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## ASYMPTOMATIC COVID-19 INFECTIONS: ITS SIGNIFICANCE AND PLAUSIBLE REASON

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**Abstract:** SARS-CoV-2 induced COVID-19 is continued to spread. In this present situation, where the virus has spread rapidly all over the world, and a meaningful treatment or vaccine is yet to be available, the biggest challenge arises on how to combat its spread. Human infection by SARS-CoV-2 results extremely heterogenous symptoms, ranging from asymptomatic or mild cases to severe hypoxia and acute respiratory distress syndrome (ARDS) depending upon host immune status. However, the exact mechanism of occurrence of an asymptomatic carrier of COVID-19 is not clearly understood. The major and yet to be resolved question is however, the role of “asymptomatic carrier” in spreading the disease. Herein, we summarize our current understanding on the possible clinical significance of asymptomatic COVID-19 infection. Particularly, the evolutionary significance, host antiviral response to SARS-CoV-2 infection and possible outcome in terms of asymptomatic carrier are briefly discussed. The resulting “asymptomatic carrier” may be the outcome of an efficient host antiviral defense, that effectively limits but could not block SARS-CoV-2 replication, and asymptomatic shedding might occur.

*Index Terms - COVID-19, Asymptomatic infection, Disease transmission, Immune response, Immune defense, Evolutionary response*

### INTRODUCTION

The recent outbreak of SARS-CoV-2 induced Coronavirus disease 2019 (COVID-19) pandemic has emerged as an unprecedented threat for humanity. According to the World Health Organization (WHO), the pandemic has more than 20.5 million confirmed cases worldwide with over 745 thousand deaths, as of August 12, 2020. These numbers are changing continuously, and an up-to-date information can be found at <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>. Treatment has been empirical, and there is no licensed COVID-19 vaccine or drugs for humans so far. Without any definitive treatment, the current standard care is mainly supportive treatment. In this present situation, where the virus has spread rapidly all over the world infecting more than 20million people, many urgent questions arise on how to combat its spread and stop deleterious effects in infected patients. One of the major unresolved question is the role of “asymptomatic subjects” in spreading the disease. While the controversy exists on transmission of the disease through asymptomatic patients, COVID-19’s rapid spread throughout the world *via* asymptomatic and pre-symptomatic subjects cannot be ruled out.

### HISTORICAL CONTEXT

SARS-CoV-2 is the seventh human pathogenic coronavirus to jump from its animal host to humans. Of the seven CoVs, four cause mild symptoms similar to the common cold and three (SARS-CoV, MERS-Cov, and SARS-Co-2) cause severe respiratory illness in humans (Fung et al. 2020).

Asymptomatic infections occur in both humans and animals. In fact, the SARS-CoV and the cause of the current pandemic SARS-CoV-2 arise from ostensibly asymptomatic animals (Fung et al. 2020). It is likely that these animals either completely asymptomatic, or just mildly ill, which were either unnoticed or unstudied. Asymptomatic carriers of the pathogen constitute a reservoir maintaining their persistence in nature (Fung et al. 2020). Carriage of viruses is not rare and reported for many viruses including influenza virus, SARS-CoV, HIV, herpesvirus, hepatitis B virus (Levo et al. 1980), etc. However, the specific mechanism how some of the individuals remain asymptomatic is not very clearly understood. Viruses causing infectious diseases exhibit a rich variety of life history strategies, shaped by natural selection (Saad-Roy et al. 2020). An important pathogen life history characteristic is the propensity to induce an asymptomatic yet transmissible stage at the beginning of an infection, subjected to complex trade-offs, ranging from immunological considerations to population-level social processes (Saad-Roy et al. 2020).

