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

Diana C Buitrago-Garcia (0000-0001-9761-206X),¹ ¹ Dianne Egli-Gany (0000-0002-4725-0475),¹
Michel J Counotte (0000-0003-1039-6873),¹ Stefanie Hossmann (0000-0003-1600-5925),¹ Hira Imeri
(0000-0002-0412-1649),¹ Georgia Salanti (0000-0002-3830-8508),¹ Nicola Low (0000-0003-4817-
8986).¹

1. Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
2. Graduate School of Health Sciences, University of Bern, Bern, Switzerland

* These authors contributed equally to the study

Funding: Swiss National Science Foundation, project number 320030_176233; European Union
Horizon 2020 research and innovation programme, project EpiPose (No 101003688).

Correspondence to: Nicola Low, MD FFPH, Professor of Epidemiology and Public Health, Institute of
Social and Preventive Medicine, University of Bern, Mittelstrasse 43, Bern, CH-3012, Switzerland.
NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
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.
Background

There is substantial disagreement about the level of asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in a population. The differences are extreme. Authors of a World Health Organization report stated that, “The proportion of truly asymptomatic infections is unclear but appears to be relatively rare and does not appear to be a major driver of transmission.” In contrast, reports of new infections found on a single day have led to statements that “the large majority of coronavirus infections do not result in symptoms.” 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. These studies include both people who will remain asymptomatic throughout and those, known as pre-symptomatic, who will develop symptoms of coronavirus disease 2019 (COVID-19) if followed until at least the end of the incubation period of 14 days. The full spectrum and distribution of COVID-19, from completely asymptomatic, to mild and non-specific symptoms, viral pneumonia, respiratory distress syndrome and death are not yet known. Without follow up, however, the proportions of asymptomatic and pre-symptomatic infections cannot be determined.

Accurate estimates of the proportions of true asymptomatic and pre-symptomatic infections are needed urgently because their contribution to overall SARS-CoV-2 transmission at the population level will determine the appropriate balance of control measures. If the predominant route of transmission is from people who have symptoms, then strategies should focus on testing, followed by isolation of infected individuals and quarantine of their contacts. If, however, most transmission is from people without symptoms, social distancing measures that reduce contact with people who might be infectious, should be prioritised. The objectives of this study were to address three 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**

We conducted a rapid systematic review to provide relevant evidence during this public health emergency of international concern.⁷ The protocol for this review is published in the Open Science Framework (https://osf.io/9ewys/). We report our findings according to the preferred reporting items for systematic reviews and meta-analyses.⁸ We conducted the search on March 25, 2020.

**Search strategy**

We searched the living evidence database at the University of Bern Institute of Social and Preventive Medicine (ISPM) (https://ispbern.github.io/covid-19/living-review/collectiondata.html), which includes daily updates of searches of four electronic databases: Medline-Pubmed, Embase, bioRxiv and medRxiv, for articles with medical subject headings and keywords for SARS-CoV-2 infection and COVID-19. We reviewed results that contained "asympt*" in the title or abstract (https://osf.io/9ewys/). We also examined articles suggested by experts and the reference lists of retrieved mathematical modelling studies and systematic reviews.

**Eligibility criteria**

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. We included contact tracing investigations, case series, cohort studies, case control studies and statistical and mathematical modelling studies. We did not apply any language restrictions to the search. We excluded the following study types: case reports of a single patient, surveillance data, case series where patients were not enrolled consecutively, reports in which the primary data were found in another included publication, and mathematical modelling studies that did not specifically estimate the quantities specified in the review questions.
Study selection and data extraction
One reviewer selected studies based on our predefined inclusion and exclusion criteria. A second reviewer verified all included and excluded studies. We reported the identification, exclusion and inclusion of studies in a flowchart (Figure S1).

One reviewer extracted data using a pre-piloted extraction form in an electronic data capture system (REDCap, Vanderbilt University, USA). A second reviewer verified the extracted data using the query system in REDCap. In case of disagreements, a third reviewer was consulted. When disagreements were not resolved by discussion, we contacted study authors for clarification. The extracted variables included, but were not limited to, study design, country and/or region, study setting, population, age, review outcomes and length of follow-up.

