept] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields]) OR “Pandemics”[MeSH Terms])
SCOPUS	
LILACS	
PsycINFO	
CNKI	#3 (“COVID-19 diagnostic testing” [Supplementary Concept] OR “COVID-19 testing” [All Fields] OR “LAMP assay” [Supplementary Concept] OR “LAMP assay COVID-19” [All Fields] OR LAMP assay SARS-CoV-2” [All Fields] OR OR LAMP assay Coronavirus Infections/*diagnosis [All Fields]))
	#4 #1 AND #2 AND #3

45 Abbreviations: MEDLINE, Medical Literature Analysis and Retrieval System Online; CENTRAL, Cochrane
46 Central Register of Controlled Trials; EMBASE, Excerpta Medica Database; LILACS, Latin American and
47 Caribbean Health Sciences Literature; PsycINFO, Psychology Information; CNKI, Chinese National Knowledge
48 Infrastructure.
49

50 51 **Study Selection**

52 The PICO acronym [Population (P), Interventions/Exposure (I), Comparators (C) and
53 Outcomes (O)] are detailed in Table 2.
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Table 2 Inclusion and exclusion criteria

PICO Acronym ²³	Inclusion criteria	Exclusion criteria
P – Population	Infant, Child, Adolescents, Young Adult, Adult and Aged (according to MeSH terms)* of both sexes, of any ethnicity, and symptomatic and / or suspect for COVID-19.	–
I – Intervention/Exposure	COVID-19 testing	Testing for other previous pandemics
C – Comparison	Symptomatic individuals for COVID-19 who have not been tested	–
O – Outcome	The primary outcomes includes better notification, control and timely monitoring of COVID-19 cases	–

Abbreviations: MeSH, Medical Subject Headings; COVID-19, Coronavirus Disease 2019.

* In this systematic review we will using as a definition the following terms in accordance with the MeSH terms indexing, such as “Infant” - a child between 1 and 23 months of age; “Child, Preschool”- a child between the ages of 2 and 5; “Child”- a person 6 to 12 years of age; “Adolescent”- a person 13 to 18 years of age; “Young Adult”- a person between 19 and 24 years of age; “Adult”- a person having attained full growth or maturity. Adults are of 19 through 64 years of age; “Aged”- a person 65 through 79 years of age; “Aged, 80 and over”- a person 80 years of age and older.

Regarding the study design, we will include all designs with quantitative approach (descriptive studies, observational studies and experimental studies), as well as the gray literature (editorials, opinion articles, reviews, clinical guidelines, conference proceedings, abstracts, book chapters, etc.) as recommended by the Cochrane Handbook.²⁶ Thus, studies that have investigated epidemiological and clinical aspects of testing the symptomatic and suspected population for COVID-19 will be included in this systematic review. Nevertheless, studies evaluating the mass testing for other Severe Acute Respiratory Syndromes (SRAG) than COVID-19 will be excluded. The selection of studies will also be carried out by two reviewers independently (LCLJ and EOB) and blindly. After this selection, a third reviewer (RAGL) will be responsible for analyzing and deciding on the inclusion or exclusion of each article, especially in relation to those containing a conflicting decision. In this inclusion stage of articles, we will use the Rayyan™ application, developed by the *Qatar Computing Research Institute*,²⁴ as an auxiliary tool in the archiving, organization and selection of articles. With regards to the setting of the population to be testing we will include people living in community, nursing homes, also outpatients and hospitalized people.

Screening and Data Extraction

First of all, the screening of studies will be based on the information retrieved in their titles and abstracts and will be carried out by two independent researchers (LCLJ and EB).

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3 When the reviewers disagree, the article will be reevaluated and, if the disagreement
4 persisted, a third reviewer (RAGL) will make a final decision, using Rayyan™ app. Secondly,
5 the full-paper screening will be done by the same independent investigators. In order to
6 measure inter-coder agreement in each screening phase, Cohen's kappa will be performed.
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8 Once consensus is reached on the selected studies, a standardized form based on previous
9 studies^{27 28 29 30} will be used for data extraction. Information to be extracted including four
10 domains: I) identification of the study (article title; journal title; impact factor; authors;
11 country of the study; idiom; publication year; host institution of the study [hospital;
12 university; research center; single institution; multicenter study]; conflict of interest and study
13 sponsorship); ii) methodological characteristics (study design; study objective or research
14 question or hypothesis; sample characteristics, e.g. sample size, age, race, baseline
15 characteristics; groups and controls; recruitment methods and study completion rates; stated
16 length of follow-up; validated measures; statistical analyses, adjustments; iii) main findings
17 and implications for clinical practice; and iv) conclusions. The same two reviewers will be
18 carried out the data extraction independently. Discrepancies between the reviewers will be
19 resolved either by discussion or, in the lack of agreement, by a third reviewer (RAGL).
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32 **Methodological appraisal**

34 The internal validity and risk of bias for RCTs will be assessed with the appraisal tool
35 from the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0,²⁶ which
36 assesses which assesses the seven domains: I) Randomization Sequence Allocation; II)
37 Allocation concealment; III) Blinding of participants and team involved; IV) Blindness of
38 outcome evaluators; V) Incomplete outcomes; VI) Report of selective outcome and VII)
39 Other sources of bias. Based on these domains evaluated, studies are classified as at risk of
40 low, high or uncertain bias. For assessing Non-Randomized Controlled Trials, the
41 Methodological Index for Non-Randomized Studies (MINORS),³¹ will be used. This
42 instrument MINORS contains eight items for non-comparative studies: 1) A clearly stated
43 aim; 2) Inclusion of consecutive patients; 3) Prospective collection of data; 4) Endpoints
44 appropriate to the aim of the study; 5) Unbiased assessment of the study endpoint; 6) Follow-
45 up period appropriate to the aim of the study; 7) Loss to follow-up less than 5%; and 8)
46 Prospective calculation of the study size.³¹ Again, the same two reviewers (LCLJ and EB)
47 will held the critical appraisal independently. Disagreements will be resolved by a third
48 reviewer (RAGL). The risk of bias for each outcome across individual studies will be
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3 summarized as a narrative statement and supported by a risk of bias table. A review-level
4 narrative summary of the risk of bias will also be depicted.
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6 **Data synthesis**

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8 Narrative syntheses about the risk of bias of RCT will be made for the included and
9 analyzed studies. The studies will be classified according to the risk of bias as follows: “low”
10 if all the main domains were classified as “low risk”; “Uncertain” if one or two main domains
11 were classified as “uncertain risk”; and “high” if more than two main domains have been
12 classified as “uncertain” or “high risk”. When no information was available, we assigned
13 “uncertain risk”.³² For assessing the Non-Randomized Studies, each item from MINORS will
14 be rated from 0 to 2, which means: the score 0 indicates that the information was not reported,
15 1 indicated that the information was inadequately reported, and 2 that the information was
16 adequately reported.³¹ We will provide a qualitative synthesis of the findings from the
17 included studies, structured around the type of intervention, target population characteristics,
18 focused on the primary outcome and intervention follow-up. In order to select particular
19 studies for data synthesis, we will consider the subgroups based on study design (RCT, non-
20 randomized studies), risk of bias assessments (for example, low, uncertain and high risk of
21 bias), sample size, the relevance of the evidence (outcome, population/context, or
22 intervention) comprising to the research question, or the certainty of the evidence, directness
23 in relation to the research question).
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26 Informal methods will involve ordering tables or structuring figures such as
27 methodological characteristics (for example, study design), subpopulations (for example, sex,
28 age), intervention components, and/or contextual/setting factors. The assessment of the
29 certainty of the evidence will search to take into consideration the precision of the synthesis
30 finding (confidence interval if available), the number of studies and participants, the
31 consistency of effects across studies, the risk of bias of the studies, how directly the included
32 studies address the planned question (directness), and the risk of publication bias.³³
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35 Study findings will be presented in tables or graphs in the same way as the syntheses
36 are reported in the narrative text to facilitate the comparison of findings from each included
37 study. Key characteristics, such as study design, sample size, and risk of bias, which may
38 affect interpretation of the data, will be also presented. Outcomes will be analyzed according
39 to sex and population subgroups (children, adolescents, young adults, adults and the elderly),
40 and also according to classification of country (low, middle or high-income country).
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43 Furthermore, whenever possible, continuous and dichotomous outcomes will be
44 pooled together for meta-analysis purposes. All effect sizes will be transformed into a
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3 common metric, in order to make them comparable across studies – the bias-corrected
4 standardized difference in means by Hedges' g score, for both fixed and random effect
5 models. Heterogeneity will be assessed using I^2 .³⁴
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10 **Patient and public involvement, ethics and dissemination**

