SYSTEMATIC REVIEW

A rapid review and meta-analysis of the asymptomatic proportion of PCR-confirmed SARS-CoV-2 infections in community settings [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Cross-sectional studies indicate that up to 80% of active SARS-CoV-2 infections may be asymptomatic. However, accurate estimates of the asymptomatic proportion require systematic detection and follow-up to differentiate between truly asymptomatic and pre-symptomatic cases. We conducted a rapid review and meta-analysis of the asymptomatic proportion of PCR-confirmed SARS-CoV-2 infections based on methodologically appropriate studies in community settings.

Methods: We searched Medline and EMBASE for peer-reviewed articles, and BioRxiv and MedRxiv for pre-prints published before 25/08/2020. We included studies based in community settings that involved systematic PCR testing on participants and follow-up symptom monitoring regardless of symptom status. We extracted data on study characteristics, frequencies of PCR-confirmed infections by symptom status, and (if available) cycle threshold/genome copy number values and/or duration of viral shedding by symptom status, and age of asymptomatic versus (pre)symptomatic cases. We computed estimates of the asymptomatic proportion and 95% confidence intervals for each study and overall using random effect meta-analysis.

Results: We screened 1138 studies and included 21. The pooled asymptomatic proportion of SARS-CoV-2 infections was 23% (95% CI 16%-30%). When stratified by testing context, the asymptomatic proportion ranged from 6% (95% CI 0-17%) for household contacts to 47% (95% CI 21-75%) for non-outbreak point prevalence surveys with follow-up symptom monitoring. Estimates of viral load and duration of

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viral shedding appeared to be similar for asymptomatic and symptomatic cases based on available data, though detailed reporting of viral load and natural history of viral shedding by symptom status were limited. Evidence into the relationship between age and symptom status was inconclusive.

Conclusion: Asymptomatic viral shedding comprises a substantial minority of SARS-CoV-2 infections when estimated using methodologically appropriate studies. Further investigation into variation in the asymptomatic proportion by testing context, the degree and duration of infectiousness for asymptomatic infections, and demographic predictors of symptom status are warranted.

Keywords

SARS-CoV-2, asymptomatic, COVID-19, pandemic, epidemiology

This article is included in the [Coronavirus \(COVID-19\)](#) collection.

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Introduction

Reports of asymptomatic SARS-CoV-2 infection and potential transmission^{1–3} have generated concern regarding the implications of undetected asymptomatic transmission on the effectiveness of public health interventions in the current COVID-19 pandemic⁴. However, estimating the proportion of asymptomatic SARS-CoV-2 infections with viral shedding is challenging as the majority of testing is carried out on symptomatic individuals⁵. Furthermore, longitudinal designs that include symptom follow-up are required to differentiate truly asymptomatic cases, i.e. those that never develop symptoms during infection, from pre-symptomatic cases, i.e. those that shed virus and therefore test positive prior to symptom onset (see Figure 1). While asymptomatic viral shedding has been suggested to comprise up to ~80% of SARS-CoV-2 infections^{6–8}, data informing these figures are largely confined to cross-sectional reports that cannot distinguish truly asymptomatic cases from those who are pre-symptomatic at the point of testing (see Figure 1). Interchangeable use of these concepts, i.e. asymptomatic and pre-symptomatic, precludes accurate estimation of the asymptomatic proportion of potentially infectious SARS-CoV-2 cases. Detectable SARS-CoV-2 shedding based on reverse transcriptase polymerase chain reaction (PCR) testing cannot conclusively establish infectiousness in the absence of viral culture^{9,10}. However, PCR cycle threshold values provide an informative estimate of viral load and, by extension, probable infectiousness⁹; consequently, PCR-confirmed infection can provide a useful and accessible indicator of potentially infectious cases, including those without symptoms, for epidemiological modelling.

Differences in demographic characteristics of asymptomatic versus symptomatic individuals are also poorly understood.

Age is an important risk factor for COVID-19 severity, with greater risk of poor prognostic outcomes including mortality in older adults^{11,12}. Consequently, asymptomatic infection may be less common with increasing age. Understanding the relationship between age and symptom status has important implications for public health interventions.

Given the widespread discussion and potential implications of asymptomatic transmission of SARS-CoV-2, we aimed to rapidly synthesize studies to estimate the asymptomatic proportion of PCR-confirmed cases in community settings (primary outcome). We also aimed to synthesize available data from these studies regarding viral load and duration of viral shedding in asymptomatic community cases compared to pre-symptomatic cases or those symptomatic from baseline (secondary outcome), and the relationship between symptom status and age (secondary outcome). We limited the review to include studies from community settings rather than hospitals and other medical facilities to prevent selection bias towards symptomatic cases. Only studies reporting PCR-confirmed cases rather than exclusive serological studies were included to estimate the proportion of asymptomatic SARS-CoV-2 infection with viral shedding. The review was not extended to estimate the overall asymptomatic proportion including non-shedding serological cases due to the limited number of serological studies, varying interpretation, and ongoing development of valid serological assays for SARS-CoV-2.

Methodology

This review was reported in line with the PRISMA guidelines¹³. A protocol was not registered due to its status as a rapid review.

Figure 1. Timeline of symptom development and viral shedding in relation to timing of virological testing. This figure demonstrates two trajectories of symptom development in cases with detectable viral shedding. The symptomatic case trajectory comprises a period of pre-clinical viral shedding, in which the individual demonstrates no symptoms but tests PCR positive (pre-symptomatic PCR-confirmed). These individuals subsequently develop symptoms and continue to shed virus (symptomatic PCR-confirmed). Consequently, cases with a symptomatic trajectory may appear to be asymptomatic if tested in the pre-clinical shedding period and not followed-up. Asymptomatic cases with viral shedding, conversely, test PCR positive and never go on to develop symptoms across the course of infection (asymptomatic PCR-confirmed).

Search strategy

We used Ovid to search the Medline and EMBASE databases of peer-reviewed literature (2019- May 05 2020 and search repeated to include period of May 06 2020 to June 10 2020, and subsequently to include June 11 2020 to August 25 2020) using the following search terms for titles and abstracts: (*Coronavirus** OR *Covid-19* OR *SARS-CoV-2* OR *nCoV*) AND (*asymptomatic*) AND (*polymerase chain reaction* OR *PCR* OR *laboratory-confirmed* OR *confirmed*). We also searched BioRxiv and MedRxiv for titles and abstracts of pre-print manuscripts using the terms “*Covid-19*” + “*asymptomatic*”. We hand-searched the reference lists of all included studies to identify any additional relevant literature.

