

## NERVTAG paper: Asymptomatic SARS-CoV-2 infection

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### Summary

#### 1. Reason for bringing to SAGE

- Understanding of the proportion of SARS-CoV-2 infections that are asymptomatic or paucisymptomatic and the relative infectiousness of asymptomatic / paucisymptomatic infections versus symptomatic infections is important for modelling purposes and screening/return to work policies.
- Note that this paper is not addressing the proportion of a group of people who are asymptomatic and infected, which will vary with the infection prevalence and setting (e.g. institutional outbreak).

#### 2. Key conclusions of the paper (and level of confidence in these)

- Asymptomatic / paucisymptomatic SARS-CoV-2 infection does occur (high confidence);
- The proportion of infections that are asymptomatic / paucisymptomatic may vary by age, with an increasing proportion of infections being symptomatic with increasing age (moderate confidence), however this may decline again in the oldest age groups.<sup>1</sup>

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<sup>1</sup> <https://www.medrxiv.org/content/10.1101/2020.03.24.20043018v2>

- Estimates of the proportion of infections that are asymptomatic / paucisymptomatic vary very widely, between 4% and 50%. Some of the highest estimates are from nursing home studies, and information on the completeness of follow up data are not always available. In elderly nursing home residents, symptoms may be difficult to ascertain.
- Current data (see summary table) suggest that the proportion of infections that are asymptomatic / paucisymptomatic is likely to be in the range of 10-35% (moderate confidence).

### Summary table

Paper	Source		Proportion of infections asymptomatic			
I	Beale et al	Meta analysis	11% of PCR-confirmed COVID-19 cases were truly asymptomatic with a 95% confidence interval between 4% -18%.			
II	Buitrago-Garcia et al	Meta analysis	Estimated an upper bound for the proportion of asymptomatic SARS-CoV-2 infections of 29% (95% confidence interval 23 to 37%)			
NA	PHE data on Easter 6 nursing homes	Care home cohort of residents	Of the 268 residents, 107 (49.1%) were SARS-COV-2 positive and 51/107 (47.7%) did not develop any symptoms during the two weeks before or after swabbing 16 (15.0%) were pre- symptomatic and 12 (11.2%) were post-symptomatic.			
		Care home cohort of staff	Of the 51 SARS-CoV-2 positive staff members, 26 (51.0%) did not develop any symptoms in the two weeks before or after the swab, 4 (7.8%) were pre-symptomatic and 11 (21.6%) were post-symptomatic.			
NA	Sheffield NHS Trust data on HCW screening	HCW screening, with 14 days follow up after PCR test.		n	% of positives (n=22)	% of total (n=1660)
			Symptomatic	9	41%	0.54%
			Pre-symptomatic	8	36%	0.48%
			True asymptomatic	5	<u>23%</u>	0.30%
			Total positives	22	-	1.33%

- The proportion of infections that are asymptomatic / paucisymptomatic may change over time as individuals are re-exposed to SARS-CoV-2 and the severity of infection is moderated by prior exposure to SARS-CoV-2;

- Data are variable, but RT-PCR cycle threshold values over time are either similar or lower in asymptomatic / paucisymptomatic infections compared to symptomatic infections <sup>2,3,4,5</sup>
- If it is assumed that lower viral loads as determined by RT-PCR cycle threshold values correlate with infectiousness, and symptoms such as coughing increase the risk of transmission via respiratory droplets, the infectiousness of asymptomatic / paucisymptomatic infections is likely lower than symptomatic infections (low confidence) but at this time a numerical value cannot be put on this.

3. What are the key questions to be considered by SAGE?

- See below.

4. Recommendations or proposed next steps (if any)

- Since the detection of RNA through a PCR test can be prolonged but does not necessarily indicate the presence of infectious virus, longitudinal studies of infectiousness are needed. These could be done in the context of HCW screening programmes.
- Such studies should consider serial viral culture, sub-genomic RNA detection (to detect RNA indicative of viral replication), and parallel serology to determine if the presence of neutralising antibody is likely to indicate that subjects are no longer infectious even though PCR +ve.
- Results from screening of health and social care workers should be centralised and made available to PHE and SPI-M.

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<sup>2</sup> <https://doi.org/10.1101/2020.04.27.20082347>.

