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Estimating the extent of true asymptomatic COVID-19 and its potential for community transmission: systematic review and meta-analysis

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Abstract

Background: The prevalence of true asymptomatic COVID-19 cases is critical to policy makers considering the effectiveness of mitigation measures against the SARS-CoV-2 pandemic. We aimed to synthesize all available research on the asymptomatic rates and transmission rates where possible.

Methods: We searched PubMed, Embase, Cochrane COVID-19 trials, and European PMC for pre-print platforms such as MedRxiv. We included primary studies reporting on asymptomatic prevalence where: (a) the sample frame includes at-risk population, and (b) there was sufficiently long follow up to identify pre-symptomatic cases. Meta-analysis used fixed effect and random effects models.

Results: We screened 571 articles and included five low risk-of-bias studies from three countries (China (2), USA (2), Italy (1)) that tested 9,242 at-risk people, of which 413 were positive and 65 were asymptomatic. Diagnosis in all studies was confirmed using a RT-qPCR test. The proportion of asymptomatic cases ranged from 6% to 41%. Meta-analysis (fixed effect) found that the proportion of asymptomatic cases was 16% (95% CI: 12% - 20%) overall; higher in non-aged care 19% (15% - 24%), and lower in long-term aged care 8% (4% - 14%). Two studies provided direct evidence of forward transmission of the infection by asymptomatic cases but suggested lower rates than symptomatic cases.

Conclusion: Our estimates of the prevalence of asymptomatic COVID-19 cases are lower than many highly publicized studies, but still substantial. Further robust epidemiological evidence is urgently needed, including in sub-populations such as children, to better understand the importance of asymptomatic cases for driving spread of the pandemic.

Introduction

Asymptomatic cases of any infection are of considerable concern for public health policies to manage epidemics. Such asymptomatic cases complicate the tracking of the epidemic, and prevent reliable estimates of transmission, tracing, and tracking strategies for containing an epidemic by isolating and quarantining. This has been a significant concern for the current COVID-19 pandemic. Multiple reports have quoted the reproduction number to be 3; this is the number of cases estimated to be infected by an index case in a susceptible population.¹ Some modelling experts doubt this low R_0 could explain the global exponential spread we have observed. Using data from 13 countries they have estimated the number could be as high as 15.4 (range 5.5-25.4) if asymptomatic carriers were incorporated in the equation.²

The possibility of asymptomatic transmission of COVID-19 cases was first raised by a case report in China where a traveler from Wuhan was presumed to have transmitted the infection to 5 other family members in other locations while she remained asymptomatic for the entire 21-day follow-up period.³ Subsequently a number of other reports confirmed not only the possibility but began quantifying the potential proportions. For example, the outbreak on the Diamond Princess cruise ship⁴ demonstrated a significant proportion of asymptomatic cases once widespread testing of those on board the ship had been undertaken. A recent review by the Centre for Evidence Based medicine in Oxford⁵ found a range of estimates of asymptomatic COVID19 cases which ranged from 5% to 80%. However, many of the identified studies were either poorly executed or poorly documented, making the validity of these estimates questionable.

We therefore sought to identify all studies that had attempted to estimate the proportion of asymptomatic COVID-19 cases, select those with minimal or no bias, and synthesize these to provide an overall estimate and potential range. We also aimed to estimate the asymptomatic transmission rates if sufficient data were found.

Methods

We conducted a systematic review and a meta-analysis. We searched PROSPERO database to rule out existence of a similar review; then on the 8th of April 2020 systematically searched PubMed, Embase, Cochrane COVID-19 trials, and European PMC for pre-print platforms such as MedRxiv. We did not include government websites in the initial search due to the difficulty in systematically searching them, but considered them during full text screening and citation analysis stages. The selected search strategy for all databases is presented in Supplement 1.

We restricted publication types to reports of primary data collection released in full (including pre-prints) with sufficient details to enable a risk of bias assessment. We anticipated cross-sectional prevalence surveys with follow up, and cohort studies would be the bulk of eligible reports. No restrictions on language were imposed.

We excluded studies for following reasons: unclear sampling frame; no or unclear follow up; no data on asymptomatic cases; single case study/small cluster; modelling or simulation studies (but sources of real data were checked for possible inclusion); non-SARS-CoV-2 virus study; antiviral treatment

studies; study protocols, guidelines, editorials or historical accounts without data to calculate primary outcomes.