11 Since this is a systematic review protocol the participant recruitment as well as their
12 involvement was not applicable. Moreover, any amendments to this protocol will be
13 documented with reference to saved searches and analysis methods, which will be recorded in
14 bibliographic databases for data collection and synthesis. In addition, our findings will be
15 disseminated via peer-reviewed publication as well as in different media, such as, symposia,
16 and congresses.
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23 **DISCUSSION**

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27 One of the strengths of the proposed systematic review is to apply a reproducible and
28 transparent procedure for systematic review of the literature. In this protocol, we clearly
29 describe the types of studies, participants, intervention and outcomes that will be considered
30 according to the research question, as well as the data sources, search strategy, data extraction
31 methods (including critical appraisal of the studies included) and data synthesis.³⁵ By
32 publishing the research protocol, we reinforce the clarity of the strategy and minimize the risk
33 of bias, i.e., selective outcome reporting.³⁵ These results shall provide high-level evidence to
34 inform, support and customize shared decision making from the healthcare providers,
35 stakeholders and governments.
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43 Potential limitations of this systematic review might include the heterogeneity of
44 measures and outcomes evaluated and the potentially reduced number of studies in subgroup
45 analyses (give the recent COVID-19 outbreak), which may influence the external validity.
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48 Antibody tests are used primarily to determine whether a person has ever had COVID-
49 19. Specific IgM and IgG antibodies should begin to be detectable after 4-5 days, with
50 positive IgM antibodies in 70% of symptomatic patients on days 8 to 14 and 90% of the total
51 positive antibody tests on days 11 to 24.^{36 37} The testing of all symptomatic patients,
52 according to the Imperial College study and the Chinese experience,³⁸ is essential for the
53 strategy of combining recommended measures to contain the epidemic to be successful.³⁸
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58 While the virus spreads worldwide, the scientific community are doing many efforts to
59 generate and spread knowledge about COVID-19. On February 13, 2020, the COVID-19
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3 vocabulary had already been added to the MeSH terms as a subject descriptor indexed in the
4 Medical Literature Analysis and Retrieval System Online - MEDLINE database. On May 11,
5 the new coronavirus had already been cited in 10,750 publications indexed in PubMed,
6 including descriptive analyzes of the first cases, analysis of genomic sequences,
7 epidemiological analyzes, mathematical and statistical models to monitor the new virus and
8 define action strategies, in addition to clinical outcomes, and the unbridled search for the
9 treatment of the new coronavirus. However, there is still no systematic review on the actual
10 effectiveness of testing COVID-19 symptomatic patients for the control and monitoring of
11 cases.
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14 In this sense, the present systematic review will delivery relevant evidence on the on
15 the effectiveness of testing capacity for symptomatic individuals for the control of COVID-19
16 in order to address this gap in the literature with regards to achieving better notification,
17 control and timely monitoring of COVID-19 cases as well as guiding important strategies and
18 health policies decision-making to the several countries.
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For peer review only

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Syst Rev.* 2015;4(1):1.

		Reporting Item	Page Number
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
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1 and 2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1
	#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
Sources	#5a	Indicate sources of financial or other support for the review	1

1	Sponsor	#5b	Provide name for the review funder and / or sponsor	1
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3	Role of sponsor or	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any,	1
4	funder		in developing the protocol	
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7	Rationale	#6	Describe the rationale for the review in the context of what is	3 and 4
8			already known	
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11	Objectives	#7	Provide an explicit statement of the question(s) the review will	5
12			address with reference to participants, interventions, comparators,	
13			and outcomes (PICO)	
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16	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design,	5 and 6
17			setting, time frame) and report characteristics (such as years	
18			considered, language, publication status) to be used as criteria for	
19			eligibility for the review	
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23	Information	#9	Describe all intended information sources (such as electronic	5
24	sources		databases, contact with study authors, trial registers or other grey	
25			literature sources) with planned dates of coverage	
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28	Search strategy	#10	Present draft of search strategy to be used for at least one electronic	5 and 6
29			database, including planned limits, such that it could be repeated	
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32	Study records -	#11a	Describe the mechanism(s) that will be used to manage records and	5 and 7
33	data management		data throughout the review	
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36	Study records -	#11b	State the process that will be used for selecting studies (such as two	7
37	selection process		independent reviewers) through each phase of the review (that is,	
38			screening, eligibility and inclusion in meta-analysis)	
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41	Study records -	#11c	Describe planned method of extracting data from reports (such as	7 and 8
42	data collection		piloting forms, done independently, in duplicate), any processes for	
43	process		obtaining and confirming data from investigators	
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46	Data items	#12	List and define all variables for which data will be sought (such as	7
47			PICO items, funding sources), any pre-planned data assumptions and	
48			simplifications	
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52	Outcomes and	#13	List and define all outcomes for which data will be sought, including	6
53	prioritization		prioritization of main and additional outcomes, with rationale	
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56	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of individual	8
57	individual studies		studies, including whether this will be done at the outcome or study	
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1		level, or both; state how this information will be used in data	
2		synthesis	
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4	Data synthesis	#15a Describe criteria under which study data will be quantitatively	9
5		synthesised	
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8		#15b If data are appropriate for quantitative synthesis, describe planned	9
9		summary measures, methods of handling data and methods of	
10		combining data from studies, including any planned exploration of	
11		consistency (such as I ² , Kendall's τ)	
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14		#15c Describe any proposed additional analyses (such as sensitivity or	9 and 10
15		subgroup analyses, meta-regression)	
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18		#15d If quantitative synthesis is not appropriate, describe the type of	9 and 10
19		summary planned	
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22	Meta-bias(es)	#16 Specify any planned assessment of meta-bias(es) (such as	n/a
23		publication bias across studies, selective reporting within studies)	
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26	Confidence in	#17 Describe how the strength of the body of evidence will be assessed	n/a
27	cumulative	(such as GRADE)	
28	evidence		
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 32 4.0. This checklist was completed on 06. September 2018 using <http://www.goodreports.org/>, a tool made by
 33 the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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BMJ Open

EFFECTIVENESS OF MASS TESTING FOR CONTROL OF COVID-19: A SYSTEMATIC REVIEW PROTOCOL

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Title Page – BMJ Open

EFFECTIVENESS OF MASS TESTING FOR CONTROL OF COVID-19: A SYSTEMATIC REVIEW PROTOCOL

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None do declare.

Author Contributions: LCLJ conceptualized and designed the protocol, drafted the initial manuscript and reviewed the manuscript. EB, DSCS, RMP, SIPCS, RAGL and LCLJ defined the concepts and search items, data extraction process as well as methodological appraisal of the studies. EB, DSCS, RMP, SIPCS, and LCLJ planned the data extraction and statistical analysis. RAGL, EB, DSCS, LCLJ provided critical insights. All authors have approved and contributed to the final written manuscript.

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ABSTRACT

Introduction: Since the COVID-19 outbreak has been declared a pandemic by the WHO, the new coronavirus spreading has been the focus of attention of scientists, governments and communities around the world. One of the great concerns and challenges, mainly in low and middle-income countries, is the notification and monitoring of COVID-19's cases. The large-scale availability of the test is a fundamental aspect in the control of COVID-19, but this is currently the biggest challenge faced by many countries in the world. We aim to synthesize and critically evaluate the scientific evidence on the effectiveness of testing capacity for symptomatic individuals for the control of COVID-19.

Methods and analysis: A systematic review will be conducted through eight databases: MEDLINE, ISI-of-Knowledge, CENTRAL, EMBASE, SCOPUS, LILACS, PsycINFO and CNKI, from inception until June 30, 2020. No restriction regarding the publication date, settings or languages will be employed. Primary outcomes will include sensitivity as well as the specificity of the tests for COVID-19. Study selection will follow the PRISMA checklist. Methodological appraisal of the studies will be assessed by the Cochrane Risk-of-Bias tool for Randomized Controlled Trials, besides MINORS for Non-Randomized Studies and Newcastle-Ottawa Scale for case-control or cohort studies. Findings will be structured according to the test type, target population characteristics, focused on the primary outcomes (sensitivity and specificity). Additionally, if sufficient data are available, a meta-analysis will be conducted. Pooled standardized mean differences and 95% CIs will be calculated. Heterogeneity between the studies will be determined by the I^2 statistics. Subgroup analyzes will be also performed. Publication bias will be assessed with funnel plots and Egger's test. Heterogeneity will be explored by random-effects analysis.

Ethics and dissemination: Ethical approval was not required. Findings will be disseminated widely via peer-reviewed publication and presented at conferences related to this field.

PROSPERO registration number: CRD42020182724.