<sup>3</sup> <https://elifesciences.org/articles/58728>

<sup>4</sup> Clin Infect Dis. 2017 Mar 15;64(6):736-742

<sup>5</sup> DOI: 10.1056/NEJMoa2008457

## Paper I.

### **A Rapid Review of the Asymptomatic Proportion of COVID-19 PCR-Confirmed Cases in Community Settings**

**Report for:** NERVTAG / SAGE

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**Date:** 11 May 2020

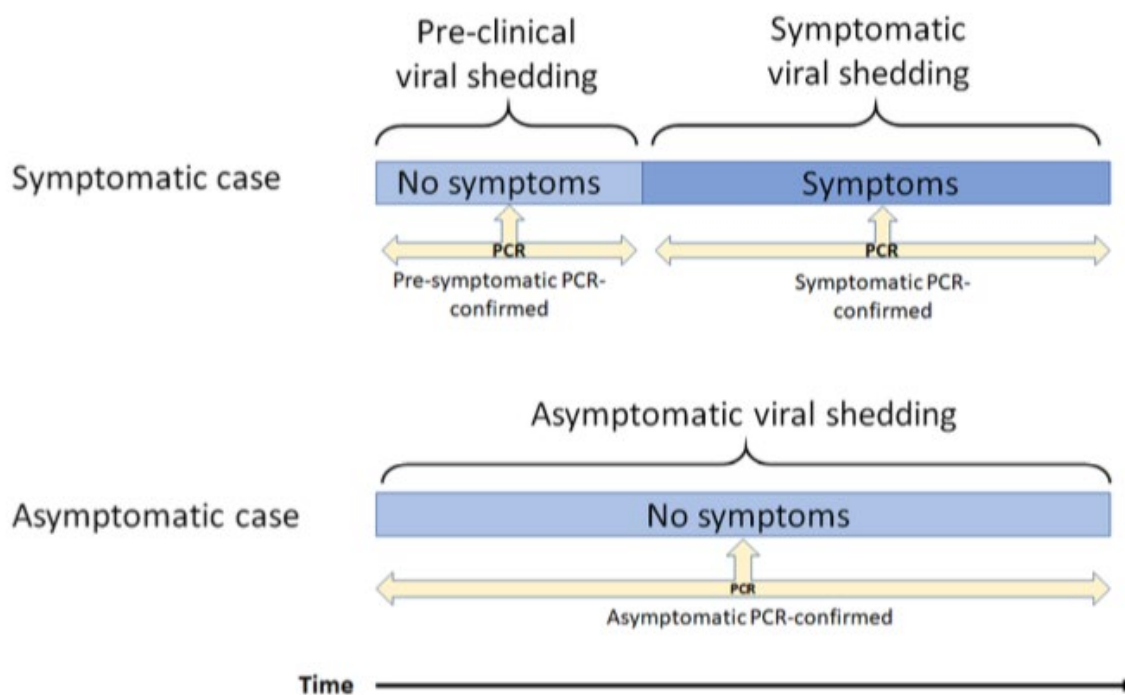
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#### **Introduction**

Reports of asymptomatic COVID-19 cases and potential transmission<sup>1,2,3</sup> have generated concern regarding the implications of undetected asymptomatic transmission on the effectiveness of public health interventions in the current pandemic<sup>4</sup>. However, estimating the proportion of asymptomatic COVID-19 cases shedding virus, and therefore potentially infectious, is challenging because the majority of testing is carried out on symptomatic individuals<sup>5</sup>. Furthermore, longitudinal designs including 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 prior symptom onset (see Figure 1). While asymptomatic virus shedders have been suggested to comprise up to 78% of COVID-19 cases<sup>6</sup>, 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 COVID-19 cases.

Given the widespread discussion and potential implications of asymptomatic transmission of COVID-19, we aimed to rapidly synthesize current evidence regarding the asymptomatic proportion of COVID-19 PCR-confirmed cases in community settings.

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



## Methodology

### Search Strategy

We used Ovid to search the Medline and EMBASE databases of peer-reviewed literature (2019- May 05 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 BioArxiv and MedArxiv for titles and abstracts of pre-print manuscripts using the mandatory terms "Covid-19" + "asymptomatic". We hand-searched the reference lists of all included studies to identify any additional relevant literature, but identified no further studies.

