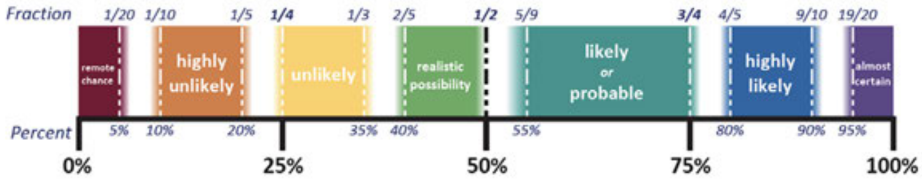
PHIA probability yardstick – to be used when expressing likelihood or confidence



A Rapid Review of the Asymptomatic Proportion of PCR-Confirmed SARS-CoV-2 Infections in Community Settings

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Abstract

Background: Up to 80% of active SARS-CoV-2 infections are proposed to be asymptomatic based on cross-sectional studies. 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 current evidence regarding 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 prior to 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.

Findings: We screened 1138 studies and included 22. The pooled estimate for the asymptomatic proportion of SARS-CoV-2 infections was 28% (95% CI 20%-35%). Estimates of viral load and duration of 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 was limited. Evidence of the relationship between age and symptom status was inconclusive.

Interpretation: Asymptomatic virus shedding comprises a substantial minority of SARS-CoV-2 infections when estimated using methodologically-appropriate studies. Further investigation into the degree and duration of infectiousness for asymptomatic infections and demographic predictors of symptom status is warranted.

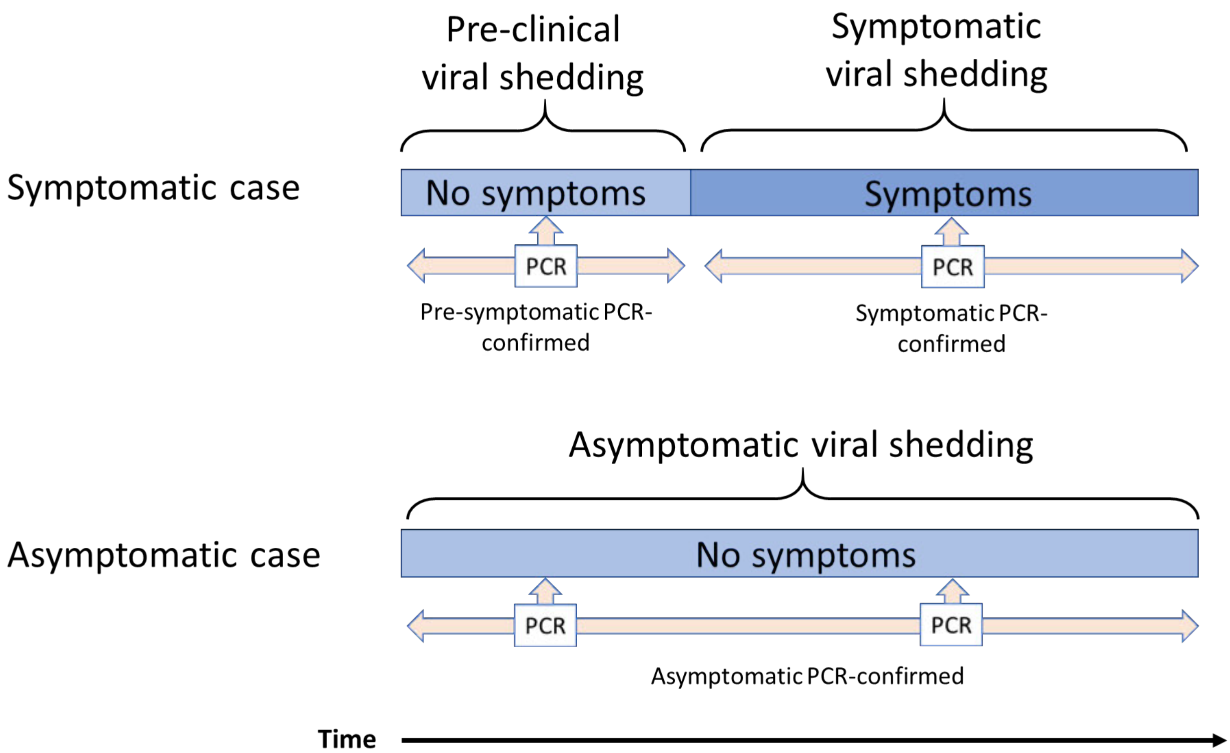
Background

Reports of asymptomatic SARS-CoV-2 infection and potential transmission[1,2,3] have generated concern regarding the implications of undetected asymptomatic transmission on the effectiveness of public health interventions in the current COVID-19 pandemic[4]. 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 individuals[5]. Furthermore, longitudinal designs that include symptom follow-up are required to differentiate truly asymptomatic cases, i.e. those that never develop symptoms during illness, from pre-symptomatic cases, i.e. those that shed virus and therefore test positive prior to symptom onset (see Figure 1). While asymptomatic virus shedding has been suggested to comprise up to ~80% of SARS-CoV-2 infections [6,7,8], 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 infections. Detectible 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 infectiousness [9]; 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 symptomatic status (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.

