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

Authors: Sarah Beale¹,², Andrew Hayward², Laura Shallcross¹, Robert W Aldridge¹, Ellen Fragaszy*¹,³

¹UCL Institute of Health Informatics, 222 Euston Rd, London NW1 2DA
² UCL Research Department of Epidemiology & Public Health, 1-19 Torrington Place, London WC1E 7HB
³ LSHTM Department of Infectious Disease Epidemiology, Keppel Street, London WC1E 7HT

*corresponding author: Ellen Fragaszy (ellen.fragaszy@ucl.ac.uk)

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 05/05/2020. 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 values and/or duration of viral shedding by symptom status. We computed estimates of the asymptomatic proportion and 95% confidence intervals for each study and overall using random effect meta-analysis.

Findings: We screened 270 studies and included 6. The pooled estimate for the asymptomatic proportion of SARS-CoV-2 infections was 11% (95% CI 4%-18%). Estimates of baseline viral load appeared to be similar for asymptomatic and symptomatic cases based on available data in three studies, though detailed reporting of cycle threshold values and natural history of viral shedding by symptom status was limited.

Interpretation: The asymptomatic proportion of SARS-CoV-2 infections is relatively low when estimated from methodologically-appropriate studies. Further investigation into the degree and duration of infectiousness for asymptomatic infections is warranted.

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Introduction

Reports of asymptomatic SARS-CoV-2 infection and potential transmission\textsuperscript{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\textsuperscript{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\textsuperscript{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 shedders have been suggested to comprise up to \textasciitilde80\% of SARS-CoV-2 infections \textsuperscript{6,7}, 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 \textsuperscript{8,9}. However, PCR cycle threshold values provide an informative estimate of viral load and, by extension, probable infectiousness \textsuperscript{8}; consequently, PCR-confirmed infection can provide a useful and accessible indicator of potentially infectious cases, including those without symptoms, for epidemiological modelling.

Given the widespread discussion and potential implications of asymptomatic transmission of SARS-CoV-2, we aimed to rapidly synthesize studies to enable us to estimate the asymptomatic proportion of PCR-confirmed cases in community settings (primary outcome) and viral load and duration of viral shedding in asymptomatic community cases compared to pre-symptomatic cases or those symptomatic from baseline (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

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 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 or schools). 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 values, viral culture results, and duration of viral shedding for asymptomatic and pre-/symptomatic cases if reported.

We performed random-effects meta-analysis using the metaprop programme\textsuperscript{10} 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 \textsuperscript{11}. 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 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 and duration of viral shedding for 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 studies\textsuperscript{12} (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.

Role of Funding Source

The funders were not involved in the design, delivery, analysis, or write-up of this study.
Results

Records Identified

Figure 3 presents an adapted PRISMA flow diagram\textsuperscript{13} of the study selection procedure. The search yielded 216 published articles indexed on OVID 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\textsuperscript{14,15,16,17,18,19}, including two studies based in nursing homes\textsuperscript{15,16} and four studies from general population samples potentially exposed to confirmed cases\textsuperscript{14,17,18,19} and/or returning from travel to high-risk countries\textsuperscript{18}. No further eligible studies were identified from hand-searching reference lists of included studies.

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

Estimates of the the asymptomatic proportion of PCR-positive SARS-CoV-2 infections for included studies ranged from 4\% (95\% CI 2-10\%; Park et al., 2020) to 43\% (95\% CI 27%-61\%; Chau et al., 2020). 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 11\% (95\% CI 4\%-18\%; 95\% prediction interval 0-32\%). There was considerable heterogeneity: $Q(5)= 20.75$, $p<.001$, $\tau^2 = 0.00$, $I^2 = 75.90\%$ (Figure 4). Chau et al. (2020)\textsuperscript{17,18} - which the Galbraith plot indicated to be the most heterogeneous study - 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.

Viral Load and Duration of Viral Shedding

Three of the six included studies reported data regarding the cycle threshold values and/or duration of viral shedding for asymptomatic cases versus pre-symptomatic cases and/or those symptomatic from baseline. Arons et al. (2020)\textsuperscript{15} reported similar baseline median cycle threshold values (CT) for asymptomatic (CT =25.5), pre-symptomatic (CT=23.1), and
symptomatic (CT=24.5) cases; duration of viral shedding was not reported by symptom status. 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\textsuperscript{15}.

Danis et al. (2020)\textsuperscript{17} 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. Further details of cycle threshold values were not presented numerically. Chau et al. (2020)\textsuperscript{17,18} reported similar baseline cycle threshold values for asymptomatic and symptomatic cases, though further numeric detail was not reported. Across follow-up, asymptomatic cases were reported to demonstrate lower viral loads, possibly indicating faster viral clearance for asymptomatic cases. This difference was not statistically significant if comparing PCR-positive follow-up samples only and details of cycle threshold values were not available.