### Selection Criteria

Inclusion criteria were: 1) original research or public health data; 2) presented data on polymerase chain reaction (PCR) confirmed COVID-19 cases; 3) systematic PCR testing of exposed or potentially exposed individuals regardless of symptom status (to avoid bias towards symptomatic cases); 4) systematic follow-up and reporting of symptom status

among PCR confirmed cases (to differentiate pre-clinical shedding from truly asymptomatic cases); 5) presented data from a community setting (i.e. community and home contact tracing, population screening, traveller screening, non-hospital institutional settings). Exclusion criteria were: 1) no primary data; 2) non-human studies; 3) not available in English; 4) studies or case series with <5 positive cases and/or <20 total cases (small sample size); 5) not possible to consistently ascertain the symptomatic status of participants across follow-up; 6) inadequate detail about testing strategy (i.e. not possible to discern if all cases tested systematically).

We limited the search to include studies from community settings rather than hospitals to prevent selection bias towards symptomatic cases. Only studies reporting PCR-confirmed cases were included to estimate the proportion of asymptomatic COVID-19 cases shedding virus; exclusive serological studies were not included as serologically confirmed cases do not necessarily shed virus. 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. Very small studies or case series (<5 positive cases, <20 total cases) were excluded due to likely low generalisability of asymptomatic proportions.

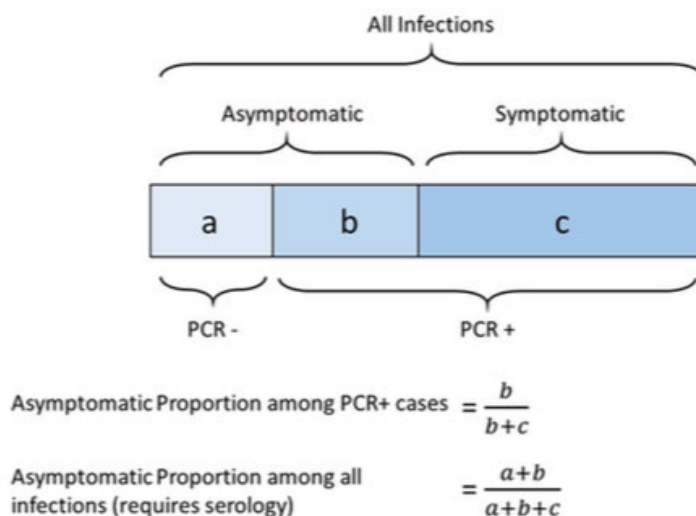
### Data Extraction and Analysis

One researcher (SB) performed the search and extracted study details, and two researchers (SB and EF) extracted primary outcome data independently and resolved any disagreement by consensus. We extracted the following variables of interest to assess the primary outcome 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, method of assessing symptoms, 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, and number of confirmed cases who remained asymptomatic throughout follow-up.

We performed random-effects meta-analysis to assess the asymptomatic proportion for each study and overall. The asymptomatic proportion is given as the number of consistently asymptomatic confirmed cases over 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 refer to the asymptomatic proportion of all infections including those that do not shed virus and would not be PCR-confirmed (see Figure 2).

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



## ***Risk of Bias Assessment***

Two researchers (SB and EF) independently assessed the risk of bias for each included study and resolved any disagreement by consensus. Bias was graded as very low, low, moderate, or high based on the following criteria deemed relevant to the topic of this review:

**Table 1.** *Risk of Bias Assessment*

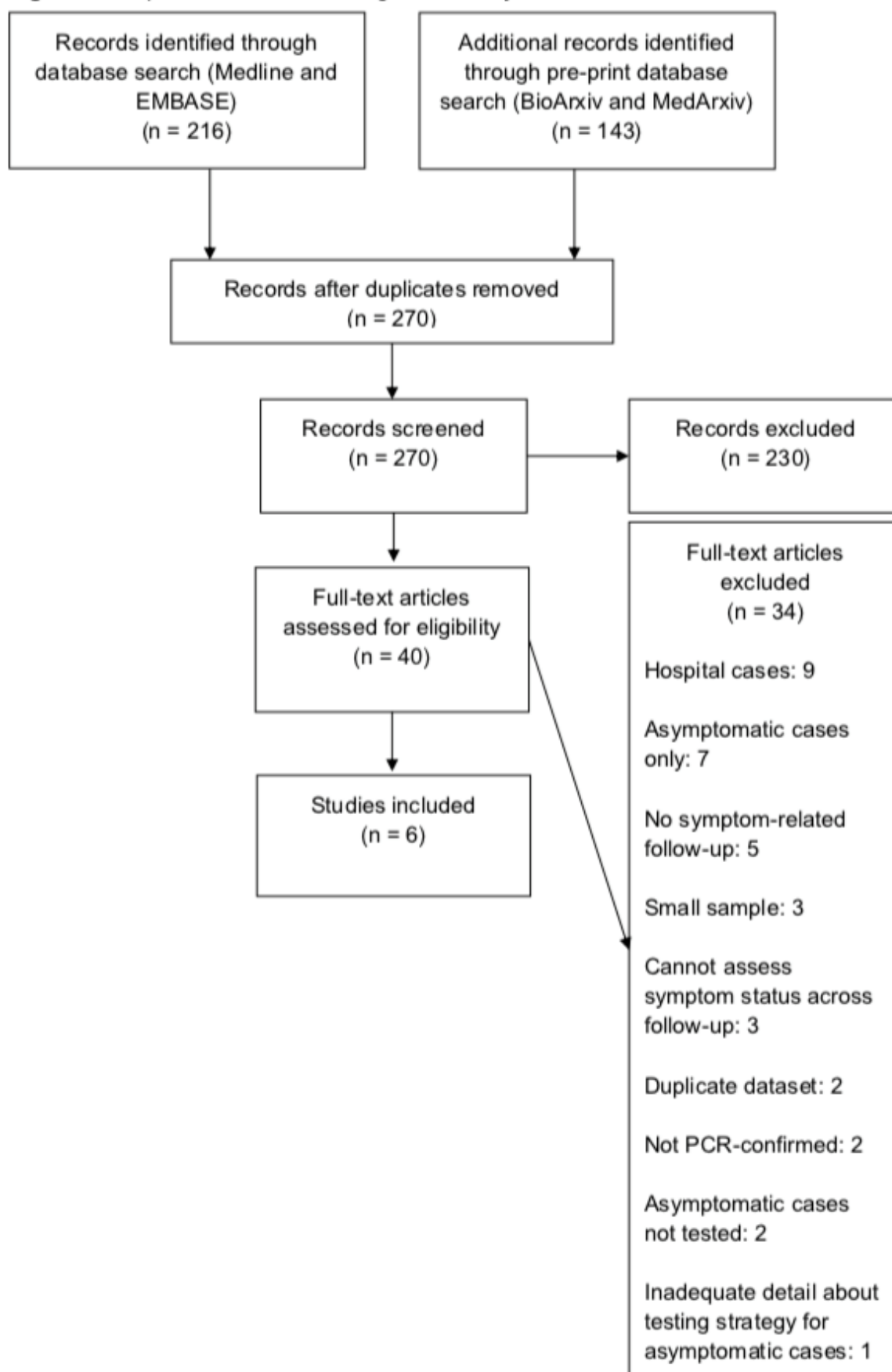
<b>Potential Issue</b>	<b>Direction of Bias</b>
Information Bias: Initial testing doesn't identify all infected people shedding virus	Effect estimate could be biased downwards if PCR testing is more likely to pick up symptomatic shedders compared to asymptomatic shedders. This could be because asymptomatics shed less virus or shed for a shorter period of time.
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<sup>7</sup> of the study selection procedure. The search yielded 216 published articles and 143 pre-prints. Following deduplication, we screened the titles and abstracts of 270 published articles and pre-prints, of which we assessed the 40 full texts and included 6 in the present review.

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





### *Asymptomatic Proportion of PCR-Confirmed COVID-19 Cases in Community Settings*

We computed the asymptomatic proportion of PCR-positive COVID-19 cases for each of the six included studies (detailed in Table 2) and performed random-effects meta-analysis ( $Q(5) = 20.75$ ,  $p < .001$ ,  $\tau^2 = 0.00$ ,  $I^2 = 75.90\%$ ; Figure 4). The pooled estimate for the asymptomatic proportion was 11% (95% CI 4%-18%; 95% prediction interval 0-32%). Estimates ranged from 4% (95% CI 2-10%; Park et al., 2020) to 43% (95% CI 27%-61%; Chau et al., 2020). Confidence intervals for all included studies overlapped substantially with one another and with the pooled estimate with the exception Chau et al. (2020), which the Galbraith plot also indicated to be the most heterogeneous study. Chau et al. (2020) was the only study to systematically test participants using multiple specimen types (baseline saliva specimens and daily nasopharyngeal swabs) and appears to have the highest detection sensitivity for positive cases. This study was also, however, the most affected by potential non-participation bias as 39% of PCR-confirmed cases chose not to participate in the symptom monitoring. This led to a moderate risk of bias score whereas all other studies were assessed as low overall risk of bias.