Keywords: COVID-19; Coronavirus; Coronavirus Infections; Testing; Effectiveness; Public Health Nursing; Health Surveillance.

Strengths and limitations of this study:

- We will offer evidence for health surveillance support in order to help decision makers (i.e. healthcare providers, stakeholders and governments) regarding COVID-19 control.
- This systematic review will be the first to critically evaluate the scientific evidence about the effectiveness of testing capacity for symptomatic individuals of COVID-19.
- This study will be relevant to address the gap in the literature with regards to achieving better notification, control and timely monitoring of COVID-19 cases as well as guiding strategies and health policies in several countries.
- This systematic review protocol reduces the possibility of duplication, due to the transparency of the methods and processes that will be used, in addition, it reduces possible biases and also allows peer review.
- The sensitivity and specificity of the tests varies widely by test and may be the main limitation of this systematic review, in addition to the publication bias of the original researches and the methodological appraisal of the studies.

INTRODUCTION

In December 2019, an increased number of pneumonia-like cases in Wuhan, China, have led to the discovery of a new type of zoonotic Coronavirus - an enveloped RNA virus, commonly found also in humans capable of causing respiratory, enteric, liver and neurological disorders. ¹ Despite the low lethality of COVID-19, around 3%, its transmissibility is high, ¹ with respiratory secretions being the main means of spreading SARS-CoV-2. ² Since the World Health Organization declared COVID-19 outbreak a pandemic on March 11, 2020, ³ the new coronavirus spreading has been the focus of attention for scientists, government officials, and communities around the world. ⁴

A study on observations of SARS-CoV-2 infections in China, using a networked metapopulation dynamics and Bayesian inference models to infer epidemiological characteristics associated with COVID-19, estimated that the rate of transmission of undocumented infections per person was 55% of documented infections. However, due to their greater number, undocumented infections were the source of infection for 79% of documented cases. ⁵ SARS-CoV2 is already circulating in 213 countries and territories worldwide, with 8,914,787 infected and 466,718 deaths recorded on June 20, 2020, ⁶ making Brazil the new epicenter of the pandemic ⁷ with 1,070,139 confirmed cases and 50,058 deaths so far. ⁶

One of the greatest concerns and challenges in several countries, especially for low and middle-income countries, refers to the notification of cases. ⁸ Notification platforms have undergone modifications over the months. ⁹ In addition, the coexistence of several criteria and platforms can generate serious failures in the health surveillance system, resulting in underreporting. Indeed, the main reason for criticism of how health surveillance is being employed in several countries is the low capacity for mass testing. ^{8 10}

Another crucial issue that the World Health Organization (WHO) has pointed out, is that testing all suspected cases is essential for pandemic control. ¹¹ However, the access to diagnostic tests remains a challenge globally, besides the confusion among health professionals and the population about prioritizing tests and interpreting results.^{10 12} The limited availability of diagnostic tests and laboratory capacity for the detection of COVID-19 in many countries, for example in Brazil, had led the Minister of Health to limit testing only for severe cases. The Minister of Health justified its decision by stating that, in mild cases, it

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3 does not matter if the person tests negative or positive, the treatment to be delivered is the
4 same if it is a suspected mild case.¹³
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6 It should be noted that the incubation period from the infection to the appearance of
7 the first symptoms is typically 5 to 7 days, but up to 14 days. The final diagnosis depends on
8 tests to detect viruses in various body fluids.^{10 12} Nasopharyngeal smears are more sensitive
9 than oropharyngeal smears and are more effective at early stages of symptom development.¹⁴
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RESEARCH AIMS

The purpose of this systematic review is to synthesize and critically evaluate the scientific evidence on the effectiveness of testing capacity for symptomatic individuals for the control of COVID-19.

METHODS AND ANALYSIS

Search Strategy

Search strategy will be performed using resources to enhance methodological transparency and improve the reproducibility of the findings, following the PRISMA-P guidelines.²² In addition, using the PICO (Population/ Intervention/Comparison/Outcomes) acronym²³ we elaborated the research question of this review, for ensuring the systematic search of the literature: *"What are the scientific evidence from studies about the effectiveness of the testing capacity for symptomatic patients for COVID-19 pandemic control?"*. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on April 2020 (registration number CRD42020182724).

Article searches will be conducted in the following specialized and general databases: Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed, ISI of Knowledge via Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Excerpta Medica database (EMBASE), SCOPUS, Latin American and Caribbean Health Sciences Literature (LILACS), Psychology Information (PsycINFO) and Chinese National Knowledge Infrastructure (CNKI), from inception until June 30, 2020. The grey literature will be searched in five additional sources: ProQuest Dissertations and Theses Global, Mascot/Wotro, Effective Public health Practice Projects, Public Health Grey Literature Sources, Health Evidence. No restriction regarding the publication date, the setting or languages will be considered in this systematic review. Additionally, secondary searches in other sources, such as the website of clinical trials (e.g. ClinicalTrials.gov), The British Library and Google Scholar will be also performed. The reference section of the included studies and citing studies will be hand searched for additional relevant studies. The search strategy will comprise for only key terms according to a pre-established PICO acronym. It is stand out that two researchers (LCLJ and EB) will carry out the search strategy in all databases independently. Also, the bibliographic software EndNote (<https://www.myendnoteweb.com/>) as well as Rayyan™ app (Qatar Computing Research

Institute)²⁴ will be used to store, organize, and manage all the references and ensure a systematic and comprehensive search.

Firstly, we will identify the existence of specific subject headings index in each database (such as MeSH terms, Emtree terms, PsycINFO Thesaurus and DeCS-Health Science Descriptors) and their synonyms (keywords). The search terms will be combined using the Boolean operators “AND” and “OR”.²⁵ The search strategy combining MeSH terms and keywords which will be used in MEDLINE is depicted in the Table 1 and will be adapted to meet each databases’ specific syntax requirements.

Table 1 Concepts and search items

Databases	Search strategy
MEDLINE ISI of Knowledge CENTRAL EMBASE SCOPUS LILACS PsycINFO CNKI	<p>#1 (“Infant” [MeSH Terms] OR “Child, Preschool” [MeSH Terms] OR “Adolescent” [MeSH Terms] OR “Young Adult” [MeSH Terms] OR “Adult” [MeSH Terms] OR “Aged” [MeSH Terms] OR “Aged, 80 and over” [MeSH Terms])</p> <p>#2 (“Coronavirus”[MeSH Terms] OR "Coronavirus"[All Fields]) OR ("COVID-19"[All Fields] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[Supplementary Concept] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields]) OR “Pandemics”[MeSH Terms])</p> <p>#3 (“COVID-19 diagnostic testing” [Supplementary Concept] OR “COVID-19 testing” [All Fields] OR “2019 novel coronavirus disease testing” [All Fields] OR “COVID19 antibody testing” [All Fields] OR “SARS2 testing” [All Fields] OR “2019-nCoV testing” [All Fields] OR “COVID-19 antibody testing” [All Fields] OR “COVID-19 blood antibody testing” OR “SARS-CoV-2 infection antibody testing” [All Fields] OR “COVID-19 serological testing” [All Fields] OR “COVID19 serological testing” [All Fields] OR “Serology Testing for COVID-19” [All Fields] OR “COVID-19 serological testing” [All Fields] OR “Serology Testing for COVID-19” [All Fields] OR “SARS-CoV-2 infection serological testing” [All Fields] OR “LAMP assay” [Supplementary Concept] OR “LAMP assay COVID-19” [All Fields] OR LAMP assay SARS-CoV-2” [All Fields] OR LAMP assay Coronavirus Infections/*diagnosis [All Fields] OR “2019-novel coronavirus real-time reverse transcriptase diagnostic panel” [All Fields] OR “2019-nCoV RT-PCR diagnostic panel” [All Fields] OR “COVID-19 nucleic acid testing” [All Fields] OR “SARS-CoV-2 infection nucleic acid testing” [All Fields] OR “COVID19 nucleic acid testing”</p>

[All Fields] OR))

#4 #1 AND #2 AND #3

Abbreviations: MEDLINE, Medical Literature Analysis and Retrieval System Online; CENTRAL, Cochrane Central Register of Controlled Trials; EMBASE, Excerpta Medica Database; LILACS, Latin American and Caribbean Health Sciences Literature; PsycINFO, Psychology Information; CNKI, Chinese National Knowledge Infrastructure.

Study Selection

The PICO acronym [Population (P), Interventions/Exposure (I), Comparators (C) and Outcomes (O)] is detailed in the Table 2.