Participants

We included studies of people of any age who were at-risk of contracting SARS-CoV-2 virus, diagnosed by laboratory-based real time quantitative reverse transcription polymerase chain reaction (RT-qPCR) or serological tests to be positive, but remained symptomless throughout the follow up period of at least 7 days to distinguish them from pre-symptomatic cases.

Outcomes

Our primary outcome was proportion of all true SARS-Cov-2 infected people who were completely asymptomatic at the time of test and throughout the follow up period, where the denominator included all tested individuals in the study sample whose result was positive, and the numerator included those who tested positive and had no symptoms. Our secondary outcome was estimate of community spread from true asymptomatic cases.

Study selection and screening

Two authors (OB and MC) independently screened titles, abstracts, and full texts according to eligibility criteria. All discrepancies were resolved via group discussion with the other authors. Reasons for exclusion were documented for all full text articles deemed ineligible (Supplement 2) - see PRISMA diagram (Figure 1).

Data extraction

Three authors (OB, MC, KB) used a Microsoft Excel form to extract the following information:

1. Methods: study authors, year of publication, country, publication type, duration of study, duration of follow-up
2. Participants: sample size, age (mean or median; range), setting (community, province, aged care facility, hospital, screening clinic), presence or absence of symptoms, test results.
3. History of illness and diagnosis: Type of test, numerator, denominator/sampling frame, proportion of asymptomatic, mild symptomatic, or symptomatic subjects, and number or proportion of people infected by the asymptomatic case.

Case definition: Asymptomatic: confirmed via any testing specified above without report of symptom onset for the duration of sufficient follow-up to differentiate from pre-symptomatic cases. Exposure: Self-reported and/or documented contact with a confirmed case or potential contact of another pre-symptomatic person (e.g. came from an endemic area or linked with an infected traveler). The World Health Organization (WHO) recommends that “for confirmed asymptomatic cases, the period of contact is measured as the 2 days before through the 14 days after the date on which the sample was taken which led to confirmation”.⁶

Risk of bias assessment

We used a combination of risk of bias tools for prevalence studies⁷ and diagnostic accuracy⁸ and adapted the key signaling questions on sampling frame, ascertainment of infectious disease status, acceptability of methods to identify denominators, case definition of asymptomatic for the numerator, and length of follow up, as shown in Table 2 and in Supplement 3 in full.

Data analysis

We estimated the proportion of COVID-19 cases that were asymptomatic for each included study population, assuming a binomial distribution and calculating exact Clopper–Pearson confidence intervals. We then pooled data from all included studies using (1): fixed effect meta-analysis and (2): random effects meta-analysis. All analyses were conducted using SAS 9.4; the FREQ procedure was used for individual studies and the fixed effect meta-analysis; the NLMIXED procedure was used for the random effects meta-analysis.

We planned to undertake subgroup analysis for age (between studies, and within studies where age was reported separately for asymptomatic and symptomatic cases). As only studies deemed to be of high quality on items 1 and 2 after risk of bias appraisal were included in the analysis, no sensitivity analysis of high versus low quality studies was undertaken.

Results

Five hundred-seventy-one articles were screened for title and abstract and 69 full-text assessed (Figure 1). Major reasons for exclusion were inadequate sampling frame and insufficient follow-up time to accurately classify the asymptomatic cases. Full list of excluded studies with reasons is presented in Supplement 2. Five articles – three published and two pre-prints – from three countries (China (2), United States of America (USA) (2), and Italy (1)) that tested 9,242 close contacts of at least 740 confirmed COVID-19 cases, of which 413 were positive and 65 were asymptomatic, met eligibility criteria for the estimation of the primary outcome.⁹⁻¹³