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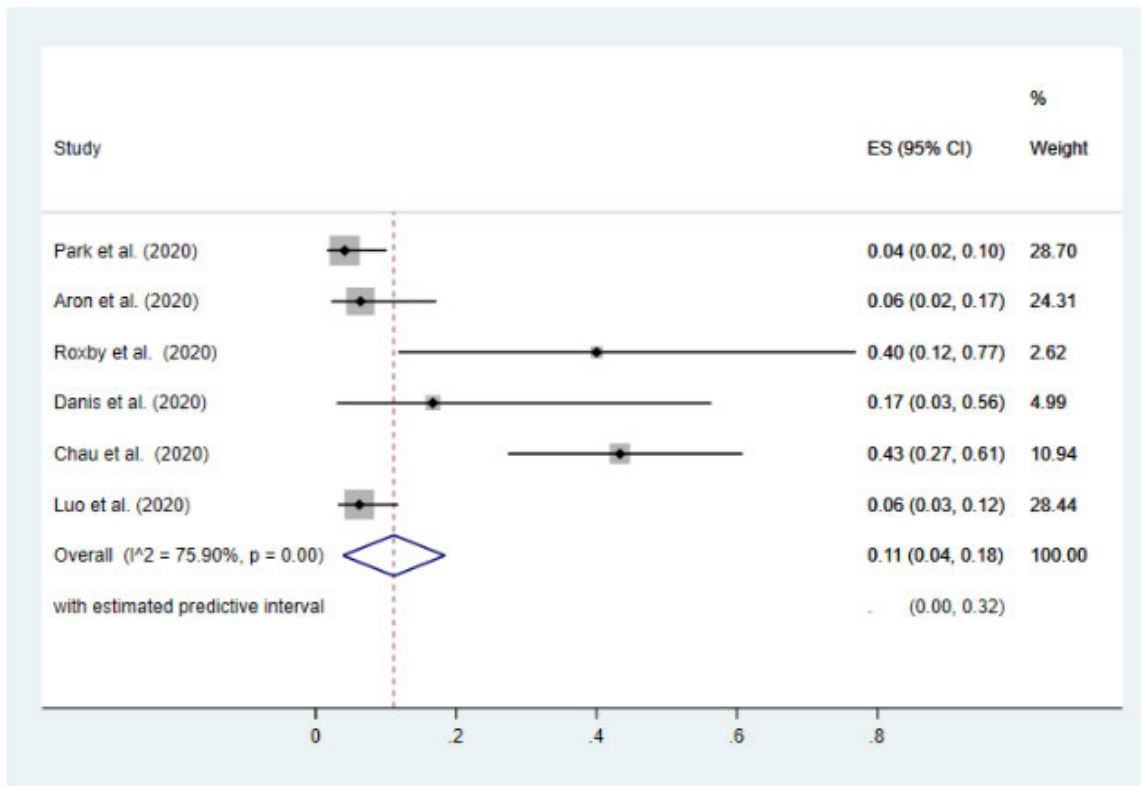
**Table 2.** Descriptive Summary of Studies Included in Meta-Analysis

Reference	Country	Group	Study design	Testing criteria	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 % ( <i>n/N</i> )	Risk of Bias
Park et al. (2020) <sup>8</sup>	South Korea	General public	Surveillance	Exposed to index case(s)	From date of first symptom onset (if any)	14 days	1143	Nasopharyngeal and oropharyngeal swabs daily	97	4.12% (4/97)	Low
Arons et al. (2020) <sup>9</sup>	USA	Nursing home residents	Serial point prevalence survey	Exposed to index case(s)	Within previous 14 days	7 days	76	Nasopharyngeal and oropharyngeal swabs twice one week apart	47 (+1 excluded as previously positive but negative at facility testing)	6.38% (3/47)	Low
Roxby et al. (2020) <sup>10</sup>	USA	Nursing home residents and staff	Surveillance	Exposed to index case(s)	Within previous 14 days	7 days	142	Nasopharyngeal swabs twice one week apart	5 (+ 1 positive at follow-up only and excluded)	40.00% (2/5)	Low
Danis et al. (2020) <sup>11</sup>	France	General public	Surveillance	Exposed to index case(s)	From date of first symptom onset (if any)	14 days	11 (isolated in France)	Nasopharyngeal swabs or endotracheal aspirates daily	6	16.67% (1/6)	Low