The primary outcomes for each review question were:

1. Proportion with asymptomatic SARS-CoV-2 infection who did not experience symptoms at all during follow-up;

2. Proportion with SARS-CoV-2 infections who did not have symptoms at the time of testing but developed symptoms during follow-up.

3. Estimated proportion (with including uncertainty interval) of SARS-CoV-2 transmission accounted for by people who are asymptomatic or pre-symptomatic.

Risk of bias in included studies
Two authors independently assessed the risk of bias. A third reviewer resolved disagreements when consensus was not achieved. For review questions 1 and 2, we adapted the Joanna Briggs Institute Critical Appraisal Checklist for Case Series. The adapted tool included items about inclusion criteria, measurement of asymptomatic status, follow-up of course of disease, and availability of numerator and denominator. We added items about the representativeness of source and target populations.
from a tool for the assessment of risk of bias in prevalence studies.\textsuperscript{10} For review question 3, we used a tool for assessing the credibility of mathematical modelling studies.\textsuperscript{11}

**Synthesis of the evidence**
We used the \textit{metaprop} function from the \textit{meta} package (version 4.11-0)\textsuperscript{12} in R (version 3.5.1) to display the study findings for questions 1 and 2 as forest plots. The 95\% confidence intervals (CI) are estimated using the Clopper-Pearson method.\textsuperscript{13} To synthesise proportions from comparable studies, in terms of design and population, we used both random and common-effect models. When the between-studies variance was close to zero we present only the results from the common-effect analysis.

**Results**
We screened 89 studies (Figure S1). We included six studies that reported family contact tracing investigations in China,\textsuperscript{14-20} two studies of populations evacuated from Wuhan and the Diamond Princess cruise ship,\textsuperscript{21,22} one statistical modelling study based on passengers on the Diamond Princess,\textsuperscript{23} and two mathematical modelling studies.\textsuperscript{24,25}

**Proportion of asymptomatic SARS-CoV-2 infections**
The six family contact investigations included 39 people, with one or more individuals who remained asymptomatic throughout follow-up (Table 1).\textsuperscript{14-20} One study contributed three clusters. The study included adolescents and young adults admitted to hospital in Chonqing with COVID-19.\textsuperscript{16} The authors reported nine case investigations it total, of which four were all symptomatic and two included a person who was asymptomatic on admission, but who developed symptoms later. Nine asymptomatic cases were identified in total, with follow-up from the last possible day of exposure ranging from 17 to 33 days (Table 1), which exceeds the accepted SARS-CoV-2 incubation period of 14 days.\textsuperscript{5} The ages were reported for six of the asymptomatic cases; two were children, aged 13 months and 10 years. For three of the asymptomatic cases, transmission to other individuals was
reported. The common-effect summary of the proportion of asymptomatic SARS-CoV-2 from contact investigations was 23% (95% CI 12 to 39%) (Figure 1).

Table 1. Characteristics of studies of asymptomatic SARS-CoV-2 infection

| ID  | Author | Location, country | Setting                        | Total SARS-CoV-2, n | Asymptomatic SARS-CoV-2, n | Sex of asymptomatic SARS-CoV-2 | Age of asymptomatic SARS-CoV-2, years | Follow-up of asymptomatic SARS-CoV-2, days after exposure | Follow-up of asymptomatic SARS-CoV-2, days after diagnosis |
|-----|--------|------------------|--------------------------------|---------------------|---------------------------|---------------------------------|-------------------------------------|-------------------------------------------------|-------------------------------------------------|
| 4   | Bai, Y | Anyang           | Contact tracing                | 6                   | 1                         | F                               | 20                                  | 32                                              | 15                                              |
| 11  | Chan, JF | Shenzhen, Guangdong | Contact tracing | 5                   | 1                         | M                               | 10                                  | 18                                              | NR                                              |
| 22  | Hu, Z  | Nanjing          | Contact tracing                | 4                   | 1                         | M                               | 64                                  | 30                                              | 17                                              |
| 36  | Liao, J | Chongqing        | Contact tracing                | 12                  | 3                         | Not reported                    | Not reported                       | 33, 32, 27                                       | 16, 11, NR²                                    |
| 42  | Luo, SH | Anhui            | Contact tracing                | 4                   | 1                         | F                               | 50                                  | 17ᵇ                                             | NR                                              |
| 54  | Qian, G | Zhejiang         | Contact tracing                | 8                   | 2                         | F, M                            | 1, 60                               | 23, 23                                          | 7, 11                                          |
| 49  | Nishiura, H | Japan | Evacuation                  | 13                  | 4                         | Not reportedᶜ                    | Not reported                       | 30ᵈ                                             | NR                                              |
| 64  | Tabata, S | Japan  | Evacuation                  | 104                 | 33                        | 18F, 15M                        | Median 70 (IQR 57-75)               | Median 10 (IQR 7-10)⁧                          | NR                                              |
| 47  | Mizumoto, K | Open sea Cruise ship | 634                 | 113                    | 313F, 321M⁰                  | Not reported                    | 14ᶠ                                             | NR                                              |