Table 2 Inclusion and exclusion criteria

PICO Acronym ²³	Inclusion criteria	Exclusion criteria
P – Population	Infant, Child, Adolescents, Young Adult, Adult and Aged (according to MeSH terms)* of all genders, of any ethnicity, and symptomatic and / or suspect for COVID-19.	–
I – Intervention/Exposure	Testing for COVID-19	Testing for other previous pandemics
C – Comparison	Symptomatic individuals for COVID-19 who have not been tested	–
O – Outcome	The primary outcomes includes sensitivity as well as the specificity of the tests.	–

Abbreviations: MeSH, Medical Subject Headings; COVID-19, Coronavirus Disease 2019.

* In this systematic review we will use the definitions in accordance with the MeSH terms indexing, such as “Infant” - a child between 1 and 23 months of age; “Child, Preschool”- a child between the ages of 2 and 5; “Child”- a person 6 to 12 years of age; “Adolescent”- a person 13 to 18 years of age; “Young Adult”- a person between 19 and 24 years of age; “Adult”- a person having attained full growth or maturity. Adults are of 19 through 64 years of age; “Aged”- a person 65 through 79 years of age; “Aged, 80 and over”- a person 80 years of age and older.

Regarding the study design, we will include all designs with quantitative approach (descriptive, observational and experimental studies), as well as the gray literature (editorials, opinion articles, reviews, clinical guidelines, conference proceedings, abstracts, book chapters, etc.) as recommended by the Cochrane Handbook.²⁶ Thus, studies that have investigated epidemiological and clinical aspects of testing capacity for symptomatic and suspected patients for COVID-19 will be included in this systematic review. Nevertheless, studies evaluating mass testing for other Severe Acute Respiratory Syndromes (SARS) than COVID-19, will be excluded. With regards to population characteristics, will be included people living in the communities, nursing homes, outpatients and hospitalized people.

The primary outcomes of this systematic review include sensitivity as well as the specificity of the tests for COVID-19. Sensitivity measures how often a test correctly

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3 generates a positive result for people who have the condition that is being tested for (also
4 known as the “true positive” rate). A test that’s highly sensitive will flag almost everyone who
5 has the disease and not generate many false-negative results. For instance, a test with 90%
6 sensitivity will correctly return a positive result for 90% of people who have the disease but,
7 will return a negative result - a false-negative - for 10% of the people who have the disease
8 and should have tested positive.²⁷ Specificity measures a test’s ability to correctly generate a
9 negative result for people who don’t have the condition that’s being tested for (also known as
10 the “true negative” rate). A high-specificity test will correctly rule out almost everyone who
11 does not have the disease and will not generate many false-positive results. For example, a
12 test with 90% specificity will correctly return a negative result for 90% of people who don’t
13 have the disease but, will return a positive result - a false-positive - for 10% of the people who
14 don’t have the disease and should have tested negative).²⁷ In other words, sensitivity is the
15 proportion of patients with disease who have a positive test, or the true positive rate and the
16 specificity is the proportion of patients without disease who have a negative test, or true
17 negative rate. These terms describe the operating characteristics of a test and can be used to
18 gauge the effectiveness of a test result.²⁸

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The screening and selection of studies will also be carried out by two reviewers (LCLJ and EB) independently and blindly. After this selection, a third reviewer (RAGL) will be responsible for analyzing and deciding on the inclusion or exclusion of each article, especially in relation to those containing a conflicting decision. The Rayyan™ application, developed by the *Qatar Computing Research Institute*,²⁴ will be used as an auxiliary tool for data management.

Screening

After importing documents retrieved from the initial searches, duplicates will be removed, and two reviewers (LCLJ and EB) will independently screen the studies for based on their titles and abstracts. If good agreement is achieved between reviewers (at least 80 percent) then each will proceed to full article screening. If there is less than 80 percent agreement, the articles will be reevaluated, and the disagreements discussed and resolved by consensus, but if the disagreement persist, a third reviewer (RAGL) will make a final decision, using Rayyan™ app.

Data Extraction

Full text screening will be done by the same independent investigators. In order to measure inter-coder agreement in each screening phase, Cohen’s kappa will be performed. Once consensus is reached on the selected studies, a standardized form based on previous

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3 studies^{29 30 31 32 33 34} will be used for data extraction. Information to be extracted including four
4 domains: I) identification of the study (article title; journal title; impact factor; authors;
5 country of the study; language; sources of funding; publication year; host institution of the
6 study [hospital; university; research center; single institution; multicenter study]; conflict of
7 interest and study sponsorship); ii) methodological characteristics (study design; study
8 objective or research question or hypothesis; sample characteristics, e.g. sample size, age,
9 eligibility criteria, ethnicity, baseline characteristics; groups and controls; recruitment
10 methods and study completion rates; comparator group; timeframe for follow-up; co-
11 interventions; validated measures; costs and/or remuneration related to participation;
12 statistical analyses, adjustments; iii) main findings and implications for clinical practice; and
13 iv) conclusions. The same two reviewers will be carried out the data extraction independently.
14 Discrepancies between the reviewers will be resolved either by discussion or, in the lack of
15 agreement, by a third reviewer (RAGL).

25 **Methodological appraisal**

27 The internal validity and risk of bias for RCTs will be assessed with the appraisal tool
28 from the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0,²⁶ which assesses
29 the following seven domains: I) Randomization Sequence Allocation; II) Allocation
30 concealment; III) Blinding of participants and team involved; IV) Blindness of outcome
31 evaluators; V) Incomplete outcomes; VI) Report of selective outcome and VII) Other sources
32 of bias. Based on these domains evaluated, studies are classified as at risk of low, high or
33 uncertain bias. For assessing Non-Randomized Controlled Trials, the Methodological Index
34 for Non-Randomized Studies (MINORS),³⁵ will be used. This instrument MINORS contains
35 eight items for non-comparative studies: 1) A clearly stated aim; 2) Inclusion of consecutive
36 patients; 3) Prospective collection of data; 4) Endpoints appropriate to the aim of the study; 5)
37 Unbiased assessment of the study endpoint; 6) Follow-up period appropriate to the aim of the
38 study; 7) Loss to follow-up less than 5%; and 8) Prospective calculation of the study size.³⁵
39 With regards to the case-control or cohort studies, we will use the Newcastle-Ottawa Scale to
40 evaluate its methodological quality.³⁶ Using the Newcastle-Ottawa Scale, the case-control
41 and cohort studies will be given star ratings in 3 categories —Selection (maximum 4 stars),
42 Comparability (maximum 2 stars), and Outcome (maximum 3 stars)—with a maximum score
43 of 9 stars.³⁶ The same two reviewers (LCLJ and EB) will hold the quality assessment
44 independently. Disagreements will be resolved by a third reviewer (RAGL).

58 **Data synthesis**

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3 A qualitative synthesis on the risk of bias of RCT will be made for the included and
4 analyzed studies. The studies will be classified according to the risk of bias as follows: “low”
5 if all the main domains were classified as “low risk”; “Uncertain” if one or two main domains
6 were classified as “uncertain risk”; and “high” if more than two main domains have been
7 classified as “uncertain” or “high risk”. When no information is available, we will assign
8 “uncertain risk”.³⁷ For assessing the Non-Randomized Studies, each item from MINORS will
9 be rated from 0 to 2, which means: the score 0 indicates that the information was not reported,
10 1 indicated that the information was inadequately reported, and 2 that the information was
11 adequately reported.³⁵ Regarding the case-control and cohort studies assessing by the
12 Newcastle-Ottawa Scale the quality of these studies will be adjudicated based on previous
13 study³⁸: good quality: Selection ≥ 3 stars AND Comparability ≥ 1 stars AND Outcome ≥ 2
14 stars; fair quality: Selection 2 stars AND Comparability ≥ 1 stars AND Outcome ≥ 2 stars; poor
15 quality: Selection ≤ 1 Star OR Comparability 0 stars OR ≤ 1 stars.³⁸

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17 In addition, we will complete a narrative synthesis, providing a comprehensive
18 descriptive summary around the type of test for COVID-19, study design, target population
19 characteristics, focused on the primary outcome (sensitivity as well as the specificity of the
20 tests for COVID-19). It will be also presented in the text and table format the methodological
21 characteristics of the studies, subpopulations characteristics, test characteristics, as well as
22 sensitivity and specificity of them. The assessment of the certainty of the evidence will take
23 into consideration the precision of the synthesis finding (i.e. confidence interval if available),
24 the number of studies and participants, the consistency of effects across studies, the risk of
25 bias of the studies, how directly the included studies address the planned question
26 (directness), and the risk of publication bias.³⁹