Figure 1. *Timeline of Symptom Development and Viral Shedding in Relation to Timing of Virological Testing*



Note: This figure demonstrates two trajectories of symptom development in cases with detectable viral shedding. The symptomatic case trajectory comprises a period of pre-clinical virus 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).

Methodology

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

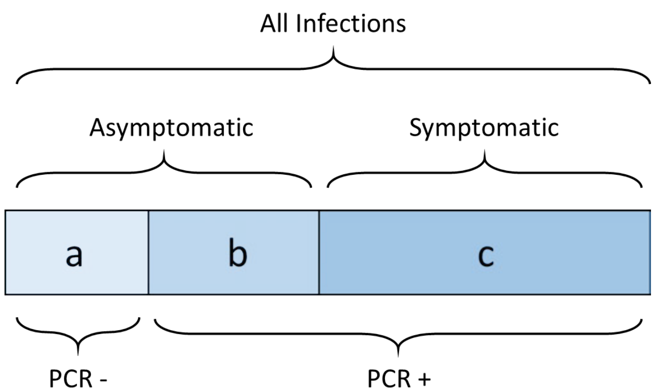
We included studies that met all of the following criteria: 1) human study; AND 2) presented original research or public health COVID-19 surveillance data; AND 3) available in English; AND 4) presented data on polymerase chain reaction (PCR) confirmed COVID-19 cases; AND 5) presented data on PCR testing 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, cruise ships or workplaces). 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 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, 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* programme[13] 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 intervals [14]. 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). We report 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.

Figure 2. *Summary Classification of Clinical and PCR Outcomes and Calculation of Asymptomatic Proportions*



Asymptomatic Proportion among PCR+ cases $= \frac{b}{b+c}$

Asymptomatic Proportion among all infections (requires serology) $= \frac{a+b}{a+b+c}$

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 studies[15] (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.

Table 1. *Risk of Bias Assessment*

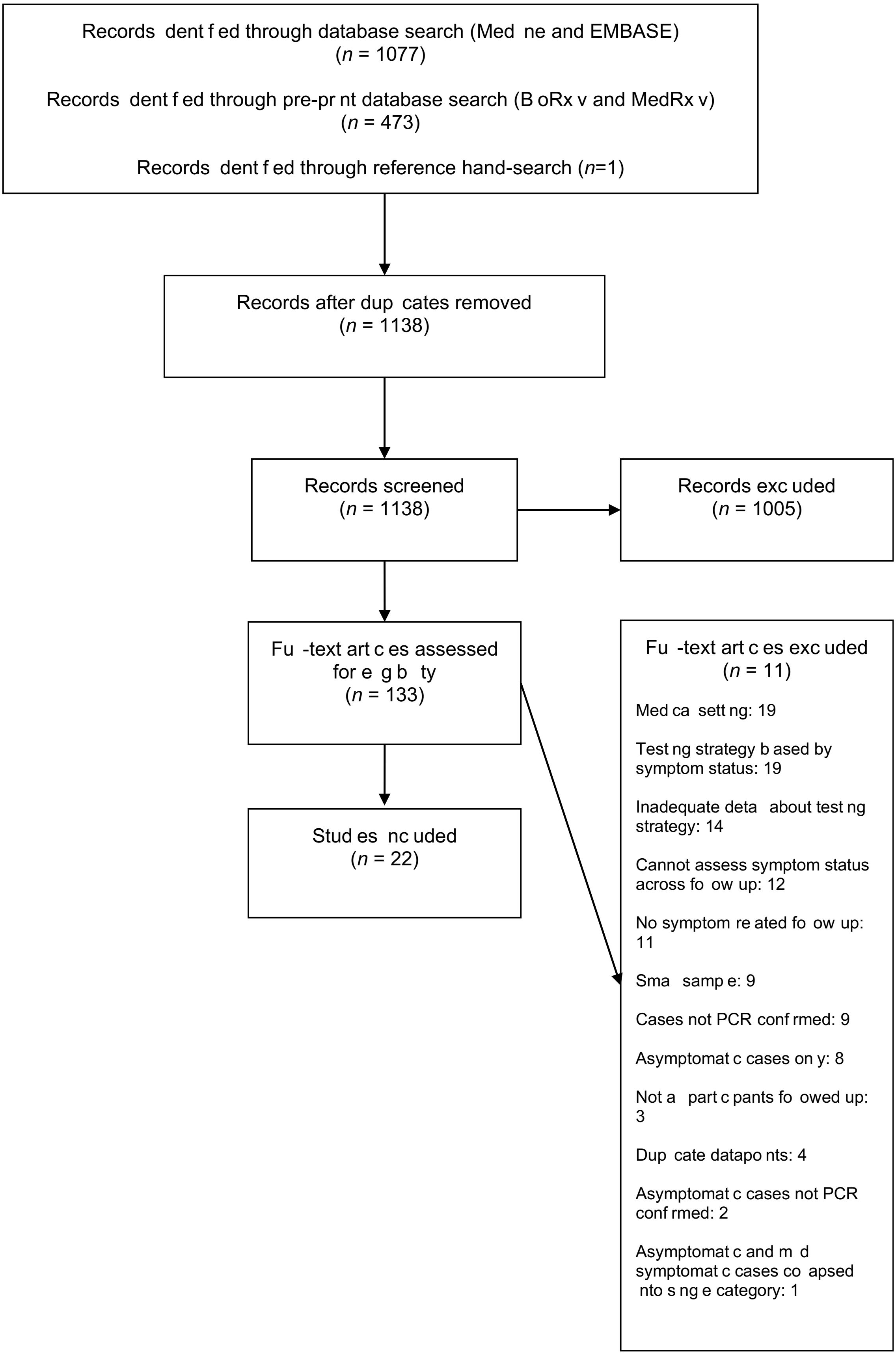
Potential Issue	Direction of Bias
Information Bias: Initial testing does not identify all infected people shedding virus	Effect estimate could be biased downwards if PCR testing is more likely to detect symptomatic shedders compared to asymptomatic shedders. This could be because asymptomatic cases shed 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

