

<b>Type of document:</b> Rapid systematic review	
<b>In response to request from:</b> NCS-TF Advisory Board	<b>Date of request:</b> 30/03/2020
<b>Expert groups involved:</b> Public health	<b>Date of response:</b> 09/04/2020
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<b>Comment on planned updates:</b> This is a living systematic review. The search was updated on 20.04.2020.	
<b>Title:</b> The role of asymptomatic SARS-CoV-2 infections: rapid living systematic review and meta-analysis	
<b>Questions:</b> 1. What is the proportion of people that becomes infected with SARS-CoV-2 infection who do not experience symptoms at all during their infection? 2. Amongst people who become infected with SARS-CoV-2, what proportion has no symptoms at the time of testing, but develops symptoms later? 3. What proportion of SARS-CoV-2 infections is accounted for by people who are either asymptomatic throughout infection, or pre-symptomatic?	
<b>Summary:</b> 1. We estimate, from empirical data, that up to 40% of people who become infected with SARS-CoV-2 will have an asymptomatic infection and will not develop symptoms during the course of their infection. 2. Based on empirical studies, the proportion of people detected to have asymptomatic SARS-CoV-2 that goes on to develop symptoms is uncertain. 3. Mathematical modelling studies predict that 50-60% of all SARS-CoV-2 transmission is the result of transmission from either asymptomatic or pre-symptomatic individuals.	
<b>Main text:</b> There is substantial disagreement about the level of asymptomatic SARS-CoV-2 infection. The authors of the World Health Organization report on the mission to China stated that, “The proportion of truly asymptomatic infections is unclear but appears to be relatively rare and does not appear to be a major driver of transmission.” (World Health Organization 2020) In contrast, commentators interpret findings such as, “... 78% [of new infections] identified in the 24 hours to the afternoon of Wednesday 1 April were asymptomatic” as an indication that “the large majority of coronavirus infections do not result in symptoms” (Day 2020). These disagreements result from differences in definitions, in the sources of data, and in interpretation. In particular, many studies reporting the proportion with asymptomatic SARS-CoV-2 are cross-sectional and include both people who will remain asymptomatic and those who would go on to develop symptoms if followed up.	

Understanding the proportions of SARS-CoV-2 infections that remain asymptomatic and go on to become symptomatic will help to determine the contribution to SARS-CoV-2 transmission of asymptomatic infection. This is an urgent priority that will influence the balance of control measures, including testing programmes for the identification and isolation of infected people, for tracing and quarantine of close contacts, and for social distancing measures (Lipsitch et al. 2020).

We conducted a rapid systematic review up to 25 March 2020, using a living evidence database of articles published in Pubmed, Embase, bioRxiv and medRxiv. The protocol is published at <https://osf.io/9ewys/>. We screened 89 studies. We included 9 follow-up studies (Bai et al. 2020, Chan et al. 2020, Hu et al. 2020, Liao et al. 2020, Luo et al. 2020, Nishiura et al. 2020, Qian et al. 2020, Tabata et al. 2020, Wang et al. 2020), one statistical modelling study (Mizumoto et al. 2020), and two mathematical modelling studies (Ferretti et al. 2020, Ganyani et al. 2020).

We conducted a descriptive synthesis and, where appropriate, calculated pooled estimates using fixed effects meta-analysis and the prediction interval. We assessed the risk of bias by adapting published tools.

**Question 1. What is the proportion of people that becomes infected with SARS-CoV-2 infection who do not experience symptoms at all during their infection?**

We estimated the proportion of asymptomatic SARS-CoV-2 from contact investigations (6 studies, 8 estimates) (Bai et al. 2020, Chan et al. 2020, Hu et al. 2020, Liao et al. 2020, Luo et al. 2020, Qian et al. 2020) and from people evacuated from either the Diamond Princess cruise ship (Tabata et al. 2020) or Japanese nationals evacuated from Wuhan (Nishiura et al. 2020) (Figure1, Table S1).