### SARS-COV-2 INDUCED ASYMPTOMATIC/ PRE-SYMPTOMATIC INFECTIONS

Current COVID-19 pandemic caused by the infection of SARS-CoV-2 is continued to spread (WHO). Almost all Governments enacted lockdown and physical distancing measures to slow down the infection and disease spread, flattening the epidemic curve and minimize case mortality. However, we are witnessing daily record spike of infection constantly as post relaxation of lockdown started along with resumption of social mixing. In the absence of definitive immunization, a large portion of the population may remain susceptible to infection and at the risk of exposure, which suggest that a better understanding is crucial as to what extent the virus can spread asymptotically (Lavezo et al. 2020, Day 2020). It has been recently reported that nearly 80% of COVID-19 infections show mild symptoms or asymptomatic, 15% exhibit severe symptoms, and 5% fall critically ill (WHO, Thomas-Rüddel et al. 2020). In a recent study by Oran and Topol (2020) have reported that 40-45% of SARS-CoV-2 infected cases remain asymptomatic, which can transmit the disease for an extended period of over 14 days.

Asymptomatic cases are devoid of any visible COVID-19 typical symptoms, however the presence or absence of any sub-clinical symptoms, such as any change in the lung or other organ is yet to be clearly understood. Currently, symptoms-based testing, contact tracing, isolation, and quarantine are the principal strategies for controlling and combating the spread of COVID-19 infections. However, viable viruses have also been reported from asymptomatic cases (Oran and Topol, 2020). Presumed transmission of SARS-CoV-2 from asymptomatic carrier to family members has been recorded recently (Bai et al. 2020). This certainly implies that the symptom-based control strategies are unlikely to be enough to contain the spread of the disease unless asymptomatic cases are significantly less infectious than symptomatic ones. Although it is too early to understand the extent of asymptomatic cases, recent reports from Italian city of Vo' (Lavezzo et al. 2020) and China (Day 2020) reported nearly 75% and 80% respectively of asymptomatic cases. However, other findings including the ship Dimond Princess (18%), Japanese people evacuated from Wuhan (42%) and children (10%) have suggested that the proportion of asymptomatic COVID-19 cases are smaller. However, there is a mixed perception prevailing with the asymptomatic cases and its role on disease transmission. Although recent studies indicated that the asymptomatic cases of COVID-19 could be a source of contagion (Zhou et al. 2020) but the epidemiological significance of asymptomatic carriers of SARS-CoV-2 are still remain controversial (Gao et al. 2020).

An understanding of asymptomatic viral infections that defined as infections with a pathogenic virus not necessarily having any sign of the disease or symptom, is important from various aspects: for understanding the pathogenesis, assessing severity and the burden of the disease (Gentile & Micozzi, 2016). This may also imply for optimizing public health control measures or strategizing the screening procedure in case of a highly infectious disease, like COVID-19. It is important to recognize that the study of asymptomatic COVID-19 is an emerging subject of the current pandemic, and part of this discussion may necessarily be speculative. The main goal of this review is to augment our understanding on asymptomatic infections and criteria for causality, and about the immunological and host-virus interactions in asymptomatic infections, focusing on COVID-19.

### SEVERITY OF COVID-19 AND ASYMPTOMATIC INFECTIONS

Clinically COVID-19 is an acute respiratory disease caused by the infection of SARS-CoV-2. The clinical manifestations of COVID-19 are variable and vary from person to person, according to age and depending on the host health and immune status. These include asymptomatic carrier, acute respiratory disease (ARD), and pneumonia of varying degrees of severity. SARS-CoV-2 infected asymptomatic cases were diagnosed based on positive viral nucleic acid test results or based on serological conversion result but without any COVID-19 symptoms, such as fever, gastrointestinal, or respiratory symptoms, or chest radiographic abnormalities. Although, recent reports have suggested plausible transmission of SARS-CoV-2 through asymptomatic carrier (Noh et al. 2020, Li et al. 2020), but there is a lack of clear consensus regarding the infectivity and transmissibility *via* asymptomatic carrier (Gao et al. 2020). Patients with ARD are defined as laboratory-confirmed COVID-19 cases with respiratory symptoms, which do not reveal signs of pneumonia based on chest computed tomography (CT) (Huang et al. 2020). These groups are categorized as mild symptomatic cases with probable recovery from or progression to advanced stages and capable of transmitting the disease. Patients with pneumonia are defined as severe COVID-19 cases having both respiratory symptoms and pneumonia on CT (Huang et al. 2020). It also includes patient with critical condition characterized by respiratory failure requiring mechanical ventilation, or another organ failure requiring ICU management.