Results

Records Identified

Figure 3 presents an adapted PRISMA flow diagram[16] 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 hand-search of the literature – and included 22 in the present review [17-38] , including 13 studies from general population samples potentially exposed to confirmed cases [17,20, 22, 23, 25,26,28,29,32,34,37] and/or returning from travel to high-risk countries[21,30], 7 studies based in nursing homes [18,19,24,33,35,36,38] , and 2 studies of healthcare workers with occupational exposure to confirmed cases[27,31].

Figure 3. *Adapted PRISMA Flow Diagram of Study Selection*



Asymptomatic Proportion of PCR-Confirmed COVID-19 Cases 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., 2020[29]) to 91% (95% CI 73%-98%; Starling et al., 2020[36]). 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 28% (95% CI 20%-35%; 95% prediction interval 0-62%). There was high heterogeneity: $Q(23)= 588.05$ $p<.001$, $\tau^2= 0.03$, $I^2= 96.43\%$ (Figure 4).

Viral Load and Duration of Viral Shedding

Nine of the twenty-four 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. (2020)[34], 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. (2020)[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 specimens[18]. Chamie et al. (2020)[37] also found that median CT values across samples were not significantly different between asymptomatic (CT=24, 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)[38] 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. (2020)[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 clearance[21].

Duration of viral shedding was directly investigated by a further three studies. Lombardi et al. (2020)[31] found that median duration from positive test to first negative test was shorter is asymptomatic participants (22 days; IQR: 15–30) than symptomatic ones (29 days; IQR: 24–31), but the difference was not statistically significant. Zhao et al. (2020)[27] found that median duration of viral shedding was shorter in asymptomatic and pre-symptomatic participants (16.4 day, IQR: 7–28) – who were combined in a single category for this analysis – than participants who developed severe or critical symptoms (28 days, IQR: 20.3–35), but similar to mild/moderate symptomatic participants (16.8 days, IQR: 7–25.2). The remaining two studies indicated similar duration of viral shedding for asymptomatic and symptomatic participants. Danis et al. (2020)[20] reported that the 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[21,28,30,32,34,38] reported information regarding the age of asymptomatic versus symptomatic cases. Variation in reported measures precluded meta-analysis and findings are presented in an effect direction plot (Table 3). Three studies indicated no significant difference in age between symptomatic and asymptomatic cases, while three studies indicated that asymptomatic cases tended to be younger than those with symptoms. Five studies were conducted in general population samples (contacts/potential contacts of confirmed case or returning travellers), and one study was conducted in nursing home residents and staff with results stratified for these groups. Only one study[30] 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).