Selection criteria

We included studies that met all of the following criteria: 1) human study; AND 2) presented original research or public health COVID-19 surveillance data; AND 3) available in English; AND 4) presented data on polymerase chain reaction (PCR) confirmed COVID-19 cases; AND 5) presented data on PCR testing of exposed or potentially exposed individuals regardless of symptom status (to avoid bias towards symptomatic cases); AND 6) had systematic follow-up at ≥ 1 time-point and reporting of symptom status among PCR confirmed cases (to differentiate pre-clinical shedding from truly asymptomatic cases); AND 7) presented data from a community setting (i.e. community and home contact tracing, population screening, traveller screening, community institutional settings such as care homes, schools, or workplaces, occupational exposure including healthcare workers). Studies were excluded if they met any of the following criteria: 1) studies or case series with <5 positive cases and/or <20 total cases (small sample size) due to likely low generalisability of asymptomatic proportions; OR 2) not possible to consistently ascertain the symptomatic status of participants across follow-up; OR 3) inadequate detail about testing strategy (i.e. not possible to discern if all cases were tested systematically); OR 4) recruitment/reporting of patients from acute healthcare settings (e.g. hospitals, medical facilities) due to selection bias towards symptomatic cases.

Data extraction and analysis

One researcher performed the search and deduplication using Ovid, screened and selected studies, and extracted study details. Two researchers extracted primary outcome data independently and resolved any disagreement by consensus. We extracted the following variables of interest to assess the primary and secondary outcomes and the characteristics and quality of included studies: author names, year of publication, publication type (peer-reviewed article or pre-print), study design, study setting, study country of location, participant age (mean, median, or range as available), participant sex distribution, symptoms comprising symptomatic case definition, duration of symptom history at PCR-confirmation, duration of follow-up symptom monitoring, testing criteria, sample size, number of participants who underwent PCR testing, number of PCR-confirmed cases, number of confirmed cases who remained asymptomatic throughout follow-up, and

cycle threshold or genome copy number values, viral culture results, duration of viral shedding for asymptomatic and pre-/symptomatic cases, and any available data regarding age or age distribution of asymptomatic versus (pre)symptomatic cases if reported.

We performed random-effects meta-analysis using the *metaprop* programme¹⁴ in Stata Version 15 to compute the study-specific and pooled asymptomatic proportion - the primary outcome of this review - with its 95% confidence intervals (Wilson score method) and 95% prediction intervals¹⁵, applying the Freeman-Tukey transformation (the same analysis can be performed in R). We decided a-priori to use a random effects model to address heterogeneity. The asymptomatic proportion is given as the number of consistently asymptomatic confirmed cases divided by the total number of PCR-confirmed cases who received follow-up (Figure 2). It is important to note that the term asymptomatic proportion is sometimes used to alternatively refer to the asymptomatic proportion of all infections including those that do not shed virus and would not be PCR-confirmed (see Figure 2). To account for potential exposure-driven heterogeneity in asymptomatic proportion, we present findings stratified by testing context as well as overall. Testing context was subdivided into studies comprising exclusive household contacts of an index case, studies comprising contacts from other settings or those (potentially) exposed to an outbreak (including travellers returning from high-prevalence regions), and point prevalence surveys not specifically linked to an outbreak that had follow-up symptom monitoring.

We reported available findings regarding the viral load, duration of viral shedding, and age of asymptomatic and (pre)symptomatic cases, but did not conduct meta-analysis due to sparse reporting and inconsistencies in data presented.

Risk of bias assessment

We assessed risk of bias based using criteria relevant to the topic of this review adapted from the Joanna Briggs Institute critical appraisal tool for prevalence studies¹⁶ (Table 1). Two researchers independently assessed the risk of bias for each included study and resolved any disagreement by consensus. Bias was assessed according to criteria described in Table 1, with studies graded as very low risk of bias if they were unlikely to have been affected by bias on any of the criteria, low if one criterion may have been affected, moderate if two may have been affected, and high if all three may have been affected. Risk of publication bias across included studies was assessed using a funnel plot and Egger's test.

Results

Records identified

Figure 3 presents an adapted PRISMA flow diagram¹³ of the study selection procedure. The search yielded 1077 published articles indexed on OVID and 473 pre-prints. Following deduplication, we screened the titles and abstracts of 1138 published articles and pre-prints, of which we assessed the 133 full texts – including a relevant text identified through

Figure 2. Summary classification of clinical and PCR outcomes and calculation of asymptomatic proportions.

Table 1. Risk of bias assessment.

Potential Issue	Direction of Bias
Information Bias: Initial testing does not identify all infected people shedding virus	Effect estimate could be biased downwards if PCR testing is more likely to detect symptomatic shedders compared to asymptomatic shedders. This could be because asymptomatic cases shed less virus or shed for a shorter duration.
Information Bias: Difficulty distinguishing pre-clinical versus truly asymptomatic	Effect estimate could be biased upwards if pre-symptomatic cases are misclassified as asymptomatic (see Figure 1)
Non-Participation Bias: Individuals opt out of initial PCR testing or out of symptom follow-up	Effect estimate could be biased in either direction if participation is influenced on symptom-status

hand-search of the literature – and included 21 in the present review^{17–37}. Three of the 21 included studies comprised household contacts of confirmed cases^{26,28,29}. A further three included studies were point prevalence surveys with symptom monitoring follow-up^{34–36}, one of which was conducted in a general population sample³⁶ and the remaining two in nursing home samples^{34,35}. The remaining 15 studies involved participants with other epidemiological links to confirmed or suspected cases/outbreaks^{17–25,27,30–33}, including five studies based in nursing homes^{18,19,24,32,37}, and one study of healthcare workers with occupational exposure to confirmed cases³⁰. The healthcare worker study was included as it comprised whole-facility testing following occupational exposure in healthcare workers rather than patients presenting to healthcare settings due to symptoms (see inclusion criteria). Studies were conducted across the following range of countries in Asia, Europe, and North America: China^{22,25–27,29}, USA^{18,19,28,32,36}, UK^{24,35,37}, South Korea¹⁷, France²⁰, Vietnam²¹, Brunei²³, Italy³⁰, Japan³¹, Hong Kong³³, and Ireland³⁴. Risk of bias was rated as very low for two studies^{30,33}, low for 15 studies^{17–20,22,23,25–29,32,34–36}, and moderate for four studies^{21,24,31,37}.