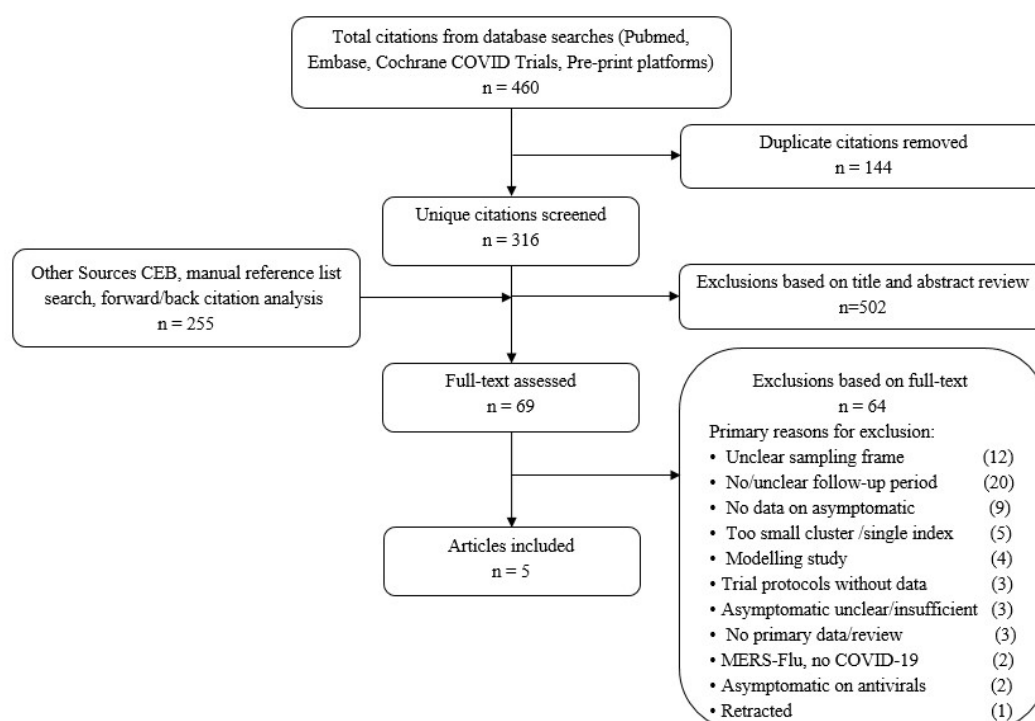


Figure 1. Screening and selection of articles

Their sampling frames were residential aged care facilities (RACF) in USA^{12,13}; a community sample of source cases and their close contacts¹¹; a community screening program of Shenzhen cases and their close contacts including hospitalized patients, fever clinics and travelers contacts¹⁰ and a whole District surveillance program in Italy⁹. The demographic characteristics (Table 1) indicate that most of the tested individuals were adults, with mean age over 70 years in the two RACF studies,^{12,13} and mean over 37 years in the three⁹⁻¹¹ community screening programs. The proportions of children and young people were reported as 8.2% aged 0-19 years¹⁰, 15.8% aged 0-17 years¹¹, and 16.6% aged 0-20 years⁹ respectively. (Table 1)

Diagnosis in all studies was confirmed via RT-qPCR and in one case supplemented with radiological evidence.¹¹ Testing intensity varied across settings and in the eligible studies intensity was generally over 85% as follows: all contacts regardless of symptoms;¹⁰⁻¹² 93% of residents¹³ and 85.9% of an entire town.⁹ The case definitions for asymptomatic cases usually included self-reported absence of fever and cough^{10,12} in addition to absence of other symptoms,⁹ self-report supplemented with chart abstraction in the RACFs for people with severe cognitive impairment,^{12,13} or described as “asymptomatic throughout” the study period.¹¹ Length of follow-up for monitored individuals in the RACF studies was 7 to 19 days;^{12,13} 14 days for the Chinese travelers and their contacts;¹¹ 7-14 days in the Italian community;⁹ and 12 days for 95% of all contacts in the Shenzhen community surveillance.¹⁰

Table 1. Characteristics of included studies (n=5)