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 *n*	Test Specimen and Frequency	PCR+ Cases *n*	Asymptomatic Proportion % (95% CI, *n/N)*	Risk of Bias
Park et al. (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 et al. (2020)	USA	Nursing home residents: 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[b]	6% (2-17%, 3/47)	Low

Roxby et al. (2020)	USA	Nursing home residents: mean age = 86 (range 69-102); 77% female (62/80) Nursing home staff: 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 et al. (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 et al. (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 et al. (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
Chaw et al. (2020)	Brunei	General public: median age 33 (IQR = 29.5); 35% female (*n*=25/71) [e]	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	71	13% (7-22%, 9/71)	Low

										worker) unspecified.			
Graham et al. (2020)	United Kingdom	Nursing home residents: median age 83 (IQR= 15); 62% female (*n*=246/394) [g]	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 (re)tested one week later. Collected by healthcare workers.	126*	35% (27-44%, 44/126)	Moderate
Wang et al. (2020)	China	General population: mean age 39.3 (SD=16.5); 46% female (*n*=29/63) [h]	Surveillance	Exposed to index case(s)	Medical reports	Full list unspecified but including cough, fever, short of breathless 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 et al. (2020)	China	General population: median age 43.5 (IQR= 35.8-62.3) for	Surveillance	Exposed to index case(s)	Internet-based questionnaires	Fever, cough, shortness of breath, diarrhoea or other common symptoms (including expectoration, haemoptysis, sore	Since exposure event	21 days	143	Nasopharyngeal and/or oropharyngeal swabs (at Day 1, 7, and 14 for	48	10% (5-22%, 5/48)	Low

		secondary cases and 37 (IQR= 14.5-58) for non-cases. 56% female *n*=80/143)				throat, nasal obstruction, runny nose, sneeze, headache, muscle ache or fatigue)				asymptomatic cases and up to 3-day intervals if showed symptoms). Collected by healthcare workers.			
Zhao et al. (2020)	China	Healthcare workers: median age 31 (IQR: 30-32); 76% female (67/88)[i]	Retrospective cohort	Exposed occupationally to suspected symptomatic cases including some confirmed case(s)	Questionnaire	Mild or worse fever (>37.5 °C), fatigue, and mild or worse dry cough, sore throat, shortness of breath, muscle ache, headache, diarrhoea, and vomiting	From date of first symptom onset (if any)	14+ days	908	Nasopharyngeal swab (at Days 7 & 14 for negative cases and every 2 days for positive cases). Collected by healthcare workers.	38	71% (55-83%, 27/38)	Moderate
Yang et al. (2020)	China	General population: median age 32 (IQR:26-33); 78% female (7/9)[e]	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 [j]	22% (6-55%, 2/9)	Low
Yousaf et al. (2020)	USA	General population: 35% (69/195) <18 years, 46% (89/195) 18-49 years, 15% (29/195) 50-64 years, 4% (8/195) 65+ years; 51%	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,	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

		female (99/195)				nausea/vomiting, diarrhoea, and abdominal pain							
Hua et al. (2020)	China	General population: mean age 8.16 (SD: 4.07); 39% female (17/43) [k]; 39% children (<14 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);	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	Unclear for study. 3711 tested on ship but	Pharyngeal swabs or sputum specimens. Further details of collection unspecified.	104	59% (55-62%, 33/104)	Low

		48% female (50/104)[e]						days (IQR: 7-10)	not all isolated in study facility.					
Patel et al. (2020)	USA	Nursing home residents: median age 82 (IQR: 72-92); 69% female (24/35) [m]	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.	29	45% (28-62%, 13/29)	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	
Kennelley et al. (2020)	Ireland	Nursing home residents and staff. 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	Nursing home residents [n]: 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[o]	29% (20-39%, 23/80)	Low

Ladhani et al. (2020)	UK	Nursing home residents and staff: 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)	Very low

[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-postive 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] includes residents identified due to symptoms, who were excluded from the asymptomatic analyses for this study (only 118 tested regardless of symptom status included here); [n] staff excluded due to requirement to be 'fit to work' biasing sample towards asymptomatic participants; [o] excluding 3 PCR-positive participants without symptom status classification/follow-up

Figure 4. *Meta-Analysis Results for COVID-19 Asymptomatic Proportion in Community Studies*

