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BMJ Open Relative infectiousness of asymptomatic SARS-CoV-2 infected persons compared with symptomatic individuals: a rapid scoping review

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ABSTRACT

Objectives The aim of this study was to determine the relative infectiousness of asymptomatic SARS-CoV-2 infected persons compared with symptomatic individuals based on a scoping review of available literature.

Design Rapid scoping review of peer-reviewed literature from 1 January to 5 December 2020 using the LitCovid database and the Cochrane library.

Setting International studies on the infectiousness of individuals infected with SARS-CoV-2.

Participants Studies were selected for inclusion if they defined asymptomatics as a separate cohort distinct from presymptomatics and if they provided a quantitative measure of the infectiousness of asymptomatics relative to symptomatics.

Primary outcome measures PCR result (PCR studies), the rate of infection (mathematical modelling studies) and secondary attack rate (contact tracing studies) - in each case from asymptomatic in comparison with symptomatic individuals.

Results There are only a limited number of published studies that report estimates of relative infectiousness of asymptomatic compared with symptomatic individuals. 12 studies were included after the screening process. Significant differences exist in the definition of infectiousness. PCR studies in general show no difference in shedding levels between symptomatic and asymptomatic individuals; however, the number of study subjects is generally limited. Two modelling studies estimate relative infectiousness to be 0.43 and 0.57, but both of these were more reflective of the infectiousness of undocumented rather than asymptomatic cases. The results from contact tracing studies include estimates of relative infectiousness of 0, but with insufficient evidence to conclude that it is significantly different from 1.

Conclusions There is considerable heterogeneity in estimates of relative infectiousness highlighting the need for further investigation of this important parameter. It is not possible to provide any conclusive estimate of relative infectiousness, as the estimates from the reviewed studies varied between 0 and 1.

INTRODUCTION

The first case of COVID-19 was first reported from Wuhan, China, in December 2019.¹

Strengths and limitations of this study

- A strength of this study is that it only included peer-reviewed studies.
- This study also had a robust screening process that was used to ensure that the relative infectiousness of asymptomatic compared with symptomatic was defined properly. It ensured that each study properly distinguished asymptomatic and presymptomatic individuals.
- Differences in the definition of infectiousness and the heterogeneity in results between studies negate the potential to provide a pooled quantitative estimate of relative infectiousness.
- The present study highlights the need for additional studies in this area.

The outbreak of COVID-19 was declared a Public Health Emergency of International Concern on 30 January 2020 and a pandemic was declared on 11 March 2020.² Since then, many countries have sought to contain the spread of the virus through a range of measures aimed at limiting transmission within the population.

At the outset of an epidemic, a key principle of control might be quarantining of individuals with clinical symptoms fitting a particular case definition. However, for many infectious diseases, a proportion of infected individuals may never present with clinical signs (ie, asymptomatic) yet still be infectious to others. The existence of this cohort of SARS-CoV-2 infected individuals is now well recognised.³

The transmission potential of such asymptomatic individuals is likely to be different from those who have clinical signs. On the one hand, they might shed lower quantities of the infectious agent; on the other hand, their potential for contacts might be greater. Being unaware that they are infected,



asymptomatic people are less likely to follow quarantine guidelines designed to restrict transmission from infected individuals.

Decision making in the midst of a pandemic often relies on predicted outcomes from infectious disease models. Such models may aid in public health decision making by predicting the number of new cases each day as well as possible trajectories of an outbreak given different management options. Estimates from these models may be sensitive to the way in which asymptomatic individuals are considered.⁴ In particular, it is important to understand the proportion of individuals who are infectious but remain asymptomatic, as well as understanding the transmission potential in that cohort, compared with symptomatic individuals, that is, the relative infectiousness.

This study sought to determine the relative infectiousness of asymptomatic SARS-CoV-2 infected persons compared with symptomatic individuals, based on a scoping review of available literature. A scoping review rather than a systematic review was undertaken given the rapidly evolving and complex literature available on SARS-CoV-2 infection and the range of ways in which 'infectiousness' might be defined and measured.

MATERIALS AND METHODS

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols with extension for scoping reviews guidelines.⁵ A review protocol was established for this work, but the review was not preregistered.

The LitCovid database, a curated literature hub for tracking up-to-date scientific information about the COVID-19, was searched up until 5 December 2020 using the following search strategy: (infectious* OR transmissibility OR spread*) AND (asymptomatic* OR symptomatic* OR pre-symptomatic*⁶). The Cochrane database was also searched.