Asymptomatic proportion of PCR-confirmed SARS-CoV-2 infections in community settings

Estimates of the asymptomatic proportion of PCR-positive SARS-CoV-2 infections for included studies ranged from 0% (95% CI 0–0.8%; Yousaf *et al.*²⁸) to 91% (95% CI 73%–98%; Starling *et al.*, 2020³⁵). Table 2 reports all asymptomatic proportions with 95% confidence intervals for as well as details of included studies. Based on random-effects meta-analysis (Figure 4), the pooled estimate for the asymptomatic proportion was 23% (95% CI 16%–30%; 95% prediction interval 0.01–57%). There was high heterogeneity: $Q(20)=253.06$, $p<.001$, $\tau^2=0.11$, $I^2=92.10\%$. Heterogeneity appeared to be partly influenced by testing context (test for subgroup heterogeneity: $Q(2)=10.49$, $p=0.01$), but remained substantial within these subgroups. Household contact studies demonstrated the lowest asymptomatic proportion estimate of 6% (95% CI 0–17%; heterogeneity $Q(2)=12.09$, $p<.001$, $\tau^2=0.07$, $I^2=83.46\%$), rising to 23% (95% CI 14–32%; $Q(14)=139.86$, $p<.001$, $\tau^2=0.12$, $I^2=89.99\%$) for studies comprising participants with other epidemiological links to SARS-CoV-2 cases or outbreaks, and 47% (95% CI 21–75%; $Q(2)=47.16$,

Figure 3. Adapted PRISMA flow diagram of study selection.

Table 2. Descriptive summary of studies included in meta-analysis.

Reference	Country of study	Participant group description	Study design	Testing criteria	Symptom assessment method	Symptoms included in symptomatic case definition	Length of baseline symptom history	Length of symptom follow-up	Tested <i>n</i>	Test Specimen and Frequency	PCR+ Cases <i>n</i>	Asymptomatic Proportion % (95% CI, <i>n/N</i>)	Risk of Bias
Park <i>et al.</i> (2020)	South Korea	General public: mean age 38 (range 20–80); 72% female (620/857 with demographic data)	Surveillance	Exposed to index case(s)	Standardised assessment form based on patient interviews	Unspecified	From date of first symptom onset (if any)	14 days	1143	Nasopharyngeal and oropharyngeal swabs daily. Collection method (self- vs healthcare worker) unspecified	97	4% (2–10%, 4/97)	Low
Arons <i>et al.</i> (2020)	USA	Residents of one nursing home: mean age: 76 ±10; 63% female (48/76)	Serial point prevalence survey	Exposed to index case(s)	Standardised assessment form based on interviews and medical records	Fever, cough, shortness of breath, chills, myalgia, malaise, sore throat, runny nose or congestion, confusion or sleepiness, dizziness, headache, diarrhoea, and nausea and/or vomiting.	Within previous 14 days	7 days	76	Nasopharyngeal and oropharyngeal swabs twice one week apart. Collection method (self- vs healthcare worker) unspecified	47 ^a	6% (2–17%, 3/47)	Low
Roxby <i>et al.</i> (2020)	USA	Residents of one nursing home: mean age = 86 (range 69–102); 77% female (62/80) Staff of one nursing home: mean age 40 (range 16–70); 72% female (45/62)	Surveillance	Exposed to index case(s)	Standardised assessment form based on patient self-report with or without staff assistance	Fever, cough, and other symptoms inc. sore throat, chills, confusion, body aches, dizziness, malaise, headaches, cough, shortness of breath, and/or diarrhoea	Within previous 14 days	7 days	142	Nasopharyngeal swabs twice one week apart. Collection method (self- vs healthcare worker) unspecified	5	40% (12–77%, 2/5)	Low
Danis <i>et al.</i> (2020)	France	General public (demographic details unknown)	Surveillance	Exposed to index case(s)	Bespoke (to study) assessment forms based on patient interviews	Full list unspecified but included fever, dry cough, wet cough, asthenia/fatigue, chills, sweats, rhinorrhoea, and/or myalgia	From date of first symptom onset (if any)	14 days	11 ^a	Nasopharyngeal swabs or endotracheal aspirates daily. Collection method (self- vs healthcare worker) unspecified	6	17% (3–56%, 1/6)	Low
Chau <i>et al.</i> (2020)	Vietnam	General public: median age 29 (range 16–60); 50% female (15/30 with follow-up)	Prospective cohort	Exposed to index case(s) and returning travellers from high-risk areas	Standardised assessment forms based on participant report	Full list unspecified but included fever, cough, rhinorrhoea, fatigue, diarrhoea, sore throat, muscle pain, headache, abdominal pain, and/or lost sense of smell	From date of first symptom onset (if any)	14+ days	14000	Nasopharyngeal swabs daily and saliva at baseline. Collection method (self- vs healthcare worker) unspecified	30 ^d	43% (27–61%, 13/30)	Moderate
Luo <i>et al.</i> (2020)	China	General public: median age 38.0 (IQR: 25.0 - 52.0); 50% female (2466/4950)	Prospective cohort	Exposed to index case(s)	Standardised assessment forms from participant self-report	Fever, cough, chill, sputum production, nasal congestion, rhinorrhoea, sore throat, headache, fatigue, myalgia, arthralgia, shortness of breath, difficulty breathing, chest tightness, chest pain, conjunctival congestion, nausea, vomit, diarrhoea, stomach-ache, and/or other	From date of first symptom onset (if any)	Until 2 consecutive negative swabs – up to 30 days	495	Oropharyngeal swabs every two days. Swabbing conducted by public health workers.	129	6% (3–12%, 8/129)	Low