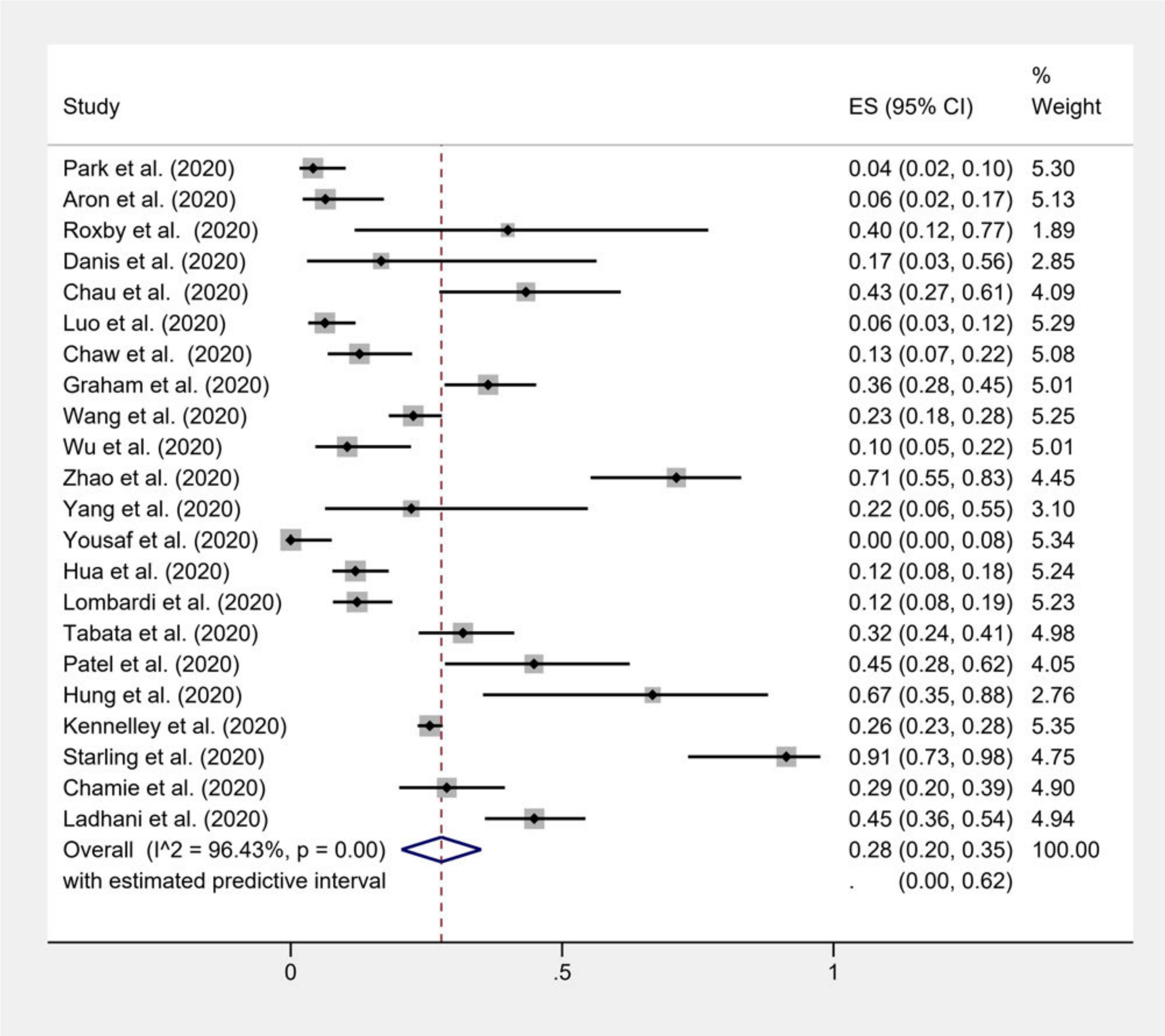


Figure 4 Note: ES (effect size) = asymptomatic proportion; I^2 = heterogeneity

Table 3. *Effect Direction Plot for Age of Asymptomatic and Symptomatic Cases*

Study	Sample	Findings	Effect Direction
Chau et a . (2020)	Genera pub c (contacts of conf rmed case or return ng trave ers)	Med an age of asymptomat c versus symptomat c part c pants: 30 (range 16-60) versus 27 (range 18-58)	◄►
Yang et a . (2020)	Genera pub c exposed to ndex case on f ght	Med an age of asymptomat c and symptomat c part c pants: 26 (IQR: 25.5-26.5) versus 33 (IQR: 29-45) *note: very sma asymptomat c samp e (*n*=2)	▼
Hua et a . (2020)	Genera pub c exposed to househo d cases or return ng from h gh-r sk areas	23% of nfected ch dren (≤14 years, *n*=10/43) were asymptomat c versus 7% of nfected adu ts (*n*=8/108), w th ch dren compr s ng 56% (*n*= 10/18) of asymptomat c cases and adu ts 44% (*n*= 8/18)	▼
Tabata et a . (2020)	Genera pub c exposed to outbreak on cru se sh p	Med an age of asymptomat c versus symptomat c part c pants: 70 (IQR: 57-75) versus 68 (IQR: 56-74)	◄►
Hung et a . (2020)	Genera pub c exposed to outbreak on cru se sh p	Med an age of asymptomat c and symptomat c part c pants: 57 (IQR: 47–59) versus 68 (IQR: 59–68)	▼
Ladhan et a . (2020)	Nurs ng home res dents and staff	Med an age of asymptomat c, post-symptomat c, pre-symptomat c, and symptomat c res dents: 84 (IQR: 78-90); 88 (IQR: 85-91); 84 (IQR: 80-91); 87 (IQR: 80-91) Med an age of asymptomat c, post-symptomat c, pre-symptomat c, and symptomat c staff:	◄►