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28 Study findings will be presented in tables or graphs in the same way as the syntheses
29 are reported in order to facilitate the comparison of similarities and differences in design and
30 outcomes between studies. Key characteristics, such as study design, sample size, and risk of
31 bias, sensitivity as well as the specificity, which may affect interpretation of the data, will be
32 also presented. Outcomes will be analyzed according to sex and population subgroups
33 (children, adolescents, young adults, adults and the elderly), test for COVID-19 type, and also
34 according to the classifying countries by income (high, upper-middle, lower-middle, and
35 low), based on The World Bank Classification using the Gross National Income (GNI) per
36 capita.⁴⁰

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38 Meta-analyses will be conducted if there is sufficient homogeneity in study design and
39 study subjects among selected articles. Therefore, continuous and dichotomous outcomes will
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3 be pooled together for meta-analysis purposes. Quantitative data from each study will be
4 extracted and inserted into an Excel sheet by two independent reviewers. Statistical analyses
5 will be carried out using the Statistical Package for the Social Sciences - SPSS, version 18.0
6 (SPSS, Inc., Chicago, IL, USA).
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10 Standardized mean differences (SMD) and 95% CI will be used to calculate the effect
11 sizes, ^{41 42} included in our meta-analysis will have reported the differences in testing for
12 COVID-19. All effect sizes will be transformed into a common metric, in order to make them
13 comparable across studies—the bias-corrected standardized difference in means (Hedges' *g*).
14 For continuous outcome measures, standardized mean differences (SMDs) and risk ratio (RR)
15 for categorical outcomes will be considered for the final assessment from individual studies.
16 SMD was chosen as a measure of pooled results considering the likely variability in the
17 measuring scales for continuous outcomes. ⁴² The effect size will be interpreted by Cohen's
18 proposal: 0.20 corresponds to a small effect size, 0.50 corresponds to a medium effect size
19 and 0.80 corresponds to a large effect size. ⁴³
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27 A random effects model will be selected under the assumption that studies included in
28 the meta-analysis have been carried out with heterogeneous populations. Heterogeneity will
29 also be tested by the I^2 statistic, which can quantify the heterogeneity ranging from 0% (no
30 heterogeneity) to 100% (the differences between the effect sizes can completely be explained
31 by chance alone), and the interpretations of the percentages are as follows: 0%–40% indicates
32 potentially unimportant heterogeneity, 30%–60% indicates moderate heterogeneity, 50%–
33 90% indicates substantial heterogeneity and 75%–100% indicates considerable heterogeneity.
34 ⁴² To explore the heterogeneity across studies, subgroup analysis will be performed using a
35 mixed effects model according to the following variables: according to sex and population
36 subgroups (children, adolescents, young adults, adults and the elderly), test for COVID-19
37 type, and also according to the classifying countries by income (high, upper-middle, lower-
38 middle, and low).
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48 **Patient and public involvement**

49 Since this is a systematic review protocol no patients and public will be involved.

51 **Ethics and dissemination**

52 Due to the characteristics of this study design, the ethical evaluation was not required.
53 The findings of this systematic review will be disseminated through peer-reviewed
54 publication as well as in different media, such as, symposia, and congresses related to this
55 field. Moreover, any amendments to this protocol will be documented with reference to the
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3 saved searches and analysis methods, which will be recorded in bibliographic databases, for
4 data collection and synthesis.
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8 **DISCUSSION**

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10 One of the strengths of the proposed systematic review is to apply a reproducible and
11 transparent procedure for systematic review of the literature. In this protocol, we clearly
12 describe the types of studies, participants, intervention and outcomes that will be considered
13 according to the research question, as well as the data sources, search strategy, data extraction
14 methods (including critical appraisal of the studies included) and data synthesis.³⁵ By
15 publishing the research protocol, we reinforce the clarity of the strategy and minimize the risk
16 of bias, i.e., selective outcome reporting.⁴⁴ These results shall provide evidences in order to
17 inform, support and customize shared decision making from healthcare providers,
18 stakeholders and government personnel.
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25 Since the sensitivity and specificity of the tests for COVID-19 varies widely by test,
26 this might be the main limitation of this systematic review, in addition to the publication bias
27 of the original studies and the methodological appraisal of the studies, which may influence
28 the external validity.
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32 The testing of all symptomatic patients, according to the Imperial College study and
33 the Chinese experience,⁴⁵ is essential to contain the epidemic. Although positive tests for
34 COVID-19 are clinically useful, negative tests need to be interpreted with caution, taking into
35 account the pre-test probability of disease. This has important implications for physicians to
36 interpret tests and policymakers who design diagnostic algorithms for COVID-19. The
37 Chinese handbook of COVID-19 prevention and treatment states "*if the nucleic acid test is*
38 *negative at the beginning, samples should continue to be collected and tested in the following*
39 *days*".⁴⁶ False negatives carry substantial risks; for instance, patients can be transferred to
40 wards not covered by COVID-19, leading to the spread of hospital-acquired COVID-19
41 infection; caregivers can also spread the infection to vulnerable dependents.^{28 47} Hence, clear
42 evidence-based guidelines on repeated testing are needed to reduce the risk of false negatives.
43 Finally, physicians must ensure that patients are informed about the limitations of the tests.
44 Patients with a single negative test, but with symptoms that are suggestive of COVID-19,
45 should be advised to isolate themselves according to the guidelines for suspected COVID-19,
46 once no test is 100% accurate.^{28 47}
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58 In this sense, the present systematic review will delivery relevant evidence on the
59 effectiveness of testing capacity for symptomatic individuals for the control of COVID-19.
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3 Ultimately, we will provide evidence to help the health sector achieving better notification,
4 control and timely monitoring of COVID-19 cases, as well as guiding important strategies and
5 health policy decision makers of several countries.
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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
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
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1 and 2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1
	#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
Sources	#5a	Indicate sources of financial or other support for the review	1

1	Sponsor	#5b	Provide name for the review funder and / or sponsor	1
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3	Role of sponsor or	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any,	1
4	funder		in developing the protocol	
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7	Rationale	#6	Describe the rationale for the review in the context of what is	3 and 4
8			already known	
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11	Objectives	#7	Provide an explicit statement of the question(s) the review will	5
12			address with reference to participants, interventions, comparators,	
13			and outcomes (PICO)	
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16	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design,	5 and 6
17			setting, time frame) and report characteristics (such as years	
18			considered, language, publication status) to be used as criteria for	
19			eligibility for the review	
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23	Information	#9	Describe all intended information sources (such as electronic	5
24	sources		databases, contact with study authors, trial registers or other grey	
25			literature sources) with planned dates of coverage	
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28	Search strategy	#10	Present draft of search strategy to be used for at least one electronic	5 and 6
29			database, including planned limits, such that it could be repeated	
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32	Study records -	#11a	Describe the mechanism(s) that will be used to manage records and	5 and 7
33	data management		data throughout the review	
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36	Study records -	#11b	State the process that will be used for selecting studies (such as two	7
37	selection process		independent reviewers) through each phase of the review (that is,	
38			screening, eligibility and inclusion in meta-analysis)	
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41	Study records -	#11c	Describe planned method of extracting data from reports (such as	7 and 8
42	data collection		piloting forms, done independently, in duplicate), any processes for	
43	process		obtaining and confirming data from investigators	
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46	Data items	#12	List and define all variables for which data will be sought (such as	7
47			PICO items, funding sources), any pre-planned data assumptions and	
48			simplifications	
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52	Outcomes and	#13	List and define all outcomes for which data will be sought, including	6
53	prioritization		prioritization of main and additional outcomes, with rationale	
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level, or both; state how this information will be used in data synthesis

Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	9
	#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)	9
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	9 and 10
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	9 and 10
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	n/a
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	n/a

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BMJ Open

EFFECTIVENESS OF MASS TESTING FOR CONTROL OF COVID-19: A SYSTEMATIC REVIEW PROTOCOL

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Health policy, Public health
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Title Page – BMJ Open

EFFECTIVENESS OF MASS TESTING FOR CONTROL OF COVID-19: A SYSTEMATIC REVIEW PROTOCOL

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None do declare.

Author Contributions: LCLJ conceptualized and designed the protocol, drafted the initial manuscript and reviewed the manuscript. EB, DSCS, RMP, SIPCS, RAGL, and LCLJ defined the concepts and search items, data extraction process as well as methodological appraisal of the studies. EB, DSCS, RMP, SIPCS, and LCLJ planned the data extraction and statistical analysis. RAGL, EB, DSCS, LCLJ provided critical insights. All authors have approved and contributed to the final written manuscript.

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ABSTRACT

Introduction: Since March 2020, when the Corona Virus Disease 2019 (COVID-19) outbreak has been deemed a pandemic by the World Health Organization (WHO), the SARS-CoV-2 spreading has been the focus of attention of scientists, authorities, public health agencies, and communities around the world. One of the great concerns and challenges, mainly in low- and middle-income countries, is the identification and monitoring of COVID-19 cases. The large-scale availability of testing is a fundamental aspect of COVID-19 control, but it is currently the biggest challenge faced by many countries around the world. We aimed to synthesize and critically evaluate the scientific evidence on the influence of the testing capacity for symptomatic individuals in the control of COVID-19.