During primary screening, all abstracts from the initial screening process were screened by the first author. Only peer-reviewed studies were considered further. We retained abstracts with subject matter relating to any of the following: the dynamics of infectiousness, contact tracing studies, mathematical studies of transmission, studies that explicitly mentioned relative infectiousness and studies that compared the infectiousness of symptomatic and asymptomatic individuals. Other studies were excluded, including those relating to transmission in animals, COVID-19 comorbidities, risk factors, diagnosis, treatment and healthcare services, immunity and vaccination.

The secondary screening, a full-paper review, was conducted by the first author. Only English language papers were considered further. At this stage, we retained those papers that specifically identified cohorts of asymptomatic and symptomatic individuals and those that provided estimates of infectiousness (or relative infectiousness) using methods that were either direct (viral load or PCR testing) or indirect (contact tracing methods

or posterior estimates from mathematical models). For the purpose of this study, we defined symptomatic and asymptomatic individuals as people who did or did not develop symptoms of COVID-19 during confirmed SARS-CoV-2 infection. Furthermore, we considered symptomatic infection to incorporate both the presymptomatic and symptomatic phases of infection. We excluded editorials, letters or commentaries. Reviews were included for further consideration during the tertiary screen. During secondary screening, all retained papers were categorised as either reviews, contact tracing studies, PCR studies and mathematical modelling studies.

During the tertiary screening process, each paper was independently reviewed by two people: the first author and either CM or SJM. For all papers, we only retained those with reported methods to differentiate presymptomatic and asymptomatic individuals (noting that presymptomatics will eventually develop symptoms, given sufficient time). For the mathematical modelling papers, we also only retained those with posterior (calculated) rather than prior (input) estimates of (relative) infectiousness. Each review was checked to identify any additional references; these were then each screened using the three-step screening process as outlined. The reviews were then excluded.

With the contact tracing studies, we calculated relative infectiousness by comparing the secondary attack rate (SAR) of asymptomatic and symptomatic primary cases. The SAR is the number of secondary cases among all those people who were considered close contacts of the primary case. In papers where the point estimate for relative infectiousness was 0, we used Fisher's exact test to test the null hypothesis that the SARs were equal (ie, relative infectiousness was 1). In those papers that identified three groups of primary cases (asymptomatic, presymptomatic and symptomatic), the latter two groups (presymptomatic and symptomatic) were combined.

With the PCR studies, we provide a narrative description of relative infectiousness by comparing the viral load from asymptomatic and symptomatic individuals, generally based on cycle threshold (Ct) values during PCR testing. The Ct is a semiquantitative value that can broadly categorise the concentration of viral genetic material in a patient sample following testing by RT PCR, with a low Ct indicating a high concentration of viral genetic material (typically associated with a high risk of infectivity) and a high Ct indicating a low concentration of viral genetic material (typically associated with a lower risk of infectivity).⁷

With the modelling studies, relative infectiousness was extracted as the model-inferred estimate of the 'infectiousness factor', which used as a multiplier on the infectiousness of asymptomatic infected individuals relative to symptomatic infectious individuals.

A quality assessment was conducted on all retained papers using the following criteria:

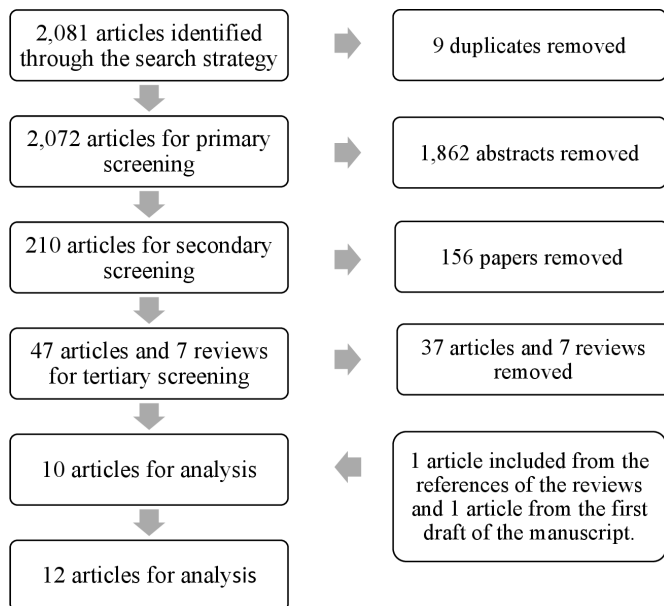


Figure 1 Screening process of the articles.