a. Date of diagnosis was assumed to be date of hospitalisation.
b. Patient did not develop symptoms after 17 days of hospitalisation.
c. Sex distribution of all passengers. Not reported separately for asymptomatic cases.
d. Individuals were observed for 30 days after departure from Wuhan, China.
e. Observation period reported for entire study population.
f. Cruise ship underwent 14 day quarantine.

F, female; IQR, interquartile range; M, male; NR, not reported.
Two studies reported on study populations evacuated from a setting where SARS-CoV-2 transmission was confirmed (Table 1, Figure 1). Nishiura et al. reported on 565 Japanese nationals evacuated from Wuhan. Of these, 13 tested positive by RT-PCR for SARS-CoV-2 and four were asymptomatic. The authors reported that after 30 days of follow up, all four remained asymptomatic. Tabata et al. reported on a sample of passengers evacuated from the Diamond Princess cruise ship who tested positive by RT-PCR for SARS-CoV-2 and were followed up at a hospital in Japan. Of 107 SARS-CoV-2-infected people in the hospital, 104 were followed for a median of 10 days (interquartile range 7 to 10 days). Thirty-three remained asymptomatic by the end of the follow-up period (February 26, 2020). The common-effect summary proportion of infected individuals remaining asymptomatic was 32% (95% CI 24 to 41%). The estimates from the two study types were statistically compatible. The common-effect summary of all studies was 29% (95% CI 23 to 37%) (Figure 1).

| Study          | Events | Total | Proportion | 95%-CI       |
|----------------|--------|-------|------------|--------------|
| Bai, Y         | 1      | 6     | 0.17       | [0.00; 0.64] |
| Chan, JF       | 1      | 5     | 0.20       | [0.01; 0.72] |
| Hu, Z          | 1      | 4     | 0.25       | [0.01; 0.81] |
| Liao, J [cluster:1] | 1 | 5 | 0.20 | [0.01; 0.72] |
| Liao, J [cluster:2] | 1 | 3 | 0.33 | [0.01; 0.91] |
| Liao, J [cluster:3] | 1 | 4 | 0.25 | [0.01; 0.81] |
| Luo, SH        | 1      | 4     | 0.25       | [0.01; 0.81] |
| Qian, G        | 2      | 8     | 0.25       | [0.03; 0.65] |
| **Fixed effect model** | **39** | | **0.23** | [0.12; 0.39] |
| **Heterogeneity:** | **I² = 0%, τ² = 0, p = 1.00** | | | |

| Study          | Events | Total | Proportion | 95%-CI       |
|----------------|--------|-------|------------|--------------|
| Nishiura, H    | 4      | 13    | 0.31       | [0.09; 0.61] |
| Tabata, S      | 33     | 104   | 0.32       | [0.23; 0.42] |
| **Fixed effect model** | **117** | | **0.32** | [0.24; 0.41] |
| **Heterogeneity:** | **I² = 0%, τ² = 0, p = 0.94** | | | |

| **Fixed effect model** | **156** | | **0.29** | [0.23; 0.37] |
| **Heterogeneity:** | **I² = 0%, τ² = 0, p = 1.00** | | | |
| **Residual heterogeneity:** | **I² = 0%, p = 1.00** | | 0.2 0.4 0.6 0.8 |

*Figure 1. Proportion of people with SARS-CoV-2 infection who do not experience symptoms at all during their infection.*
Mizumoto et al. conducted a statistical modelling analysis of data based on 634 passengers from the Diamond Princess cruise ship with RT-PCR positive test results from February 5 to February 20, 2020.23 Of these, 328 were reported to be asymptomatic when tested. The authors estimated the timing of infection, using published data, and adjusted for the proportion of people who would develop symptoms (right censoring). In a Bayesian framework, they estimated that, if all were followed up until the end of the incubation period, the true proportion of asymptomatic infections would be 17.9% (95% credibility interval, Cr I 15.5 to 20.2%).