### CLINICAL FEATURES OF SYMPTOMATIC AND ASYMPTOMATIC PATIENTS: WHY SOME SECTION OF SARS-CoV-2 INFECTED PEOPLE ARE ASYMPTOMATIC OR DEVELOP ATYPICAL SYMPTOMS

Huang et al. (2020) reported that SARS-CoV-2 infection present strong infectivity during the incubation period with rapid transmission. In another study, Giacomelli et al. (2020) reported that some patients with laboratory confirmed COVID-19 are asymptomatic, while others exhibit atypical symptoms including loss of smell (anosmia) and loss of taste (ageusia). It is now widely recognized that respiratory symptoms of COVID-19 in symptomatic patients are extremely heterogenous, ranging from asymptomatic or minimal symptoms to significant hypoxia with ARDS at severe stage (Huang et al. 2020). SARS-CoV-2 infected symptomatic patients revealed with fever, fatigue, nonproductive cough, and myalgia, as common symptoms of COVID-19 (Huang et al. 2020). At severity, the disease is characterized by significantly high serum levels of D-dimer, lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, tendency for monocytosis, lymphopenia, low number of natural killer (NK) and cytotoxic T cells, and tendency for disseminated intravascular coagulation (DIC), reflecting the involvement of Cytokine Storm Syndrome (CSS) (Cao et al. 2020, Huang et al. 2020, Fu et al. 2020, Moore & June 2020, Zhang et al. 2020, Wang et al. 2020, Chen et al. 2020). It has been generally recognized that the COVID-19 disease exaggeration till the late stage is not only attributed to direct viral damage, but also a consequence of immune-mediated inflammatory injury induced by SARS-CoV-2 (Cao et al. 2020, Moore & June 2020, Shi et al. 2020). **Table 1** compares the patterns of symptoms along with cytokines and T cell lymphopenia related to the severity of COVID-19 patients.

Host immune response clearly plays a crucial role in the host defense against SARS-CoV-2 infection and subsequent disease progression (Catanzaro et al. 2020). Notably, SARS-CoV-2 infection activates both innate and adaptive immune response, thus sustaining the resolution of COVID-19 (Catanzaro et al. 2020). The relevant changes occur in both innate and adaptive immune systems have been highlighted by several studies (Cao et al. 2020, Moore & June 2020, Shi et al. 2020, Catanzaro et al. 2020, Liu et al. 2020). While a rapid and well-coordinated immune response represents the host's first line of defense against viral infection, an excessive inflammatory innate response and dysregulated adaptive immune defense may cause severe tissue damage both at the site of virus entry and at systemic level (Zhaou et al. 2020, Shi et al. 2020). Mounting evidences suggest that excessive proinflammatory response is the cause to induce an immune pathology resulting the course of ALI, ARDS, acute cardiac injury, sepsis and multiorgan failure in COVID-19 (Huang et al. 2020, Zhang et al. 2020, Zhou et al. 2020, Wang et al. 2020, Xu et al. 2020).

**TABLE 1. PATTERNS OF SYMPTOMS ALONG WITH CYTOKINES AND CHEMOKINES, AND T CELL LYMPHOPENIA IN PATIENTS RELATED TO THE SEVERITY OF COVID-19**

(Huang et al. 2020, Zhang et al. 2020, Zhou et al. 2020, Chen et al. 2020)

