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Review

Asymptomatic SARS Coronavirus 2 infection: Invisible yet invincible


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ABSTRACT

While successful containment measures of COVID-19 in China and many European countries have led to flattened curves, case numbers are rising dramatically in other countries, with the emergence of a second wave expected. Asymptomatic individuals carrying SARS-CoV-2 are hidden drivers of the pandemic, and infectivity studies confirm the existence of transmission by asymptomatic individuals. The data addressed here show that characteristics of asymptomatic and presymptomatic infection are not identical. Younger age correlates strongly with asymptomatic and mild infections and children as hidden drivers. The estimated proportion of asymptomatic infections ranges from 18% to 81%. The current perception of asymptomatic infections does not provide clear guidance for public-health measures. Asymptomatic infections will be a key contributor in the spread of COVID-19. Asymptomatic cases should be reported in official COVID-19 statistics.

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Introduction

Transmission of SARS-CoV-2, the agent causing COVID-19, is driven by virus-containing droplets released from the upper airways and aerosols that can float, dependent on the airflow, for a prolonged period in the environment (Meselson, 2020). Aerosols can be spread by just breathing, while droplets originate from speaking, shouting, sneezing, and coughing as well as from singing and playing wind instruments (Zhang et al., 2020; Zhen-Dong et al., 2020; Asadi et al., 2019). Of great importance are super-spreading events, which are infection clusters constituting effective chains of SARS-CoV-2 transmission. For instance, such super-spreading events have been observed in Hong Kong (Adam et al., 2020), at religious mass events in Iran (Mubarak and Zin, 2020) and choir rehearsals in the US (Hamner et al., 2020), where singing contributed to a maximum emission of droplets and aerosols and, thus, to successful transmission (Asadi et al., 2019).

Defining “asymptomatic”

Transmission of the virus by infected, albeit asymptomatic individuals has been reported since the early stages of the outbreak (Pan et al., 2020; Yan et al., 2020) posing substantial COVID-19 containment challenges. The likely spread of COVID-19 occurs to a large extent via asymptomatic individuals, as these do not present to health care or testing facilities. Uncertainty about the significance of asymptomatic infections is reinforced by the vagueness with which the term “asymptomatic” is used. WHO defines an asymptomatic case as a laboratory-confirmed infected person without overt symptoms (WHO, 2020). It remains to be established how thoroughly such a person needs to be examined clinically. Moreover, the distinction between asymptomatic and presymptomatic individuals is often neglected in COVID-19 case definitions.

A distinction between asymptomatic and presymptomatic stages can currently only be made retrospectively, after the occurrence or non-occurrence of clinical symptoms. Recent evidence suggests that elevated serum/plasma lactate dehydrogenase levels may, already in the early stages, be indicative of presymptomatic infections and, thus, facilitate early

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differentiation (Ooi and Low, 2020). Diagnostic imaging cannot distinguish between the two infection stages, as, surprisingly, 30% of asymptomatic individuals showed ground-glass opacities, and 27% had diffuse consolidations (Long et al., 2020).

Pandemic is driven by asymptomatic infections

The frequency and infectivity of asymptomatically infected persons are the main reasons why COVID-19 has become a pandemic. Evidence has pointed to the need for strict tracking and testing of all contacts, regardless of apparent symptoms (Zhang et al., 2020; Ooi and Low, 2020; Baggett et al., 2020; Wei et al., 2020). However, detection of COVID-19 has long been driven by testing patients only, a practice still recommended in the EU/EEA (except Germany) and UK (European Centre for Disease Prevention and Control, 2020). Meanwhile, some countries have started to extend testing; Luxembourg and the state of Bavaria (Germany) have announced that the entire population of 600,000 and 13 million, respectively, shall be tested to prevent a second wave. The USA's Center for Disease Control (CDC) recommends diagnostic tests for both symptomatic and asymptomatic individuals with known or suspected exposure to COVID-19 (Prevention CfDCA, 2020a). At the same time, the European Centre for Disease Control (ECDC) proposes tests mainly for asymptomatic healthcare workers, when testing facilities are underutilized (Control ECfDPA, 2020).

Since April 1, 2020, China has responded to the emerging significance of asymptomatic infections by establishing a separate category of "asymptomatic cases" in its daily COVID 19 statistics (Zhang et al., 2020). Mathematical modeling clearly supports broader test strategies. A simulation applying data from the Jiangsu Province, China, compared epidemiological data with an estimated asymptomatic proportion of 44% and found that asymptomatic individuals can cause faster and larger outbreaks than imported cases (Sun and Weng, 2020). Another analysis indicated that 30% of asymptomatic and 50% of symptomatic patients must be isolated to achieve disease control (Kassa et al., 2020).