Proportion of pre-symptomatic SARS-CoV-2 infections
We included four studies (Table 2, Figure 2).15 17 21 26 In three studies in China, people who had SARS-CoV-2 detected by RT-PCR were followed in hospital. In all three studies, authors reported that the asymptomatic cases were detected during contact investigations of patients who had presented with symptoms of COVID-19. In two studies, most patients developed symptoms,15 26 including 43 of 55 patients in Shenzhen, which was the only study in which patients were followed up until clearance of SARS-CoV-2, measured by repeated negative RT-PCR test results.26 In the third hospital-based study, in Nanjing, five of 24 asymptomatic SARS-CoV-2 cases developed symptoms within one to three days of admission.17 Another thirteen showed viral clearance, with two or more negative RT-PCR test results. The remainder still had positive RT-PCR test results, but had not developed symptoms. The fourth study reported the outcome of SARS-CoV-2 infection in passengers of the Diamond Princess cruise ship who were hospitalised in Japan.21 Of 43 who were asymptomatic at the time of diagnosis, 10 developed symptoms during median follow-up of 10 days (IQR 7-10 days). The findings of the four studies were too disparate to pool in a meta-analysis (Figure 2).
Table 2. Characteristics of studies of pre-symptomatic SARS-CoV-2 infection

| ID  | Author | Location, country | Setting               | Total asymptomatic SARS-CoV-2, n | Develops symptoms, n | Sex, symptomatic/overall | Age, years | Follow-up, days |
|-----|--------|-------------------|-----------------------|---------------------------------|----------------------|--------------------------|------------|-----------------|
| 22  | Hu, Z  | Nanjing           | Contact tracing       | 24                              | 5                    | 5F/16F                   | Median 32.5 (IQR 19-57) | Median 12.5 (IQR 8-14) |
| 42  | Luo, SH| Anhui             | Contact tracing       | 8                               | 7                    | Not reported             | Not reported           | Until discharge or negative RT-PCR² |
| 64  | Tabata, S | Japan      | Evacuation            | 43                              | 10                   | 6F/34F                   | Median 69 (IQR 60.5-75) | Median 10 (IQR 7-10)³ |
| 71  | Wang, Y | Shenzhen         | Hospital              | 55                              | 43                   | NR/33F                   | Median 49 (IQR 2-69)    | Until negative RT-PCR   |

a. The one patient that not develop symptoms was observed up to 17 days after hospitalization;
b. Observation period reported for entire study population.

Figure 2. Proportion of people with asymptomatic SARS-CoV-2 infection who develop symptoms of COVID-19 during follow-up

Risk of bias in studies of asymptomatic and pre-symptomatic SARS-CoV-2 infection
All studies reporting empirical data about asymptomatic and pre-symptomatic infection reported follow-up time of at least seven days after the first positive RT-PCR test result (Figure S2). The main source of bias is a selection bias in the inclusion of asymptomatic cases in contact investigations. All clusters include at least one asymptomatic case, so there is a systematic overestimation of the
proportion of people with asymptomatic SARS-CoV-2. The pooled estimate is therefore an upper bound of the proportion asymptomatic in the population.

**Contribution of asymptomatic and pre-symptomatic infection to SARS-CoV-2 to transmission**

We included two transmission dynamic mathematical modelling studies that explicitly addressed this question.24 25 Ganyani et al. used publicly available line-listed data about clusters of COVID-19 from Tianjin, China and from Singapore. The applied statistical models in a Bayesian framework to examine generation and serial intervals for linked cases, with an assumption of the incubation period from a published study. A generation period shorter than the incubation period of the infector indicates pre-symptomatic transmission. They found that the proportion of pre-symptomatic transmission was 48% (95% CI 32 to 67%) for Singapore and 62% (95% CI 50 to 76%) for Tianjin, China.24 Ferretti et al. developed a compartmental mathematical model, informed by data on linked COVID-19 cases in Hubei province, China. They separated the transmission parameter into symptomatic, asymptomatic, pre-symptomatic and environmental components. In their baseline scenario, they assumed a fraction of 46% asymptomatic SARS-CoV-2 infections (citing data from the Diamond Princess) and reduced infectiousness from asymptomatic cases. They found, in their base case scenario, that pre-symptomatic patients account for 47% (95% credibility interval 11 to 58%) of the total transmission, and asymptomatic transmission 6% (0 to 57%) of the total. They provide a shiny app [ref:link], where different assumptions can be examined.25

