Estimating the extent of 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 Europe PMC (which covers 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. We assessed risk of bias by combination of questions adapted from risk of bias tools for prevalence and diagnostic accuracy studies.

Results: We screened 998 articles and included nine low risk-of-bias studies from six countries that tested 21,035 at-risk people, of which 559 were positive and 83 were asymptomatic. Diagnosis in all studies was confirmed using a RT-qPCR test. The proportion of asymptomatic cases ranged from 4% to 41%. Meta-analysis (fixed effect) found that the proportion of asymptomatic cases was 15% (95% CI: 12% - 18%) overall; higher in non-aged care 16% (13% - 19%), and lower in long-term aged care 8% (3% - 18%). Four studies provided direct evidence of forward transmission of the infection by asymptomatic cases but suggested considerably lower rates than symptomatic cases.

Discussion: Our estimates of the prevalence of asymptomatic COVID-19 cases and asymptomatic transmission rates are lower than many highly publicized studies, but still sufficient to warrant policy attention. 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.

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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 R0 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 ship(4) 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 Oxford(5) 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 using enhanced processes and automation tools.(6) We searched PROSPERO database to rule out existence of a similar review; searched PubMed, Embase, Cochrane COVID-19 trials for published studies, and Europe PMC for pre-prints from January 2019 to 15 May 2020. A search string composed of MeSH terms and words was developed in PubMed, and was translated to be run in other databases using the Polyglot Search Translator.(7) Search strategies for all databases is presented in Supplement 1. We also conducted forward and backward citation searches of the included studies in the Scopus citation database.

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: sampling frame in part determined by presence or absence of symptoms. Or unclear; 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 where: all those at-risk of contracting SARS-CoV-2 virus were tested regardless of presence or absence of symptoms; diagnosis confirmed by a positive result on a real-time reverse transcription polymerase chain reaction (RT-qPCR) and or positive serological test; and all cases had follow up period of at least 7 days to distinguish asymptomatic cases from pre-symptomatic cases (Figure 1).

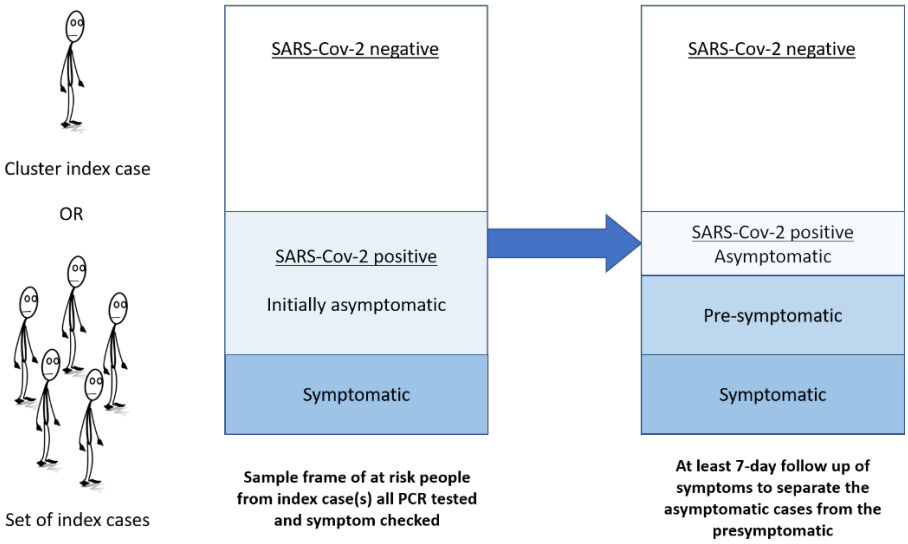

Figure 1. Depiction of ideal study flow and criteria used for study inclusion: (i) sample frame of at-risk people, and (ii) adequate follow-up on symptoms.

Outcomes

Our primary outcome was proportion of all people with SARS-Cov-2 infection 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 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 2).