Contact tracing studies

- ▶ *Asymptomatic status.* Methodology used to confirm the asymptomatic status of individuals in the asymptomatic cohort. As a minimum, evidence of observation over time. Earlier work by Buitrago-Garcia *et al*⁸ represents the gold standard, where asymptomatic status was confirmed as follows: a person with laboratory-confirmed SARS-CoV-2 infection, who has no symptoms 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 reverse transcriptase PCR (RT-PCR) test results; follow-up for 14 days or more after the last possible exposure to an index case; and follow-up for 7 days or more after the first RT-PCR positive result.
- ▶ *Identification of close contacts.* Methodology to protect against the potential for bias, between the symptomatic and asymptomatic cohorts, in the identification of close contacts.
- ▶ *Case ascertainment.* Methodology to protect against ascertainment bias, between the symptomatic and asymptomatic cohorts, when identifying close contacts.
- ▶ *Case attribution.* Methodology to minimise error during case attribution. An understanding of the period of infectiousness (including symptom onset) in the index case and exposure period for close contact(s) are each required.
- ▶ *External validity.* The representativeness of the index cases and close contacts for the broader population of interest.

PCR studies

- ▶ *Asymptomatic status.* As above.

- ▶ *Testing methods.* Methodology to maximise accuracy and precision of PCR testing.
- ▶ *Considerations relating to infectiousness profile.* Methodology to minimise bias, between the symptomatic and asymptomatic cohorts, when assessing the magnitude and/or duration of the period of infectiousness.
- ▶ *External validity.* As above.

Mathematical modelling studies

- ▶ *Representativeness of the studied compartment.* Determining whether the model compartment is reflective of the true asymptomatic cohort.
- ▶ *Consideration of the range of values within which the model estimate is confined.* How wide and what range is the parameter estimate confined within, and does the final parameter estimate indicate that this range may not be appropriate.
- ▶ *Model validation.* Whether the model was validated on different sources of data, data from different countries or data from different points in time.

RESULTS

The search strategy in LitCovid resulted in 2081 articles, whereas no results were given in the Cochrane database. After nine duplicates were removed, the abstracts of 2072 articles were reviewed in the primary screening stage yielding 210 articles for the secondary screening process. During secondary screening, 156 papers were removed leaving 47 articles and 7 review papers for the third screening process. During tertiary screening, 37 articles were removed, and the references of each of the seven review papers were examined, leaving 10 papers for analysis. All relevant references from the review papers and an earlier draft of the current paper were screened using the three-stage process, and two were included for analysis, namely Long *et al*⁹ and Li *et al*,¹⁰ respectively. Therefore 12 studies were retained for the current study. A summary of the screening process is presented in figure 1.

Table 1 provides an overview of the 12 papers, including the type and location of study, the number of relevant study subjects, either number of individuals with available PCR results (PCR studies) or the number of close contacts (contact tracing studies). Numbers of study subjects for modelling studies are not included given that these studies aimed to partition large (national) populations into disease compartments rather than following study participants per se.

In three out of the five PCR studies (namely from Uhm *et al*,¹¹ Lavezzo *et al*¹ and Danis *et al*¹²), the PCR values were similar among asymptomatic and symptomatic carriers. In Long *et al*,⁹ initial Ct values were similar in these two cohorts; however, the duration of shedding based on PCR among asymptomatics was longer than for mild symptomatic individuals. This is in contrast to the Letizia *et al*¹³ study, where the viral load, as estimated using PCR, was approximately four times higher in symptomatic compared with the asymptomatic individuals. However, this study also

Table 1 Estimates of the infectiousness of asymptomatic compared with symptomatic individuals, by study type (PCR studies, modelling studies and contact tracing studies)