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Chau et al. (2020) <sup>12</sup>	Vietnam	General public	Prospective cohort	Exposed to index case(s) and returning travellers	From date of first symptom onset (if any)	14+ days	14000	Nasopharyngeal swabs daily and saliva at baseline	30 (+19 excluded as refused follow-up)	43.33% (13/30)	Moderate
Luo et al. (2020) <sup>13</sup>	China	General public	Prospective cohort	Exposed to index case(s)	From date of first symptom onset (if any)	Until 2 consecutive negative swabs – up to 30 days	4950	Oropharyngeal swabs every two days	129	6.20% (8/129)	Low

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



## Discussion

Through meta-analysis we calculate that 11% of PCR-confirmed COVID-19 cases were truly asymptomatic with a 95% confidence interval between 4% -18%. These findings do not support claims of a very high proportion of virus-shedding infections being asymptomatic and highlights the importance of distinguishing between asymptomatic and pre-symptomatic cases as we have done here. The careful screening of study design and methodology done as part of this review was reflected in the overall low risk of bias for all but one included study. An additional strength of this study is the systematic search of both peer-reviewed published literature and preprint servers thus capturing the most up to date information 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. Small case reports, however, have indicated potential

transmission of SARS-CoV-2 from some asymptomatic index cases <sup>1,2,12</sup> and this is an important area for further research.

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\* indicates inclusion in this meta-analysis

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## Paper II. Pre-print abstract Buitrago-Garcia

### The role of asymptomatic SARS-CoV-2 infections: rapid living systematic review and meta-analysis

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#### Abstract

**Background:** There is substantial disagreement about the level of asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in a population. The disagreement results, in part, from the interpretation of studies that report a proportion of asymptomatic people with SARS-CoV-2 detected at a single point.

**Review questions:** 1. Amongst people who become infected with SARS-CoV-2, what proportion does not experience symptoms at all during their infection? 2. Amongst people with SARS-CoV-2 infection who are asymptomatic when diagnosed, what proportion will develop symptoms later? 3. What proportion of SARS-CoV-2 transmission is accounted for by people who are either asymptomatic throughout infection, or pre-symptomatic?

**Methods:** Rapid living systematic review (protocol <https://osf.io/9ewys/>). We searched Pubmed, Embase, bioRxiv and medRxiv using a living evidence database of SARS-CoV-2 literature on 25.03.2020. We included studies of people with SARS-CoV-2 diagnosed by reverse transcriptase PCR (RT-PCR) that documented follow-up and symptom status at the beginning and end of follow-up and modelling studies. Study selection, data extraction and bias assessment were done by one reviewer and verified by a second, with disagreement resolved by discussion or a third reviewer. We used a common-effect model to synthesise proportions from comparable studies.

**Results:** We screened 89 studies and included 11. We estimated an upper bound for the proportion of asymptomatic SARS-CoV-2 infections of 29% (95% confidence interval 23 to 37%) in eight studies. Selection bias and likely publication bias affected the family case investigation studies. One statistical modelling study estimated the true proportion of asymptomatic infections at 18% (95% credibility interval 16 to 20%). Estimates of the proportions of pre-symptomatic individual in four studies were too heterogeneous to combine. In modelling studies, 40-60% of all SARS-CoV-2 infections are the result of transmission from pre-symptomatic individuals, with a smaller contribution from asymptomatic individuals.

**Conclusions:** An intermediate contribution of pre-symptomatic and asymptomatic infections to overall SARS-CoV-2 transmission means that combination prevention, with enhanced hand and respiratory hygiene, testing tracing and isolation strategies and social distancing, will continue to be needed. The findings of this systematic review of publications early in the pandemic suggests that most SARS-CoV-2 infections are not asymptomatic throughout the course of infection.