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 with report of no symptoms for the duration of sufficient follow-up to differentiate from pre-symptomatic cases. Exposure: 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".(8)

Risk of bias assessment

We used a combination of risk of bias tools for prevalence studies(9) and diagnostic accuracy(10) 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 who 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

Nine hundred ninety-eight articles were screened for title and abstract and 132 full-text articles assessed for inclusion (Figure 2). 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. Nine articles – five published and four preprints – from six countries (China (3), United States of America (USA) (2), Taiwan (1), Brunei (1), Korea (1) and Italy (1)) that tested 21,035 close contacts of at least 843 confirmed COVID-19 cases, of which 599 were positive and 83 were asymptomatic, met eligibility criteria for the estimation of the primary outcome.(11-19)

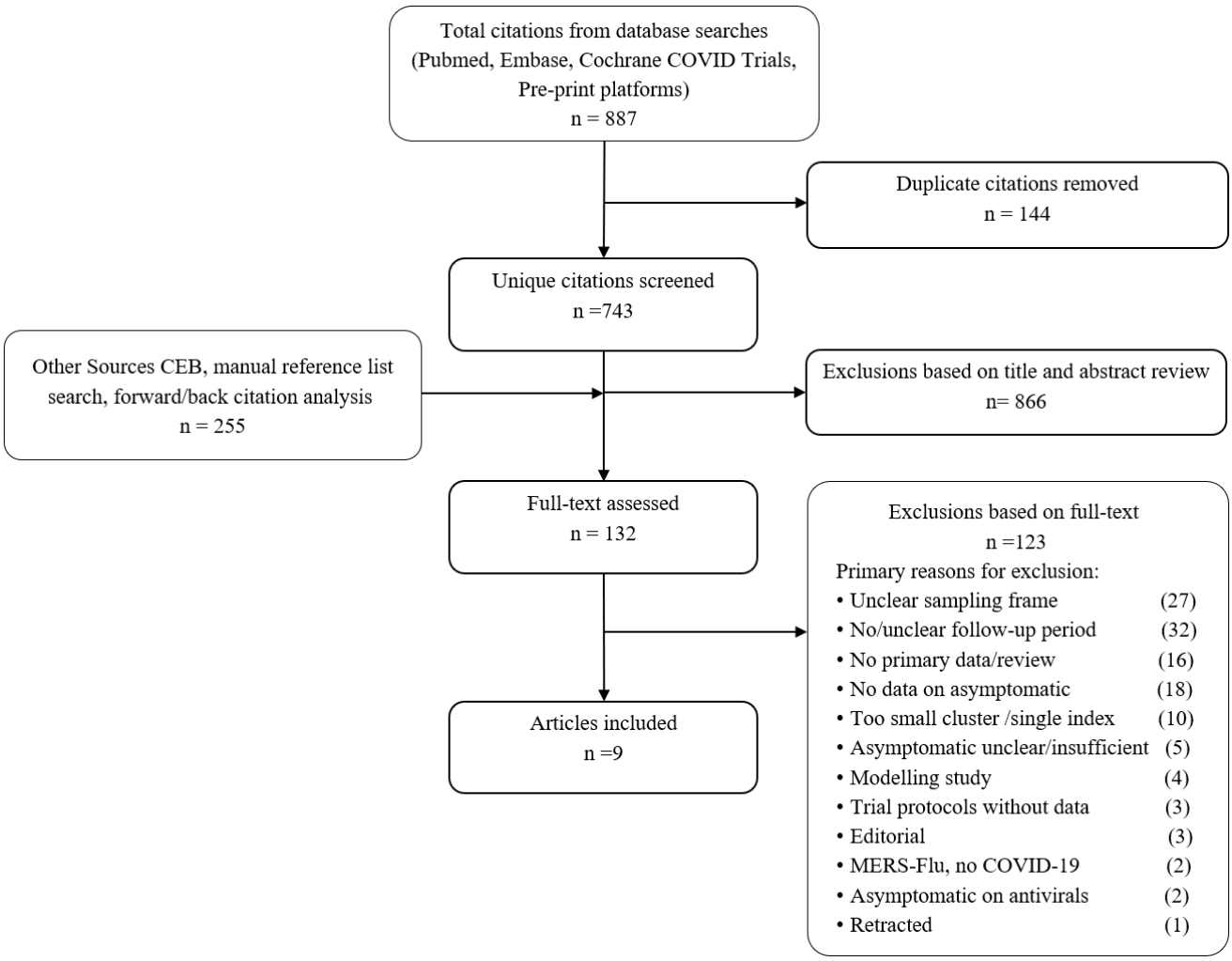

Figure 2. Screening and selection of articles

Their sampling frames included skilled nursing facilities (SNF) in USA(11, 18); high-risk close contacts of confirmed COVID-19 cases(12-14, 16, 17, 19); and a whole district surveillance program in Italy(15). The demographic characteristics (Table 1) indicate that most of the tested individuals were adults, with mean age over 79 years in the two SNF studies and mean over 31 years in the non-aged care studies. The proportions of children and young people (0-20 years) ranged from 6% to 23.5%.