Study ID, year and country	Study population (sampling frame)	Sample size, mean age	Type of diagnostic testing	Length of follow up of asymptomatic cases	Outcomes
Lavezzo et al⁹ 2020 (Italy) Preprint	Majority of population of Italian town of Vo following a COVID-19 death on 21 Feb. Quarantine measures were in place from 23 Feb – 8 Mar.	N=2,812. Mean age of cohort 47 yrs, mean age of cases 58 yrs.	Nasal swab, RT-qPCR	7-14 days	Prevalence and risk of infection, prevalence of asymptomatic cases, transmission rate
Bi et al¹⁰ 2020 (China) Preprint	Close contacts of 391 confirmed cases identified by the Shenzhen CDC before February 9th.	N=1,286. Mean age of cohort 37.9 yrs, mean age of cases 42.5yrs.	Nasal swab, RT-qPCR	95% followed up for 12+ days	Proportion of asymptomatic, mild, moderate and severe cases, transmission rate (secondary attack rate), incubation period
Luo et al¹¹ 2020 (China) Preprint	Close contacts of 347 confirmed COVID-19 patients identified between January 13 and March 6, 2020, in Guangzhou, Guangdong Province, China.	N=4,950. Mean age of cohort 38 yrs, mean age of cases 44.2 yrs.	Nasal swab, RT-qPCR	14 days	Infection rates, modes of contact, clinical characteristics of confirmed cases and source cases, risk of transmission
Kimball et al¹² 2020 (USA) Published	Residents, healthcare personnel, and visitors of Long-Term Care Facility following a SARS-CoV-2(+) case on 1 Mar.	N=76. Mean age of cohort 76.8 yrs, mean age of cases 80.7 yrs.	Nasal swab, RT-qPCR	7 days	Prevalence of SARS-CoV-2 infections, rate of asymptomatic cases, clinical features of COVID-19 among patients, transmission rate
McMichael et al¹³ 2020 (USA) Published	Residents of Long-Term Care Facility following a SARS-CoV-2(+) case on 28 Feb.	N=118. Mean age of cases 83 yrs.	Nasal swab, RT-qPCR	~19 days	Prevalence of SARS-CoV-2 infections, rate of asymptomatic cases, clinical features of COVID-19 among patients

The proportion of asymptomatic cases in the 5 included studies ranged from 6% (95% CI 3% - 12%) in China¹¹ to 41% (95% CI 30% - 53%) in Italy.⁹ Combining data from all five studies, we estimate that 16% of cases were asymptomatic (95% CI: 12% - 20%; fixed effects); for the three non-aged care studies: 19% (15% - 24%), and for the two studies of long-term aged care facilities 8% (4% -

14%). The corresponding estimated proportions in the random effects meta-analysis (not depicted) were: overall 14% (95% CI: 3% - 47%), non-aged care 19% (5% - 50%), and aged care 9% (2% - 29%). The one study that reported on age-specific proportions of asymptomatic infection, found similar proportions across all age groups.⁹

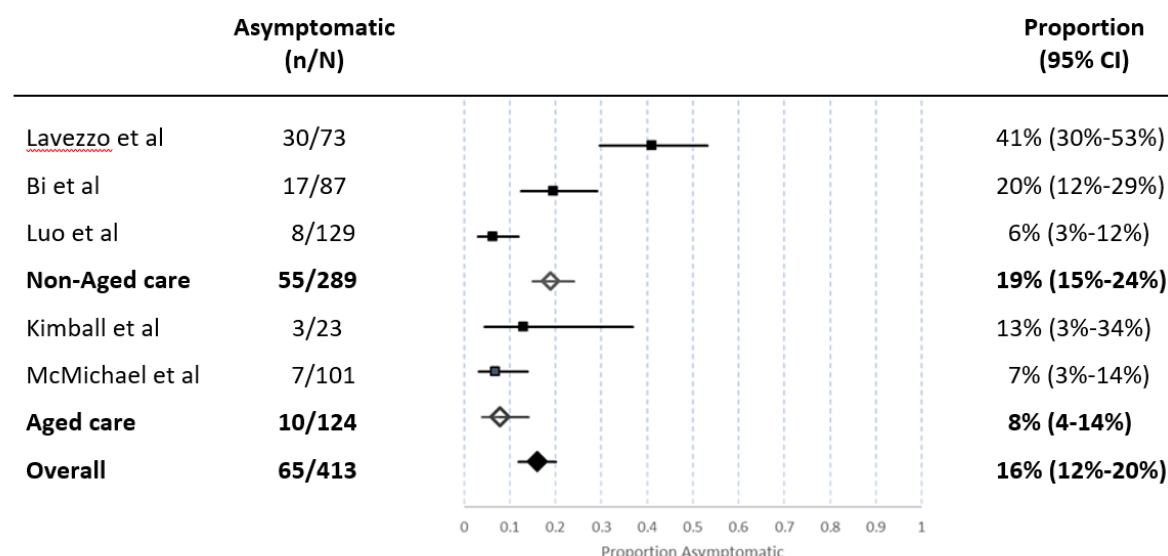

























Figure 2. Fixed effects pooled estimates of proportion of asymptomatic carriers by subpopulations. N - positive cases; n - asymptomatic cases.

