Occurrence and transmission potential of asymptomatic and 
presymptomatic SARS-CoV-2 infections: a living systematic review and 
meta-analysis

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.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

Debate about the level of asymptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection continues. The amount of evidence is increasing and study designs have changed over time. We conducted a living systematic review 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) What is the infectiousness of asymptomatic and presymptomatic, compared with symptomatic, SARS-CoV-2 infection? (3) What proportion of SARS-CoV-2 transmission in a population is accounted for by people who are asymptomatic or presymptomatic?

Methods and Findings

The protocol was first published on 1 April 2020 and last updated on 18 June 2020. We searched PubMed, Embase, bioRxiv and medRxiv, aggregated in a database of SARS-CoV-2 literature, most recently on 2 February 2021. Studies of people with PCR-diagnosed SARS-CoV-2, which documented symptom status at the beginning and end of follow-up, or mathematical modelling studies were included. Studies restricted to people already diagnosed, of single individuals or families, or without sufficient follow-up were excluded. One reviewer extracted data and a second verified the extraction, with disagreement resolved by discussion or a third reviewer. Risk of bias in empirical studies was assessed with a bespoke checklist and modelling studies with a published checklist. All data syntheses were done using random effects models. Review question (1): We included 94 studies. Heterogeneity was high and we could not reliably estimate values for the proportion of asymptomatic infections overall (interquartile range 13-45%, prediction interval 2-89%), or in studies based on screening of defined populations (interquartile range 18-59%, prediction interval 3-95%). In screening studies at low risk of information bias, the prediction interval was 4-69% (summary proportion 23%, 95% CI 14-35%). In 40 studies based on contact or outbreak investigations, the summary proportion asymptomatic was 18% (95% CI 14-24%, prediction interval 3-64%) and, in studies at low risk of selection bias, 25% (95% CI 18-33%, prediction interval 5-66%). (2) The
secondary attack rate in contacts of people with asymptomatic infection compared with symptomatic infection was 0.43 (95% CI 0.05-3.44, 5 studies). (3) In 11 modelling studies fit to data, the proportion of all SARS-CoV-2 transmission from presymptomatic individuals was higher than from asymptomatic individuals. Limitations of the evidence include high heterogeneity in studies that were not designed to measure persistently asymptomatic infection, high risks of selection and information bias, and the absence of studies about variants of concern or in people who have been vaccinated.

CONCLUSIONS

This review does not provide a summary estimate of the proportion of asymptomatic SARS-CoV-2 across all study designs. In studies based on contact and outbreak investigation, most SARS-CoV-2 infections were not persistently asymptomatic. Summary estimates from meta-analysis may be misleading when variability between studies is extreme. Without prospective longitudinal studies with methods that minimise selection and measurement biases, further updates with the study types included in this living systematic review are unlikely to be able to provide a reliable summary estimate of the proportion of asymptomatic infections caused by wild-type SARS-CoV-2.

REVIEW PROTOCOL: Open Science Framework (https://osf.io/9ewys/)
Introduction

There is ongoing debate about the true proportion of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection that remains asymptomatic [1]. A well-recognised source of overestimation arises when people without symptoms at the time of testing are reported as having asymptomatic infection, with such cross-sectional studies often reporting percentages of 80% or more [2, 3]. These studies overestimate the proportion of persistently asymptomatic infection because they misclassify people with so-called presymptomatic infection, who will develop symptoms of coronavirus disease 2019 (COVID-19) if reassessed after an adequate follow-up period [1]. Other sources of bias can result in over- or underestimation of the proportion with persistent asymptomatic infections, even when participants are adequately followed up [1]. For example, studies that assess a limited range of symptoms could overestimate the proportion asymptomatic through misclassification if they do not ask participants about all possible symptoms. Since COVID-19 was first identified as a viral pneumonia, the spectrum of symptoms has grown to include gastrointestinal symptoms and disturbances of smell and taste [1]. On the other hand, selection bias would be expected to underestimate the proportion with asymptomatic SARS-CoV-2 if people with symptoms are more likely to be tested for SARS-CoV-2 infection than those without symptoms [4].

Accurate estimates of the proportions of true asymptomatic and presymptomatic infections are needed to determine the balance and range of control measures [5]. Recognition of asymptomatic and presymptomatic infections has shown the importance of control measures such as physical distancing, active case-finding through testing of asymptomatic people [6] and the need for rapid quarantine [7]. The number of published studies about SARS-CoV-2 is increasing continuously and the types of published studies are also changing [8], including the designs of studies that report on the proportion of people with asymptomatic infection. In systematic reviews, reported estimates from random effects meta-analysis models range from 17 to 41% [9-14]. Authors of these reviews acknowledge high heterogeneity, typically reporting values of the $i^2$ statistic >90%, which is the
proportion of the variability between estimates due to study differences other than chance [15].

Sources of heterogeneity are often not explored in detail, however, with infrequent reporting of prediction intervals [9, 10], even though they give information about all between-study variability and show the range of estimates that would be expected in future studies [15]. In this fourth update of our living systematic review [10] we aimed to improve and understand the changing evidence over time for three review questions: (1) Amongst people who become infected with SARS-CoV-2, what proportion does not experience symptoms at all during their infection? (2) What is the infectiousness of people with asymptomatic and presymptomatic, compared with symptomatic SARS-CoV-2 infection? (3) What proportion of SARS-CoV-2 transmission is accounted for by people who are either asymptomatic throughout infection, or presymptomatic?

Methods

We conducted a living systematic review, a systematic review that provides an online summary of findings and is updated when relevant new evidence becomes available [16]. The protocol, which describes modifications for each update, was first published on 1 April 2020 and amended for this version on 18 June 2020, (https://osf.io/9ewys/). Previous versions of the review have been posted as preprints [17] and published as a peer-reviewed article [10]. We report our findings according to statements on preferred reporting items for systematic reviews and meta-analyses 2020 (S1 PRISMA 2020 Checklist) [18] and on synthesis without meta-analysis in systematic reviews (SWiM) [19]. Ethics committee review was not required for this review. Box 1 shows our definitions of symptoms, asymptomatic infection and presymptomatic status.