Author	Location	Number of relevant study subjects	Measure of relative infectiousness
PCR studies			
Letizia <i>et al</i> ¹³	South Carolina, USA	51	The viral load at diagnosis was approximately four times as high (4.39, S.gene; 4.3, N.gene; 5.22, ORF 1ab) in the five symptomatic participants compared with the 46 asymptomatic participants. However, some asymptomatic participants had higher viral loads estimated on the basis of the cycle threshold (Ct).
Uhm <i>et al</i> ¹¹	South Korea	396	There was no significant difference in the first follow-up Ct value for the E, RdRP and N genes between symptomatic and asymptomatic individuals.
Lavezzo <i>et al</i> ¹	Vo', Italy	58	There was no significant difference between asymptomatic and symptomatic participants based on viral PCR recovered from the nasopharyngeal swabs.
Danis <i>et al</i> ¹²	Les Contamines-Montjoie, France	††	The viral load was described as being similar among the six study subjects (one asymptomatic and five symptomatic cases).
Long <i>et al</i> ⁹	Wanzhou, China	74	The initial Ct values were similar among the asymptomatic and mild symptomatic individuals, whereas the duration of shedding among asymptomatics was longer than for mild symptomatic individuals.
Modelling studies, estimate (95% CI)			
Nabi ²	Dhaka, Bangladesh	NA*	0.57†
Li <i>et al</i> ¹⁰	China	NA*	0.55 (0.46 to 0.62)†, ** 0.50 (0.37 to 0.69)§, ** 0.43 (0.31 to 0.61)¶, **
Contact tracing studies			
Park <i>et al</i> ¹⁴	Seoul, South Korea	225	Secondary attack rate: <ul style="list-style-type: none"> ▶ Among asymptomatic primary cases=0/4=0. ▶ Among symptomatic and presymptomatic primary cases=34/221=0.05. Relative risk (RR)=0, but Fisher's exact test (null hypothesis of no difference), p=1.0. Therefore, the point estimate for RR (equivalent to relative infectiousness) is equal to 0, but we do not have sufficient evidence to conclude that it is significantly different to 1.
Cheng <i>et al</i> ¹⁵	Taiwan	2735	Secondary attack rate: <ul style="list-style-type: none"> ▶ Among asymptomatic primary cases=0/91=0. ▶ Among symptomatic primary cases=22/2644=0.008. RR=0. Fisher's exact test, p=1.0. Therefore, the point estimate for RR (equivalent to relative infectiousness) is equal to 0, but we do not have sufficient evidence to conclude that it is significantly different to 1.

Continued

Table 1 Continued

Author	Location	Number of relevant study subjects	Measure of relative infectiousness
Han ¹⁶	South Korea	192 (all contacts) and 36 (close contacts only)	Secondary attack rate among all contacts: ▲ Among asymptomatic primary cases=0/52=0 (among contacts). ▲ Among symptomatic and presymptomatic primary cases=7/140=0.05. Secondary attack rate among close contacts only: ▲ Among asymptomatic primary cases=0/14=0. ▲ Among symptomatic and pre-symptomatic primary cases=7/22=0.32. RR=0. Fisher's exact test, p=0.19 (all contacts), p<0.001 (close contacts). Conclusion: ▲ All contacts: the point estimate for RR (equivalent to relative infectiousness) is equal to 0, but we do not have sufficient evidence to conclude that it is significantly different to 1. ▲ Close contacts only: the point estimate for RR (equivalent to relative infectiousness) is equal to 0, and we have sufficient evidence to conclude that it is significantly different to 1.
Plucinski <i>et al</i> ⁸	Diamond Princess cruise ship, Japan	75	0.78 (0.58 to 1.04)
Luo <i>et al</i> ^{17,†}	Guangzhou, China	2610	Adjusted OR for transmission risk, based on the severity of the primary cases‡: ▲ Asymptomatic: 0.37 (0.04 to 3.79). ▲ Mild: 0.56 (0.33 to 0.94). ▲ Moderate: 1 (reference category). ▲ Severe: 1.04 (0.57 to 1.90).

The number of relevant study subjects refers to the number of individuals with available PCR results (PCR studies) or the number of close contacts (contact tracing studies).

*Population studied at national level.

†The average of the following set of values for relative infectiousness: {0.5249, 0.5855, 0.5995, 0.59, 0.5498}.

‡After controlling for age, sex, exposure setting and symptoms in the index (primary) cases.

§Model for the period 24 January–3 February 2020.

¶Model for the period 24 January–8 February 2020.

**Model for the period 24 January–8 February 2020.

††Asymptomatics were defined as 'undocumented cases'.



found that some asymptomatic patients had higher viral loads estimated on the basis of the Ct.

For the mathematical modelling studies, Nabi² estimated that asymptomatic were roughly half as infectious as symptomatic individuals: its approximate measure for relative infectiousness is 0.57. In Li *et al.*¹⁰ we consider the most appropriate estimate of the three estimates presented in table 1 as 0.43 (95% CI 0.31 to 0.61). This RI estimate was based on the time period of 24 January–8 February 2020. The other two estimates use earlier time windows (10–23 January and 24 January to 4 February, respectively), where it is more likely that undocumented cases included a larger proportion of symptomatic individuals given lower awareness of the disease.

