

REVIEW ARTICLE

Mildly Infected and Presumed Asymptomatic Carriers of SARS-CoV-2; Implications in Spread and Control of COVID-19Raees Khan¹, Shumaila Naz¹, Fawad Muhammad^{2,3}, Syed Babar Jamal¹, Sumra Wajid Abbasi¹, Rabail Zehra Raza¹**ABSTRACT**

The death toll and the total number of infected individuals due to the ongoing pandemic of SARS-CoV-2 infection have exceeded that of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) as the disease has raged around the world. So far the global efforts to tackle COVID-19 include the launch of Sputnik V vaccine by Russia, 42 vaccines presently undergoing clinical trials on humans and around 92 vaccines under preclinical active investigation in animals. Majority of the SARS-CoV-2 infected individuals have been reported to show mild symptoms whereas a considerable number show no symptoms at all. SARS-CoV-2 is believed to spread from infected individuals who are asymptomatic in addition to the symptomatic individuals. In this review we discussed how the mildly infected and asymptomatic individuals raise serious concerns and complicate the processes of screening, detection, quarantine, tracking and treatment that are in practice to prevent the transmission of the COVID-19.

Key Words: *Asymptomatic carriers, Community, COVID-19, SARS-CoV-2, Transmission.*

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Introduction

The first report about asymptomatic individuals and the potential of their contagion came out after a presumably asymptomatic Chinese businesswoman infected her business partners during a meeting in Germany.^{1,2} This report was criticized initially due to lack of proper evidence in investigating the said woman. It was unknown whether or not she was experiencing any symptoms at the time of contact with her business partners.

After this first cluster of cases, other asymptomatic individuals were reported to shed the virus thereby infecting others.³ Some even tested positive for SARS-CoV-2. For instance, an interesting familial

cluster of 5 patients (Patients 2 through 6) with mild to severe symptoms and 1 asymptomatic family member (Patient 1) were admitted to the Fifth People's Hospital of Anyang, Anyang, China.⁴ Patient 1 (presumed asymptomatic carrier) was originally from Wuhan and travelled to Anyang where she contacted the other five patients who developed disease later. Patient 1 tested positive for SARS-CoV-2 but had never developed any symptoms since her initial contact with other above mentioned patients (10th January 2020 through February 11, 2020; 32 days).

Another interesting cluster from Taiwan includes a woman who was potentially shedding the virus during the incubation period thereby infecting her husband. The husband of the said woman started showing symptoms just one day after the woman become symptomatic, indicating the possibility of the asymptomatic spread of the virus.⁵

Still another case of asymptomatic SARS-CoV-2 infection includes a patient from Taiwan who was completely asymptomatic though reported positive with a high viral load.⁵

In another incidence an asymptomatic child (aged 10 years) of a Guangdong familial cluster was among the five infected family members who were reported

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positive for SARS-CoV-2 and with radiological changes of viral pneumonia.⁶ Asymptomatic SARS-CoV-2 cases have been reported from Japan and Egypt as well.^{7,8,9}

Asymptomatic SARS-CoV-2 carriers are contagious
 Though the above-mentioned case reports highlight the potential transmission of the virus by asymptomatic individuals, scientific evidence is still limited. A recent study analyzed relative viral loads in nasal and throat specimens from SARS-CoV-2 infected individuals showing either typical symptoms of COVID-19 or no symptoms at all.¹⁰ Interestingly similar viral loads were observed in all individuals regardless of the symptoms type, suggesting a similar potential of the asymptomatic patients for viral transmission. However, this hypothesis of presumed asymptomatic carrier driven transmission need further investigation. In general, the existence of possible asymptomatic individuals driven transmission indicates that the spectrum of COVID-19 is much wider than was previously thought. The potential of the asymptomatic individual to infect others indicates that most of the mechanisms underlying viral transmission are shared among symptomatic and asymptomatic carriers (Fig 1).