Box 1. Definitions of symptoms and symptom status in a person with SARS-CoV-2 infections

**Symptoms**: symptoms that a person experiences and reports. We used the authors’ definitions. We searched included manuscripts for an explicit statement that the study participant did not report symptoms that they experienced. Some authors defined ‘asymptomatic’ as an absence of self-reported symptoms. We did not include clinical signs observed or elicited on examination.

**Asymptomatic infection**: a person with laboratory-confirmed SARS-CoV-2 infection, who has no symptoms, according to the authors’ report, at the time of first clinical assessment and had no symptoms at the end of follow-up. The end of follow-up was defined as any of the following:
virological cure, with one or more negative RT-PCR test results; follow-up for 14 days or more after the last possible exposure to an index case; follow-up for seven days or more after the first RT-PCR positive result.

**Presymptomatic:** a person with laboratory-confirmed SARS-CoV-2 infection, who has no symptoms, according to the authors’ report, at the time of first clinical assessment, but who developed symptoms by the end of follow-up. The end of follow-up was defined as any of the following: virological cure, with one or more negative RT-PCR test results; follow-up for 14 days or more after the last possible exposure to an index case; follow-up for seven days or more after the first RT-PCR positive result.

**Information sources and search**

We conducted the first search on 25 March 2020 and updated it on 20 April 2020, 10 June 2020 and 2 February 2021. We searched the COVID-19 living evidence database [20], which uses automated workflow processes to: (1) provide daily updates of searches of four electronic databases (Medline, PubMed, Ovid Embase, bioRxiv and medRxiv), using medical subject headings and free-text keywords for SARS-CoV-2 infection and COVID-19; (2) de-duplicate the records; (3) tag records that are preprints; and (4) allow searches of titles and abstracts using Boolean operators. We used the search function to identify studies of asymptomatic or presymptomatic SARS-CoV-2 infection using a search string of medical subject headings and free text keywords (S1 Text). We also examined articles suggested by experts and the reference lists of retrieved studies. Reports were planned to be updated at 3-monthly intervals, with continuously updated searches.

**Eligibility criteria**

We included studies, in any language, of people with SARS-CoV-2 diagnosed by RT-PCR that documented follow-up and symptom status at the beginning and end of follow-up or investigated the contribution to SARS-CoV-2 transmission of asymptomatic or presymptomatic infection. We included contact tracing and outbreak investigations, cohort studies, case-control studies, and mathematical modelling studies. We amended eligibility criteria in the protocol for this update in two ways. First, we excluded studies that only reported the proportion of presymptomatic SARS-CoV-2 because the settings and methods of these studies were very different and their results were too heterogeneous to summarise [10]. Second, we aimed to reduce the risk of bias from studies with inclusion criteria based mainly on people with symptoms, which would systematically underestimate...
the proportion of people with asymptomatic infection. We therefore excluded the following study types: case series restricted to people already diagnosed and studies that did not report the number of people tested for SARS-CoV-2, from whom the study population was derived. We also excluded case reports and contact investigations of single individuals or families, and any study without sufficient follow-up (Box 1). Where data from the same study population were reported in multiple records, we extracted data from the most comprehensive report.

Study selection and data extraction

Reviewers worked in pairs to screen records using an application programming interface in the electronic data capture system (REDCap, Vanderbilt University, Nashville, TN, USA). One reviewer applied eligibility criteria to select studies and a second reviewer verified all included and excluded studies. We reported the process in a flow diagram, adapted for living systematic reviews [21] (S1 Fig). The reviewers determined which of the three review questions each study addressed. One reviewer extracted data using a pre-piloted extraction form in REDCap and a second reviewer verified the extracted data. For both study selection and data extraction, a third reviewer adjudicated on disagreements that could not be resolved by discussion. We contacted study authors for clarification where the study description was insufficient to determine eligibility or if reported data in the manuscript were internally inconsistent. The extracted variables included, study design, country and/or region, study setting, population, age, sex, primary outcomes and length of follow-up (full list of variables in S1 Form). We extracted raw numbers of individuals with an outcome of interest and relevant denominators from empirical studies. From statistical and mathematical modelling studies we extracted proportions and 95% credibility intervals.

The primary outcomes for each review question were (1) the proportion of people with asymptomatic SARS-CoV-2 infection who did not experience symptoms at all during follow-up; (2) secondary attack rate from asymptomatic or presymptomatic index cases, compared with
symptomatic cases; (3) model-estimated proportion of SARS-CoV-2 transmission accounted for by people who are asymptomatic or presymptomatic.

Risk of bias in included studies
For this update, we developed a new tool to assess the risk of bias in studies estimating the proportion of asymptomatic infections because the study designs of included studies have changed over the course of the review. In previous versions, we used items from a tool to assess case series, which had dominated the literature early on [22] and from a tool assessing the prevalence of mental health disorders [23]. The new tool was based on possible biases in observational studies of prevalence in general and in COVID-19 in particular [4, 24]. We developed signalling questions in the domains of selection (two items), information (three items) and selective reporting (one item) biases (S2 Text). For mathematical modelling studies, we used a checklist for assessing relevance and credibility [25]. Two authors independently assessed the risk of bias, using a customised online tool, which saved responses into the REDCap database. A third reviewer resolved disagreements.