Methods and analysis: A systematic review will be conducted in eight databases, such as MEDLINE, ISI-of-Knowledge, CENTRAL, EMBASE, SCOPUS, LILACS, PsycINFO, and CNKI, from inception until July 30, 2020. No restriction regarding the language, publication date, or setting will be employed. Primary outcomes will include the sensitivity as well as the specificity of the tests for COVID-19. Study selection will follow the PRISMA checklist. Methodological assessment of the studies will be evaluated by the Cochrane Risk-of-Bias tool for randomized controlled trials, the MINORS for non-randomized studies, and the Newcastle-Ottawa Scale for cohort or case-control studies. Findings will be structured according to the test type and target population characteristics and focused on the primary outcomes (sensitivity and specificity). Moreover, if sufficient data are available, a meta-analysis will be performed. Pooled standardized mean differences and 95% CIs will be calculated. Heterogeneity between the studies will be determined by I^2 statistics. Subgroup analyses will also be conducted. Publication bias will be assessed with funnel plots and Egger's test. Heterogeneity will be explored by random-effects analysis.

Ethics and dissemination: Ethical approval is not required. The results will be disseminated widely via peer-reviewed publication and presentations at conferences related to this field.

PROSPERO registration ID: CRD42020182724.

Keywords: COVID-19; Coronavirus; Coronavirus Infections; Testing; Effectiveness; Public Health Nursing; Health Surveillance.

Strengths and limitations of this study:

- We will offer evidence for health surveillance support in order to help decision makers (i.e., healthcare providers, stakeholders and governments) regarding COVID-19 control.
- This systematic review will be the first to critically evaluate the scientific evidence about the influence of the testing capacity for symptomatic individuals in COVID-19.
- This study will be relevant to address the gap in the literature with regard to achieving better identification, control and timely monitoring of COVID-19 cases and guiding strategies and health policies in several countries.
- This systematic review protocol reduces the possibility of duplication due to the transparency of the methods and processes that will be used; in addition, it reduces possible biases and allows for peer review.
- The sensitivity and specificity of the tests varies widely by test and may be the main limitation of this systematic review, in addition to the publication bias of the original studies and the methodological appraisal of the studies.

INTRODUCTION

In December 2019, an increased number of pneumonia-like cases in Wuhan, China, led to the discovery of a new type of coronavirus—an enveloped RNA virus commonly found in humans and capable of causing respiratory, enteric, liver as well as neurological illness.¹ Despite the low lethality of COVID-19, approximately 3%, its transmissibility is high,¹ with respiratory contact droplet being the main means of spreading the new coronavirus.² Since the WHO declared the COVID-19 outbreak a pandemic on March 11, 2020,³ the spread of the new coronavirus has been the focus of attention of scientists, authorities, public health agencies, government officials, and communities around the world.⁴

Using a networked metapopulation dynamics and Bayesian inference models to gather epidemiological factors associated with COVID-19, a recent study on SARS-CoV-2 infections in China, showed that unreported infections were projected to be 55% as contagious as documented infections, per person. Besides, unreported cases were the source of infection for 79% of reported cases.⁵ A total of 213 countries, territories or areas have reported confirmed cases of SARS-CoV-2, with 8.914.787 infected and 466.718 deaths recorded as of June 20, 2020,⁶ with Brazil being the new epicenter of the pandemic⁷ with 1.070.139 confirmed cases and 50.058 deaths so far.⁶

One of the greatest concerns and challenges in several countries, especially low- and middle-income countries, refers to the identification of cases.⁸ Identification platforms have undergone modifications in recent months.⁹ In addition, the coexistence of several criteria and platforms can generate serious failures in the health surveillance system, resulting in underreporting. Indeed, the main reason for the problem with how health surveillance is being performed in several countries is the low capacity for mass testing.^{8 10}

Another crucial issue that the WHO has pointed out is that testing all suspected cases is essential for pandemic control.¹¹ However, access to diagnostic tests remains a challenge globally, in addition to the confusion among health professionals and the population about prioritizing tests and interpreting results.^{10 12} The limited availability of diagnostic tests and laboratory capacity for the detection of COVID-19 in many countries, for example, in Brazil, has led the Ministry of Health to limit testing only for severe cases. The Ministry of Health justified its decision by stating that, in mild cases, it does not matter if the person tests negative or positive, the treatment to be delivered is the same as if it was a suspected mild case.¹³

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3 It should be noted that the incubation period from infection to the appearance of the
4 first symptoms is typically 5 to 7 days but up to 14 days. The final diagnosis depends on tests
5 to detect viruses in several body fluids.^{10 12} Nasopharyngeal smears are more sensitive than
6 oropharyngeal smears and are more effective at early stages of symptom development.^{14 15 16}
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RESEARCH AIMS

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METHODS AND ANALYSIS

Search Strategy

The search strategy will be performed using resources to enhance methodological transparency and improve the reproducibility of the findings, following the PRISMA-P guidelines.²² In addition, using the PICO (Population/ Intervention/Comparison/Outcomes) approach,²³ we elaborated the research question of this review to ensure a systematic search of the literature: *"What is the scientific evidence from studies about the influence of the testing capacity for symptomatic patients in COVID-19 pandemic control?"*. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in April 2020 (registration ID: CRD42020182724).

Article searches will be conducted in the following specialized and general databases from inception until July 30, 2020: Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed, the ISI of Knowledge via Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), Excerpta Medica dataBASE (EMBASE), SCOPUS, Latin American and Caribbean Health Sciences Literature (LILACS), Psychology Information (PsycINFO) and Chinese National Knowledge Infrastructure (CNKI). The gray literature will be searched in five additional sources: ProQuest Dissertations and Theses Global, Mascot/Wotro, Effective Public Health Practice Projects, Public Health Gray Literature Sources, and Health Evidence. No restriction regarding the publication date, setting or language will be considering in this systematic review. Additionally, secondary searches in other sources, such as the clinical trials website (e.g., ClinicalTrials.gov), The British Library and Google Scholar, will also be performed. The reference sections of the included studies and cited studies will be manually searched for additional relevant studies. The search strategy will comprise only key terms according to a pre-established PICO strategy. Two researchers (LCLJ and EB) will independently carry out the search in all databases. Additionally, the bibliographic software EndNote (<https://www.myendnoteweb.com/>) as well as the Rayyan™ app (*Qatar Computing Research Institute*)²⁴ will be used to store, organize, and manage all the references and ensure a systematic and comprehensive search.

First, we will identify the existence of a specific subject heading index in each database (including MeSH terms, Emtree terms, PsycINFO Thesaurus and DeCS-Health Science Descriptors) and their synonyms (keywords). The search terms will be combined using the Boolean operators "AND" and "OR".²⁵ The search strategy combining MeSH terms

and keywords that will be used in MEDLINE is depicted in Table 1; it will be adapted to meet each database's specific syntax requirements.

Table 1 Concepts and search items

Databases	Search strategy
MEDLINE ISI of Knowledge CENTRAL EMBASE SCOPUS LILACS PsycINFO CNKI	<p>#1 (“Infant” [MeSH Terms] OR “Child, Preschool” [MeSH Terms] OR “Adolescent” [MeSH Terms] OR “Young Adult” [MeSH Terms] OR “Adult” [MeSH Terms] OR “Aged” [MeSH Terms] OR “Aged, 80 and over” [MeSH Terms]).</p> <p>#2 (“Coronavirus” [MeSH Terms] OR "Coronavirus"[All Fields]) OR ("COVID-19" [All Fields] OR "Severe Acute Respiratory Syndrome Coronavirus 2" [Supplementary Concept] OR "Severe Acute Respiratory Syndrome Coronavirus 2" [All Fields] OR "2019-nCoV" [All Fields] OR "SARS-CoV-2" [All Fields]) OR “Pandemics” [MeSH Terms]).</p> <p>#3 (“COVID-19 diagnostic testing” [Supplementary Concept] OR “COVID-19 testing” [All Fields] OR “2019 novel coronavirus disease testing” [All Fields] OR “COVID19 antibody testing” [All Fields] OR “SARS2 testing” [All Fields] OR “2019-nCoV testing” [All Fields] OR “COVID-19 antibody testing” [All Fields] OR “COVID-19 blood antibody testing” OR “SARS-CoV-2 infection antibody testing” [All Fields] OR “COVID-19 serological testing” [All Fields] OR “COVID19 serological testing” [All Fields] OR “Serology Testing for COVID-19” [All Fields] OR “COVID-19 serological testing” [All Fields] OR “Serology Testing for COVID-19” [All Fields] OR “SARS-CoV-2 infection serological testing” [All Fields] OR “LAMP assay” [Supplementary Concept] OR “LAMP assay COVID-19” [All Fields] OR LAMP assay SARS-CoV-2” [All Fields] OR LAMP assay Coronavirus Infections/*diagnosis [All Fields] OR “2019-novel coronavirus real-time reverse transcriptase diagnostic panel” [All Fields] OR “2019-nCoV RT-PCR diagnostic panel” [All Fields] OR “COVID-19 nucleic acid testing” [All Fields] OR “SARS-CoV-2 infection nucleic acid testing” [All Fields] OR “COVID19 nucleic acid testing” [All Fields] OR)).</p> <p>#4 #1 AND #2 AND #3</p>

Abbreviations: MEDLINE, Medical Literature Analysis and Retrieval System Online; CENTRAL, Cochrane Central Register of Controlled Trials; EMBASE, Excerpta Medica dataBASE; LILACS, Latin American and Caribbean Health Sciences Literature; PsycINFO, Psychology Information; CNKI, Chinese National Knowledge Infrastructure.