**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 11% of PCR-confirmed SARS-CoV-2 infections in community settings were asymptomatic, with a 95% confidence interval between 4%-18%. These findings do not support claims\textsuperscript{6,7} of a very high asymptomatic proportion for PCR-confirmed infections (up to 80%) and highlights the importance of distinguishing between asymptomatic and pre-symptomatic cases. 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 one included study. 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. Small case reports, however, have indicated potential transmission of SARS-CoV-2 from some asymptomatic index cases\textsuperscript{1,2,8,18}. Limited evidence regarding the viral load and dynamics of SARS-CoV-2 in the present review indicates that asymptomatic cases had
similar baseline viral loads to pre-symptomatic and symptomatic cases\textsuperscript{15,17,18}, though the natural history of viral excretion by symptom status remains unclear.

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)\textsuperscript{20}. While median baseline cycle threshold values for all symptom status groups (23.1-25.5) reported by Arons et al. (2020)\textsuperscript{14} 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. Further inquiry into the degree of preclinical shedding for pre-symptomatic cases, although not the focus of this review, is similarly 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\textsuperscript{21}.

Only three of the six included studies\textsuperscript{15,16,19} described the full range of symptoms included within their symptomatic case definitions, while a further two studies\textsuperscript{17,17,18} reported details of symptoms endorsed by participants but did not specify whether additional symptoms were assessed as part of their case definitions. 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 one study\textsuperscript{17,18} - and dysgeusia/ageusia -not referred to in any included study - may be the primary or sole symptom for some COVID-19 cases\textsuperscript{22–24}. Demographic reporting across studies was also limited and it was not possible to stratify findings by age and sex. Estimates of the asymptomatic proportion may vary across population subgroups and this is a relevant area for future enquiry.

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. 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. Overall, this review provides preliminary evidence that, when investigated using methodologically-appropriate studies, a relatively low proportion of active SARS-CoV-2 infections with viral shedding are truly asymptomatic.

**Competing Interests:** ACH serves on the UK New and Emerging Respiratory Virus Threats Advisory Group. The other authors declare no competing interests.

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* indicates inclusion in this meta-analysis

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

![Figure 1](image)

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

All Infections

- Asymptomatic
- Symptomatic

PCR -  c

PCR +  a + b

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

Asymptomatic Proportion among all infections (requires serology) = \frac{a+b}{a+b+c}
Figure 3. Adapted PRISMA Flow Diagram of Study Selection

Records identified through database search (Medline and EMBASE) (n = 216)

Additional records identified through pre-print database search (BioRxiv and MedRxiv) (n = 143)

Records after duplicates removed (n = 270)

Records screened (n = 270)

Records excluded (n = 230)

Full-text articles assessed for eligibility (n = 40)

Studies included (n = 6)

Full-text articles excluded (n = 34)

Hospital cases: 9
Asymptomatic cases only: 7
No symptom-related follow-up: 5
Small sample: 3
Cannot assess symptom status across follow-up: 3
Duplicate dataset: 2
Cases not PCR-confirmed: 2
Asymptomatic cases not PCR-confirmed: 2
Inadequate detail about testing strategy for asymptomatic cases: 1
Figure 4. Meta-Analysis Results for COVID-19 Asymptomatic Proportion in Community Studies

Note: ES (effect size) = asymptomatic proportion; I² = heterogeneity
| 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                                                 |
| 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)⁵⁸ | 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 | 4.12% (2-10%, 4/97) | Low |
| Arons et al. (2020)⁵⁹ | 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 | 47⁰ | 6.38% (2-17%, 3/47) | Low |
| Roxby et al. (2020)⁶⁰ | USA | Nursing home residents: mean age = 86 (range 69-102); 77% female (62/80) | 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 | 40.00% (12-77%, 2/5) | Low |
| Study (Year) | Country | Population Details | Surveillance Method | Exposed to Index Case(s) | Bespoke (to study) Assessment Forms | Full List of Symptoms Included | Duration from First Symptom Onset | Test Frequency | Test Collection Method | Test Collection Method Details | Case Detection Rate | Risk Level |
|-------------|---------|---------------------|---------------------|--------------------------|------------------------------------|-------------------------------|-------------------------------|----------------|-------------------------|--------------------------------|----------------|-----------|
| 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, rhinorrhea, and/or myalgia | From date of first symptom onset (if any) | 14 days | Nasopharyngeal swabs or endotracheal aspirates daily | Collection method (self- vs healthcare worker) unspecified | 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 | Standardised assessment forms based on participant report | Full list unspecified but included fever, cough, rhinorrhea, fatigue, diarrhea, sore throat, muscle pain, headache, abdominal pain, and/or lost sense of smell | From date of first symptom onset (if any) | 14+ days | Nasopharyngeal swabs daily and saliva at baseline | Collection method (self- vs healthcare worker) unspecified | 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, rhinorrhea, sore throat, headache, fatigue, myalgia, arthralgia, shortness of breath, difficulty breathing, chest tightness, chest pain, conjunctival congestion, nausea, vomit, diarrhea, stomach-ache, and/or other | From date of first symptom onset (if any) | Until 2 consecutive negative swabs – up to 30 days | Oropharyngeal swabs every two days. Swabbing conducted by public health workers. | | 129 | Low |