Synthesis of the evidence
The data extracted from the included studies and the code used to display and synthesise the results are publicly available: https://github.com/leonieheron/LSR_Asymp_v4. We used the metaprop and metabin functions from the meta package (version 4.11-0) [26] and the ggplot2 package (version 3.3.5) in R (version 3.5.1) to display the study findings in forest plots and synthesise their results, where appropriate. The 95% confidence intervals (CI) for each study were estimated using the Clopper-Pearson method [27]. For review question 1, in studies that identified participants through investigation of contacts or in outbreak investigations, we subtracted the index cases from the total number of people with SARS-CoV-2 infection, because these people were likely to have been identified because of their symptoms and their inclusion might lead to underestimation of the asymptomatic proportion [14]. For all meta-analyses, we used stratified random effects models. Where a meta-analysis was not done, we present the interquartile range (IQR) and describe heterogeneity visually in forest plots, ordered by study sample size [19]. For statistical examination
of heterogeneity, we calculated the $I^2$ statistic, which is the approximate proportion of between-study variability that is due to heterogeneity other than chance and $\tau^2$, the between-study variance, which is used to generate the 95% prediction interval for the likely range of proportions that would be obtained in subsequent studies conducted in similar settings [15]. The protocol pre-specified subgroup analyses according to study design, setting and risk of bias. We did a $\chi^2$ test to compare subgroups of studies assessed as being at low risk of bias in each domain versus those of unclear or high risk of bias and between studies assessed as being at low risk of bias in all domains with those at unclear or high risk of bias in any domain. In additional analyses, we examined studies with at least ten cases of SARS-CoV-2 infection and according to publication date. To compare our findings with other studies, we extracted the raw data from three large systematic reviews [12-14] and calculated prediction intervals. For review question 2, as a measure of infectiousness, we calculated the secondary attack rate as the number of SARS-CoV-2-infected contacts as a proportion of all close contacts ascertained. For each included study, we compared the secondary attack rate from asymptomatic or presymptomatic index cases with that from symptomatic cases in the same study. If there were no events in a group, we added 0.5 to each cell in the 2x2 table. We did not account for potential clustering of contacts because the included studies did not report the number and size of infection clusters consistently. We used the Hartung-Knapp method for random effects meta-analysis to estimate a summary risk ratio (with 95% CI) [28]. For review question 3, we reported the findings descriptively because of large differences between study settings, methods and results. We did not construct funnel plots to examine bias across studies because their utility in studies reporting on proportions is not clear.

**Results**

The searches for studies about asymptomatic or presymptomatic SARS-CoV-2, on 25 March, 20 April and 10 June 2020 and 2 February 2021 resulted in 89, 230, 688 and 4,293 records for screening, respectively (S1 Fig). In the first version of the review [17], 11 articles were eligible for inclusion [7, 29-38], version 2 identified another 26 eligible records, version 3 [10] identified another 61 eligible
records and this update, version 4, identified another 74 articles [39-112]. Owing to the change in eligible study designs, this update excludes 66 articles from earlier versions, comprising 23 contact tracing studies or outbreak investigations, 39 screening studies, and four mathematical models (S1 Table). This review version included a total of 107 studies addressing one or more objectives; 94 empirical studies that estimate the proportion of people with asymptomatic SARS-CoV-2 (summarised in Table 1 and S2 Table) [39-48, 50-54, 56-80, 82-90, 92-97, 99-102, 104-138], five studies reporting on secondary attack rates [119, 129, 138-140], and 11 mathematical modelling studies reporting on the contribution of asymptomatic or presymptomatic infection to all SARS-CoV-2 transmission [7, 49, 55, 81, 91, 98, 103, 141-144].

Proportion of people with asymptomatic SARS-CoV-2 infection

The 94 studies reported on 16,193 people with SARS-CoV-2 infection (5,905 defined as having asymptomatic infection) in 31 countries [39-48, 50-54, 56-80, 82-90, 92-97, 99-102, 104-138] (Table 1). Thirty-two studies, including 9,121 infected people, were done in the United States (S3 Table). At time of the latest search date, 17 records were preprints, 14 of which had been published in peer-reviewed journals by 23 November 2021 [7, 49, 55, 89, 92, 98, 102, 105, 125, 126, 128, 133, 141, 145] and 3 were still preprints [95, 96, 144]. In all included studies, 86 followed participants for seven days or more, 19 followed participants for at least 14 days after a known exposure, 27 followed participants until they had at least one negative RT-PCR test and 29 studies used more than one method of follow-up (Table 1, S2 Table). Most studies included adults (39 studies) or people of all ages (35 studies); only three studies included children only [65, 69, 132] and seven included older adults [48, 71, 84, 94, 114, 121, 122]. Ten studies did not report the age of the participants. Only 15 studies reported the median age [39, 47, 57, 59, 61, 64, 86, 107, 118, 121, 123, 124, 127, 137, 145] and only 21 studies reported the sex distribution of people with asymptomatic SARS-CoV-2 [39, 40, 46, 48, 50, 57, 59, 61, 63, 64, 72, 86, 87, 107, 113, 118, 121, 123, 124, 127, 137] (Table 1, S2 Table).

The types of included studies changed across the four versions of the review. In the first version [17], six of nine studies were contact tracing investigations of single-family clusters. In this version, two
main types of study design generated the study populations of people with SARS-CoV-2: contact tracing or outbreak investigation methods were used to identify and test potentially infected contacts (40 studies, referred to as contact and outbreak investigations); and studies that involved screening of a defined group of people in settings in the community, institutions, such as long-term care facilities, or occupational groups (54 studies, referred to as screening studies).
### Table 1. Summary of characteristics of studies reporting on proportion of asymptomatic SARS-CoV-2 infections (review question 1)