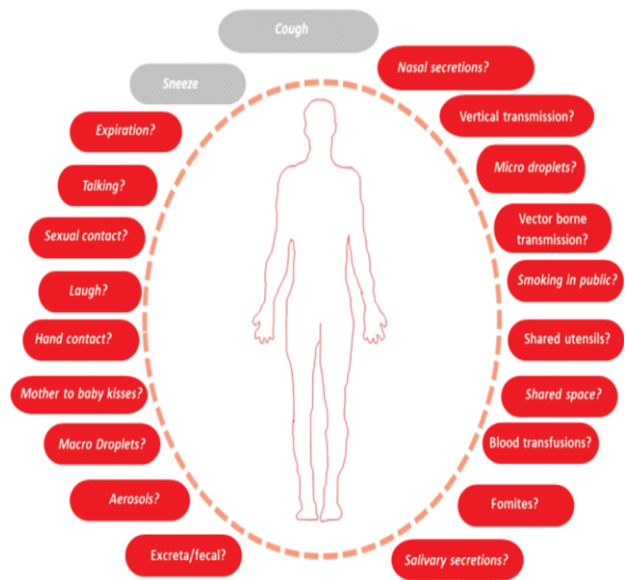


Fig 1: Transmission and spread of SARS-CoV-2. Possible ways of transmission and spread that might be shared among symptomatic and asymptomatic patients are highlighted in red. The cough and sneeze mediated transmission (highlighted in grey) are generally perceived to be limited to symptomatic individuals

The proportion of mild and asymptomatic individuals among SARS-CoV-2 infected populations

The very first comprehensive report from China CDC which analyzed data from 72,314 patient records revealed remarkably interesting aspects of this novel corona virus infection.¹ Whereas the majority of the SARS-CoV-2 infected individuals (80.9%) have been reported to show mild symptoms, and only 1.2% has shown no symptoms at all. Though the proportion of asymptomatic individuals seems small, this is perhaps due to the inability to track and test all asymptomatic individuals. However, if asymptomatic goes unchecked, it could result in silent spread of the disease.

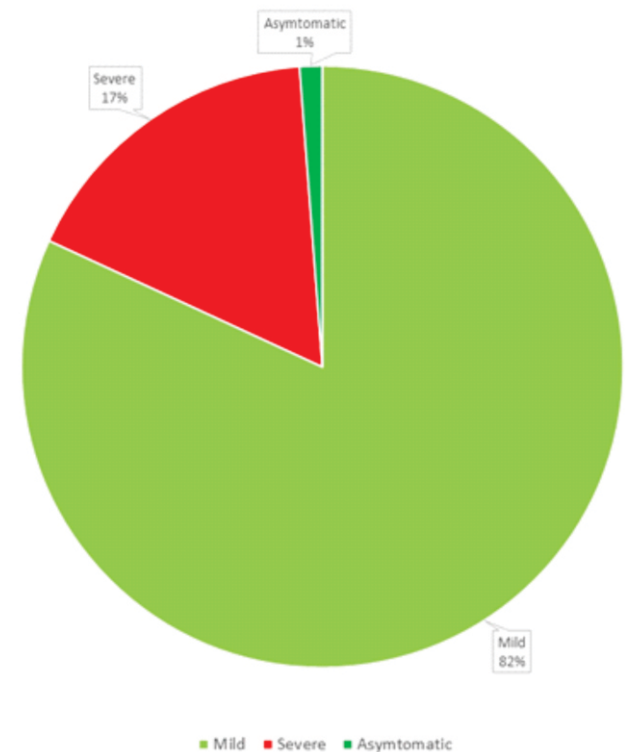


Fig 2: Proportion of the severe, mild and asymptomatic individuals from 72,314 patients record released by China CDC weekly.¹

Immunological assessment and relative contagiousness of asymptomatic individuals

An important question which is still waiting to be answered is for how long the immune response lasts in symptomatic and asymptomatic individuals. A recent report which evaluated and compared levels of virus specific antibodies (IgM and IgG) as well as various cytokines among both groups suggests that the immune response is not similar among these two

groups.¹¹ The asymptomatic group revealed to have significantly lower IgG levels both in acute as well as in convalescent phase. Moreover, the immune response was of shorter duration and approximately 40% of these individuals were found seronegative for IgG in the convalescent phase as compared to 12% in case of symptomatic individuals. This strengthens the suggestion that the low immune response might be the key factor resulting in overall symptoms, their severity as well as the various pathological forms of the disease.