		50 (IQR: 40-56); 54, (41-59); 38 (IQR 34-49); 40 (IQR: 26-55)	

Note: ◄► = no difference; ▼ = asymptomatic group younger; all ages given in years

Discussion

Accurate estimates of the asymptomatic proportion of SARS-CoV-2 infections depend on appropriate study designs that systematically detect asymptomatic virus-shedding and follow these cases up to differentiate truly asymptomatic infection from pre-clinical shedding. We calculated that 28% of PCR-confirmed SARS-CoV-2 infections in community settings were asymptomatic, with a 95% confidence interval between 20%-35%. These findings do not support claims [6,7,8] of a very high asymptomatic proportion for PCR-confirmed infections (up to 80%) and highlight the importance of distinguishing between asymptomatic and pre-symptomatic cases. 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 repeatedly[8]. However, these cases had not been systematically followed-up regarding symptoms across the course of illness, potentially overestimating the asymptomatic proportion. More recently questionnaires have been changed to capture symptoms over the week prior to testing. This should allow more confidence that symptoms are captured. Although the more recent data is not yet in the public domain it is reported that the change in methodology has not impacted on the proportion estimated to be asymptomatic. (Personal communication Sarah Walker). Furthermore, findings are affected by the small number of positive cases and consequently wide confidence intervals due to testing at a period of relatively low COVID-19 incidence in the population. While some of these issue 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 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)[39]. While median baseline cycle threshold values for all symptom status groups (23.1-25.5) reported by Arons et al. (2020)[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 inconclusive, with the majority of studies suggesting no significant difference in viral clearance times for asymptomatic and symptomatic cases. One study suggested that asymptomatic cases may have more rapid viral clearance than those that develop severe, but not mild, symptoms[32]. 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 cases[40].

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 subsample[30] 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.

Only nine of the twenty-two included studies[18,22-24,27,31,33,36,38] described the full range of symptoms included within their symptomatic case definitions, while a further ten studies[19,20,23,25,26,28,29,30,34,35] 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[17,32,37] provided no detail. While a similar range of symptoms appear to have been monitored/endorsed across 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. This is particularly relevant given that unusual symptoms such as dysosmia/anosmia - only explicitly investigated by four studies[21,29,31,38] - and dysgeusia/ageusia -only explicitly investigated by two studies[29,31] - may be the primary or sole symptom for some COVID-19 cases [41-43]. 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 Zhao et al. (2020)[27.], if baseline symptomatic participants are classified as index cases and systematically excluded from the asymptomatic proportion. Removing this study did not substantially impact the overall estimate or heterogeneity, with a pooled asymptomatic proportion of 26% (95% CI: 18-33%, 95% prediction interval: 0-59%, I^2=96.24%).

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 methods[44]. 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 infection[45]. 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.

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** indicates inclusion in current meta-analysis*