Asymptomatic infections during the pandemic

Asymptomatic infections have increasingly been recognized in family clusters with unknown index cases. The first cluster study comprised five family members from Anyang, China, who developed COVID-19 symptoms and tested positive by RT-PCR after acquiring the infection from the index case, an asymptomatic visitor from Wuhan who later tested positive (Bai et al., 2020). Another study with five family members from Luzhou, China, described a patient who developed severe COVID-19 pneumonia after attending a family reunion. Apparently, he had acquired COVID-19 from an asymptomatic relative from Wuhan (Ye et al., 2020).

Several studies have focused on determining the incidence of asymptomatic infections. On the cruise ship *Diamond Princess*, with 3711 passengers, a major outbreak of 634 cases occurred after an infected asymptomatic passenger had boarded in Hong Kong. Due to the dense living conditions and frequent passenger contacts, the R_0 value was initially four times higher than in Wuhan (Rocklöv et al., 2020). The true asymptomatic proportion, defined as those who never developed symptoms, among all infected passengers was 18% (Mizumoto et al., 2020). Similar to the *Diamond Princess*, another study of an Argentinian expedition cruise ship found that 59% of the 217 passengers tested positive for COVID-19; 81% of those infected were asymptomatic virus carriers (Ing et al., 2020). In Vo, the first Italian city with a confirmed COVID-19 fatality, 3711 were surveyed twice. 2.6 % of the population tested positive before the lockdown, and 1.2 % tested positive after the lockdown; of these, 41% and 45% were asymptomatic before and after the lockdown, respectively (Lavezzo et al., 2020). When screening individuals in Gangelt, Germany, 22% of individuals positive for COVID-19 remained asymptomatic (Streeck et al., 2020). In another study of individuals repatriated from Wuhan to Japan, 13 of the 565 (2%) evacuated tested positive, and 31% of those evacuated remained asymptomatic after a sufficiently long time to complete the incubation period (Nishiura et al., 2020). A first nationwide population-based study from Spain, including 61,000 participants from 35,883 households, concluded that one in three infections seems to be asymptomatic and emphasized the need to maintain public health measures to avoid a second epidemic wave (Pollán et al., 2020).

As these findings differ significantly, it is difficult to accurately determine the extent of asymptomatic infections. Discrepancies could result from imprecise definitions of the term "asymptomatic" or a different understanding of "asymptomatic" in the various studies (Table 1). Extremely high incidences could result from the unintended inclusion of presymptomatic and very mild cases. The true incidence of asymptomatic infections can only be determined if close surveillance is initiated and continued at least over the estimated average incubation period of at least five days in order not to miss a possible onset of symptoms.

Asymptomatic infectivity: viral load and viral shedding

When assessing public health risks raised by asymptomatic COVID-19 cases, it is important to determine whether the infectivity varies between asymptomatic, presymptomatic, and symptomatic individuals. A study of the first 243 patients in Singapore revealed a proportion of 6% presymptomatic cases with transmission occurring 1–3 days before the onset of symptoms (Wei et al., 2020). Data from three Chinese hospitals, including 24 asymptomatic subjects, showed an average SARS-CoV-2 carrier period of 22 days. The time from exposure to eventual negativity indicates that asymptomatically infected persons likely carry the virus for a relatively long period (Yan et al., 2020). Infectivity exists

Table 1
Limited overview of reported studies on asymptomatic infection among adults and children.

Reported studies	Sample size	Country	Estimates	References
Passenger ship: <i>Diamond Princess</i>	n = 3711	Yokohama, Japan	18%	Rocklöv et al. (2020); Mizumoto et al. (2020)
Argentinian expedition cruise ship	n = 217	Montevideo, Uruguay	81%	Ing et al. (2020)
Two-point prevalence survey	n = 2343	Vo, Padua, Italy	41% and 45%	Lavezzo et al. (2020)
Sero-epidemiological study	n = 919	Gangelt, Germany	22%	Streeck et al. (2020)
Repatriated passengers	n = 565	Japan	31%	Nishiura et al. (2020)
Nationwide population-based study	n = 61,000	Spain	22 to 36%	Pollán et al. (2020)
Presymptomatic surveillance study	n = 243	Singapore	6%	Wei et al. (2020)
Followed up case series	n = 78	Wuhan, China	42%	Yang et al. (2020)
Viral dynamics: Asymptomatic patients	n = 31	Guangzhou, China	29%	Zhou et al. (2020)
Nationwide case series: Children	n = 2135	China	4%	Dong et al. (2020)

in presymptomatic and/or asymptomatic men; however, further analyses of the viral loads and viral shedding duration are required. Viral shedding is the release of the virus from somatic cells after replication; it does not necessarily imply that it is infectious (Atkinson and Petersen, 2020). The virus load is measured by the cycle threshold (Ct value), which corresponds to the diagnostic RT-PCR assays' amplification cycles. Ct values increase with decreasing viral load; low Ct values indicate a high viral load. Also, the duration of virus detectability serves as an indicator of infectivity.