Reference	Country of study	Participant group description	Study design	Testing criteria	Symptom assessment method	Symptoms included in symptom case definition	Length of baseline symptom history	Length of symptom follow-up	Tested <i>n</i>	Test Specimen and Frequency	PCR+ Cases <i>n</i>	Asymptomatic Proportion % (95% CI, <i>n/N</i>)	Risk of Bias
Chaw <i>et al.</i> (2020)	Brunei	General public: median age 33 (IQR = 29.5); 3.5% female (<i>n</i> =25/71) ^a	Surveillance	Exposed or epidemiological link to outbreak	Digital records on the national health information system database	Fever, cough, runny nose, sore throat	From date of first symptom onset (if any)	14 days	127	Nasopharyngeal swab. Those with positive swab or who developed symptoms re-tested until two consecutive negative tests (for positives) at unreported frequency. Collection method (self- vs healthcare worker) unspecified.	71	13% (7-22%, 9/71)	Low
Graham <i>et al.</i> (2020)	United Kingdom	Residents of four nursing homes: median age 83 (IQR= 15); 62% female (<i>n</i> =246/394) ^a	Serial point prevalence survey	Exposed to nursing home outbreak	Case note review and information from medical and nursing team	New fever, cough and/or breathlessness, newly altered mental status or behaviour, anorexia, diarrhoea or vomiting	Within previous 14 days	7 days	313	Nasopharyngeal and oropharyngeal swabs collected at baseline, with previously unavailable or test-negative participants (retested one week later. Collected by healthcare workers.	126*	35% (27-44%, 44/126)	Moderate
Wang <i>et al.</i> (2020)	China	General population: mean age 39.3 (SD=16.5); 46% female (<i>n</i> =29/63) ^b	Surveillance	Exposed to index case(s)	Medical reports	Full list unspecified but including cough, fever, shortness of breath and muscle soreness	From 2 days after exposure event	Until discharge from quarantine (median 10-13 days for those with and without normal chest x-ray respectively)	Unclear (only 279 positives reported on)	Nasopharyngeal swabs daily. Collection method (self- vs healthcare worker) unspecified.	279	23% (18-28%, 63/279)	Low
Wu <i>et al.</i> (2020)	China	General population: median age 43.5 (IQR= 35.8-62.3) for secondary cases and 37 (IQR= 14.5-58) for non-cases. 56% female <i>n</i> =80/143	Surveillance	Exposed to index case(s)	Internet-based questionnaires	Fever, cough, shortness of breath, diarrhoea or other common symptoms (including expectoration, haemoptysis, sore throat, nasal obstruction, runny nose, sneeze, headache, muscle ache or fatigue)	Since exposure event	21 days	143	Nasopharyngeal and/or oropharyngeal swabs (at Day 1, 7, and 14 for asymptomatic cases and up to 3-day intervals if showed symptoms). Collected by healthcare workers.	48	10% (5-22%, 5/48)	Low
Yang <i>et al.</i> (2020)	China	General population: median age 32 (IQR: 26-33); 78% female (7/9) ^c	Retrospective cohort	Exposed to confirmed case on flight	Medical records	Full list unspecified but including cough, expectoration, myalgia, headache, sore throat, anorexia, fatigue, diarrhoea, nausea, vomiting, chest distress, and dyspnoea	From date of first symptom onset (if any)	14 days	325	Throat swab at baseline. Subsequent frequency and collection method (self- vs healthcare worker) unspecified.	9	22% (6-55%, 2/9)	Low

Reference	Country of study	Participant group description	Study design	Testing criteria	Symptom assessment method	Symptoms included in symptomatic case definition	Length of baseline symptom history	Length of symptom follow-up	Tested <i>n</i>	Test Specimen and Frequency	PCR+ Cases <i>n</i>	Asymptomatic Proportion % (95% CI, <i>n/N</i>)	Risk of Bias
Yousaf et al. (2020)	USA	General population: mean age 8.16 (SD: 3.5); 69/195 <18 years, 46% (89/195) 18–49 years, 15% (29/195) 50–64 years, 4% (8/195) 65+ years, 51% female (99/195)	Prospective cohort	Household contacts of confirmed case(s)	Standardised questionnaire and symptom diary	Full list unspecified but including fever, chills, myalgia, or fatigue, runny nose, nasal congestion, or sore throat, cough, difficulty breathing, shortness of breath, wheezing, or chest pain, headache, loss of taste, or loss of smell, nausea/vomiting, diarrhoea, and abdominal pain	From date of first symptom onset (if any)	14 days	195	Nasopharyngeal swab on first and last day of study and if new symptoms were reported	47	0% (0–0.08%, 0/9)	Low
Hua et al. (2020)	China	General population: mean age 8.16 (SD: 4.07); 39% female (17/43); 39% children (<4 years; 325/835), 61% (510/835) adults	Retrospective cohort	Family contacts of confirmed case(s) or returning from high-risk areas	Medical and public health records	Full list unspecified but including fever, cough, stuffy/runny nose, fatigue, diarrhoea, vomiting/abdominal pain, shortness of breath, chest tightness, and headache	Since exposure to index case(s)	Until discharge from quarantine (mean=20.2, SD: 7.9, range 3–32 days)	835	Respiratory specimens. Further details of collection unspecified.	151	12% (8–18%, 18/151)	Low
Lombardi et al. (2020)	Italy	Healthcare workers: mean age 44.5 years; 64% female (1010/1573)	Surveillance	Exposed occupationally to confirmed case(s)	Infectious disease notification form	Fever, cough, dyspnoea, asthenia, myalgia, coryza, sore throat, headache, ageusia or dysgeusia, anosmia or parosmia, ocular symptoms, diarrhoea, nausea, and vomiting	14 days	Until end of study for patients asymptomatic at baseline	1573	Nasopharyngeal swabs at baseline and subsequently for positive cases at unspecified frequency. Collection method (self vs healthcare workers) unspecified.	139	12% (8–19%, 17/139)	Very low
Tabata et al. (2020)	Japan	General population: median age 68 (IQR: 47–75); 48% female (50/104)*	Surveillance/Retrospective cohort	Exposed to confirmed case(s) on cruise ship – whole ship screening	Medical records based on clinical interviews	Unspecified	From beginning of quarantine period	Until discharge or end of study (whichever was earliest); median 10 days (IQR: 7–10)	Unclear for study. 3711 tested on ship but not all isolated in study facility.	Pharyngeal swabs or sputum specimens. Further details of collection unspecified.	104	32% (24–41%, 33/104)	Moderate
Patel et al. (2020)	USA	Residents of one nursing home: median age 82 (IQR: 72–92); 69% female (24/35)	Surveillance	Exposed to nursing home outbreak	Interview by nursing staff	Fever, cough, shortness of breath, hypoxia, sore throat, nasal congestion, diarrhoea, decreased appetite, chills, myalgias, headaches, new onset confusion	From baseline	30 days	118	Nasopharyngeal swab at single time-point. Collected by healthcare workers.	35	37% (23–54%, 13/35)	Low
Hung et al. (2020)	Hong Kong	General population: median age 58 (IQR: 56–61) for positive participants and for negative 64 (IQR: 56–70); 59% female (127/215)	Prospective cohort	Exposed to confirmed case(s) on cruise ship	Questionnaire	Full list unspecified but including chills and rigors, cough, sputum, malaise, myalgia, diarrhoea, rhinorrhoea, and fever	From baseline	14+ days	215	Nasopharyngeal, throat, and rectal swabs at baseline, and Days 4, 8, and 12. Collected by healthcare workers.	9	67% (35–88%, 6/9)	Very low