| Study designs and settings | Contact investigation | Outbreak investigation | Screening of defined study population | All studies |
|---------------------------|-----------------------|------------------------|---------------------------------------|-------------|
|                           |                       |                        | Community | Institutional | Occupational |             |
| Total studies, n          |                       |                        |           |              |              | 94          |
| Study characteristics a   |                       |                        |           |              |              |             |
| Publication date, n studies |                       |                        |           |              |              |             |
| January 2020 – June 2020  | 6                     | 9                      | 3         | 3            | 4            | 25          |
| July 2020 – December 2020| 5                     | 17                     | 11        | 17           | 6            | 56          |
| January 2021 – June 2021  | 1                     | 2                      | 3         | 4            | 3            | 13          |
| Region b, n studies       |                       |                        |           |              |              |             |
| Africa                    | 0                     | 0                      | 1         | 0            | 0            | 1           |
| Americas                  | 4                     | 9                      | 3         | 12           | 5            | 33          |
| South-East Asia           | 0                     | 3                      | 1         | 1            | 1            | 6           |
| Europe                    | 2                     | 11                     | 5         | 11           | 4            | 33          |
| Eastern Mediterranean     | 0                     | 0                      | 3         | 0            | 1            | 4           |
| Western Pacific           | 6                     | 5                      | 4         | 0            | 2            | 17          |
| Follow-up method, n studies |                       |                        |           |              |              |             |
| 14 days after last possible exposure | 1 | 1 | 0 | 0 | 0 | 2 |
| ≥7 days after diagnosis   | 4                     | 16                     | 8         | 18           | 6            | 52          |
| Until negative RT-PCR result | 1 | 2 | 2 | 4 | 2 | 11 |
| Two or more follow-up methods | 6 | 9 | 7 | 2 | 5 | 29 |
| Age range of study participants |       |                        |           |              |              |             |
| Children (<18 years), n studies | 1 | 1 | 0 | 1 | 0 | 3 |
| Adults (18 – 65 years), n studies | 2 | 9 | 7 | 10 | 11 | 39 |
| Older adults (>65 years), n studies | 0 | 5 | 0 | 2 | 0 | 7 |
| All ages, n studies       | 7                     | 12                     | 7         | 8            | 1            | 35          |
| Not reported, n studies   | 2                     | 1                      | 3         | 3            | 1            | 10          |

**Participant characteristics**

| Total SARS-CoV-2 infections, n individuals | 1055 | 4620 | 2378 | 7045 | 1095 | 16193 |
| Total asymptomatic SARS-CoV-2 total, n individuals | 246 | 1316 | 1093 | 3003 | 247 | 5905 |
| Gender of asymptomatic cases (if available c) |       |      |      |      |      |       |
| Male, n | 1     | 11   | 140  | 10   | 16   | 178   |
| Female, n | 0   | 1    | 169  | 294  | 26   | 490   |

SARS-CoV-2, severe acute respiratory syndrome coronavirus.

a Table 1 reports the characteristics of each study included for review question 1; b World Health Organization regions; c 80 studies did not report the gender of asymptomatic cases.
Between-study heterogeneity was considerable and we could not reliably estimate a range of plausible values for the proportion of asymptomatic infections for all included studies, or for screening studies (Fig 1). The IQR of estimates for all 94 included studies was 13-45% and the prediction interval from random-effects meta-analysis was 2-89% (S2 Fig). In studies enrolling people found through contact or outbreak investigations, for example in long-term care facilities, in aeroplanes, or on cruise ships, we estimated a summary estimate for the proportion asymptomatic (18%, 95% CI 14-24%, prediction interval 3-64%, IQR 8-35%, 40 studies [53, 60, 62, 65-68, 71, 73, 74, 82-86, 88, 90, 92, 93, 101, 105, 111, 112, 114-117, 119-123, 128-130, 132, 133, 136-138]. The estimated proportions of asymptomatic SARS-CoV-2 infections were similar in studies of contact investigations (16%, 95% CI 10-25%) and outbreak investigations (19%, 95% CI 14-26%) (S3 Fig).

In 54 screening studies, the IQR for estimates from individual studies was 18-59% and the prediction interval from random-effects meta-analysis was 3-95% [39-48, 50-52, 54, 56-59, 61, 63, 64, 69, 70, 72, 75-80, 88, 89, 94-97, 99, 100, 102, 104, 106-110, 113, 118, 124-127, 131, 134, 135]. We distinguished three settings in which screening studies were conducted; people in a community setting (17 studies, prediction interval 1-97%), institutional settings such as nursing homes (23 studies, prediction interval 5-95%), and occupational settings such as amongst groups of healthcare workers (13 studies, prediction interval 2-95%) (S3 Fig).

Risk of bias in individual studies
There were risks of bias in all types of empirical studies (S4 Fig). In pre-specified subgroup analyses according to risk of bias domains (Table 2), statistical heterogeneity remained very high (I² ≥ 84%) and the prediction intervals remained wide. In contact and outbreak investigations, the estimated proportion of asymptomatic individuals was associated with the risk of selection bias. In studies judged to be at low risk, 25% (95% CI 18-33%, prediction interval 5-66%) and 13% (95% CI 8-20%,
prediction interval 1-61%) in studies at unclear or high risk of bias (p=0.02 from χ² test for subgroup differences). In screening studies, heterogeneity was lower in studies judged to be at low risk of information bias in the assessment of symptoms (p>0.01, test for subgroup differences), with a summary estimate of the proportion asymptomatic of 23% (95% CI 14-35%, prediction interval 4-69%). Only nine studies were judged to be at low risk of bias in all domains, with some evidence of reduced heterogeneity (p=0.05, test for subgroup differences). For all other domains, estimates of heterogeneity were not associated with the assessment of the risk of bias.