Importance of asymptomatic driven transmission

Recently, Wuhan aggressively tested nearly 10 million individuals to have an idea about the overall infection types (mild, severe, asymptomatic) within Wuhan. Interestingly only 300 SARS-CoV-2 asymptomatic individuals were found positive.¹² In another step, all the contacts of these 300 (asymptomatic but test positive) patients were tracked and were tested for SARS-CoV-2 but none tested positive. Although this indicates that the spread of the disease from asymptomatic individuals is relatively less but this may be due to the strict isolation and lockdown measures that Wuhan took to prevent the spread of the disease. This in turn probably led to the reduction in overall transmission of the virus. Such large-scale tests if conducted in other populations may further shed light on to what extent asymptomatic individuals are responsible for the transmission of the disease.

Since SARS-CoV-2 is considered to be transmitted via droplets when infected individuals sneeze or cough, the general perception is that the risk and extent of infection spread from asymptomatic individuals or those with mild symptoms may be relatively low. However, this may not be the case and the asymptomatic and most probably mildly infected individuals may be the real culprits in driving the major proportion of the infection spread. This is because like a healthy individual, an asymptomatic carrier will travel, move, talk and contact people like usual thus shedding the virus over greater distances and to a greater number of people. Furthermore, unaware of being a carrier of the virus, these individuals will not be concerned with self-quarantine and taking precautionary measures such as wearing a mask, to protect others. Additionally, asymptomatic individuals and those with mild

unnoticeable symptoms will not be considered as a threat by their close contacts as well as by the community surrounding them. Thus, it is more likely that these individuals may shed more virus and thus infect more people as compared to those with severe symptoms. Moreover, such asymptomatic carriers will be of extreme importance in countries and territories with no cases yet or where only a few cases have been reported. Such individuals will not only spread the virus silently, but it will make the tracking process of clusters quite complicated.

At this stage, our understanding of the nature of asymptomatic spread is in its infancy and more in-depth studies are needed to better understand the potential risks posed by such individuals. Tracking of the asymptomatic individuals' and their close contacts may shed light on the extent and mechanism of the asymptomatic individuals driven transmission of COVID-19.

Future Perspective

The complex nature of asymptomatic carriage poses serious threats to control infectious diseases like COVID-19., The inability to track all asymptomatic carriers makes the understanding of the natural history of infection difficult and complicated. Also, the existence of asymptomatic individuals or those with mild symptoms greatly reduce the effectiveness of control interventions that solely depend on identifying individuals with noticeable symptoms, such as cross-border movement of people or isolation and treatment of infected individuals. Moreover, infected individuals without any symptoms may potentially influence the efficiency of processes such as vaccination or widespread prophylaxis specifically intended to target susceptible individuals. The reason being distinguishing individuals that are carriers but show no symptoms from susceptible individuals can be challenging. Treating asymptomatic carriers without prior knowledge poses the risk of selective pressure potentially leading to the emergence of drug-resistance.

Conclusion

The possibility that a proportion of the mildly infected and asymptomatic individuals may bypass screening, detection, quarantine, tracking and treatment processes indicate that the SARS-CoV-2 may keep spreading in human populations without

causing severe symptoms in the majority of the individuals and even no symptoms at all in others. This in turn suggests that over time COVID-19 may be taken as a common cold or seasonal flu caused by other coronaviruses (229E, OC43, NL63) and influenza viruses, respectively. If so, COVID-19 will further add to the overall burden on healthcare services and may become a common community virus.

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