Reference	Country of study	Participant group description	Study design	Testing criteria	Symptom assessment method	Symptoms included in symptomatic case definition	Length of baseline symptom history	Length of symptom follow-up	Tested <i>n</i>	Test Specimen and Frequency	PCR+ Cases <i>n</i>	Asymptomatic Proportion % (95% CI, <i>n/N</i>)	Risk of Bias
Kennelley et al. (2020)	Ireland	Residents and staff of 28 nursing homes. Further demographic detail unspecified.	Surveillance	National point-prevalence testing programme for nursing homes	Survey	Cough, fever, dyspnoea, and any new-onset symptoms deemed notable by medical officer/general practitioner	7 days	7 days	2718	Nasopharyngeal swab at single time-point. Further details of collection unspecified.	1374	26% (23-28%, 352/1374)	Low
Starling et al. (2020)	UK	Residents of 15 nursing homes ^a ; median age ranged across homes from 36.0-90.5 (range 18-106); sex distribution ranged across homes from 40.0-78.6% female	Surveillance	Local authority point-prevalence testing programme for nursing homes	Interview with care home managers	New continuous cough or fever	From baseline	14 days	441	Upper respiratory tract specimens at single time-point. Collected by healthcare workers.	23	91% (73-98%, 21/23)	Low
Chamie et al. (2020)	USA	General population: 3% 4-10 years (118/3953); 4% 11-17 years (141/3953); 64% 18-50 years (2532/3953); 24% 51-70 years (951/3953); 5% > 70 years (211/3953); 43% female (1699/3953)	Prospective cohort	Resident, bordering, or employed within a local inner-city census-tract area	In-person interview at baseline and follow-up by community team if positive	Unspecified	Unspecified but includes symptoms prior to testing	14 days	3953	Oropharyngeal or mid-turbinate nasal swab at single time-point. Collected by healthcare workers.	80 ^b	29% (20-39%, 23/80)	Low
Ladhani et al. (2020)	UK	Residents and staff of 6 nursing homes: median age for positive participants 85 (78-90) for residents and 47 (38-57) for staff; for negative participants 85 (80-91) for residents and 47 (35-56) for staff; 74% female (386/518)	Surveillance	Exposed to nursing home outbreak	Datasheet and daily phone call with research worker	Fever, persistent cough, sore throat, shortness of breath, anosmia, new-onset confusion, reduced alertness, fatigue, lethargy, reduced mobility, diarrhoea	14 days	14 days	518	Nasal swabs at single time-point. Collected by healthcare workers for residents and self-collected by staff.	158	45% (36-54%, 77/158)	Moderate

^a includes only high-risk contacts isolated and followed-up in France; ^b excludes one case that had history of previous positive test but was negative at facility-wide study testing; ^c excludes one case with negative PCR at baseline and positive PCR at follow-up PCR, as symptom monitoring not possible; ^d not including 19 PCR-positive cases that refused follow-up; ^e demographics only reported for PCR- positive cases; ^f includes one case excluded from present analyses as identified via symptoms and not systematic PCR-testing; ^g only residents included as staff testing was not systematic and was partially based on symptom status; ^h demographics reported for asymptomatic participants only; ⁱ demographics reported for PCR-positive cases or those with clinical abnormalities only; ^j excludes index case and two PCR-positive case without symptom follow-up; ^k demographics for children only but adults included in clinical outcomes; ^l 8 participants excluded because of insufficient data; ^m staff excluded due to requirement to be 'fit to work' biasing sample towards asymptomatic participants; ⁿ excluding 3 PCR-positive participants without symptom status classification/follow-up

Figure 4. Meta-analysis results for COVID-19 asymptomatic proportion in community studies. ES (effect size) = asymptomatic proportion; I^2 = heterogeneity; asymptomatic proportions are given in decimal form.

$p < .001$ $\tau^2 = 0.23$, $I^2 = 95.76\%$) for point prevalence surveys with symptom follow-up and without direct links to outbreaks/cases. Data were limited for studies exclusively involving household contacts or point prevalence surveys (both $n=3$ studies).

The funnel plot (Figure 5) and Egger's test did not indicate publication bias across studies included in the meta-analysis: $t=0.23$, $p=0.82$, 95% CI: -0.97, 1.20.

Viral load and duration of viral shedding

Eight of the twenty-one included studies reported data regarding the CT values/viral load and/or duration of viral shedding for asymptomatic cases versus pre-symptomatic cases and/or those symptomatic from baseline. Differences in methodology and reporting precluded meta-analysis.

Five studies reported CT values and/or genome copy number by symptom status. One of these studies, Hung *et al.*³³, found lower median baseline genome copy number in asymptomatic (3.86 log₁₀ copies/mL) than symptomatic participants (7.62 log₁₀ copies/mL). The remaining four studies all reported similar CT values for asymptomatic and symptomatic participants. Arons *et al.*¹⁸ reported similar baseline median cycle threshold values (CT) for asymptomatic (CT=25.5), pre-symptomatic (CT=23.1), and symptomatic (CT=24.5) cases. Infectious virus was isolated by viral culture from 33% (1/3) of available asymptomatic case specimens, 70.8% (17/24) of pre-symptomatic case specimens, and 65.0% (16/20) for symptomatic case specimens¹⁸. Chamie *et al.* (2020)³⁶ also found that median CT values across samples were not significantly different between asymptomatic (CT=24,

Figure 5. Funnel plot for meta-analysis of COVID-19 asymptomatic proportion in community studies.

IQR: 19-26) and symptomatic individuals (CT=24, IQR: 19-25). Pre-symptomatic individuals appeared to have higher median CT values if seronegative and similar values if seropositive, but numerical detail was not reported overall for this group. Ladhani *et al.* (2020)³⁷ also found no significant difference in baseline CT values between asymptomatic, pre-symptomatic, symptomatic, and post-symptomatic (i.e. reported symptoms in the two weeks prior to positive PCR result) participants; exact values were not provided. Chau *et al.*²¹ also reported similar baseline cycle threshold values for asymptomatic and symptomatic cases, though further numeric detail was not reported. When including all PCR results across follow-up for asymptomatic versus symptomatic cases (including negative PCR results), asymptomatic cases appeared to demonstrate lower CT values overall, which was proposed to indicate faster viral clearance²¹.

Direct investigation of duration of viral shedding was limited. Lombardi *et al.*³⁰ found that median duration from positive test to first negative test was shorter in asymptomatic participants (22 days; IQR: 15–30) than symptomatic ones (29 days; IQR: 24–31), but the difference was not statistically significant. Danis *et al.*²⁰ reported that the single asymptomatic case demonstrated the same viral load dynamics as one of the five symptomatic cases, with respective viral shedding periods of 7 and 6 days.