Additional analyses

When restricted to studies with more than ten people with SARS-CoV-2 infection (S5 Fig), the estimated proportions with asymptomatic infection were very similar to the overall estimates (Fig 1, Table 2). The estimates of the proportion asymptomatic in the three periods of publication date were similar (S6 Fig, S7 Fig). In the three systematic reviews that we re-analysed, prediction intervals were: 1-83% (241 studies [12]); 4-97% (95 studies [13]); and 3-89% (170 studies [14]). I² values were between 94% and 99% (S4 Table).
Table 2. Summary of findings from subgroup analyses according to risk of bias in studies estimating the proportion of asymptomatic SARS-CoV-2 infections

| Risk of selection bias | Contact and outbreak investigations | Screening of defined study population | Subgroup diff, p value |
|------------------------|------------------------------------|--------------------------------------|------------------------|
| Low (S8 Fig)           | 22                                 | 16                                   | 0.02                   |
| Unclear/high (S8 Fig)  | 23                                 | 40                                   |                        |
| **n**                  | **Summary estimate (95% CI)**      | **Prediction interval**               | **I²**                 |
| 22                     | 0.25 (0.18-0.33)                   | 0.05-0.66                            | 84%                    |
| 23                     | 0.13 (0.08-0.20)                   | 0.01-0.61                            | 87%                    |
| **n**                  | **Summary estimate (95% CI)**      | **Prediction interval**               | **I²**                 |
| 16                     | 0.40 (0.27-0.56)                   | 0.05-0.90                            | 93%                    |
| 40                     | 0.42 (0.29;057)                    | 0.02-0.97                            | 93%                    |
| **n**                  | **Summary estimate (95% CI)**      | **Prediction interval**               | **I²**                 |
| 11                     | 0.23 (0.14-0.35)                   | 0.04-0.69                            | 92%                    |
| 47                     | 0.49 (0.33;0.59)                   | 0.03-0.97                            | 93%                    |
| **n**                  | **Summary estimate (95% CI)**      | **Prediction interval**               | **I²**                 |
| 9                      | 0.23 (0.14-0.35)                   | 0.04-0.69                            | 92%                    |
| 47                     | 0.49 (0.33;0.59)                   | 0.03-0.97                            | 93%                    |
| **n**                  | **Summary estimate (95% CI)**      | **Prediction interval**               | **I²**                 |
| 9                      | 0.23 (0.14-0.35)                   | 0.04-0.69                            | 92%                    |
| 47                     | 0.49 (0.33;0.59)                   | 0.03-0.97                            | 93%                    |

*Assessed in the risk of bias tool (S2 Text), with full assessments in S4 Fig.

*n = number of clusters analysed, which exceeds the total number of studies.
Infectiousness of people with asymptomatic or presymptomatic SARS-CoV-2

Five of the studies that conducted detailed contact investigations provided enough data to calculate a secondary attack rate according to the symptom status of the index cases and to compare the secondary attack rates by symptom status (Fig 2) [119, 129, 138-140]. The updated search did not identify any new studies. Four studies compared the secondary attack rate from asymptomatic with symptomatic index cases (summary risk ratio 0.43 (95% CI 0.05-3.44, prediction interval 0-67%) [119, 129, 139, 140]. One study compared asymptomatic with presymptomatic index cases (summary risk ratio 0.19, 95% CI 0.02-1.46) [138] and three studies compared presymptomatic with symptomatic index cases (summary risk ratio 0.71 (95% CI 0.36-1.41, prediction interval 0.10-5.28) [119, 129, 139]. The risk of information bias, specifically in symptom assessment, was judged to be high or unclear in all five studies included (S4 Fig).

Contribution of asymptomatic and presymptomatic infection to SARS-CoV-2 to transmission

We included 11 mathematical modelling studies (Fig 4) [7, 49, 55, 81, 91, 98, 103, 141-144]. Four studies were new [49, 81, 91, 98] and one study from the previous version [31] was replaced by a more recent analysis based on the same data [103]. The models in eight studies were informed by analyses of data from contact investigations in China, South Korea, Singapore, and from an outbreak on the Diamond Princess cruise ship, using data to estimate the serial interval or generation time [7, 49, 55, 91, 98, 103, 141, 142]. In the other three studies the authors did not analyse any original data sources [81, 143, 144].

Estimates of the contributions of both asymptomatic and presymptomatic infections SARS-CoV-2 transmission were very heterogeneous. For asymptomatic SARS-CoV-2 infection, three studies contributed four estimates [7, 55, 81]. Three estimates suggested a contribution to SARS-CoV-2 transmission of asymptomatic infection of less than 10%. One study estimated a higher proportion (69%, 95% CrI 20–85%) with a wide credibility interval [55] (Fig 4). The estimates have large
uncertainty intervals, and the disparate predictions result from differences in the proportion of 
asymptomatic infections and relative infectiousness of asymptomatic infection.

We included 11 studies providing 16 estimates of the contribution of presymptomatic transmission. 
The models examined a range of epidemic settings and used different assumptions about the 
durations and distributions of infection parameters such as incubation period, generation time and 
serial interval [7, 49, 55, 81, 91, 98, 103, 141-144]. In seven studies, point estimates for the 
estimated contribution of presymptomatic infection to all SARS-CoV-2 transmission in at least one 
reported scenario were 40% or greater [7, 81, 91, 98, 103, 142, 144] (Fig 3). In one study that 
estimated a contribution of <1% [143], the model-fitted serial interval was longer than observed in 
empirical studies. The credibility of most modelling studies was limited by the absence of external 
validation and of uncertainty intervals for the estimates cited. (S18 Fig). The estimates from studies 
that relied on data from different published sources that might not have been compatible were 
assessed as providing low quality evidence (S5 Table).

Discussion

Summary of main findings

Between-study heterogeneity precluded a reliable estimate of a range of plausible values for the 
proportion of asymptomatic infections for all included studies, or for screening studies. In studies 
that identified participants through contact tracing of index cases and outbreak investigations, the 
proportion of asymptomatic infections was 18% (95% CI 14-24%, prediction interval 3-64%, 40 
studies). In 54 studies that identified SARS-CoV-2 infection through screening of defined populations, 
the prediction interval was 3-94% (IQR 18-59%). The risk ratio for the secondary attack rate from 
asymptomatic compared with symptomatic infections was 0.43 (95% CI 0.05-3.44, prediction interval 
0.0-67.1) and for presymptomatic infections compared with symptomatic infection was 0.71 (95% CI 
0.36-1.41, prediction interval 0.10-5.28). In mathematical modelling studies, estimated proportions 
of all SARS-CoV-2 infections that result from transmission from asymptomatic individuals were 
mostly below 10%, and from presymptomatic individuals mostly higher than 40%.
Strengths and weaknesses of the living systematic review methods