Diagnosis in all studies was confirmed via RT-qPCR and in two cases supplemented with radiological evidence(16, 19). Testing of individuals within the study sample varied across settings but was generally very high: all contacts regardless of symptoms(12-14, 16, 17, 19); >97% of SNF residents(11, 18) and 85.9% of an entire town(15). Length of follow-up for monitored individuals in the SNF studies was 7 days(11, 18); 14 days for the Bruneian(13), Taiwanese(14), Korean(17) and Chinese close contacts(16); 7-14 days in the Italian community(15); 12 days for 95% of all contacts in the Shenzhen community surveillance(12), and 16±6 days in Liaocheng, China(19).

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
Arons et al(11) 2020 (USA) Published	Residents of skilled nursing facility (Facility A) in Seattle following a confirmed case on 1 Mar.	N=86. Mean age of cohort 77 yrs, mean age of cases 79 yrs.	Nasal swab, RT-PCR	7 days	Prevalence of infections, rate of asymptomatic cases, mortality, viral load and mutation sequencing
Bi et al(12) 2020 (China) Published	Close contacts of confirmed cases identified by the Shenzhen CDC between Jan 14, 2020 and Feb 12, 2020.	N=1,286. Mean age of cohort 38 yrs, mean age of cases 43yrs.	Nasal swab, RT-PCR	95% followed up for 12+ days	Proportion of asymptomatic, mild, moderate, and severe cases, transmission rate (secondary attack rate), incubation period
Chaw et al(13) 2020 (Brunei) Preprint	Bruneian attendants of a religious event in Malaysia, where a confirmed case was present.	N=1830. Mean age of cohort 31 yrs, mean age of cases 33 yrs.	Nasal swab, RT-PCR	14 days	Incubation period, serial interval, attack rates, mean reproductive number
Cheng et al(14) 2020 (Taiwan) Published	High risk close contacts (household members, HCWs) of first 100 cases in Taiwan.	N=849. Mean age of cohort 42 yrs, mean age of cases 41 yrs.	Nasal swab, RT-PCR	14 days	Secondary clinical attack rate for different exposure time windows of the index cases and for different exposure settings
Lavezzo et al(15) 2020 (Italy) Preprint	Majority of population of Italian town of Vo following a COVID-19 death on 21 Feb.	N=2,812. Mean age of cohort 47 yrs, mean age of cases 58 yrs.	Nasal swab, RT-PCR	7-14 days	Prevalence and risk of infection, prevalence of asymptomatic cases, transmission rate
Luo et al(16) 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 yrs.	Nasal swab, RT-PCR	14 days	Infection rates, modes of contact, clinical characteristics of confirmed cases and source cases, risk of transmission
Park et al(17) 2020 (Korea) Published	Employees, residents, and visitors of a commercial+ residential building where a confirmed case worked.	N=1143. Mean age of cohort 38 yrs.	Nasal swab, RT-PCR	14 days	Prevalence of infection and asymptomatic cases, secondary transmission rates
Roxby et al(18) 2020 (USA) Published	Residents of independent and assisted living communities (Facility 1) in Seattle following two confirmed cases between 5-9 Mar.	N=79. Mean age of cohort was 86 yrs.	Nasal swab, RT-PCR	7 days	Prevalence of infections, rate of asymptomatic cases in the facility
Tian et al(19) 2020 (China) Preprint	Close contacts (co-workers, family members, customers) of a confirmed supermarket employee (super-spreader) in Liaocheng city, China.	N~8000. Mean age of cases 48 yrs.	Nasal swab, RT-PCR	16±6.15 days	Clinical characteristics of confirmed cases, transmission rates, severity, biomedical data

RT-PCR: Reverse Transcription-Polymerase Chain Reaction; HCWs: health care workers.

The proportion of asymptomatic cases in the 9 included studies ranged from 4% (95% CI 1% - 10%) in Korea(17) to 41% (95% CI 30% - 53%) in Italy(15). Combining data from all nine studies, we estimate that 15% of cases were asymptomatic (95% CI: 12% - 18%; fixed effects); for the seven non-aged care studies: 16% (13% - 19%), and for the two studies of SNFs 8% (3% - 18%) (Figure 3). The corresponding estimated proportions in the random effects meta-analysis (not depicted) were: overall 14% (95% CI: 4.9% - 24.0%), non-aged care 15% (4.5% - 25.8%), and aged care 12% (0% - 31.1%). The 95% prediction interval was 3.2%-45.9%. The one study that reported on age-specific proportions of asymptomatic infection, found similar proportions across all age groups.(15)