Study Selection

The PICO strategy [Population (P), Interventions/Exposure (I), Comparators (C) and Outcomes (O)] is detailed in Table 2.

Table 2 Inclusion and exclusion criteria

PICO component ²³	Inclusion criteria	Exclusion criteria
P – Population	Infant, Child, Adolescents, Young Adult, Adult and Aged (according to MeSH terms)* of all sexes, of any ethnicity, and symptomatic and/or suspect for COVID-19.	–
I – Intervention/Exposure	Testing for COVID-19.	Testing for other previous pandemics.
C – Comparison	Individuals symptomatic for COVID-19 who have not been tested.	–
O – Outcome	The primary outcomes include the sensitivity as well as the specificity of the tests.	–

Abbreviations: MeSH, Medical Subject Headings; COVID-19, Coronavirus Disease 2019.

* In this systematic review, we will use definitions in accordance with the MeSH term indexing, such as “Infant” - a child between 1 and 23 months of age; “Child, Preschool” - a child between the ages of 2 and 5; “Child” - a person 6 to 12 years of age; “Adolescent” - a person 13 to 18 years of age; “Young Adult” - a person between 19 and 24 years of age; “Adult” - a person having attained full growth or maturity. Adults are 19 through 64 years of age; “Aged” - a person 65 through 79 years of age; “Aged, 80 and over” - a person 80 years of age and older.

Regarding the study design, we will include all studies with quantitative approaches (descriptive, observational and experimental studies), as well as the gray literature (editorials, opinion articles, reviews, clinical guidelines, conference proceedings, abstracts, book chapters, etc.) as recommended by the Cochrane Handbook.²⁶ Thus, studies that have investigated epidemiological and clinical aspects of testing capacity for symptomatic and suspected COVID-19 patients will be included in this systematic review. Nevertheless, studies evaluating mass testing for severe acute respiratory syndromes (SARSs) other than COVID-19 will be excluded. With regard to population characteristics, people living in the community and in nursing homes, outpatients and hospitalized people will be included.

The primary outcomes of this systematic review include the sensitivity as well as the specificity of the tests for COVID-19. The sensitivity of a test corresponds to the probability of “true positive”. In other words, it indicates the percentage of people with the disease that correctly tested positive. Therefore, a test is highly sensitive if it identifies the actual positive cases which are clinically identified as such.²⁷ The specificity of a test corresponds to the probability of a “true negative”. It indicates the true percentage of people who did not have the disease that correctly tested negative.²⁷ These terms describe the performance characteristics of a test and can be used to gauge the effectiveness and validity of a test result.²⁸

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3 The screening and selection of studies will be carried out by two reviewers (LCLJ and
4 EB) independently and blindly. After this selection, a third reviewer (RAGL) will be
5 responsible for analyzing and deciding on the inclusion or exclusion of each article, especially
6 in relation to those about which there is a conflicting decision. The Rayyan™ application,
7 developed by the *Qatar Computing Research Institute*,²⁴ will be used as an auxiliary tool for
8 data management.
9

13 **Screening**

15 After importing documents retrieved from the initial searches, duplicates will be removed,
16 and two reviewers (LCLJ and EB) will independently screen the studies based on their titles
17 and abstracts. If good agreement is achieved between reviewers (at least 80%), then each will
18 proceed to full article screening. If there is less than 80% agreement, the articles will be
19 reevaluated, and the disagreements will be discussed and resolved by consensus; if a
20 disagreement persists, a third reviewer (RAGL) will make a final decision using the
21 Rayyan™ app.
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27 **Data Extraction**

29 Full-text screening will be performed by the same independent investigators. To
30 measure intercoder agreement during each screening phase, Cohen's kappa will be performed.
31 Once consensus is reached on the selected studies, a standardized form based on previous
32 studies^{29 30 31 32 33 34} will be used for data extraction. The information to be extracted includes
33 four domains: I) identification of the study (article title; journal title; impact factor; authors;
34 country of the study; language; sources of funding; publication year; host institution of the
35 study [hospital; university; research center; single institution; multicenter study]; conflicts of
36 interest; and study sponsorship); ii) methodological characteristics (study design; study
37 objective or research question or hypothesis; sample characteristics, e.g., sample size, age,
38 eligibility criteria, ethnicity, baseline characteristics; groups and controls; recruitment
39 methods and study completion rates; comparator group; timeframe for follow-up;
40 cointerventions; validated measures; costs and/or remuneration related to participation;
41 statistical analyses; and adjustments); iii) main findings and implications for clinical practice;
42 and iv) conclusions. The same two reviewers will independently perform the data extraction.
43 Discrepancies between the reviewers will be resolved either by discussion or, in the lack of
44 agreement, by a third reviewer (RAGL).
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56 **Methodological appraisal**

58 The internal validity and risk of bias for RCTs will be assessed with the appraisal tool
59 from the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0,²⁶ which assesses
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3 the following seven domains: I) Randomization sequence allocation; II) Allocation
4 concealment; III) Blinding of participants and team involved; IV) Blindness of outcome
5 evaluators; V) Incomplete outcomes; VI) Report of selective outcome; and VII) Other sources
6 of bias. Based on the evaluation of these domains, studies are classified as at risk of low, high
7 or uncertain bias. For assessing nonrandomized controlled trials, the Methodological Index
8 for Non-Randomized Studies (MINORS)³⁵ will be used. This MINORS instrument contains
9 eight items for noncomparative studies: 1) A clearly stated aim; 2) Inclusion of consecutive
10 patients; 3) Prospective collection of data; 4) Endpoints appropriate to the aim of the study; 5)
11 Unbiased assessment of the study endpoint; 6) Follow-up period appropriate to the aim of the
12 study; 7) Loss to follow-up less than 5%; and 8) Prospective calculation of the study size.³⁵
13 With regard to the case-control or cohort studies, we will use the Newcastle-Ottawa Scale to
14 evaluate the methodological quality of the studies.³⁶ Using the Newcastle-Ottawa Scale, the
15 case-control and cohort studies will be given star ratings in 3 categories—Selection
16 (maximum 4 stars), Comparability (maximum 2 stars), and Outcome (maximum 3 stars)—
17 with a maximum score of 9 stars.³⁶ The same two reviewers (LCLJ and EB) will conduct the
18 quality assessment independently. Disagreements will be resolved by a third reviewer
19 (RAGL).