A strength of the methodology of this review is the transparent reporting, with openly available data and changes over different versions reported in the protocol. Our inclusion criteria attempted to reduce risks of bias and we developed a new tool to address potential biases in the studies included in this review. In contact investigations, we subtracted index cases from the total number of people with SARS-CoV-2 to avoid underestimation of the proportion asymptomatic [14]. We examined heterogeneity in detail and, as a result of the wide prediction interval, we chose not to report an overall summary estimate [19, 146]. A limitation of the methods for this living systematic review is that this update only includes published studies up to 2 February 2021. Although we made extensive efforts to comply with the planned 3-monthly updates, with weekly searches and a continuous process of screening, data extraction and risk of bias assessment, the pace of publications about SARS-CoV-2 exceeds the capacity of our crowd of reviewers [8, 20]. In reviews of observational epidemiological studies, search terms are broad so the number of studies that needs to be screened is high, but the yield of included studies is low. We are in the process of updating our findings and preliminary analyses show that the main findings do not change when including studies published up to April 2021. The four databases that we searched are not comprehensive, but they cover the majority of publications and we do not believe that we have missed studies that would change our conclusions. We have also not considered the possible impact of false negative RT-PCR results, which might be more likely to occur in asymptomatic infections [147] and would underestimate the proportion of asymptomatic infections [148]. We found no published studies of people infected with SARS-CoV-2 variants of concern or of vaccinated people, in line with another systematic review that includes studies published up to April 2021 [14]. Other limitations related to the studies included are discussed below.

Comparison with other reviews and interpretation

The type of studies that provide estimates of the proportion of asymptomatic SARS-CoV-2 infections and heterogeneity between them has changed over the course of the pandemic. In our living systematic review, the prediction interval has widened from 23-37% in studies published up to 25
March 2020 [17], to 3-67% up to June 2020 [10] and 2-89% up to 2 February 2021. We found three systematic reviews, in which authors reported restriction of inclusion to studies with adequate follow-up [9, 11, 14]. In two reviews of studies published up to mid-2020, authors also applied inclusion criteria to reduce the risks of selection bias, with summary estimates of 18% (95% CI 9–26%, I² 84%, 9 studies) [11] and 23% (95% CI 16–30%, I² 92%, 21 studies) [9]. In both reviews, many included studies used designs that we defined as contact or outbreak investigations (Fig 1, S2 Table).

Sah et al. reviewed studies published up to April 2021 and their subgroup estimate from studies in long-term care facilities, which include many outbreak investigations, was 17.8%, 95% CI 9.7-30.3%, 15 studies [14]. The summary estimates from all these reviews are compatible with our estimate from 40 studies in similar settings (18%, 95% CI 0.14-24%, prediction interval 3-64%, I² 91%) (S3 Fig).

It may not be possible to obtain a single summary estimate from published literature of the proportion of persistently asymptomatic SARS-CoV-2 infection. Systematic reviews from meta-analysis might be precise, but are likely to be unreliable owing to unacceptably high levels of heterogeneity. In the three largest systematic reviews, other than ours, authors provided overall estimates with narrow confidence intervals [12-14]. I² values were 94-99%, describing heterogeneity other than that due to chance, but prediction intervals, which show the extent of all between-study variability were not reported [15]. The prediction intervals that we calculated extended more or less from zero to 100%, making the summary estimates, and any differences in estimates between these studies, uninterpretable. We expected this update to our living systematic review to provide a more precise and less heterogeneous estimate of the proportion of people with asymptomatic SARS-CoV-2 than in the previous version [10]. In particular, we expected that studies that detect SARS-CoV-2 through screening of defined populations and follow up of those infected would be less affected by biases in study methodology [24] and would provide a more accurate estimate of persistently asymptomatic SARS-CoV-2, which should be influenced mainly by properties of the virus and the host response to infection [149]. Information bias, resulting from the way in which asymptomatic status is determined, was the factor most strongly associated with the estimated proportion of
asymptomatic infection in screening studies (Table 2). Studies in which a wide range of possible
COVID-19 symptoms are assessed frequently will classify more people as having symptoms than
studies with a limited symptom list. Studies based on contact and outbreak investigations might
obtain more detailed data about symptoms, resulting in lower estimates of the proportion that is
classified as asymptomatic. Selection bias affected studies based on contact and outbreak
investigations more than screening studies, however. These studies include people identified mainly
through contact tracing and differential inclusion of contacts with symptoms might underestimate
the true proportion of asymptomatic SARS-CoV-2. Age might play a role as children appear more
likely than adults to have an asymptomatic course of infection, but age was poorly reported in
studies included in this review (Table 1).

The analysis of secondary attack rates in this update provides some evidence of lower infectiousness
of people with asymptomatic than symptomatic infection, but the small number of studies and wide
confidence intervals are compatible with both no difference in transmissibility or higher
transmissibility (Fig 2) [128, 129, 139]. The difference in secondary attack rates between
asymptomatic and symptomatic index cases in our meta-analysis is smaller than that obtained when
groups of studies of asymptomatic index cases and of symptomatic cases are analysed separately
[149, 150]. In meta-analyses of two proportions, the direct comparison within studies reduces
heterogeneity and is less biased [28]. Since SARS-CoV-2 can be transmitted a few days before the
onset of symptoms [151], presymptomatic transmission likely contributes substantially to overall
SARS-CoV-2 epidemics. If both the proportion and transmissibility of asymptomatic infection are
relatively low, people with asymptomatic SARS-CoV-2 infection should account for a smaller
proportion of overall transmission than presymptomatic individuals. This is consistent with the
findings of modelling studies in our review.