In three of the five contact tracing studies (namely Park *et al.*¹⁴ Cheng *et al.*¹⁵ and Han¹⁶), there was no evidence of transmission from asymptomatic individuals. This is in contrast to the Plucinski *et al.*³ study, using data from the *Diamond Princess* cruise ship, with an estimated relative infectiousness of 0.78 (95% CI 0.58 to 1.04). The adjusted ORs for transmission risk based on the severity of the primary cases from asymptomatic, mild, moderate and severe are reported in the Luo *et al.*¹⁷ study. The moderate cases are set as the reference category equal to one and the asymptomatic OR is 0.37 (95% CI 0.04 to 2.79), the mild OR is 0.56 (95% CI 0.33 to 0.94) and the severe OR is 1.04 (95% CI 0.57 to 1.90).¹⁷

The quality assessment for these 12 papers is presented in the supplementary material. The quality of the five PCR study papers varied, based on the criteria used. The quality of Lavezzo *et al.*¹ and Danis *et al.*¹² was assessed to be high quality, although the number of cases in Danis *et al.*¹² was very small (five symptomatic, one asymptomatic). Several of the studies will need to be generalised with care, either because they represent a limited age cohort (Letizia *et al.*¹³; young Marine Corp recruits) or only a subset of the spectrum of symptoms that could present (Long *et al.*⁹; Uhm *et al.*¹¹; mild symptoms only, among symptomatics). The quality of the two modelling studies was considered to be low with respect to our parameter of interest. The primary reason for this was that these models were generally developed for a purpose other than estimating relative infectiousness. Therefore, the compartments used sometimes indirectly represented asymptomatics (eg, by assuming that asymptomatic cases were always undocumented). Furthermore, since relative infectiousness was not the primary parameter of interest, the value was often estimated within a relatively small range of possible values. The five contact tracing studies were assessed to be of generally good quality against the five quality criteria that were used, based on the reported information. However, some indication of a longitudinal study component was reported in Luo *et al.*¹⁷ and Plucinski *et al.*³; however, it is unclear whether preasymptomatic and asymptomatic individuals were successfully separated. The study population

considered by Plucinski *et al.*³ is primarily older Americans, which will limit generalisability.

DISCUSSION

Determining the relative infectiousness of asymptomatics is important in informing public health decision making in the midst of a pandemic. Even if asymptomatic individuals are a smaller proportion of the overall cohort of infected individuals, their potential to transmit could be significant since they are unlikely to undertake the same controls (eg, self-isolation) to limit the spread of infection to others as they are unlikely to be aware that they are infected. It is also an important parameter that is used as a prior value in mathematical models that measure the dynamics of COVID-19. Relative infectiousness can be estimated using three methods as outlined previously, namely PCR studies, mathematical modelling and contact tracing.

A number of studies have used PCR results to estimate viral load, which offers one means to estimate the relative infectiousness of symptomatic and asymptomatic individuals. In four of the five PCR studies reviewed here (Uhm *et al.*¹¹ Lavezzo *et al.*¹ Danis *et al.*¹² and Long *et al.*⁹), no substantial difference between asymptomatic and symptomatic individuals was observed, mainly relating to Ct values at an initial test. In contrast, Letizia *et al.*¹³ report viral load at diagnosis approximately four times higher in symptomatic compared with asymptomatic individuals. Furthermore, Long *et al.*⁹ found that the duration of shedding among asymptomatic was longer than for mild symptomatic individuals. We note, however, that these conclusions need to be interpreted with care because PCR is a proxy for viral load; it measures genetic material and does not distinguish infectious and non-infectious virus. As noted by Atkinson and Petersen,¹⁸ measurable virus shedding does not equate with viral infectivity, and further evaluation is needed to determine the respiratory SARS-CoV-2 viral load that is correlated with culturable virus.¹⁸ Nonetheless, this method could still be valid in a comparative sense, as long as testing was conducted at equivalent time points during the infectious profile of symptomatic and asymptomatic individuals. It is unclear whether this was achieved in the reviewed studies, based on testing frequencies described as either on consecutive days for a period (Danis *et al.*¹²) or weekly (Letizia *et al.*¹³ and Lavezzo *et al.*¹). The testing frequency in Long *et al.*⁹ was not specified, whereas Uhm *et al.*¹¹ focused on the duration of infectiousness, rather than its magnitude. Most of the studies are based on a small number of cases, which may limit the ability to detect differences if present. A further challenge with these studies, and indeed with all studies in this scoping review, relates to the concern that presymptomatics (ie, those individuals that do not yet have clinical signs but will go on to develop symptoms) could be included in the definition of asymptomatics. This will occur in the absence of sufficient follow-up. In each of the reviewed studies, we sought evidence of

follow-up at the very least and ideally the gold standard methodology proposed by Buitrago-Garcia *et al.*⁸ With the five PCR studies, it was generally the former rather than the latter that is described. Finally, the external validity of the PCR studies was variable. For three of the studies, generalisability was limited due to the individuals under investigation: Uhm *et al.*¹¹ and Long *et al.*⁹ limited their studies to symptomatics with mild symptoms, and Letizia *et al.*¹³ was undertaken with Marine Corp recruits. In contrast, Lavezzo *et al.*¹ investigated all residents in the village of Vo', Italy, accounting for all age groups, thus ensuring greater external validity in this study.

