

Asymptomatic transmission during the COVID-19 pandemic and implications for public health strategies

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Summary:

This narrative review summarizes evidence demonstrating transmission potential of SARS-CoV-2 from asymptomatic and pre-symptomatic individuals, and their contribution to COVID-19 pandemic. This implicates consideration of widespread testing with emphasis on health care workers and urgent revision of global health strategies.

ABSTRACT

SARS-CoV-2 spread rapidly within months despite global public health strategies to curb transmission by testing symptomatic patients and encouraging social distancing. Here, we summarize rapidly emerging evidence highlighting transmission by asymptomatic and pre-symptomatic individuals. Viral load of asymptomatic carriers is comparable to symptomatic patients, viral shedding is highest before symptom onset suggesting high transmissibility before symptoms. Within universally tested subgroups, surprisingly high percentages of COVID-19 positive asymptomatic individuals were found. Asymptomatic transmission was reported in several clusters. A Wuhan study showed an alarming rate of intrahospital transmission, and several countries reported higher prevalence among healthcare workers than the general population. This raises concern that health workers could act as silent disease vectors. Therefore, current public health strategies relying solely on 'symptom onset' for infection identification need urgent reassessment. Extensive universal testing irrespective of symptoms may be considered with priority placed on groups with high frequency exposure to positive patients.

Keywords: COVID-19, SARS-CoV-2, Public Health, Asymptomatic, Transmission

1. INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic has rapidly spread across the globe infecting more than 4.7 million people, causing more than 316,000 deaths and overwhelming health care systems [1]. Despite these staggering numbers, the best strategies to save lives continue to be investigated. At the time of publication, no effective standard of treatment has been established and an effective vaccine is yet to be developed. In the absence of an effective treatment, the current focus remains on human-to-human transmission prevention, including among close contacts and health care workers [1]. This is a huge challenge as evidence is rapidly emerging suggesting transmission by asymptomatic or pre-symptomatic carriers of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19.

Exposure prevention strategies across the globe have included use of personal protective equipment (PPE), social distancing of community members, quarantining known COVID-19 positive patients and contact tracing in order to identify exposed individuals [2]. Current strategies of relying on presence of symptoms to identify SARS-CoV-2-infected individuals for transmission control have proven to be a challenge given emerging evidence that transmissibility can occur prior to symptom onset. The median incubation period is estimated to be about 5 days (95% CI, 4.5 to 5.8 days), with a majority of those who develop symptoms doing so within 14 days after exposure [3]. However, majority of patients develop mild to moderate disease and some remain asymptomatic [4]. Transmissibility has been shown to begin 2 to 3 days before the appearance of the first symptoms [5], peaks at 0.7 days before symptom onset [5] and may last for as long as 21 days in asymptomatic individuals [6].

In most countries, viral PCR testing to determine SARS-CoV-2 infection status has focused on symptomatic patients while testing capabilities are being improved upon [7]. The emerging evidence presented below makes a compelling case that asymptomatic and pre-symptomatic individuals are the major drivers of the COVID-19 pandemic and argues for reassessment of public health strategies. Certain groups serving vulnerable populations (e.g. health care workers (HCWs), long-term care facility (LTCF) staff, first responders, etc.) have a higher probability of exposure to SARS-CoV-2, and thus are at high risk of unknowingly contributing to disease transmission during asymptomatic and pre-symptomatic phases. It is proposed here that the early identification of infected asymptomatic and pre-symptomatic individuals should be an area of focus with priority on universal testing of those who interact with vulnerable populations.

2. CURRENT EVIDENCE

2a. Characteristics of SARS-CoV-2 leading to transmission without symptoms:

The importance of asymptomatic carriers in transmission of infectious diseases has been established in similar respiratory viral outbreaks prior to the SARS-CoV-2 pandemic. In Middle East Respiratory Syndrome Coronavirus (MERS-CoV), 12% of patients who tested positive for MERS-CoV were asymptomatic [8, 9]. During the SARS-CoV outbreak in Singapore in 2003, 7.5% of serology positive HCWs and 13% of cases in the general population were asymptomatic [10]. Data suggest that SARS-COV-2 can be highly contagious in individuals before symptom onset and in individuals who never develop symptoms. Researchers have hypothesized that salivary glands may function as potential reservoirs of SARS-CoV-2 in asymptomatic infected individuals [11]. A study on quantitative viral load found that an asymptomatic individual had similar viral load as symptomatic patients, suggesting a similar

transmission potential [12]. An asymptomatic 6-month old infant with COVID-19 had a high viral load on nasopharyngeal (NP) swab, with similar viral load as his symptomatic mother. Daily NP swabs for this infant remained positive for SARS-CoV-2 and eventually became negative on day 17 of his admission. His symptomatic mother's NP swabs became negative on day 18 of her illness [13]. A mathematical model incorporating asymptomatic carriers indicated that basic reproduction number R_0 is likely to be from 5.5 to 25.4, with a point estimate of 15.4. This suggests that asymptomatic individuals are major drivers for the growth of COVID-19 pandemic [14].