**Discussion**

**Summary of main findings**

This rapid systematic review found that an upper bound for of 29% (95% CI 23 to 37%) for the proportion of asymptomatic SARS-CoV-2 infection. A statistical modelling study estimated that 17.9% (95% CrI 15.5 to 20.2%) remain asymptomatic. In empirical studies, the estimated proportions of people who are pre-symptomatic but who go on to develop symptoms 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.
Strengths and weaknesses
A strength of this review is that we clearly distinguish between SARS-CoV-2 infections that remain asymptomatic throughout their course from those that become symptomatic, and we separate the proportions of people with infection from their contribution to overall transmission in a population. This rapid systematic review follows a published protocol and uses methods to minimise bias whilst increasing the speed of the review process. As a living systematic review, we will update it regularly using a living evidence database that includes preprints. One main limitation of the review is that the database does not include all sources. The four databases cover the majority of publications and we do not believe that we have missed studies that would change our conclusions.

Comparison with other reviews
We identified one online summary of asymptomatic SARS-CoV-2 infection that listed 21 articles found through searches of five electronic databases. There was no published protocol. The authors did not distinguish between asymptomatic and pre-symptomatic infection and present cross-sectional studies alongside longitudinal studies and mathematical modelling studies. The review gave a wide range (5 to 80%) of infections that might be asymptomatic. The advantage of our review is that it is a systematic review and, although we included fewer studies, we only report findings from empirical studies that followed participants for at least 14 days from the last exposure and we quantify the proportion of asymptomatic infection in a meta-analysis.

Interpretation
The findings from this systematic review do not support the claim that a large majority of SARS-CoV-2 infections is asymptomatic. Our estimate, 29% (95% CI 23 to 37%) is an upper bound of SARS-CoV-2 infections that remain asymptomatic throughout. We believe that our analysis is likely to have overestimate the true proportion because all the included contact investigations included at least one asymptomatic individual. At this stage of a pandemic of a new infectious disease, there is likely publication bias, with rapid publication of case reports of newsworthy findings, such as person-to-person transmission by asymptomatic individuals. The denominator of all contact investigations is not known, but the study by Liao et al. also included clusters with no asymptomatic case. The large
number of case reports of novel manifestations of disease was also a feature of the Zika epidemic.

Analysis of published studies showed that estimates of the duration of infection decreased over time as less biased studies were published. We anticipate that, as larger, more representative studies are conducted and published, the proportion estimated to be asymptomatic will decrease. The statistical modelling study by Mizumoto, which accounted for right censoring, provides an upper uncertainty interval of 20% asymptomatic infections, which might be closer to the true proportion if that assumed incubation period distribution is accurate. The level and duration of transmissibility from individuals with asymptomatic infections is not known, but in this review, three asymptomatic cases were reported to be the source of subsequent SARS-CoV-2 infections within families. The proportion of people who are pre-symptomatic could not be determined with certainty, presumably because the distribution of dates at which SARS-CoV-2 was detected differed between studies. Nevertheless, transmission from pre-symptomatic individuals has been found to occur one to three days before symptom onset.

Only mathematical modelling studies can determine the overall contribution to SARS-CoV-2 transmission of individuals with asymptomatic and pre-symptomatic infection at the population level because of the non-linear dynamics of infection transmission. In the studies included in this review, three estimates from two studies found that 40-60% of all SARS-CoV-2 infections are the result of transmission whilst pre-symptomatic, with a smaller contribution from asymptomatic infections.