Age of symptomatic versus asymptomatic cases

Six studies^{21,27,29,31,33,37} reported information regarding the age of asymptomatic versus symptomatic cases. Variation in measurement and reporting precluded meta-analysis. Findings are reported in Table 3. Three studies indicated no significant difference in age between symptomatic and asymptomatic cases, while three studies suggested that asymptomatic cases tended to be younger than those with symptoms. Five studies were conducted in general population samples (contacts/potential contacts of confirmed cases or returning travellers), and one study was conducted in nursing home residents and staff with results stratified for these groups. Only one study²⁹ reported a substantial child sub-sample (<14 years old), and found a higher asymptomatic proportion for infected children (23% $n=10/43$) than adults (7%, $n=8/108$).

Discussion

Accurate estimates of the asymptomatic proportion of SARS-CoV-2 infections depend on appropriate study designs that systematically detect asymptomatic viral shedding and follow these cases up to differentiate truly asymptomatic infections from pre-clinical shedding. We calculated that an overall estimate of 23% of PCR-confirmed SARS-CoV-2 infections in community settings were asymptomatic, with a 95% confidence interval between 16%–30%. These findings do not support claims^{6–8} of a very high asymptomatic proportion

Table 3. Reported findings for age of asymptomatic versus symptomatic cases.

Study	Sample	Findings
Chau <i>et al.</i> (2020)	General public (contacts of confirmed case or returning travellers)	Median age of asymptomatic versus symptomatic participants: 30 (range 16-60) versus 27 (range 18-58)
Yang <i>et al.</i> (2020)	General public exposed to index case on flight	Median age of asymptomatic and symptomatic participants: 26 (IQR: 25.5-26.5) versus 33 (IQR: 29-45) *note: very small asymptomatic sample ($n=2$)
Hua <i>et al.</i> (2020)	General public exposed to household cases or returning from high-risk areas	23% of infected children (≤ 14 years, $n=10/43$) were asymptomatic versus 7% of infected adults ($n=8/108$), with children comprising 56% ($n=10/18$) of asymptomatic cases and adults 44% ($n=8/18$)
Tabata <i>et al.</i> (2020)	General public exposed to outbreak on cruise ship	Median age of asymptomatic versus symptomatic participants: 70 (IQR: 57-75) versus 68 (IQR: 56-74)
Hung <i>et al.</i> (2020)	General public exposed to outbreak on cruise ship	Median age of asymptomatic and symptomatic participants: 57 (IQR: 47-59) versus 68 (IQR: 59-68)
Ladhani <i>et al.</i> (2020)	Nursing home residents and staff	Median age of asymptomatic, post-symptomatic, pre-symptomatic, and symptomatic residents: 84 (IQR: 78-90); 88 (IQR: 85-91); 84 (IQR: 80-91); 87 (IQR: 80-91) Median age of asymptomatic, post-symptomatic, pre-symptomatic, and symptomatic staff: 50 (IQR: 40-56); 54 (IQR: 41-59); 38 (IQR: 34-49); 40 (IQR: 26-55)

for PCR-confirmed infections (up to 80%) and highlight the importance of distinguishing between asymptomatic and pre-symptomatic cases. Heterogeneity in estimates of the asymptomatic proportion, however, was partly influenced by variation between testing contexts. Subgroup estimates range from 6% (95%CI 0-17%) for household contacts, increasing to 23% (95% CI 14-32%) for participants with other epidemiological links to case(s) or outbreaks, and the highest estimate of 47% (95% CI 21-74%) for point prevalence studies not directly linked to contact(s)/outbreaks.

These findings should be interpreted with caution in terms of the relationship between exposure and symptom status³⁸. The assumption that household contacts of index cases may experience frequent and intense exposure with limited protection compared to other groups, and conversely that participants in non-outbreak studies may have more limited exposure, could not be empirically verified in the present review. Confidence intervals for subgroup asymptomatic proportions overlapped substantially, and data were limited for both the household contact and the point prevalence survey with symptom follow-up categories (both $n=3$ included studies). Furthermore, the estimate for point prevalence surveys was affected by one study³⁵ with a very high asymptomatic proportion (91%); this estimate was likely influenced by the limited symptomatic case definition of new-onset cough or fever. Estimates for the other two studies were similar to the 'other epidemiological link' category (26% and 29%). Only one of the point prevalence studies with symptom follow-up³⁶ was conducted in a general population sample. Furthermore, the 'other epidemiological link' category comprised a variety of study

testing contexts, including studies that combined household contacts with participants with less intensive exposure, which likely contributed to substantial within-category heterogeneity. Despite these substantial limitations, further investigation is warranted into variability in the asymptomatic proportion across testing contexts as more data become available.

This effect of study context may partially account for differences between the overall estimate of the asymptomatic proportion in the current review and higher estimates from other studies. Notably, early population-based data collected from English households by the Office for National Statistics suggested that only 22% (95% CI 14-32%) of the 88 individuals who tested positive for COVID-19 thus far reported any symptoms, rising to 29% (95% CI 19-40%) of the 76 individuals tested repeatedly⁸. Similarly, 69% of another English community sample recruited regardless of symptom status reported no symptoms in the seven days up to their positive PCR result³⁹. However, neither of these studies systematically followed-up cases regarding their symptoms across the course of infection, potentially overestimating the asymptomatic proportion and precluding inclusion in this review. Furthermore, findings were affected by the small sample size and consequently wide confidence intervals due to testing at a period of relatively low COVID-19 incidence in the population, as well as potential false positive PCR tests leading to an overestimate of asymptomatic cases. While some of these issues may have impacted studies included in the present review, the careful screening of study design and methodology done as part of this review was reflected in the overall very low or low risk of bias on assessed criteria for all but four included

studies. An additional strength of our review is the systematic search of both peer-reviewed published literature and preprint studies which has enabled us to capture the most up to date estimates available.

Although this review identifies PCR-confirmed cases, PCR-confirmation and symptom-status alone cannot establish whether cases are infectious and, if so, the degree or duration of their infectiousness. Case reports, however, have indicated potential transmission of SARS-CoV-2 from some asymptomatic index cases^{1,2,9,21}. The balance of evidence regarding viral load in the present review indicates that asymptomatic cases had similar baseline or overall median viral loads to pre-symptomatic and symptomatic cases. Virological evidence suggests that infectious SARS-CoV-2 can be isolated by viral culture from samples with cycle threshold values up to 33, though the proportion of infectious virus decreases at higher cycle threshold values (i.e. lower viral load)⁴⁰. While median baseline cycle threshold values for all symptom status groups (23.1-25.5) reported by Arons *et al.*¹⁸ fell well within this limit, infectious virus was isolated from only 33% of asymptomatic baseline samples, compared to 71% of pre-symptomatic and 65% of symptomatic samples. These findings should be interpreted with caution given the very small sample of asymptomatic specimens ($n=3$). Overall, clear reporting of cycle threshold values across follow-up by symptom status was lacking in included studies. This is an important area for further research given that the degree and duration of the infectious period for asymptomatic cases, as well as the overall proportion of virus-shedding cases that are asymptomatic, influence the contribution of asymptomatic cases to SARS-CoV-2 transmission at a population level.