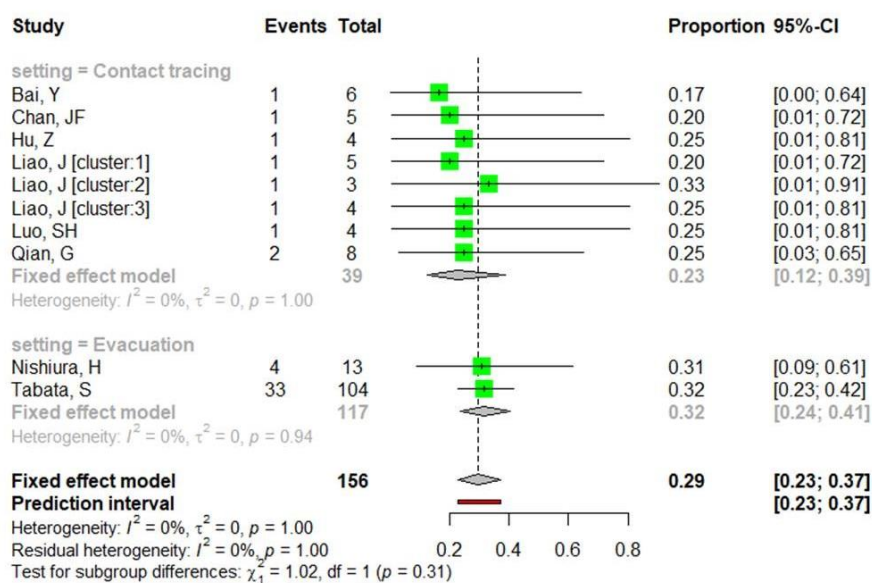


Figure 1. Proportion of people with SARS-CoV-2 infection who do not experience symptoms at all during their infection

The findings of contact tracing investigations and evacuation studies are consistent. We estimate the pooled proportion of SARS-CoV-2 infections that is, and remains asymptomatic is 29% (prediction interval 23 – 37%).

The estimate is an upper limit of the true proportion because: 1) the identified contact tracing studies all included at least one asymptomatic person. These reports are published because they are seen to be newsworthy. The size of the denominator (all contact investigations, including those in which all people developed symptoms) is unknown; 2) in both contact tracing and evacuation studies, follow up time might be incomplete and some people might develop symptoms if follow-up continued.

One study used data from the evacuation of the Diamond Princess cruise ship (Mizumoto et al. 2020). The authors used a statistical model to estimate the proportion of infected people who would remain asymptomatic if all were followed up until the end of the incubation period, based on assumptions from a previous study. They estimated that the true proportion of asymptomatic infections is 17.9% (95% credibility interval 15.5 – 20.2%).

**Question 2. Amongst people who become infected with SARS-CoV-2, what proportion has no symptoms at the time of testing, but develops symptoms later?**

We included four studies (Figure 2, Table S2) (Hu et al. 2020, Luo et al. 2020, Tabata et al. 2020, Wang et al. 2020). In three studies in China, people who had SARS-CoV-2 detected by RT-PCR and were asymptomatic on admission to hospital were followed until either discharge. In all three studies, the asymptomatic cases were detected during contact investigations of patients who had presented with symptoms of COVID-19. In two studies, the proportion that developed symptoms was high; 7 of 8 patients in Anhui province (Luo et al. 2020) and 43 of 55 patients in Shenzhen (Wang et al. 2020). In the third hospital-based study, in Nanjing, 24 asymptomatic SARS-CoV-2 cases were detected through contact investigations; five were reported to have developed symptoms within one to three days of admission and the rest remained asymptomatic for 17 days. The fourth study reported the outcome of SARS-CoV-2 infection in passengers of the Diamond Princess cruise ship who were hospitalised in Japan (Tabata et al. 2020). Of 43 who were asymptomatic at the time of diagnosis, 10 developed symptoms during median follow-up of 10 days (interquartile range, IQR 7-10 days). The findings of the four studies were too disparate to pool in a meta-analysis (Figure 2).

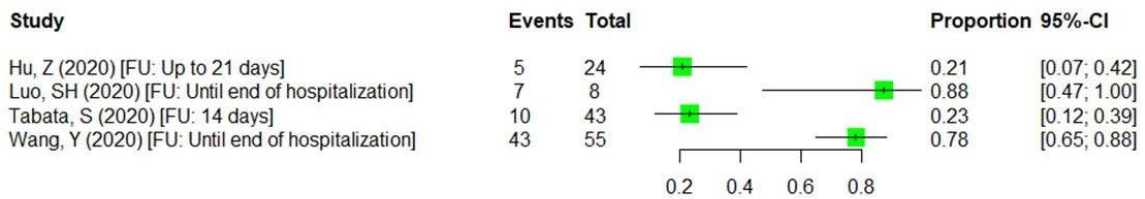


Figure 2. Proportion of people with asymptomatic SARS-CoV-2 infection who develop symptoms of COVID-19 during follow-up

**Question 3. What proportion of SARS-CoV-2 infections is accounted for by people who are either asymptomatic throughout infection, or pre-symptomatic?**