The consistency of the findings is reassuring because the studies used different methods. Of note, Ganyani et al. used data about the serial interval to derive their estimate and did not use assumptions about the proportion of asymptomatic infections. Our finding differs from a modelling study that has been interpreted as showing that up to 90% of SARS-CoV-2 transmission is asymptomatic. Li and colleagues found that 86% of infections were defined as undocumented, but it appears that this proportion is a composite of asymptomatic infections, infections that were symptomatic and diagnosed but unreported, and infections that were mild and undiagnosed.
Implications and unanswered questions

This systematic review gives important information that can inform future research and public health decision-making. 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. Social distancing measures will need to be sustained at some level because droplet transmission from close contact with people with asymptomatic and pre-symptomatic infection is occurring. Easing of restrictions will, however, only be possible with wide access to testing, contact tracing and rapid isolation of infected individuals. Quarantine of close contacts is also essential to prevent onward transmission during asymptomatic or pre-symptomatic periods of those that have become infected. Digital, proximity tracking will need to supplement classical contact tracing to speed up detection of contacts. Future studies to improve determination of the true proportion of asymptomatic and pre-symptomatic infection should ensure careful documentation of symptoms and adequate follow-up. Future larger cohort studies should improve certainty around the estimates of the proportions of asymptomatic and pre-symptomatic SARS-CoV-2 infections. The search for this rapid living systematic review was updated on 20.04.2020. 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.
References

1. World Health Organization. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19), 16-24 February 2020. Geneva, 2020.

2. Day M. Covid-19: four fifths of cases are asymptomatic, China figures indicate. BMJ 2020;369:m1375. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32241884 (Apr 2 Accessed).

3. Sutton D, Fuchs K, D’Alton M, Goffman D. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. N Engl J Med 2020. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32283004 (Apr 13 Accessed).

4. Low N, Egli-Gany D, Hossmann S, Buitrago-Garcia D, Imeri H, Counotte M. Re: Covid-19: four fifths of cases are asymptomatic, China figures indicate. BMJ 2020. Available from: https://www.bmj.com/content/369/bmj.m1375/rr-5 (Accessed 25.04.2020).

5. World Health Organization. Coronavirus disease 2019 (COVID-19) situation report - 73. Geneva, 2020.

6. Lipsitch M, Swerdlow DL, Finelli L. Defining the Epidemiology of Covid-19 - Studies Needed. The New Engl J Med 2020;382(13):1194-96. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32074416 (Mar 26 Accessed).

7. Tricco AC, Langlois EV, Straus SE, editors. Rapid reviews to strengthen health policy and systems: a practical guide. Geneva: World Health Organization, 2017.

8. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6(7):e1000100. Available from: PM:19621070 https://air.unimi.it/retrieve/handle/2434/168817/170979/PRISMA%20annals%202009%20exple natory.pdf.

9. Joanna Briggs Institute. The Joanna Briggs Institute Critical Appraisal tools for use in JBI systematic reviews—checklist for case series Adelaide. 2017. Available from: https://joannabriggs.org/ebp/critical_appraisal_tools.

10. Boyle MH. Guidelines for evaluating prevalence studies. Evid Based Ment Health 1998;1(2):37-40. Available from: http://ebmh.bmj.com/content/1/2/37.full.pdf.

11. Jaime Caro J, Eddy DM, Kan H, Kaltz C, Patel B, Eldessouki R, Briggs AH, Forces I-A-NMCT. Questionnaire to assess relevance and credibility of modeling studies for informing health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. Value Health 2014;17(2):174-82. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24636375 (Mar 5 Accessed).

12. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evid Based Mental Health 2019;22(4):153-60. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31563865 (5 Nov Accessed).

13. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998;17(8):857-72. Available from: PM:9595616 http://onlinelibrary.wiley.com/store/10.1002/(SICI)1097-0258(19980430)17:8.
14. Qian G, Yang N, Ma AHY, Wang L, Li G, Chen X, Chen X. A COVID-19 Transmission within a family cluster by presymptomatic infectors in China. *Clin Infect Dis* 2020. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32201889.

15. Luo SH, Liu W, Liu ZJ, Zheng XY, Hong CX, Liu ZR, Liu J, Weng JP. A confirmed asymptomatic carrier of 2019 novel coronavirus (SARS-CoV-2). *Chin Med J (Engl)* 2020. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32149768.