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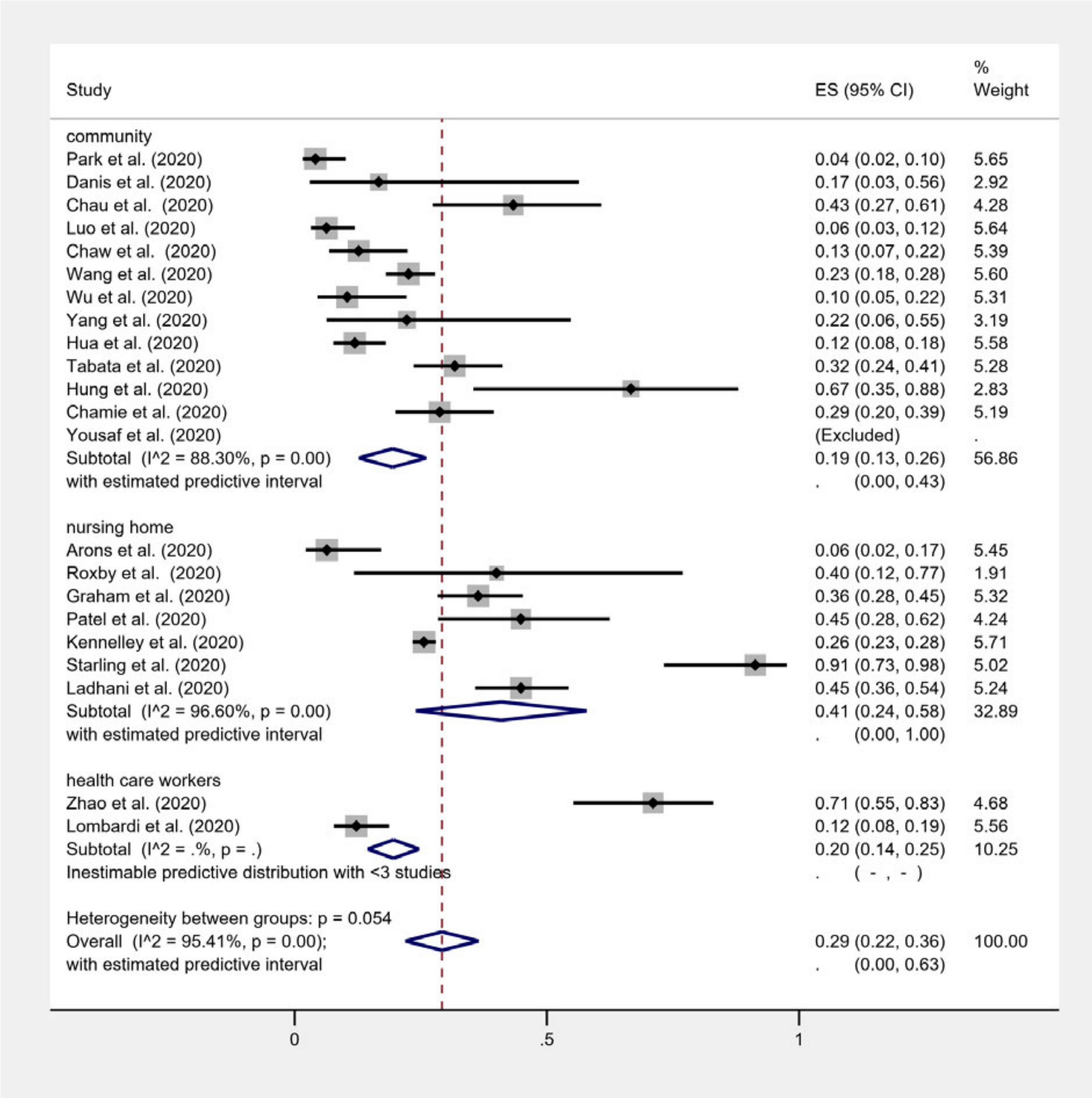
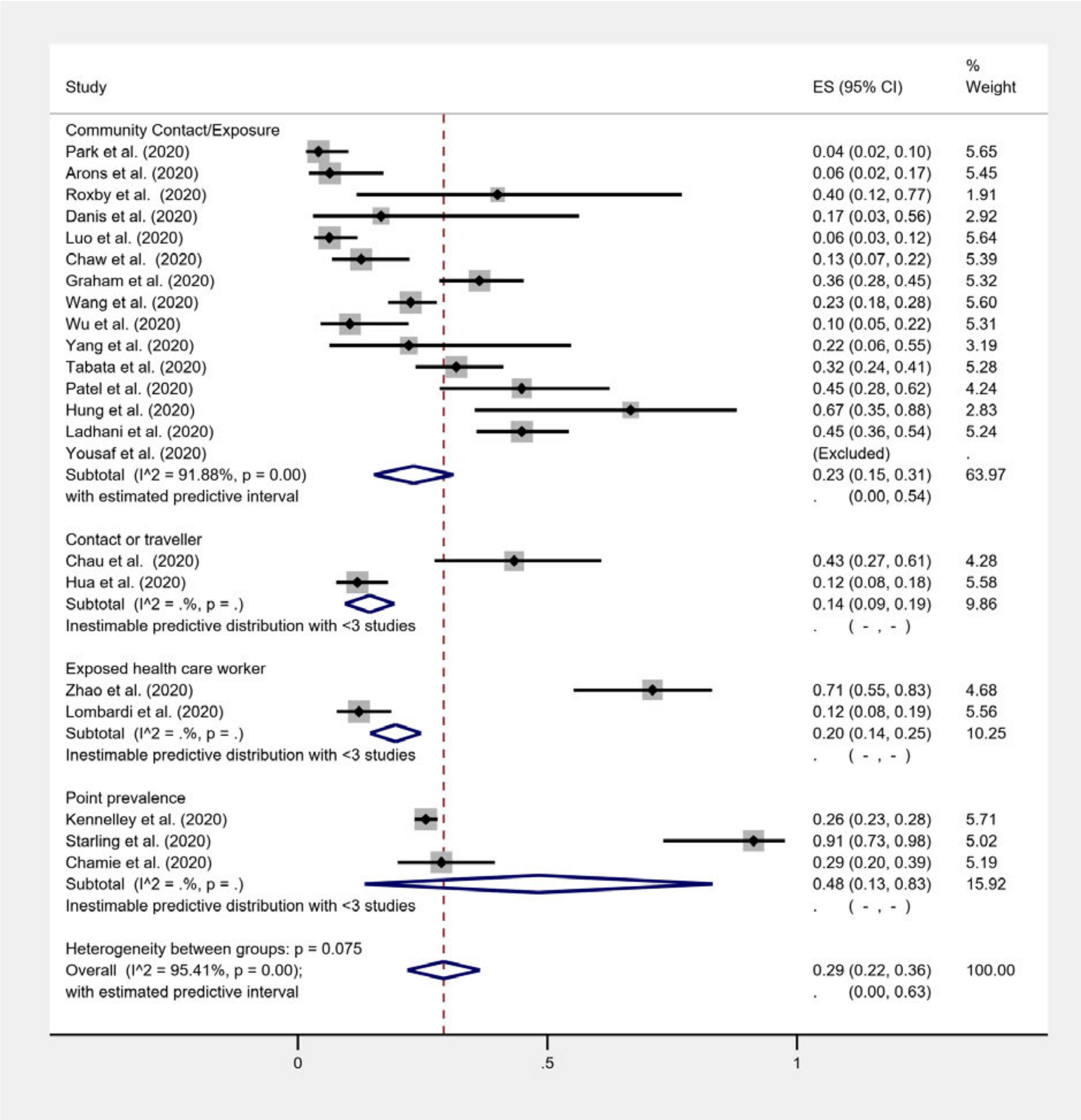
Appendix A - Stratified Analyses