We included two transmission dynamic mathematical modelling studies that explicitly addressed this question (Ferretti et al. 2020, Ganyani et al. 2020). Ganyani et al. used publicly available line-listed data about clusters of COVID-19 from Tianjin, China and from Singapore. They applied statistical models in a Bayesian framework to examine generation and serial intervals for linked cases, with an assumption of the incubation period from a published study. A generation period shorter than the incubation period of the infector indicates pre-symptomatic transmission. They found that the proportion of pre-symptomatic transmission was 48% (95% CI 32 to 67%) for Singapore and 62% (95% CI 50 to 76%) for Tianjin, China (Ganyani et al. 2020). Ferretti et al. developed a compartmental mathematical model, informed by data on linked COVID-19 cases in Hubei province, China. They separated the transmission parameter into symptomatic, asymptomatic, pre-symptomatic and environmental components. They assumed a fraction of 40% asymptomatic SARS-CoV-2 infections (citing data from the Diamond Princess) and reduced infectiousness from asymptomatic cases. They found that pre-symptomatic patients account for 47% (95% credibility interval 11 to 58%) of the total transmission, and asymptomatic transmission 6% (0 to 57%) of the total. They provide a shiny app [ref:[link](#)], where different assumptions can be evaluated (Ferretti et al. 2020).

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**Recommendations from the Task Force:**

**Open points for further discussion:**

This review clearly separates studies that investigate the proportion of people who will not experience symptoms throughout the course of SARS-CoV-2 and those who are asymptomatic at the time of testing but will develop symptoms (pre-symptomatic). The empirical studies of the proportion of asymptomatic SARS-CoV-2 infections should be seen as an upper bound of the true proportion because of the selection of families included in published case investigations and the limited follow-up in some studies. The

heterogeneity in studies of the proportion pre-symptomatic was not clearly explained by the study populations enrolled. As the population studies gets closer to 'screening' of a whole population, it would be expected to include people earlier on infection and a lower proportion might be expected to develop symptoms.

The empirical data provided in this review should be able to inform future mathematical models.

This review did not cover the transmissibility or duration of infectiousness of asymptomatic SARS-CoV-2 infection.

#### **References (included studies in alphabetical order):**

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

Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK and Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;**395**(10223): 514-523. <https://www.ncbi.nlm.nih.gov/pubmed/31986261>

Day M. Covid-19: four fifths of cases are asymptomatic, China figures indicate. BMJ 2020;**369**: m1375. <https://www.ncbi.nlm.nih.gov/pubmed/32241884>

Ferretti L, Wymant C, Kendall M, Zhao L, Nurtay A, Abeler-Dorner L, Parker M, Bonsall DG and Fraser C. Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. medRxiv 2020: 2020.2003.2008.20032946. <https://www.medrxiv.org/content/medrxiv/early/2020/03/31/2020.03.08.20032946.full.pdf>.

Ganyani T, Kremer C, Chen D, Torneri A, Faes C, Wallinga J and Hens N. Estimating the generation interval for COVID-19 based on symptom onset data. medRxiv 2020: 2020.2003.2005.20031815. <https://www.medrxiv.org/content/medrxiv/early/2020/03/08/2020.03.05.20031815.full.pdf>.

Hu ZL, Song C, Xu CJ, Jin GF, Chen YL, Xu X, Ma HX, Chen W, Lin Y, Zheng YS, Wang JM, Hu ZB, Yi YX and Shen HB. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Science China-Life Sciences 2020. <Go to ISI>://WOS:000518479200001.

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

Lipsitch M, Swerdlow DL and Finelli L. Defining the Epidemiology of Covid-19 - Studies Needed. N Engl J Med 2020;**382**(13): 1194-1196. <https://www.nejm.org/doi/pdf/10.1056/NEJMp2002125?articleTools=true>.

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

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

Nishiura H, Kobayashi T, Suzuki A, Jung SM, Hayashi K, Kinoshita R, Yang Y, Yuan B, Akhmetzhanov AR, Linton NM and Miyama T. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). *Int J Infect Dis* 2020. <https://www.ncbi.nlm.nih.gov/pubmed/32179137>.

Qian G, Yang N, Ma AHY, Wang L, Li G, Chen X and Chen X. A COVID-19 Transmission within a family cluster by presymptomatic infectors in China. *Clin Infect Dis* 2020. <https://www.ncbi.nlm.nih.gov/pubmed/32201889>.

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

Wang Y, Liu Y, Liu L, Wang X, Luo N and Ling L. Clinical outcome of 55 asymptomatic cases at the time of hospital admission infected with SARS-Coronavirus-2 in Shenzhen, China. *J Infect Dis* 2020. <https://www.ncbi.nlm.nih.gov/pubmed/32179910>

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