16. Liao J, Fan S, Chen J, Wu J, Xu S, Guo Y, Li C, Zhang X, Wu C, Mou H, Song C, Li F, Wu G, Zhang J, Guo L, Liu H, Lv J, Xu L, Lang C. Epidemiological and clinical characteristics of COVID-19 in adolescents and young adults. *medRxiv* 2020. Available from: http://dx.doi.org/10.1101/2020.03.10.20032136.

17. Hu ZL, Song C, Xu CJ, Jin GF, Chen YL, Xu X, MaHX, Chen W, Lin Y, ZhengYS, Wang JM, Hu ZB, Yi YX, Shen HB. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Science China-Life Sciences* 2020. Available from: <Go to ISI>:://WOS:000518479200001 (Mar 4 Accessed).

18. Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020;395(10223):514-23. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31986261.

19. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, Wang M. Presumed Asymptomatic Carrier Transmission of COVID-19. *JAMA* 2020;54(0):E017. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32083643.

20. Bai SL, Wang JY, Zhou YQ, Yu DS, Gao XM, Li LL, Yang F. [Analysis of the first cluster of cases in a family of novel coronavirus pneumonia in Gansu Province]. *Zhonghua Yu Fang Yi Xue Za Zhi* 2020;54(0):E005. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32064855.

21. Tabata S, Imai K, Kawano S, Ikeda M, Kodama T, Miyoshi K, Obinata H, Mimura S, Kodera T, Kitagaki M, Sato M, Suzuki S, Ito T, Uwabe Y, Tamura K. Non-severe vs severe symptomatic COVID-19: 104 cases from the outbreak on the cruise ship 'Diamond Princess' in Japan. *medRxiv* 2020. Available from: http://dx.doi.org/10.1101/2020.03.18.20038125).

22. Nishiura H, Kobayashi K, Zarebski A, Chowell G. Estimating the asymptomatic ratio of novel coronavirus infections (COVID-19). *Int J Infect Dis* 2020. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32179137).

23. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Euro Surveill* 2020;25(10). Available from: https://www.ncbi.nlm.nih.gov/pubmed/32183930 (Mar 5 Accessed).

24. Ganyani T, Kremer C, Chen D, Torneri A, Faes C, Wallinga J, Hens N. Estimating the generation interval for COVID-19 based on symptom onset data. *medRxiv* 2020:2020.03.05.20031815. Available from: https://www.medrxiv.org/content/medrxiv/early/2020/03/08/2020.03.05.20031815.full.pdf).

25. Ferretti L, Wymant C, Kendall M, Zhao L, Nurtay A, Abeler-Dorner L, Parker M, Bonsall DG, Fraser C. Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing.
medRxiv 2020:2020.03.08.20032946. Available from: https://www.medrxiv.org/content/medrxiv/early/2020/03/31/2020.03.08.20032946.full.pdf).

26. Wang Y, Liu Y, Liu L, Wang X, Luo N, Ling L. Clinical outcome of 55 asymptomatic cases at the time of hospital admission infected with SARS-Coronavirus-2 in Shenzhen, China. J Infect Dis 2020. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32179910 (Mar 17 Accessed).

27. Heneghan C, Brassey J, Jefferson T. COVID-19: What proportion are asymptomatic? Oxford: Centre for Evidence Based Medicine; 2020 [updated 06.04.2020. Available from: https://www.cebm.net/covid-19/covid-19-what-proportion-are-asymptomatic/ accessed 23.04.2020.

28. Counotte M, Meili KW, Low N. Emergence of evidence during disease outbreaks: lessons learnt from the Zika virus outbreak. medRxiv 2020Available from: https://doi.org/10.1101/2020.03.16.20036806).

29. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic Transmission of SARS-CoV-2 - Singapore, January 23-March 16, 2020. MMWR Morb Mortal Wkly Rep 2020;

30. Li R, Pei S, Chen B, Song Y, Zhang T, Yang W, Shaman J. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). Science 2020Available from: https://www.ncbi.nlm.nih.gov/pubmed/32179701 (Mar 16 Accessed).