Implications and unanswered questions
The finding that, in studies of contact and outbreak investigations, a substantial minority of people
with SARS-CoV-2 infection remains asymptomatic throughout the course of infection, and that
almost half of all transmission might occur before symptoms develop has already had implications for prevention. When SARS-CoV-2 community transmission levels are high, physical distancing measures and mask-wearing need to be sustained to prevent transmission from close contact with people with asymptomatic and presymptomatic infection. Integration of evidence from epidemiological, clinical and laboratory studies will help to clarify the relative infectiousness of asymptomatic SARS-CoV-2. Studies using viral culture as well as RNA detection are needed since RT-PCR defined viral loads appear to be broadly similar in asymptomatic and symptomatic people [147, 152]. Since late 2020, several SARS-CoV-2 variants of concern have spread internationally [153]. The omicron variant is substantially different from both wild type SARS-CoV-2 and other variants of concern and, owing to high infectiousness and immune evasion, is the dominant variant globally [154]. The clinical characteristics of SARS-CoV-2 infection caused by the omicron variant are not yet known. Future studies and systematic reviews should address evidence about the effects of both variants of concern and vaccines on asymptomatic and presymptomatic SARS-CoV-2. Studying the proportion of asymptomatic infection have become more complicated, however, because of the availability of vaccines that reduce the risk of infection and transmission, and which might also change the clinical presentation of breakthrough infection.

This living systematic review shows the challenges of synthesising evidence from observational epidemiological studies and has implications for the design and reporting of both systematic reviews and the methodology of individual studies. Methodological guidance to refrain from meta-analysis when the variability between studies is extreme is often ignored in favour of summary estimates, which are easy to cite [146]. Heterogeneity in systematic reviews of proportions is a recognised challenge [28, 155]. Part of the heterogeneity arises from the fact that many studies included in this review were not designed to estimate the proportion of asymptomatic SARS-CoV-2 infection. The incomplete descriptions of inclusion criteria, follow-up and definitions of symptom status required in this review made it difficult to assess the risks of bias. To estimate the true proportion of asymptomatic SARS-CoV-2 infections, researchers need to design studies to address this specific...
research question. Prospective longitudinal studies with methods that minimise selection and measurement biases, with frequent prospective documentation of symptom status, based on a defined symptom list [1]. More studies that assess symptom status carefully in index cases and assess transmission to contacts are needed to quantify the relative transmissibility of SARS-CoV-2 more precisely. Transparent reporting in all studies will help to assess the risks of bias. Without prospective longitudinal studies with methods that minimise selection and measurement biases, further updates to this living systematic review are unlikely to provide a reliable summary estimate of the proportion of asymptomatic infections caused by wild-type SARS-CoV-2.
Figure legends

Figure 1. Forest plot of proportion of people with asymptomatic SARS-CoV-2 infection, stratified by study design. The x-axis displays proportions. Where more than one cluster was reported, clusters are annotated with '[cluster]'. The interquartile range is given below the individual study estimates. The red bar and grey text show the prediction interval.

Figure 2. Forest plot of the secondary attack rate of SARS-CoV-2 infections comparing infections in contacts of asymptomatic and presymptomatic index cases with infections in contacts of symptomatic cases. The RR is on a logarithmic scale. The diamonds show the summary estimate and its 95% confidence interval. CI, confidence interval; E, number of secondary transmission events; N, number of close contacts; RR, risk ratio; Symp. = symptomatic individuals.

Figure 3. Forest plot of proportion ('Prop.') of SARS-CoV-2 infection resulting from asymptomatic or presymptomatic transmission. For studies that report outcomes in multiple settings, these are annotated in brackets. CI, confidence interval; SI, serial interval.
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Competing interests
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S15 Fig. Forest plot of proportion of people with asymptomatic SARS-CoV-2 infection in screening studies by risk of attrition bias.

S16 Fig. Forest plot of proportion of people with asymptomatic SARS-CoV-2 infection in contact and outbreak investigations by risk of bias in all domains.

S17 Fig. Forest plot of proportion of people with asymptomatic SARS-CoV-2 infection in screening studies by risk of bias in all domains.