NOTE TO NERVTAG: These analyses are a work in progress. Yousaf et al. (2020) requires a continuity correction and will not be excluded from the final version; this also accounts for small discrepancies in the pooled statistics to those reported above. Age is currently classified according to mean, median, or distribution of proportions across age categories. Older adults are currently defined as average sample age >50.

Forest Plot of Asymptomatic Proportion by Study Setting



Forest Plot of Asymptomatic Proportion by Testing Criteria


Study
ES (95% CI)
% Weight
Community Contact/Exposure
Park et al. (2020) 0.04 (0.02, 0.10) 5.65
Arons et al. (2020) 0.06 (0.02, 0.17) 5.45
Roxby et al. (2020) 0.40 (0.12, 0.77) 1.91
Danis et al. (2020) 0.17 (0.03, 0.56) 2.92
Luo et al. (2020) 0.06 (0.03, 0.12) 5.64
Chaw et al. (2020) 0.13 (0.07, 0.22) 5.39
Graham et al. (2020) 0.36 (0.28, 0.45) 5.32
Wang et al. (2020) 0.23 (0.18, 0.28) 5.60
Wu et al. (2020) 0.10 (0.05, 0.22) 5.31
Yang et al. (2020) 0.22 (0.06, 0.55) 3.19
Tabata et al. (2020) 0.32 (0.24, 0.41) 5.28
Patel et al. (2020) 0.45 (0.28, 0.62) 4.24
Hung et al. (2020) 0.67 (0.35, 0.88) 2.83
Ladhani et al. (2020) 0.45 (0.36, 0.54) 5.24
Yousaf et al. (2020) (Excluded) .
Subtotal (I^2 = 91.88%, p = 0.00) 0.23 (0.15, 0.31) 63.97
with estimated predictive interval . (0.00, 0.54)
Contact or traveller
Chau et al. (2020) 0.43 (0.27, 0.61) 4.28
Hua et al. (2020) 0.12 (0.08, 0.18) 5.58
Subtotal (I^2 = .%, p = .) 0.14 (0.09, 0.19) 9.86
Inestimable predictive distribution with <3 studies . (- , -)
Exposed health care worker
Zhao et al. (2020) 0.71 (0.55, 0.83) 4.68
Lombardi et al. (2020) 0.12 (0.08, 0.19) 5.56
Subtotal (I^2 = .%, p = .) 0.20 (0.14, 0.25) 10.25
Inestimable predictive distribution with <3 studies . (- , -)
Point prevalence
Kennelley et al. (2020) 0.26 (0.23, 0.28) 5.71
Starling et al. (2020) 0.91 (0.73, 0.98) 5.02
Chamie et al. (2020) 0.29 (0.20, 0.39) 5.19
Subtotal (I^2 = .%, p = .) 0.48 (0.13, 0.83) 15.92
Inestimable predictive distribution with <3 studies . (- , -)
Heterogeneity between groups: p = 0.075
Overall (I^2 = 95.41%, p = 0.00); 0.29 (0.22, 0.36) 100.00
with estimated predictive interval . (0.00, 0.63)
0
.5
1

Forest Plot of Asymptomatic Proportion by Primary Age Group of Study