Two studies^{9,11} reported data on possible community spread from asymptomatic cases. Luo et al reported on 2610 close contacts of 186 source cases where severity of disease was known. One new case resulted from 305 close contacts of asymptomatic source cases (0.3%), compared to 19 new cases from 576 close contacts of mildly symptomatic source cases (3%), and 98 new cases from 1729 case contacts of moderate, severe or critical source cases (6%). Lavezzo et al reported that of the 8 new cases identified during the second population survey, the source cases were asymptomatic in 3, and unknown in 2. Two studies of the cycle threshold (Ct) from real-time RT-PCR assays both found that asymptomatic and symptomatic individuals did not differ on this measure of potential viral transmission.^{9,12}

Risk of bias of included studies

Table 2 summarizes the overall risk of bias assessment of the five included studies (full list of risk of bias questions in Supplement 3). All of the studies were evaluated as low risk of bias in majority of the categories. Two studies had potential non-response bias for not testing all of the eligible participants: 7% (6/82) of participants in Kimball et al study and 14% (463/3275) of the target population was not tested in Lavezzo et al study. Two studies in aged-care patients posed an additional risk of bias concern because of large proportion who had cognitive impairment who might not report symptoms fully. Only one study explicitly stated the asymptomatic case definition they adhered to.

Table 2. Risk of bias in 5 included studies. Green smiley face denotes low risk, yellow straight face - unclear risk.

Included studies	Risk of bias assessment questions				
	1. Was the sampling frame a true or close representation of the target population?	2. Was the likelihood of non-response bias among those at risk of infection minimal?	3. Is the reference standard used likely to correctly classify all SARS-CoV-2 infections?	4. Was an acceptable case definition used in the study?	5. Was the length of follow-up to define case definition appropriate?
Lavezzo et al					
Bi et al					
Luo et al					
Kimball et al					
McMichael et al					

Excluded studies

Several well publicized studies did not meet our inclusion criteria. The outbreak on the Diamond Princess cruise ship involved 3,711 passengers of whom over 600 acquired COVID-19.⁴ Many of the positive cases were relocated to medical facilities in Japan without details of their clinical progression. To correct for the lack of follow-up, Mizumoto and colleagues applied a statistical adjustment for the right censoring and estimated that 17.9% (95% CI 15.5% - 20.2%) of positive cases were asymptomatic.

An open invitation screening of the Icelandic population suggested around 0.8% of the population were SARS-CoV-2 positive, with half classified as (initially) asymptomatic.³ However, as there was no follow-up, we cannot separate asymptomatic from pre-symptomatic. Furthermore, the study excluded symptomatic people undergoing targeted testing, which impeded an estimate of an overall asymptomatic rate.

A study of 215 pregnant women in New York identified 33 SARS-CoV-2 positive women.¹⁴ On admission to the delivery unit, 4 of the 33 positive cases were symptomatic and 3 became symptomatic before postpartum discharge, suggesting an asymptomatic rate of 26/33 (79%). However, the 2 days of follow-up was insufficient to meet our inclusion criteria.

A case report of a pre-symptomatic Chinese businessman transmitting COVID-19 to a German business partner was also excluded because despite three other people acquiring the infection from the affected German source, none of them was asymptomatic at follow-up.¹⁵ A 5-day point-prevalence testing of adults living in homeless shelters in Boston found 147 positive cases of which “the majority” had mild or no symptoms.¹⁶ We excluded this study, as there was no numeric estimate for true asymptomatic, and no follow-up assessment.

Two studies examined people repatriated from overseas to their home countries by plane. Neither study was clear whether symptomatic people could be included - and if excluded, they would overestimate the asymptomatic rates. The study of 565 Japanese citizens repatriated from China,¹⁷ found 13 positives: 4 asymptomatic and 9 symptomatic, based on screening on arrival. The other of 383 Greek citizens repatriated from UK, Spain, and Turkey¹⁸ found 40 asymptomatic positives on arrival, 4 of whom later self-reported symptoms. Again, the likely initial exclusion of symptomatic people, and the lack of comprehensive follow up would both overestimate the asymptomatic rates.

Discussion

Though the rate of asymptomatic COVID-19 cases has received considerable attention, we could find only five studies that provided an adequate sample frame and follow-up to ascertain a valid estimate of the proportion of asymptomatic. The combined estimate of the asymptomatic proportion was 16% (95% CI 12% - 20%), but with considerable residual uncertainty even with the five studies pooled. Aged care facilities appear to give a lower asymptomatic rate though with insufficient data for a firm conclusion. Only two of the five studies provided any valid data on transmission rates from asymptomatic cases, the larger Chinese study suggesting lower rates of transmission than from symptomatic cases.