Estimates from modelling studies provide the second method of estimating relative infectiousness for this virus. Li *et al.*¹⁰ reported the infectiousness of 'undocumented' rather than asymptomatic individuals. Three separate estimates of the infectiousness of undocumented infections were reported for the Li *et al.* study. The proportion of undocumented cases (compared with documented) consecutively decreased with time points corresponding to greater restrictions. The authors argue that this was likely to have occurred since, with greater restrictions, it was more likely that symptomatic individuals would be tested and therefore become documented. Furthermore, individuals were more likely to be tested as time progressed given the growing awareness of COVID-19. Consequently, we recommend that the most recent value, 0.43 (95% CI 0.31 to 0.61), should be used for the measure of relative infectiousness from this study.¹⁰ Relative infectiousness is estimated to be 0.57 (the average of five values (see table 1)) in the Nabi study.² CM carried out a quality appraisal of the two studies. The authors subsequently agreed that the Li *et al.*¹⁰ study appeared to have a high level of quality in terms of its consideration of the range of values within which the model estimate was confined and its model validation; it used synthetic data initially, and the model was applied separately to different time points in the outbreak. However, both studies do not appear to have properly represented the asymptomatic cohort appropriately; in both Nabi and Li *et al.*¹⁰, asymptomatics are referred to 'undocumented' rather than 'asymptomatic' per se.² Estimates from these studies must therefore be treated with significant caution.

Contract tracing studies have formed the basis for a third method to estimate relative infectiousness. In these studies, investigations are conducted to calculate the secondary attack rate among different cohorts of primary cases (either symptomatic or asymptomatic), based on the number of secondary contacts who become infected. In three out of five reviewed studies (Park *et al.*,¹⁴ Cheng *et al.*¹⁵ and Han¹⁶ (when considering all contacts of primary cases)), the point estimate for relative risk (RR) (equivalent to relative infectiousness) is equal to 0, but we do not have sufficient evidence to conclude that it is significantly different to 1. When considering close contacts of primary cases in Han¹⁶, the point estimate for RR is equal to 0, and we have sufficient evidence to conclude that it is significantly different to 1. In the remaining two

studies, the overall estimate of relative infectiousness for asymptomatics was either low (0.37 (95% CI 0.04 to 3.79, in comparison with moderate symptomatics) in Luo *et al.*¹⁷) or relatively high (Plucinski *et al.*⁸: 0.78 (95% 0.58 to 1.04)). The latter study needs to be interpreted with care, both in terms of generalisability (the study subjects were primarily over 60 years of age) and the proper identification of asymptomatic individuals (the authors mention that 'longitudinal follow-up of asymptomatic individuals can help to determine the true asymptomatic rate'³). Given the differences between these contact tracing studies, it is not possible to draw any conclusions with respect to relative infectiousness.

Collectively, there is considerable heterogeneity in estimates of relative infectiousness, as reflected in the study results presented in table 1, which highlights the need for further investigation of this important parameter. The current review has identified a range of quality criteria, relevant to different study types, for consideration in future studies. For example, there is a need for careful identification of asymptomatic individuals (which are clearly differentiated from presymptomatics) for study subjects to facilitate generalisability, the use of accurate testing methods and the validation of COVID-19 models using different data sources.

It is not possible to provide any conclusive estimate of relative infectiousness, as the estimates from the reviewed studies varied between 0 and 1, including within the same study type. Previously, Ferguson *et al.*¹⁹ assumed that symptomatics were 50% more infectious than asymptomatics. When converted to a ratio (ie, 1/1.5), this corresponds to a relative infectiousness of 0.67. Tuite *et al.*²⁰ did not model asymptomatics as a distinct cohort to symptomatics.

Modelling studies requiring informative estimates of the relative infectiousness of asymptomatic individuals should seek to ensure that the precise definition of the estimate used equates to the same definition used in the model. Some definitions may be more population specific than others. In particular, it is important to note whether the definition of infectiousness incorporates contact rates (which might be different for symptomatic or asymptomatic individuals) (or is independent of it) or whether it incorporates the proportion of asymptomatic individuals in the population (or is independent of it).