In a study of 21 infected Chinese, a subgroup of five asymptomatic patients had the longest period of RNA positivity, with prolonged viral shedding. The virus was thriving in asymptomatic subjects for a median of 18 days compared to mild (median 10 days) and severe COVID-19 cases (median 14 days) (Yongchen et al., 2020). Another study from Wanzhou district, China, compared 37 asymptomatic with 37 symptomatic individuals. Although the initial Ct values were similar, asymptomatic individuals showed prolonged virus release (asymptomatic individuals: median 19 days, symptomatic individuals 14 days) (Long et al., 2020). Of interest is also another study of 18 patients from Zhuhai, China, where viral loads in asymptomatics were similar to those in patients (Zou et al., 2020). In the Vo community study in Italy, no significant differences were found between viral loads of asymptomatic and presymptomatic individuals, and no differences in the duration of virus detectability were seen (Lavezzo et al., 2020).

Data of 78 infected subjects from Wuhan identified 33 (42%) asymptomatic infections with shorter periods of viral shedding compared to symptomatic patients (eight vs. 19 days) (Yang et al., 2020). A cohort of 71 South Koreans included three presymptomatic and ten asymptomatic subjects. Asymptomatics had lower Ct values than presymptomatic subjects over a period of 15 days, indicating a higher viral load (Kim et al., 2020). Of 31 infected persons from Guangzhou, China, who tested positive, 22 proved to be presymptomatic on admission and developed symptoms later, whereas nine remained asymptomatic. There was a statistically significant difference between asymptomatic and presymptomatic infection, with higher Ct values in asymptomatic than in presymptomatic individuals. However, there was no significant difference in viral shedding (Zhou et al., 2020). Also, infectivity was found to be highest roughly a day before symptom onset; it was estimated that 44% of secondary cases were infected by a presymptomatic carrier (He et al., 2020).

To ascertain an asymptomatic who does not meet the case definition, the detection of SARS-CoV-2 by RT-PCR on nasopharyngeal and oropharyngeal swabs is the only currently available standard diagnosis (Younes et al., 2020). Recent studies raise the question of the reliability of RT-PCR based on increasing evidence of false-negative cases and concerns about its applicability (Arevalo-Rodriguez et al., 2020; Piras et al., 2020). False-negative results can have a significant negative impact on efforts to contain the epidemic. The probability of false-negative results in RT-PCR tests is influenced by the time since exposure and the onset of symptoms (Kucirka et al., 2020). On the other hand, technical problems, insufficient virus load, and inadequate and inappropriate sampling may be other reasonable causes of false-negative results. The challenges in laboratory diagnosis of SARS-CoV-2 by RT-PCR are multifactorial, and well-defined guidelines are warranted to fill the gaps in the detection of SARS-CoV-2 in asymptomatics.

Age stratified asymptomatic infection

When analyzing common characteristics of patients, young age often correlated with asymptomatic or mild manifestations of COVID-19. Among 78 patients from Wuhan, China, asymptomatic

individuals were younger than symptomatic patients (median age 37 vs. 56 years) (Yang et al., 2020). In Nanjing, China, of 24 initially asymptomatic subjects, 29% who never showed symptoms were significantly younger than the presymptomatic group (Hu et al., 2020). These results are supported by the data from the cruise ship, Diamond Princess; of 96 asymptomatic persons, eleven later developed symptoms that made them presymptomatic. The probability of evolving to a presymptomatic stage increased with age (Sakurai et al., 2020).

In fact, a much lower prevalence of COVID-19 is observed in children than in adults, with people under 18 years accounting for only 5% of cases in the USA compared to 22% in the total population (Prevention CfDca, 2020b). Of 1412 Chinese children with infection, 4% and 51% were categorized as asymptomatic and mild, respectively (Dong et al., 2020).

Recent evidence suggests that the entry of SARS-CoV-2 via the ACE2 receptor is facilitated by the membrane-bound serine protease TMPRSS2, which primes the viral S protein for fusogenic activity (Hoffmann et al., 2020; Zang et al., 2020). Since TMPRSS2 is a gene associated with androgen levels, a higher expression occurs in males, which provides one explanation of why they are more likely to develop severe COVID-19 (Bhowmick et al., 2020). This association also applies to the distinction between preadolescents and adults and is in line with low incidences and relatively mild disease courses in children (Wambier et al., 2020). Since this also indicates a higher incidence of asymptomatic infections in younger people, it needs to be examined whether this group, especially children, could silently, yet efficiently, contribute to the spread of COVID-19.