In a study reviewing the temporal dynamics of SARS-CoV-2 viral shedding, clinical and epidemiologic data was analyzed between cases in transmission chains. The study suggests that viral shedding may begin 2 to 3 days before the appearance of the first symptoms and 44% (95% CI, 25–69%) of secondary cases acquired their infection during the index case's pre-symptomatic period [5]. Additionally, it was found that viral loads decreased each day following symptom onset in a monotonical manner. The infectiousness was determined to peak at 0.7 days (95% CI -0.2 - 2.0 days) before symptom onset, suggesting highest viral loads were present immediately prior to or on the day of symptom onset [5]. Similarly, a study using 28 pairs of index cases and their respective secondary cases estimated the serial interval for SARS-CoV-2. Serial interval was defined as the time from symptom onset in the index case (infector) to symptom onset in the secondary case (infectee). This interval was found to be 4.0 days (95% CrI, 3.1- 4.9) and is shorter than the estimated mean incubation period of 5 days, suggesting pre-symptomatic transmission occurs more frequently than symptomatic transmission [15].

Not only does the period of transmissibility begin soon after exposure, it can also last longer than a week. Among 24 asymptomatic cases exposed to COVID-19-confirmed patients in

Nanjing, China, the median period of transmissibility was 9.5 days (with maximum of 21 days). Period of transmissibility, or communicable period, was defined in the study as the period during which the case had positive PCR test results. 12 (50%) of these asymptomatic cases had typical changes of ground-glass opacities in their lungs. Despite this, only 5 (20%) went on to develop mild symptoms and none developed severe pneumonia or critical illness leading to death. Several patients who acquired disease from this group of 24, however, developed severe illness [6]. This suggests that individuals with SARS-CoV-2 infection who are asymptomatic or have mild disease can unknowingly transmit disease to others who may go on to develop severe disease, and this transmission can happen for up to 21 days.

2b. Evidence of asymptomatic infection within universally tested populations:

After the first COVID-19 related death in Italy, the entire Italian town of Vo' Euganeo with a population of 3000, was put into quarantine. Every inhabitant of this isolated village was tested for SARS-CoV-2. This revealed that at the time of the first symptomatic case, 3% (89) of the population was positive [16]. It was suggested that 50-75% of positive individuals were asymptomatic [17]. The rapid identification and isolation of asymptomatic infected individuals led to "eradication" of SARS-CoV-2 from the town of Vo' Euganeo [16].

Universal PCR testing of Japanese nationals evacuated from Wuhan, China on chartered flights suggested that 30.8% of positive patients were asymptomatic (95% confidence interval (CI): 7.7%, 53.8%) [18]. Data from the Diamond Princess Cruise line in which all passengers were tested for SARS-CoV-2 found an estimated asymptomatic proportion of 17.9% (95%CI: 15.5–20.2%) [19]. Sailors on the United States Navy aircraft carrier Theodore Roosevelt were potentially exposed on March 5 to COVID-19. Despite isolating the exposed, almost 94% of the 4,500 crew members tested positive by April 16th. About 60% of the people who tested positive

have remained asymptomatic [20]. The above data came from unique populations in which all cases were geographically confined without significant turnover.

Through the Boston Healthcare for the Homeless Program, all individuals in a single large shelter were tested over the course of a two-day period regardless of symptom status. This testing was undertaken after expeditiously removing 15 symptomatic COVID-19 confirmed patients from the shelter. Of 408 guests tested, 36% (147) were PCR-positive for SARS-CoV-2 and vast majority of the PCR positive guests had no symptoms. Prevalence of fever (0.7%), cough (7.5%), shortness of breath (1.4%), was very low and not different among the SARS-CoV-2 positive guests when compared to those who tested negative. The rapid transmission of SARS-CoV-2 infection and high prevalence of asymptomatic carriers suggests a universal testing approach instead of symptom-based approach is needed to prevent spread of infection to vulnerable populations from asymptomatic carriers [21].