CONCLUSION

Overall, there is currently only a limited number of published studies from which it is possible to derive a quantitative estimate of the relative infectiousness of asymptomatics. Three approaches to estimating relative infectiousness were identified, based on differing study types, which may help to indicate the value for this parameter. However, there are issues with each of these approaches with respect to informing the parameter of interest. There is considerable heterogeneity in estimates of relative infectiousness highlighting the need for further investigation of this important parameter. It is

not possible to provide any conclusive estimate of relative infectiousness, as the estimates from the reviewed studies varied between 0 and 1, including within the same study type.

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Supplementary material. Quality assessment of the 12 studies, by study type (PCR studies, modelling studies and contact tracing studies).

PCR Studies				
Author	Asymptomatic Status	Testing Methods	Considerations relating to infectiousness profile	External Validity
Letizia et al, 2020 [11]	Participants were followed for 14 days following enrolment, including testing (and ascertainment of symptoms during the previous 7 days, based on self-reporting) on days 0, 7 and 14.	qPCR testing was conducted in a single laboratory using an authorised test.	Sampling was conducted at 7 day intervals, with the potential for some differences in the infectiousness profiles of individuals. Bias (between symptomatic and asymptomatic individuals) is unlikely	Conducted with Marine Corp recruits, which would limit generalisability
Uhm et al, 2020 [12]	A definition for asymptomatic patients is presented. There is some suggestion of a longitudinal component, including <i>'retrospective cohort study'</i> and <i>'throughout the disease course'</i>	There were differences in testing methods (kits, cut-offs) in different hospitals. Further, Ct values were presented as categorical data.	There is a focus on duration rather than magnitude of infectiousness. Equivalence across cohorts in terms of the infectiousness profile is uncertain, given that the first follow-up RT-PCR assay was performed 7 days after diagnosis for the asymptomatic patients and immediately after the disappearance of symptoms or improvement in pneumonia stage for symptomatic patients.	Among symptomatics, only includes those with mild symptoms, which would limit generalisability
Lavezzo et al, 2020 [1]	Epidemiological data were collected on 2 occasions, at sampling conducted 2 weeks apart. Symptomatic is defined, whereas asymptomatic and pre-symptomatic is not. However, as explained in the response to reviewers for that paper, the authors	A consistent approach to testing and laboratory work was undertaken	Sampling was conducted at 7 day intervals, for all participants. Bias (between symptomatic and asymptomatic individuals) is unlikely	The population under investigation includes the population of Vo' (that is, people of all age groups)

	accounted for follow up information on symptom occurrence during the period after sample collection of each positive subject. All identified asymptomatic infections at the time of swab sampling were contacted by phone after the second survey (i.e. at the end of March 2020) for clinical follow up.			
Danis et al, 2020 [13]	The asymptomatic case was under observation until 18 Feb when s/he returned to the UK. There was considerable medical intervention, including testing, throughout this period	Testing was conducted at the National Reference Center for Respiratory Viruses (Lyon)	Testing was conducted over sequential days between 7-12 (or 13) February. Given the chronology with respect to the index case, the likely exposure period is likely similar for all of the 6 cases under investigation	The cluster related to British citizens in the French Alps in February 2020
Long et al, 2020 [9]	Detailed investigations were conducted to confirm the appropriate classification of asymptomatic cases	Detailed testing methodology is described, which was common across all cases in the study	The schedule of testing is unclear, in terms of the timing of the initial test. The text states <i>'To identify asymptomatic individuals, the Wanzhou District Centers for Disease Control and Prevention (CDC) then conducted extensive RT-PCR screening for 2,088 close contacts under quarantine. Individuals with positive RT-PCR results then were screened by point prevalence surveys carried out by the local CDC and symptoms assessments reported by clinicians.'</i>	Among symptomatics, only includes those with mild symptoms, which would limit generalisability
Modelling Studies				