S18 Fig. Assessment of credibility of mathematical modelling studies.
| Study | Contact and outbreak investigations | Events | Total | Proportion 95%CI |
|------|-----------------------------------|--------|-------|-----------------|
| Corcoran MA | 3 | 8 | 0.38 (0.09, 0.77) |
| Pinney JP | 4 | 9 | 0.44 (0.14, 0.70) |
| Ying N | 2 | 10 | 0.20 (0.05, 0.53) |
| Hirten D | 1 | 11 | 0.09 (0.00, 0.41) |
| Schweizer V | 2 | 11 | 0.18 (0.02, 0.52) |
| Danski K | 1 | 12 | 0.08 (0.00, 0.38) |
| Zhang W | 4 | 12 | 0.33 (0.05, 0.70) |
| Romao VC | 0 | 14 | 0.00 (0.00, 0.23) |
| Böhmer MM | 1 | 16 | 0.06 (0.00, 0.30) |
| Dors AV | 6 | 16 | 0.38 (0.16, 0.57) |
| Yeu K | 7 | 20 | 0.35 (0.15, 0.59) |
| Cheng HY | 4 | 22 | 0.18 (0.04, 0.34) |
| Reddit V | 3 | 24 | 0.13 (0.02, 0.32) |
| Tian S | 7 | 24 | 0.29 (0.13, 0.51) |
| Harada S [Patients] | 8 | 24 | 0.33 (0.16, 0.55) |
| Park JH | 4 | 25 | 0.14 (0.04, 0.33) |
| Patel MC | 13 | 35 | 0.37 (0.21, 0.55) |
| Brandtletter S | 2 | 36 | 0.06 (0.01, 0.19) |
| Kittang BR | 0 | 46 | 0.00 (0.00, 0.09) |
| Pavl A | 7 | 46 | 0.15 (0.06, 0.26) |
| Yousaf AR | 0 | 47 | 0.00 (0.00, 0.08) |
| Arora MM | 3 | 47 | 0.06 (0.01, 0.18) |
| Wu J | 5 | 48 | 0.10 (0.03, 0.23) |
| Harada S [Healthcare workers] | 25 | 49 | 0.51 (0.36, 0.66) |
| Ladhan SN [SNs] | 29 | 51 | 0.58 (0.49, 0.67) |
| van den Besselaar JH [Healthcare workers] | 1 | 54 | 0.02 (0.00, 0.10) |
| Pirolski | 14 | 66 | 0.21 (0.12, 0.33) |
| Nijhuis H | 20 | 77 | 0.26 (0.13, 0.41) |
| Bi Q | 17 | 87 | 0.20 (0.12, 0.39) |
| Jones A | 24 | 87 | 0.28 (0.19, 0.38) |
| Park SY | 4 | 91 | 0.04 (0.01, 0.10) |
| Taylor J [Healthcare personnel] | 9 | 99 | 0.09 (0.04, 0.17) |
| Grigova | 34 | 103 | 0.33 (0.24, 0.43) |
| Ladhan SN [SNs] | 46 | 105 | 0.44 (0.34, 0.54) |
| van den Besselaar JH [Patients] | 7 | 113 | 0.06 (0.03, 0.13) |
| Graham N | 46 | 122 | 0.38 (0.28, 0.48) |
| Taylor J | 7 | 127 | 0.06 (0.02, 0.11) |
| Luo L2 | 8 | 127 | 0.06 (0.03, 0.12) |
| Shi Q | 60 | 183 | 0.33 (0.26, 0.40) |
| Pham QT | 89 | 208 | 0.43 (0.35, 0.50) |
| Hurst JH | 87 | 293 | 0.30 (0.25, 0.35) |
| Kennelly SP [nursing home staff] | 97 | 355 | 0.27 (0.23, 0.31) |
| Lee JY | 80 | 694 | 0.12 (0.09, 0.15) |
| Kennelly SP [nursing home residents] | 193 | 710 | 0.27 (0.24, 0.31) |
| Kasper MR | 572 | 1271 | 0.45 (0.42, 0.48) |

**Preliminary interval**

| Interquartile range | 0.06 | 0.35 |

**Prediction interval**

| Interquartile range | 0.01 |

**Heterogeneity:** $I^2 = 91\%$, $t^2 = 0.0298$, $p < 0.01$

*Test for subgroups differences*: $\chi^2 = 17.05$, $df = 1$ ($p < 0.01$)
| Author                  | E/N       | E/N (Symp.) | Risk Ratio | RR       | 95%-CI    |
|-------------------------|-----------|-------------|------------|----------|-----------|
| **Asymptomatic vs. Symptomatic** |           |             |            |          |           |
| Cheng HY                | 0/91      | 22/2644     | 0.64       | [0.04;   | 10.51]   |
| Park SY                 | 0/4       | 34/210      | 0.68       | [0.05;   | 9.42]    |
| Luo L1                  | 1/305     | 117/2305    | 0.06       | [0.01;   | 0.46]    |
| Chaw L                  | 3/106     | 28/1010     | 1.02       | [0.32;   | 3.30]    |
| Random effects model    |           |             |            | 0.43     | [0.05;   | 3.44]    |
| Prediction interval     |           |             |            | [0.00;   | 67.08]   |
| Heterogeneity: $I^2 = 47\%$, $\tau^2 = 0.9514$, $p = 0.13$ | | | | | |
| **Asymptomatic vs. Presymptomatic** |           |             |            |          |           |
| Zhang W                 | 1/119     | 11/250      | 0.19       | [0.02;   | 1.46]    |
| Random effects model    |           |             |            | 0.19     | [0.02;   | 1.46]    |
| Prediction interval     |           |             |            | [0.02;   | 1.46]    |
| Heterogeneity: not applicable | | | | | |
| **Presymptomatic vs. Symptomatic** |           |             |            |          |           |
| Park SY                 | 0/11      | 34/210      | 0.27       | [0.02;   | 4.06]    |
| Cheng HY                | 2/299     | 22/2644     | 0.80       | [0.19;   | 3.40]    |
| Chaw L                  | 12/585    | 28/1010     | 0.74       | [0.38;   | 1.44]    |
| Random effects model    |           |             |            | 0.71     | [0.36;   | 1.41]    |
| Prediction interval     |           |             |            | [0.10;   | 5.28]    |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.76$ | | | | | |

Test for subgroup differences: $\chi^2 = 2.10$, df = 2 ($p = 0.35$).
| Study                                      | Prop. | 95% CI     |
|-------------------------------------------|-------|------------|
| **Asymptomatic transmission**             |       |            |
| Ferretti L                                | 0.06  | [0.00;0.57]|
| Moghadas SM [17.9% asymptomatic]          | 0.03  |            |
| Emery JC                                  | 0.69  | [0.20;0.85]|
| Moghadas SM [30.8% asymptomatic]          | 0.07  |            |
| **Pre-symptomatic transmission**          |       |            |
| Ferretti L                                | 0.47  | [0.11;0.58]|
| Zhang W [Early Transmission]              | 0.20  |            |
| Zhang W [Imported Cases]                  | 0.80  |            |
| He X                                      | 0.44  | [0.25;0.69]|
| Peak CM [Short SI]                        | 0.20  | [0.00;0.91]|
| Peak CM [Long SI]                         | 0.00  | [0.00;0.01]|
| Tindale LC [Singapore]                    | 0.74  |            |
| Tindale LC [Tianjin]                      | 0.81  |            |
| Moghadas SM [17.9% asymptomatic]          | 0.48  |            |
| Moghadas SM [30.8% asymptomatic]          | 0.47  |            |
| Ren X                                     | 0.40  |            |
| Chun JY                                   | 0.37  | [0.16;0.52]|
| Bushman M                                 | 0.34  | [0.28;0.41]|
| Sun K                                     | 0.53  |            |