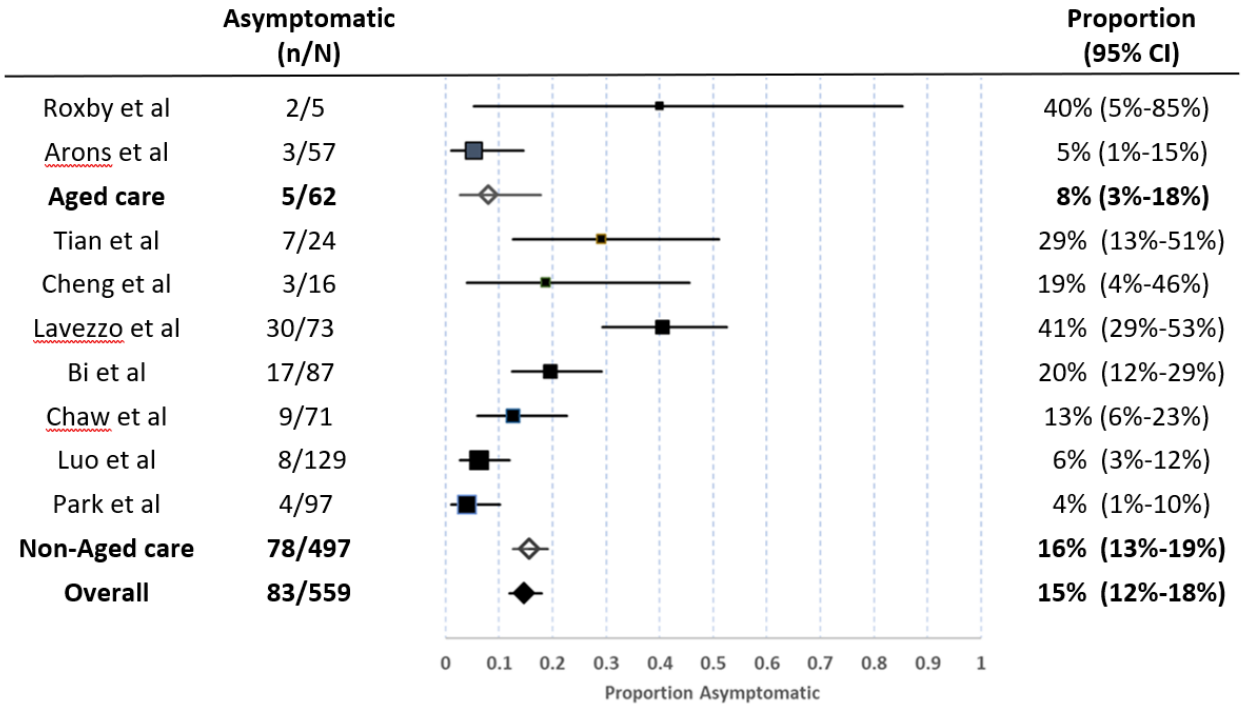

Figure 3. Fixed effects pooled estimates of proportion of asymptomatic carriers by subpopulations. N - positive cases; n - asymptomatic cases.

Four studies reported data on secondary infection transmission from asymptomatic cases (Table 2). The asymptomatic transmission rates ranged from none to 2.2%, whereas symptomatic cases' transmission rates ranged between 0.8-15.4%. Three of the included studies reported that the cycle threshold (Ct) from real-time RT-PCR assays did not differ between asymptomatic and symptomatic individuals.(11, 14, 15)

Table 2. Comparison of secondary transmission rates

Study ID	Asymptomatic transmission rate	Symptomatic transmission rate	Relative risk
Chaw et al	15/691 (2.2%)	28/1010 (2.8%)	0.79
Cheng et al	0/91 (0%)	22/2644 (0.8%)	0.0
Luo et al	1/305 (0.3%)	117/2305 (5.1%)	0.06
Park et al	0/4 (0%)	34/221 (15.4%)	0.0

Risk of bias of included studies

Table 3 summarizes the overall risk of bias assessment of the nine included studies (full list of risk of bias questions in Supplement 3). All of the studies were evaluated as low risk of bias for the sampling frame and length of follow up domains, which were part of the inclusion exclusion criteria (Domain 1 and 5). Two studies had potential non-response bias for not testing all of the eligible participants (14% (463/3275) of the target population was not tested in Lavezzo et al study(15)) or not reporting all tested participants results (87/98 cases were reported in Bi et al study(12)) (Domain 2). Four studies either had not tested the study population at least twice during the follow up period or had not provided clear information on it (Domain 3). Five of the studies did not explicitly state the asymptomatic case definition they adhered to or had additional bias due to high percentage of people in the SNFs with severe cognitive impairment(11, 18)(Domain 4).