Author	Representativeness of the studied compartment	Consideration of the range of values within which the model estimate is confined	Model validation:		
Khondoker Nazmoon Nabi, 2020 [2]	Low. Lambda is the relative infectiousness of undetected infected rather than asymptomatic per se.	Low. Lambda is confined within a tight range (0.4-0.6). Many estimates are at the upper edge of this range.	Medium. Model is applied to multiple regions independently. Estimates are broadly similar.		
Li et al, 2020 [10]	Low. Mu is the relative infectiousness of undocumented infections	High. Prior range of 0.2 - 1.0 used	High. Use of synthetic data initially and application of the model separately to different time points in the outbreak		
Contact Tracing Studies					
Author	Asymptomatic Status	Identification of close contacts	Case ascertainment	Case attribution	External Validity
Park et al, 2020 [14]	Methodology to define asymptomatic cases is presented, including observation over a 14-day period. However, the authors admit <i>'not all clinical information was available for all confirmed cases, prohibiting detailed description of clinical syndromes'</i> .	The study was restricted to household members only, thereby minimising the potential for differential bias in the identification of contacts	The study team investigated, tested, and monitored household contacts of all confirmed case-patients for 14 days after discovery, regardless of symptoms.	Not directly address in this paper, however, attribution is likely less to be confused in a household setting	The index cases emerged in a call centre in Seoul. The study only considered household contacts of these index cases
Cheng et al, 2020 [15]	There is a longitudinal nature to the epidemiological investigation. For asymptomatics, it is stated <i>'For asymptomatic confirmed cases, the period of investigation was based on the date at confirmation (instead of date at onset) and was determined according to epidemiological investigation.'</i>	The paper clearly presents the period of investigation and definition of a close contact	All cases were followed up until 14 days after the last exposure to the index case, and details of observation and testing is outlined. The testing protocol may have missed asymptomatic secondary cases	The period of investigation for each primary case is defined, and all contacts during this period were investigated	The study focuses on the first 100 COVID-19 cases in Taiwan, identified between 15 January and 18 March 2020, and their close contacts

Taewon Han, 2020 [16]	An asymptomatic was defined as <i>'a patient who showed no symptoms from the time of contact until a COVID-19 diagnostic test where the patient tested positive for COVID-19'</i> . There is a longitudinal component to the assessment, although the possibility for misclassification is not eliminated.	The paper clearly presents the period of investigation and definition of a close contact	All cases were followed up until 14 days after the last exposure to the index case, and details of observation and testing is outlined.	Errors in attribution are very unlikely. As stated in the text <i>'Aside from two confirmed cases from Sinchonji Church in Daegu that occurred 40 days prior to the outbreak associated with Spa facility A, no other confirmed case was reported in Region A.'</i>	The study concerns an outbreak in a spa with the information that <i>'Approximately 250 people visit the spa facility every day, and many are regular users of the spa facility and the accompanying gym. Many people from other regions visit the facility on the weekends.'</i>
Plucinski et al, 2020 [3]	Not clearly addressed in this paper. In the discussion, the authors state <i>'nearly two-thirds of SARS-CoV-2-positive persons who were originally classified as asymptomatic at the time of specimen collection reported having symptoms while onboard the ship'</i> . Further, they indicate that <i>'longitudinal follow-up of asymptomatic individuals can help determine the true asymptomatic rate'</i> .	The study was restricted to household members only, avoiding the potential for differential bias in the identification of contacts	Substantial efforts were made to identify secondary cases: <i>'Anyone who had fever or respiratory symptoms was tested for SARS-CoV-2, along with their close contacts. Anyone testing positive was hospitalized regardless of illness severity. On February 11, testing was expanded to asymptomatic passengers, and eventually included everyone who remained on board.'</i>	Errors in attribution is unlikely given the focus on roommate contacts. Further, room-based quarantine commenced on 5 February. Symptoms were first observed on the ship on 23 January, but infection was not confirmed until 1 February.	The study individuals were mainly >60 years, which would limit generalisability
Luo et al, 2020 [17]	Each case was reviewed by the CDC. It is not clear whether there was a	A definition of close contacts is provided: <i>'Close contacts are individuals</i>	Considerable detail is provided, as follows: <i>'after</i>	In the investigation, care was taken to distinguish potential exposures, by <i>'household, public</i>	Index cases were identified through <i>'surveillance testing, screening</i>

	<p>longitudinal component to this review, however, this is implied in Figure 1.</p>	<p><i>who have had contact, without effective protection regardless of duration of exposure, with 1 or more persons with suspected or confirmed COVID-19 any time starting 2 days before onset of symptoms in persons with a suspected or confirmed case, or 2 days before sampling for laboratory testing of asymptomatic infected persons', and contact tracing was conducted by the county or district CDC.</i></p>	<p><i>identification, close contacts were quarantined for 14 days from last contact with index cases and followed up clinically after quarantine until 6 April 2020.' 'During the quarantine period, monitoring of clinical symptoms and RT-PCR assay of SARS-CoV-2 nucleic acid was performed approximately every 24 hours.'</i></p>	<p><i>transportation, health care settings, entertainment venues or workplaces, and multiple settings'. Some limitations during case attribution are inevitable</i></p>	<p><i>individuals with symptoms who presented to a health care facility, or tracing and screening close contact'</i></p>
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