31. Salathe M, Althaus CL, Neher R, Stringhini S, Hodcroft E, Fellay J, Zwahlen M, Senti G, Battegay M, Wilder-Smith A, Eckerle I, Egger M, Low N. COVID-19 epidemic in Switzerland: on the importance of testing, contact tracing and isolation. Swiss Med Wkly 2020;150:w20225. Available from: https://www.ncbi.nlm.nih.gov/pubmed/32191813 (Mar 9 Accessed).
Supplementary material

Figure S1: Flow chart

Figure S2: Risk of bias assessment

Table S1. PRISMA checklist
Records identified through database searching (bioRxiv/medRxiv=843, Embase=269, PubMed=1,154) n=2,266

Records excluded after filter (asympt*) applied n=2,177

Full-texts articles assessed for eligibility (bioRxiv/medRxiv=38, Embase=13, PubMed=35, expert=3) n=89

Records excluded after screening n=76
Study design in appropriate=33
Aim of mathematical model not in scope=13
Insufficient data=10
Other=9
Duplicate data=5
No original data=4
Not about SARS-CoV-2=1
Data included in other publication=1

Studies included in qualitative synthesis n=13

Included in question 1 n=9
Included in question 2 n=4
Included in question 3 n=2

Included in meta-analysis for question 1 n=8
Included in meta-analysis for question 2 n=4

Figure S1. Flow chart of identified, excluded and included records, as of 25 March 2020
| Question | Bai, Y | Chan, JF | Hu, Z | Liao, J | Luo, SH | Nishiura, H | Qian, G | Tabata, S | Wang, Y |
|----------|--------|---------|-------|--------|--------|----------|--------|---------|--------|
| Q1. Were there clear criteria for inclusion in the study? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Q2. Was SARS-CoV-2 infection measured in a standard, reliable way (RT-PCR) for all participants in the study? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Q3. Were asymptomatic participants clearly documented at the start of follow-up? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Q4. Did the study have consecutive inclusion of participants? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Q5. Did the study have complete inclusion of participants? | Yes | Yes | Yes | No | Yes | Yes | Yes | Yes | Yes |
| Q6. Was there clear reporting of the demographics of the participants in the study? | No | Yes | Yes | Yes | No | No | No | Yes | Yes |
| Q7. Was there clear reporting of clinical information (i.e. type of symptoms) for the participants? | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | No |
| Q8a. Was the symptom status of cases at the end of follow-up clearly reported? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No |
| Q8b. Did participants have 14 days or more of follow-up, or documented RT-PCR negative result at end of study? | Yes | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes |
| Q9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? | Yes | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes |
| Q10. Were both numerator and denominator available? | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Q11a. Was the study population an adequate sample of the source population? | Yes | Yes | Yes | Yes | Yes | No | Yes | No | Yes |
| Q11b. Was the study population an adequate sample of the target population? | No | No | No | No | No | Yes | No | No | No |

*Figure S2. Risk of bias in studies of asymptomatic and pre-symptomatic infection*
# PRISMA 2009 Checklist

| Section/topic | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|---------------|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| **TITLE**     |   |                                                                                                                                                                                                                |                   |
| Title         | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                              | 1                 |
| **ABSTRACT**  |   |                                                                                                                                                                                                                | 2-3               |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. |                   |
| **INTRODUCTION** | |                                                                                                                                                                                                                |                   |
| Rationale     | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                   | 4                 |
| Objectives    | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 4-5               |
| **METHODS**   |   |                                                                                                                                                                                                                |                   |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                         | 5                 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                         | 5                 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                              | 5                 |
| Search        | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                  | 5                 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                          | 6                 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                   | 6                 |
| Data items    | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                           | 6                 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 6                 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                     | 6                 |
### PRISMA 2009 Checklist

| Section/topic | # | Checklist item                                                                 | Reported on page # |
|---------------|---|--------------------------------------------------------------------------------|-------------------|
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 7                 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | Not done          |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | Not applicable    |

#### RESULTS

| Section/topic | # | Checklist item                                                                 | Reported on page # |
|---------------|---|--------------------------------------------------------------------------------|-------------------|
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 7                 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 8, 11             |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 21                |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 9, 11             |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 9                 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Not done          |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | Not applicable    |

#### DISCUSSION

| Section/topic | # | Checklist item                                                                 | Reported on page # |
|---------------|---|--------------------------------------------------------------------------------|-------------------|
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 12                |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 13                |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 13-15             |

#### FUNDING
**Funding**

|   | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. |   |

*From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097*

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

Page 2 of 2