Table 3. Risk of bias in 9 included studies. Green smiley face denotes low risk, yellow straight face – moderate or unclear risk.

Risk of bias assessment questions / **Included studies**	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?
Arons et al	🙂	🙂	🙂	😐	🙂
Bi et al	🙂	😐	😐	😐	🙂
Chaw et al	🙂	🙂	😐	🙂	🙂
Chen et al	🙂	🙂	😐	😐	🙂
Lavezzo et al	🙂	😐	🙂	😐	🙂
Luo et al	🙂	🙂	🙂	🙂	🙂
Park et al	🙂	🙂	🙂	🙂	🙂
Roxby et al	🙂	🙂	🙂	😐	🙂
Tian 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.(20) 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.(21) 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.(22) 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 board the plane and be included - and if excluded, they would overestimate the asymptomatic rates. The study of 565 Japanese citizens repatriated from China,(23) found 13 positives: 4 asymptomatic and 9 symptomatic, based on screening on arrival. The other of 383 Greek citizens repatriated from UK, Spain, and Turkey(24) 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

Principal findings

Though the rate of asymptomatic COVID-19 cases has received considerable attention, we could find only nine studies that provided an adequate sample frame and follow-up to ascertain a valid estimate of the proportion of asymptomatic cases. The combined estimate of the asymptomatic proportion was 15% (95% CI 12% - 18%), but with considerable residual uncertainty even with the nine studies pooled. Aged care facilities appear to give a lower asymptomatic rate though with insufficient data for a firm conclusion. Only four of the nine studies provided any valid data on transmission rates from asymptomatic cases, all suggesting lower rates of transmission than from symptomatic cases.

Strengths and weaknesses of the study

Strengths of our systematic review include achieving full methodological rigor within a much shorter time frame than traditional reviews using enhanced processes and automation tools.(6) We also critically assessed the risk of bias of all full text articles we screened to include studies with the least risk of bias in sampling frame and length of follow up domains to be able to differentiate between the asymptomatic and pre-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, especially where study participants were only tested once.(25) If the tests missed more asymptomatic cases, then the true prevalence of asymptomatic cases could be higher than our estimates. On the other hand, false positive results which may occur in low prevalence settings, would mean the true prevalence of asymptomatic cases was lower than our estimates.

Strengths and weaknesses compared to other studies

A few other reviews have examined the asymptomatic case rate. A review by the Centre for Evidence Based Medicine in Oxford identified 21 articles with asymptomatic rates that vary between 5% and 80%.(5) However, they only included early cross-sectional reports and did not critically appraise the study design, nor attempted to pool the most valid studies. Buitrago-Garcia et al included 28 studies in their systematic review and arrived at a pooled estimated rate similar to ours, with an overall rate of 15% and 95% prediction interval of 3-55%.(26) However, the similarity in overall estimates of the two reviews appears to be mostly by chance, as they included 25 studies we excluded due to high risk of bias in sampling frame and missed six of our nine included studies and the most recent report on a further one.(11, 27) Ongoing monitoring of new studies is warranted, but should include measures to minimize risk of bias by using more robust methodological assessment. Our review also has more recent search and provide empirical data on asymptomatic transmission rate.

Meaning of the study

Estimates of asymptomatic rate and transmission rate are vital parameters for modelling studies. Our estimates of the proportion of asymptomatic cases and their transmission rates suggest that asymptomatic spread is unlikely to be a major driver of clusters or community transmission of infection, but the extent for pre-symptomatic and minor symptomatic transmission remains unknown. 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 asymptomatic cases take longer to develop active disease or remain silent.

Unanswered questions and future research

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 study(28) 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,(29) 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 are likely to have been estimated in study populations only including symptomatic cases and may not only apply to broader clinical populations

that include asymptomatic cases. Without repeated PCR tests and follow-up with antibody tests our infection prevention strategies for asymptomatic cases remain uncertain.

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 presymptomatic and mild cases from asymptomatic cases in result tables. A reliable estimate of the proportion of asymptomatic cases and the burden of disease is imperative in our understanding of infection transmission capacity of asymptomatic cases. Until we have further 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 (WHO) Health Emergencies Program Experts Advisory Panel for Infection Prevention and Control (IPC) Preparedness, Readiness and Response to COVID-19 and WHO IPC Guidance Development Group for COVID-19. All other authors declare no competing interests.

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