In Geneva, Switzerland, 79% of all RT-PCR-positive children under 16 years of age were infected in household clusters (Posfay-Barbe et al., 2020), and in Wuhan, China, as many as 90% of this group were infected by a family member (Lu et al., 2020). A systematic review identified 31 household clusters, of which only 10% had pediatric index cases compared to 54% in H5N1 influenza (Zhu et al., 2020). Together with evidence of lower viral loads and milder respiratory symptoms in children, these observations have led to the conclusion that children are unlikely to be the leading cause of the pandemic (Ludvigsson, 2020). Consequently, the re-opening of kindergartens and schools has been proposed. A low attack rate among children may yet be biased because the risk of infection is lowest for children (García-Salido, 2020). Current data from Berlin, Germany, did not show significant differences in viral loads between age groups, suggesting that children may be as infectious as adults (Jones et al., 2020).

Neglecting the role of children in the spread of COVID-19 is precarious. It is important in modeling the pandemic to undertake careful surveillance, including asymptomatic children with rates of infections assessed by serology, to better characterize childhood infection and the role of children in transmission networks (Velavan et al., 2020). Children need protection, as some become ill, although severely ill only in a minority of cases. COVID-19 vaccination of children may provide protection for older, unvaccinated populations. Vaccination of children will lead to a great deal of immunity required for overall protection in any population (Velavan et al., 2020; Kao et al., 2020).

Asymptomatic infection: hope for herd immunity

Studies suggesting high incidences of transmission through asymptomatic individuals have raised hope that comprehensive immunization of the population may occur unnoticed. In general, about two-thirds of a population must be immunized to achieve herd immunity. On June 24, 2020, the countries with the highest incidences of COVID-19 were the USA, Brazil, Russia, India, and the United Kingdom, with case numbers representing 0.71%, 0.54%,

0.43%, 0.03%, and 0.47% of the population, respectively; these percentages are far from herd immunity (Johns Hopkins University and Medicine, 2020).

In Gangelt (Germany), an event linked to carnival celebrations caused SARS-CoV-2 to spread throughout the city, resulting in 3% of the population with positive RT-PCR results. Serological screening revealed later that 16% of the population were exposed (Streeck et al., 2020). Even in densely populated and severely affected areas, the prevalence of anti-SARS-CoV-2 antibodies is still relatively low, e.g., 11% in Madrid, Spain (Gobierno de España MdCel et al., 2020), 15% in London, UK (England, 2020), and 20% in New York City, USA (State of NY, 2020).

It is still unclear whether asymptomatic infections lead to protective immunity. It was observed that, although all patients with severe and mild COVID-19 experienced seroconversion during or after hospitalization, only one in five asymptomatic patients seroconverted (Yongchen et al., 2020). Another comparison between an asymptomatic and a symptomatic cohort showed that IgG levels were significantly higher in the symptomatic group (Long et al., 2020). However, data from two hospitals in Hong Kong suggest that the disease's severity is not correlated with serum antibody levels (To et al., 2020). It would not only be misleading but dangerous to rely on silent immunization. Apparently, so far, only a small proportion of the population has been exposed to SARS-CoV-2.

Public health implications

The current perception of asymptomatic infections does not provide clear guidance for public health measures. As asymptomatic and presymptomatic infections are not distinguishable at first sight, they may pose a significant threat to public health during the unlocking of lockdown strategies currently being implemented in many countries.

Therefore, public health measures need to further include—mandatorily and for an unforeseeable period—proper hygiene measures and personal protective equipment to prevent spread by asymptomatic individuals. All contacts of infected persons must test for COVID-19, regardless of symptoms. Asymptomatic cases should be reported separately in official COVID-19 statistics, and shifts from asymptomatic to symptomatic stages must be reported to health authorities. Mass rallies and major events continue to need to be postponed or canceled.

Conclusions

Asymptomatic infections are an important aspect of SARS-CoV-2 infection, and the data addressed here show that the characteristics of asymptomatic and presymptomatic infection are not identical. Asymptomatic infections will be a key contributor to COVID-19 spread. Infectivity studies confirm the existence of transmission by asymptomatic individuals but are contradictory when comparing viral loads and virus shedding in symptomatic and asymptomatic infections. Younger age correlates strongly with asymptomatic and mild infections and consequently suggests children as hidden drivers of the pandemic. However, since childhood infections are usually far below the age average in COVID-19 infections, children's role in transmission events is not yet clear.

While public health measures might be practical in wealthy countries with well-established and relatively stable health care systems, the question of how the pandemic will affect low- and middle-income countries, as observed in South America or on the African continent, still remains unanswered (Ntoumi and Velavan, 2020; Wang et al., 2020). The international community is obliged to pay attention to the spread of COVID-19 in low-income

countries, as health systems could become severely overburdened, and the pandemic could continue to elude control, hitting hardest those with the least protection.

Conflict of interest

All authors disclose no conflict of interest.

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