Evidence regarding the duration of SARS-CoV-2 shedding by symptom status was very limited, with two studies suggesting no substantial difference in viral clearance times for asymptomatic and symptomatic cases. Duration of shedding varied widely between participants across all symptom status groups in included studies. The sample of asymptomatic cases in studies that reported duration of viral shedding also tended to be small, and the natural history of viral excretion by symptom status remains unclear. Further inquiry into the degree of preclinical shedding for pre-symptomatic cases, although not the focus of this review, is also warranted. The contribution of asymptomatic and pre-symptomatic cases to the overall spread of infection cannot be accurately inferred in the absence of high-quality evidence assessing the infectiousness of such cases⁴¹.

Evidence was also split regarding age and symptom status, with three studies indicating no difference in age between asymptomatic and symptomatic cases and three studies indicating that asymptomatic cases may tend to be younger than those with symptoms. Samples in the present study – both within the age-related analysis and in the meta-analysis overall – tended to comprise primarily or exclusively of adults, and one study with a substantial child subsample²⁹ found that a larger proportion of infected children were asymptomatic (23%) than

adults (7%). Further comparison of the asymptomatic proportion for children and adults is required.

An important limitation of this review was the variability between symptomatic case definitions across included studies. Only eight of the twenty-one included studies^{18,22–24,30,32,35,37} described the full range of symptoms included within their symptomatic case definitions, while a further ten studies^{19,20,23,25–29,33,34} reported details of symptoms endorsed by participants but did not specify whether or which additional symptoms were assessed as part of their case definitions and three^{17,31,36} provided no detail. While a similar range of symptoms appear to have been monitored/endorsed across most included studies, it is possible that symptomatic case identification may have been affected by reporting bias and consequently that the true proportion of symptomatic cases was underestimated. Notably, Starling *et al.*³⁵ – the study with the highest reported asymptomatic proportion (91%) – used a very limited case definition of new-onset cough or fever. The reported proportion likely reflects individuals not meeting this case definition and excludes cases with other symptom profiles. This issue is particularly relevant given that unusual symptoms such as dysosmia/anosmia – only explicitly investigated by four studies^{21,28,30,37} – and dysgeusia/ageusia – only explicitly investigated by two studies^{28,30} – may be the primary or sole symptom for some COVID-19 cases^{42–44}. Demographic reporting across studies was also limited and it was not possible to stratify findings by further demographic characteristics. Estimates of the asymptomatic proportion may vary across population subgroups and this is a relevant area for future enquiry.

We included only studies with symptom-related follow-up to prevent symptom status misclassification. However, overestimation of the asymptomatic proportion may still occur in contact tracing studies initiated during established outbreaks, such as Graham *et al.*²⁴, if baseline symptomatic participants are classified as index cases and systematically excluded from the asymptomatic proportion. This review was also limited to estimating the asymptomatic proportion of virologically confirmed infections. The asymptomatic proportion of infection varies depending on whether infections are identified using virological or serological methods⁴⁵. PCR confirmation, which identifies infection with viral shedding, is informative for modelling transmission potential. However, review of the asymptomatic proportion of total infections based on emerging serological evidence – which identifies infections regardless of viral shedding – will be informative to understand how far SARS-CoV-2 has spread within populations and investigate evidence of immunity following asymptomatic infection⁴⁶.

Overall, this review provides preliminary evidence that, when investigated using methodologically appropriate studies, a substantial minority of SARS-CoV-2 infections with viral shedding are truly asymptomatic. These findings indicate that testing should not be exclusively limited to symptomatic individuals. Further research identifying distinguishing features

(e.g. age) and testing contexts for truly asymptomatic cases, as well as their transmission potential, is recommended to inform testing programmes. These findings also highlight the importance of other public health measures, such as promoting social distancing and wearing face coverings in public places, regardless of symptom status.

Data availability

Underlying data

University College London Research Data Repository: A Rapid Review and Meta-Analysis of the Asymptomatic Proportion of PCR-Confirmed SARS-CoV-2 Infections in Community Settings. <http://doi.org/10.5522/04/12344135.v3>⁴⁷.

This project contains the following underlying data:

- Asymptomatic meta-analysis V2.csv. (Data used to conduct meta-analysis of asymptomatic proportion.)

Reporting guidelines

University College London Research Data Repository: PRISMA checklist for 'A rapid review and meta-analysis of the asymptomatic proportion of PCR-confirmed SARS-CoV-2 infections in community settings'. <http://doi.org/10.5522/04/12344135.v3>⁴⁷.

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Study Summary

This study is a rapid review and meta analysis aiming to estimate the proportion of PCR-confirmed SARS-CoV-2 cases that have symptoms. They searched online databases for relevant studies and identified 21 studies. Asymptomatic proportion ranged from 6% (95% CI 0-17%) -47% (95% CI 21-75%) for household contact and point prevalence surveys respectively. The authors conclude that a substantial proportion of cases are asymptomatic.

Major comments

Search criteria – I wonder if restricting to studies with the word asymptomatic in title or abstract may be too restrictive – for example a study might report the symptomatic fraction and be missed by this review. How were the terms chosen and was there any validation done to see if you might be missing important studies?

While it takes time to compile these studies there may be numerous additional studies since your period which seems to be until 2020 (so no papers from 2021?) just and as an examples I list 2 highly relevant papers which should meet your criteria and there are likely many others. I would propose the review to be updated and certainly if this is not done that it be strongly brought out in the limitations.