There are several limitations to our findings. First, our search focused on published and pre-print articles, and may have missed some public health reports that are either unpublished or only available on organisational websites. Second, the design and reporting of most of the studies had a number of important deficits that could impact their inclusion or our estimates. These deficits include the poor reporting of the sample frame, the testing and symptom check, and the follow-up processes. Such reporting would have been considerably aided by a flow chart of cases (as Lavezzo et al does) of identification, testing, and follow-up including missing data. A further important limitation was the poor reporting of symptoms, which was often simply dichotomised into symptomatic versus asymptomatic without clear definitions and details of possible mild symptoms. The included studies did not report sufficient data to examine the impact of age and underlying comorbidities on the asymptomatic rate. Finally, all included studies relied on RT-qPCR, hence some cases might have been missed due to false negative result.¹⁹ If the tests missed more asymptomatic cases, then the true prevalence of asymptomatics could be higher than our estimates.

While several previous articles have discussed the research on asymptomatic rates, the only systematic attempt we could identify was by the Centre for Evidence Based Medicine in Oxford. Their rapid review identified 21 articles with asymptomatic rates that vary between 5% and 80%, including three of the five articles eligible for our review.⁵ However, their rapid review did not include a critical appraisal of the article methods nor an attempt to pool the most valid studies. Given the importance of this topic to decision-making, an ongoing “living review” is warranted to refine estimates as new and better data appear. For example, when it becomes available, the CDC report on the 600 cases onboard the Theodore Roosevelt will be important, as reports suggest the initial asymptomatic rate was 60% but no follow up details are available.

There are still many unanswered questions about asymptomatic cases remain. In four of the studies the asymptomatic cases were not retested for RT-qPCR status, and none tested for IgG and IgM antibodies. A recent USA seroprevalence study²⁰ reported that based on antibody testing, the infection was potentially more widespread than the inference from the number of confirmed cases. With the majority of symptomatic cases developing detectable IgM and IgG antibodies between day 12 and 14 after disease onset respectively,²¹ follow-up of asymptomatic cases may need to be extended to prevent incorrectly labelling a person as a case or infectious. The estimated sensitivity and specificity of IgG and IgM tests and PCR tests may only apply to study populations that exclude asymptomatic cases. Without repeated PCR tests and follow-up with antibody tests our infection prevention strategies for asymptomatic cases remain uncertain.

Estimates of asymptomatic rate and transmission rate are vital parameters for modelling studies. Our findings do not however suggest that up to these proportions of asymptomatic cases drive clusters or imply a role in undetected outbreaks. Other unknowns include whether there is a difference in age (particularly children vs adults), sex and underlying comorbidities that differentiate asymptomatic from pre-symptomatic cases; development of long-term immunity; and whether asymptomatics take longer to develop active disease or remain silent.

Clear evidence of a true asymptomatic state has implications for our approach to containment of infection and surveillance strategies. For example, if asymptomatic cases are important drivers of outbreak, then extensive community surveillance programs will need to include everyone for testing. Quarantining all positive RT-qPCR asymptomatic cases have cost benefit implications for authorities and the individual. Quarantining may even be unnecessary and extensive immunological follow-up of asymptomatic cases will determine whether wearing a mask and keeping social distancing is a better approach than isolation.

Our recommendations for future research also include improved clearer reporting of methods, sampling frames, case definition of asymptomatic, extent of contact tracing, duration of follow-up periods, presentation of age distribution of asymptomatic cases and separation of mild cases from asymptomatics in result tables. A reliable estimate of the proportion of true asymptomatic cases and the burden of disease is imperative in our understanding of infection transmission capacity of asymptomatic cases. Until we have the immunological and epidemiological evidence, we advise that the importance of asymptomatic cases for driving the spread of pandemic to be considered with caution.

Authors' contributions: PG conceived the study and co-designed with OB, MC, and KB. JC led the literature searches including backward and forward citation analysis. OB and MC conducted the parallel title, abstract and full text screening. OB, MC, PG, KB did data extraction and analysis. MLM provided expertise in interpretation of the findings. All authors contributed to resolving disagreements throughout the study conduct and to writing of the manuscript.

Conflict of interest: Prof Mary-Louise McLaws is a member of World Health Organization Health Emergencies Program Experts Advisory Panel for Infection Prevention and Control Preparedness, Readiness and Response to COVID-19. All other authors declare no competing interests.

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