2c. Evidence of asymptomatic infection among pediatric and obstetric patients:

According to a large pediatric national case series from China, among 2143 pediatric COVID-19 cases, 4.4 % were asymptomatic. Among the age groups of 6-10 year-old and 11-15 year-old patients, the asymptomatic percentage was as high as 5.7% (30 out of 521) and 6.5% (27 out of 413), respectively. Overall, around 94% of patients were asymptomatic, mild or moderate cases [22]. A study mentioned earlier, suggested that the viral load in a 6 month old infant was similar to the viral load in his symptomatic mother. His NP swabs remained positive for >2 weeks [13]. Several familial clusters with asymptomatic pediatric patients have been described in literature, leading to concern that asymptomatic children may act as facilitators of viral transmission [23, 24].

Early during the New York City SARS-CoV-2 outbreak, pregnant women were screened based on symptoms and exposures. However, when asymptomatic pregnant women later developed symptoms during admission, several health care workers were exposed with inadequate PPE, risking further transmission of infection [25]. This led to initiation of universal SARS-CoV-2 PCR testing for all patients admitted to Labor units irrespective of symptoms, exposure and travel history [26]. Among 214 women who had PCR testing, 15% (33) were positive for SARS-CoV-2 infection and 87.9% (n=29) of these women were asymptomatic at the time of testing. This universal approach led to changes in patient isolation and PPE practices with goal of limiting asymptomatic transmission to newborns as well as hospital staff [27].

2d. Demonstration of transmissibility by asymptomatic infected individuals:

As more wide-spread viral PCR is being obtained, the presence of asymptomatic COVID-19 positive individuals in the population is becoming increasingly obvious. In a family cluster of 6 COVID-19 PCR positive patients from China, 5 symptomatic family members contracted the virus from an asymptomatic family member with absence of CT chest findings [28]. Another study in Singapore identified seven clusters of COVID-19 positive individuals among whom pre-symptomatic transmission likely occurred [29].

In a case report, asymptomatic transmission occurred from a Chinese business woman (index patient) to two German businessmen (patient 1 and 2) at a meeting in Germany [30]. The index patient later became symptomatic 1-2 days after contact with patients 1 and 2; and tested positive for COVID-19. Patient 1 developed symptoms 3-4 days after his exposure to the index patient. Two patients (patient 3 and 4) contracted the virus from patient 1 within the first 2 days of patient 1's exposure to the index patient while he was still asymptomatic. This cluster

suggests that transmission occurs before symptom onset and can often occur very soon after exposure.

2e. Evidence of transmission of SARS-CoV-2 within health care settings:

The transmission of SARS-CoV-2 in the hospital settings, whether it is from patient to patient or patient to HCW has been shown. In a single center case series of 138 patients with COVID-19 from Wuhan, China, 57 (41.3%) of these patients were presumed to have been infected in the hospital. This population was made up of 17 (12.3%) patients who were already hospitalized for other reasons and 40 (29%) who were health care workers [31].

In Washington State, 76 residents of a LTCF were tested for SARS-CoV-2 with PCR after a staff member tested positive. Of the 76 tested, 48 (63%) had positive results. Of these 48 residents, 27 (56%) were asymptomatic on the day of testing. 24 of these asymptomatic individuals subsequently developed symptoms [32]. Staff from one UK hospital reported that 50% of the emergency room workforce tested positive for coronavirus [33]. In Italy, 10% (12,252) of COVID-19 positive cases were HCWs by April 5, 2020 [34]. A pediatric hospital in Iran, reported that rate of COVID-19 infection was higher among pediatric faculty members (8.3%, n=5) than the pediatric patients (0.1% admitted patients, n=3) or general population (0.02%) [35].

According to data from 315,531 COVID-19 positive cases reported to CDC using a standardized form between February 12 -April 9, 49,370 cases included information on whether the patient was a HCW. Among these, 19% (9,282) were identified as HCWs. Among the HCWs who reported exposures, 55% (780) had contact with a COVID-19 patient only in health care settings [36]. As only symptomatic cases were included, HCWs with mild or asymptomatic infections might have been less likely to be tested or reported. These numbers, suggesting that 1 in every

5 COVID-19 patients who reported work status was a HCW, highlight the possibility of frequent health care worker disease transmission. It also raises concern for an underrepresentation of infected health care workers with potential for transmission if they remain asymptomatic and continue to work.