Dawood FS, Varner M, Tita A, et al. Incidence, Clinical Characteristics, and Risk Factors of SARS-CoV-2 Infection among Pregnant Individuals in the United States. *Clin Infect Dis*. August 2021. doi:10.1093/cid/ciab713¹

Dawood FS, Porucznik CA, Veguilla V, et al. Incidence Rates, Household Infection Risk, and Clinical Characteristics of SARS-CoV-2 Infection Among Children and Adults in Utah and New York City, New York. *JAMA Pediatr*. October 2021. doi:10.1001/jamapediatrics.2021.4217²

I am also aware of this systematic review of similar question – there may be others. In the discussion you should compare your findings to other systematic reviews and discuss why your results may differ

Buitrago-Garcia D, Egli-Gany D, Counotte MJ, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. *PLoS Med.* 2020;17(9):e1003346. doi:10.1371/journal.pmed.1003346³

The symptomatic fraction may differ for SARS-CoV-2 variants, did you account for this in the analysis? I don't see any discussion of this and yet if some variants eg. Delta are associated with more severe illness, similar effects might be expected on symptomatic fraction. Suggest reporting the period and predominant variants for each study and discussing this also and whether it could account for some heterogeneity. If all the included studies are from the pre-variant period then this should be discussed.

To note over representation of high income countries in the included studies and none from Africa. Please discuss this as studied settings may not be representative of much of the worlds population. Also the relatively small number of included studies should be mentioned.

Minor comments

Abstract – if space allows suggest adding in a comment as to the representivity of studies identified eg geographic spread.

Your discussion about serologic studies does not make sense to me. You seem to be implying that some people who seroconvert may never actually shed virus and while this is possible as a hypothesis it is not established whether this does occur. Similarly figure 2 doesn't make sense to me for the same reason. It seems to me the bigger issue with serologic studies would be people not PCR tested with sufficient frequency and that the infection could have occurred any time prior and there was no active symptom ascertainment at the time of infection.

Table 1 as written its not entirely clear what you mean by effect estimate biased up or down – suggest add a footnote to clarify what the effect estimate is or state it in brackets. This can be very confusing in these studies as some people thinking of symptomatic fraction and others asymptomatic fraction.

The inclusion of nursing home samples could have biased symptomatic fraction upwards or downward as may be older and more frail. Please discuss this.

References

1. Dawood FS, Varner M, Tita A, Newes-Adeyi G, et al.: Incidence, Clinical Characteristics, and Risk Factors of SARS-CoV-2 Infection among Pregnant Individuals in the United States. *Clin Infect Dis.* 2021. [PubMed Abstract](#) | [Publisher Full Text](#)
2. Dawood F, Porucznik C, Veguilla V, Stanford J, et al.: Incidence Rates, Household Infection Risk, and Clinical Characteristics of SARS-CoV-2 Infection Among Children and Adults in Utah and New York City, New York. *JAMA Pediatrics.* 2022; **176** (1). [Publisher Full Text](#)
3. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, et al.: Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. *PLoS Med.* **17** (9): e1003346 [PubMed Abstract](#) | [Publisher Full Text](#)

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Partly

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease epidemiology, Influenza, SARS-CoV-2, respiratory disease transmission and burden

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 08 March 2021

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Beale S. *et al.* conducted a systematic review to estimate asymptomatic proportion of PCR-confirmed cases in community settings, explore viral load and duration of viral shedding among different symptom status, and preliminarily examine the relationship between symptom status and age. The review has clear goals on the study settings - only focus on community settings to prevent selection bias towards symptomatic cases; only on PCR-confirmed to focus on current infection with viral shedding (not serological only studies). The review generally had a rigorous screening process and statistical analysis. Some definitions are clearly defined in the paper, for example, using Figure 1 to differentiate the definitions of asymptomatic v.s. Presymptomatic status; Table 1 defines the potential biases. The stratified analysis on different settings (household v.s. Community settings v.s point prevalence studies) is very interesting and the heterogeneity behind them is worthy of a good discussion. The manuscript is well-written. But several concerns exist.

Major concerns:

1. Asymptomatic case definition is a critical point in this review, which could be mainly affected by the included symptoms of COVID-19 in the original studies and the length of symptom follow-up. The definitions can be different in different studies -- Table 2 showed so. Though in the discussion, the authors explained a bit about the impacts or limitations of different definitions in different studies on the estimation of the asymptomatic proportion. However, some further "sensitivity" analysis can be done to explore the potential impacts. For example, in Table 2, some studies are followed up by 14 days; some are only 7 days; some are unclear. How would this difference affect the estimation of asymptomatic proportion? A stratified analysis based on the length of symptom follow-up can be conducted; or just focus on the high quality of sufficient follow-up time to have a sense of the impacts. Furthermore, in the methods, the definition of asymptomatic status is only described as the "remained asymptomatic through follow-up", which is very vague until reading Table 2. Please make sure to clarify the different definitions in these included studies.
2. Although the risk of bias is assessed, the quality assessment of each study is not thorough. For example, not only these potential biases will impact the quality of the study, but also the types of study designs, length of follow up, and testing frequency can critically impact the goal of the review. For example, the Arons *et al.* (2020) paper in Table 2, with serial point prevalence survey and only 7 day of follow-up, may not be the same quality compared to Luo *et al.* (2020) with prospective study design and follow up for 2 consecutive negative swabs, etc.
3. How would the two ways of calculating asymptomatic proportions in Figure 2 impact the evaluation of the asymptomatic proportion?
4. To avoid confusion, that PCR positive is not a direct measure of viral shedding (or transmissibility) should be mentioned in the methods not only in the discussions.
5. Another thing is that the interpretation of Ct value to represent viral load (or more accurately to say the amount of genetic materials in each sample) should be cautious. Ct value is a relative concept - it is very lab specific. Comparing across different studies may not be accurate.
6. The discussion on the different proportions based on different testing contexts can dig a bit deeper. For example, are these differences real? Or due to the nature of the study designs? Are point prevalence surveys tend to overestimate the asymptomatic proportion because of unrigorous follow up?
7. The systematic review has understandably delays on the updated information due to the process of reviewing a large body of literature, however, in the discussion, it is necessary to include/compare with some new and important studies to inform these related questions. For example, Buitrago-Garcia's study also reported asymptomatic proportion¹; Cevik *et al* study on the viral load and viral shedding²; Davies's studies on age and symptom status³.

Minor issues:

1. Figure 4. Heterogeneity is not reported. I^2 is a notation under the legend, but not used in the figure.

2. Figure 5 needs more legends to explain the x-axis and y-axis of the figure.

References

1. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, et al.: Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. *PLoS Med.* **17** (9): e1003346 [PubMed Abstract](#) | [Publisher Full Text](#)
2. Cevik M, Tate M, Lloyd O, Maraolo A, et al.: SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *The Lancet Microbe.* 2021; **2** (1): e13-e22 [Publisher Full Text](#)
3. Davies NG, Klepac P, Liu Y, Prem K, et al.: Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nat Med.* **26** (8): 1205-1211 [PubMed Abstract](#) | [Publisher Full Text](#)

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Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious disease epidemiology, study designs, pathogen molecular evolution and population dynamics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.