32 **Data synthesis**

34 A qualitative synthesis on the RCT risk of bias will be made for the included and
35 analyzed studies. The studies will be classified according to the risk of bias as follows: “low”
36 if all the main domains were classified as “low risk”; “uncertain” if one or two main domains
37 were classified as “uncertain risk”; and “high” if more than two main domains have been
38 classified as “uncertain” or “high risk”. When no information is available, we will assign
39 “uncertain risk”.³⁷ For assessing the nonrandomized studies, each item from the MINORS
40 will be rated from 0 to 2, which means that a score of 0 indicates that the information was not
41 reported, 1 indicates that the information was inadequately reported, and 2 indicates that the
42 information was adequately reported.³⁵ Regarding the case-control and cohort studies
43 assessed by the Newcastle-Ottawa Scale, the quality of these studies will be adjudicated based
44 on a previous study³⁸: good quality: Selection ≥ 3 stars AND Comparability ≥ 1 stars AND
45 Outcome ≥ 2 stars; fair quality: Selection 2 stars AND Comparability ≥ 1 stars AND Outcome
46 ≥ 2 stars; poor quality: Selection ≤ 1 star OR Comparability 0 stars OR ≤ 1 star.³⁸

56 In addition, we will complete a narrative synthesis, providing a comprehensive
57 descriptive summary around the type of COVID-19 test, the study design, and the target
58 population characteristics, that is focused on the primary outcome (the sensitivity as well as
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3 the specificity of the tests for COVID-19). In text and table formats, the methodological
4 characteristics of the studies, subpopulation characteristics, test characteristics, and sensitivity
5 and specificity of the tests will also be presented. The assessment of the certainty of the
6 evidence will take into consideration the precision of the synthesis findings (i.e., confidence
7 interval if available), the number of studies and participants, the consistency of effects across
8 studies, the risk-of-bias of the studies, how directly the included studies address the planned
9 question (directness), and the risk of publication bias.³⁹

15 Study findings will be presented in tables or graphs in the same way as the syntheses
16 are reported in order to facilitate the comparison of similarities and differences in designs and
17 outcomes among studies. Key characteristics, such as study design, sample size, risk of bias,
18 sensitivity and specificity, which may affect interpretation of the data, will also be presented.
19 Outcomes will be analyzed according to sex, population (children, adolescents, young adults,
20 adults and aged), and the type of COVID-19 test and according to the income classification of
21 the countries (high, upper-middle, lower-middle, and low), based on The World Bank
22 Classification using the Gross National Income (GNI) per capita.⁴⁰

29 Meta-analyses will be conducted if there is sufficient homogeneity in study design and
30 study subjects among the selected articles. Therefore, continuous and dichotomous outcomes
31 will be pooled together for meta-analysis purposes. Quantitative data from each study will be
32 extracted and inserted into an Excel sheet by two independent reviewers. Statistical analyses
33 will be carried out using the Statistical Package for the Social Sciences - SPSS, version 18.0
34 (SPSS, Inc., Chicago, IL, USA).

40 Standardized mean differences (SMDs) and 95% CIs will be used to calculate the
41 effect sizes;^{41 42} studies included in our meta-analysis will have reported the differences in
42 methods of testing for COVID-19. All effect sizes will be transformed into a common metric,
43 i.e., the bias-corrected standardized difference in means (Hedges' g), to make them
44 comparable across studies. For continuous outcome measures, standardized mean differences
45 (SMDs) and risk ratios (RRs) for categorical outcomes from individual studies will be
46 considered for the final assessment. The SMD was chosen as a measure of the pooled results
47 considering the likely variability in the measuring scales for continuous outcomes.⁴² The
48 effect size will be interpreted by Cohen's proposal: 0.20 corresponds to a small effect size,
49 0.50 corresponds to a medium effect size, and 0.80 corresponds to a large effect size.⁴³

56 A random effects model will be selected under the assumption that the studies
57 included in the meta-analysis were carried out with heterogeneous populations. Heterogeneity
58 will also be tested by the I^2 statistic, which can quantify the heterogeneity as ranging from 0%

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3 (no heterogeneity) to 100% (the differences between the effect sizes can completely be
4 explained by chance alone), and the interpretations of the percentages are as follows: 0%–
5 40% indicates potentially unimportant heterogeneity, 30%–60% indicates moderate
6 heterogeneity, 50%–90% indicates substantial heterogeneity, and 75%–100% indicates
7 considerable heterogeneity.⁴² To explore the heterogeneity across studies, subgroup analysis
8 will be performed using a mixed effects model according to the following variables: sex,
9 population (children, adolescents, young adults, adults and aged), COVID-19 test type, and
10 country income classification (high, upper-middle, lower-middle, and low).
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17 **Patient and public involvement**

18 Since this is a systematic review protocol, no patients or public will be involved.
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20 **Ethics and dissemination**

21 Due to the characteristics of this study design, ethical approval was not required. The
22 findings of this systematic review will be disseminated through peer-reviewed publication as
23 well as via different media, such as symposia and conferences related to this field. Moreover,
24 any amendments to this protocol will be documented with reference to the saved searches and
25 analysis methods, which will be recorded in bibliographic databases, for data collection and
26 synthesis.
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34 **DISCUSSION**

35 In this systematic review protocol, we clearly describe the studies' designs,
36 participants, interventions and outcomes that will be considered in line with the research
37 question and the data sources, search strategy, data extraction, methodological quality of the
38 studies, and data synthesis approach.³⁵ In addition, with this protocol study, we reinforce the
39 clarity of the search strategy and minimize the risk of bias.⁴⁴ These results will provide
40 evidence to inform and customize shared decision making to the healthcare providers,
41 stakeholders, and government personnel.
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48 Since the sensitivity and specificity of the tests for COVID-19 vary widely by test, this
49 might be the main limitation of this systematic review, followed by the publication bias of the
50 original studies and the methodological appraisal of the studies, which may influence the
51 external validity.
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55 The testing of all symptomatic patients, according to the Imperial College study and
56 the Chinese experience,⁴⁵ is essential to contain the epidemic. In a clinical context, although
57 positive tests for COVID-19 are extremely useful, due caution must be taken while
58 interpreting negative tests. Particularly, it must be taken into account the pretest probability of
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3 disease. This has important implications for health care professionals who interpret tests and
4 policymakers who design diagnostic algorithms for COVID-19. ¹⁰ The Chinese handbook of
5 COVID-19 prevention and treatment states "*if the nucleic acid test is negative at the*
6 *beginning, samples should continue to be collected and tested in the following days*". ⁴⁶ False
7 negatives carry substantial risks; for instance, patients can be transferred to wards not affected
8 by COVID-19, leading to the spread of hospital-acquired COVID-19 infection, and caregivers
9 can also spread the infection to vulnerable dependents. ^{10 28 47} Therefore, guidelines on
10 repeated testing are needed to reduce the risk of false negatives. Finally, physicians must
11 ensure that patients are informed about the limitations of the tests. Patients with a single
12 negative test, but with symptoms that are suggestive of COVID-19, should be advised to
13 isolate themselves according to the guidelines for suspected COVID-19, since no test is 100%
14 accurate. ^{10 28 47}

15 Hence, this systematic review will deliver relevant evidence on the influence of the
16 testing capacity for symptomatic individuals. Ultimately, we will provide evidence to help the
17 health sector achieve better identification, control, and timely monitoring of COVID-19 cases
18 and to guide important strategies and health policy decision-makers in several countries.

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Reporting checklist for protocol of a systematic review.

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Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

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		Reporting Item	Page Number
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
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	1 and 2
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	1
	#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
Sources	#5a	Indicate sources of financial or other support for the review	1

1	Sponsor	#5b	Provide name for the review funder and / or sponsor	1
2				
3	Role of sponsor or	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any,	1
4	funder		in developing the protocol	
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6				
7	Rationale	#6	Describe the rationale for the review in the context of what is	3 and 4
8			already known	
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11	Objectives	#7	Provide an explicit statement of the question(s) the review will	5
12			address with reference to participants, interventions, comparators,	
13			and outcomes (PICO)	
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15				
16	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design,	5 and 6
17			setting, time frame) and report characteristics (such as years	
18			considered, language, publication status) to be used as criteria for	
19			eligibility for the review	
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22				
23	Information	#9	Describe all intended information sources (such as electronic	5
24	sources		databases, contact with study authors, trial registers or other grey	
25			literature sources) with planned dates of coverage	
26				
27				
28	Search strategy	#10	Present draft of search strategy to be used for at least one electronic	5 and 6
29			database, including planned limits, such that it could be repeated	
30				
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32	Study records -	#11a	Describe the mechanism(s) that will be used to manage records and	5 and 7
33	data management		data throughout the review	
34				
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36	Study records -	#11b	State the process that will be used for selecting studies (such as two	7
37	selection process		independent reviewers) through each phase of the review (that is,	
38			screening, eligibility and inclusion in meta-analysis)	
39				
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41	Study records -	#11c	Describe planned method of extracting data from reports (such as	7 and 8
42	data collection		piloting forms, done independently, in duplicate), any processes for	
43	process		obtaining and confirming data from investigators	
44				
45				
46	Data items	#12	List and define all variables for which data will be sought (such as	7
47			PICO items, funding sources), any pre-planned data assumptions and	
48			simplifications	
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52	Outcomes and	#13	List and define all outcomes for which data will be sought, including	6
53	prioritization		prioritization of main and additional outcomes, with rationale	
54				
55				
56	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of individual	8
57	individual studies		studies, including whether this will be done at the outcome or study	
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level, or both; state how this information will be used in data synthesis

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4	Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised
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8		#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)
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14		#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
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18		#15d	If quantitative synthesis is not appropriate, describe the type of summary planned
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22	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
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26	Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)
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