3. DISCUSSION:

Continued prioritization of SARS-CoV-2 transmission prevention is essential to reduce global disease burden until an effective vaccine and treatments are developed. Current WHO guidelines for interrupting transmission include: reducing secondary infections among close contacts and health care workers by focusing on rapid identification, diagnosis and management of cases, and identification and follow up of contacts [1]. The US CDC recommends “source control” to control for possibility of asymptomatic and pre-symptomatic transmission. This involves use of universal face covers whenever leaving one’s house. All individuals entering health care facilities should be screened for symptoms and have face coverings regardless of symptoms [2]. Evidence discussed earlier suggests that viral loads for SARS-CoV-2 are similar in asymptomatic and symptomatic patients, and that asymptomatic patients may continue to test positive for up to 21 days [5, 13]. Current CDC guidelines prioritize symptomatic individuals for testing, and asymptomatic individuals are given least priority [2].

Viral shedding in symptomatic patients can begin 2 to 3 days before appearance of symptoms, and peaks 0.7 days before symptom onset, after which it decreases [5]. This suggests that testing symptomatic individuals only will miss those infected individuals who have highest transmissibility, and thus universal testing irrespective of symptoms may be needed.

Several population clusters where patients acquired SARS-CoV-2 from infected sources without symptoms have been described [28-30]. In several geographically limited sub-populations where almost all inhabitants were universally tested, asymptomatic carrier prevalence was >50% among those who tested positive (50-75% in Vo'Euganeo [16], 60% in USS Theodore Roosevelt [20], >90% in the Boston Homeless shelter study [21]). Thus, testing of only symptomatic cases may miss more than half of the infected individuals contributing to viral transmission in the community.

Lastly, studies from around the globe show that HCWs make up a significant proportion of COVID-19 cases, as shown in the US where HCW were 19% of cases who reported HCW status to CDC [36] and in China where HCW made up 29% of all cases in single-center case series [31]. Since asymptomatic and mildly symptomatic HCWs may have been underreported, the prevalence is likely even higher due to recurring encounters with infected individuals. HCWs also frequently interact with vulnerable, at-risk populations and could transmit the disease unknowingly. Thus, when resources are limited, testing should prioritize HCWs and other sub-populations (LTCF staff, first responders etc.) who have frequent contact with infected individuals.

Much is still unknown regarding SARS-CoV-2; its virulence, transmissibility, and the immune system response it elicits. Above evidence is based on highly heterogeneous studies, some of which have been reported in the news media or in pre-print journals awaiting peer-review. There are still gaps in the understanding of effective screening methods during the asymptomatic and pre-symptomatic phase [37]. Limitations still exist in the effectiveness of current PCR testing as an infection identification tool [38]. Antibody testing for SARS-CoV-2 is now being used in population-based studies to estimate prevalence of infection and studies report many seropositive patients had no history of symptoms [39]. Antibody testing, however, is not a

reliable method to screen for asymptomatic carriers due to the temporal lag between viral exposure and development of antibodies, persistence of antibodies beyond infection clearance, and false negative rates with low titers [40]. Therefore, in this review, we focus on PCR testing as a means to identify asymptomatic carriers while they are infectious in order to limit transmission through early identification.

4. CONCLUSIONS:

Transmission prevention remains at the forefront of current public health strategies for the COVID-19 pandemic with focus on community social distancing, use of PPE and testing symptomatic individuals to isolate positive patients. This review summarizes evidence that SARS-CoV-2 transmission is not only possible but likely highest during pre-symptomatic and asymptomatic phases. It also highlights the high prevalence of asymptomatic carriers in several universally tested sub-populations with some studies showing that more than 50% of positive individuals were asymptomatic at the time of testing. Therefore, strategies to curb viral spread can no longer solely rely on 'symptom onset' to identify all infected individuals. An approach that focuses on universal source control and early identification of infected individuals regardless of symptoms is of utmost importance. Universal testing of asymptomatic exposed individuals using PCR testing must be considered. Further investigation is needed into transmission by asymptomatic carriers and rapid methods of identification of such carriers. Additional epidemiologic research is also needed for the optimal approach in resource limited settings where universal testing cannot be undertaken. Surveillance with interval testing of vulnerable populations can be considered, and targeted testing of those with high frequency contact with infected individuals (HCWs, LTCF staff, first responders etc.) may be prioritized.

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