State of COVID-19	Asymptomatic/pre-symptomatic	Mild or moderate	Severe
Symptoms	No symptoms	Fever, headache, dry cough, myalgia, fatigue, dyspnea	Fever, dry cough, fatigue, ALI, ARDS or MOF
Cytokines & chemokines	No change	↑IL-6, ↑IL-10, ↑TNF-α	↑↑ IL-2, ↑↑IL-6, ↑↑ IL-10, ↑↑TNF-α, ↑↑MCP-1, ↑↑CRP, ↑GM-CSF
T cell lymphopenia	No change	↓Lymphocytes (CD4+ T, CD8+ T)	↓↓Lymphocytes (CD4+ T, especially CD8+ T)
↑increased; ↑↑ severe increased; ↓ decreased; ↓↓ severe decreased			

Taken together, these studies clearly argue that the virus-induced immunopathological events play a crucial role in the fatal pneumonia induced by SARS-CoV-2 infections in severe symptomatic patients, while such events are unlikely to occur in asymptomatic infections and mild cases of COVID-19. It has also been reported by WHO that nearly around 80% of the mild symptomatic patients get recovered of its own without any clinical interventions. Nevertheless, no clear explanations to such mild and asymptomatic SARS-CoV-2 infections or COVID-19 cases are available. However, it is presumed that due to the presence of neutralizing antibodies and or due to cross protective immunity from previous seasonal coronavirus, or their antiviral innate immune response efficiently diminish but not fully stop viral replication. In either case, low numbers of infectious virus would be shed. Alternatively, the process of virus replication could be decoupled from the immune system. Similar phenomenon was described in simian immunodeficiency virus (SIV) and local immune evasion but suppression of specific cytokines was reported to occur in upper respiratory infection with human rhinovirus (Schimid-Hempel 2008, 2009).

Virus infection is encountered by the host immune responses. Depending on the severity, the infection may be acute infections or chronic infections (Stebbins & Gazzaard 2003). During the acute infection, both viral and host immune strategies compete for dominance until infection is resolved (Virgin et al. 2009). In acute infections, there may be two major outcomes, either death of the host or recovery following termination of the infection. In chronic infections, the period is longer with the persistence of the virus (Stebbins & Gazzaard 2003, Virgin et al. 2009). In such cases, as also observed in Coronaviridae infection (Bergmann et al. 2006) and likely for SARS-CoV-2 infection, both virus replication and host immune response mechanism present to an extended period of time. Although such capacity of SARS-CoV-2 is yet to be proven, the shedding of viral nucleic acid that persist long after resolution of the acute disease might be consider as evidence for either re-infection or reactivation of latent infection (Ye et al. 2020, Alpalhão et al. 2020).

An inefficient immune response, as observed in case of COVID-19 patients with “immunocompromised” state may lead to exacerbation of the disease. This stage can be defined as patients with serious co-morbidity resulting an “acute infection” and unable to cope up with the complications of SARS-CoV-2 infections resulting rapid deterioration and possible demise. The initial survival group depending on their innate immune response may become either “disinfected or recovered” post clearance of the viral particles or may develop chronic infection with the persistence of the virus. This group also includes individuals infected with SARS-CoV-2 and remain asymptomatic or manifest only mild disease. For such asymptomatic individual, immune response contains the viral inoculum and subsequent viral replication occurs without leading to a degree of damage that alters homeostasis (Pirofski and Casadevall, 2020). In a recent study, Long et al (2020) have reported that patient may fall in the second group, where due to an efficient immune response in the early stage effectively reduce the viral load keeping the proinflammatory elements under control resulting asymptomatic or mild cases of COVID-19.

#### IS ASYMPTOMATIC INFECTION OF SARS-CoV-2 A RESULT OF EVOLUTIONARY RESPONSE?

SARS-CoVs are zoonotic viruses, which have spilled off from animals to human causing enormous public health challenges due to our limited understanding about the pathogen during the initial stages of the outbreak. The current COVID-19 pandemic is a stark example. As zoonotic viruses are often poorly adapted following a host-shift, it is natural that they undergo evolutionary stages in response to their novel human host including medical and public health interventions (Day et al, 2020). Examples where some evidence exist for adaptation following host-shifts include Avian flu, Ebola, and Zika virus in humans (Geoghegan et al. 2018). Similarly, it is extremely likely that we can expect further adaption of SARS-CoV-2 in human host. For instance, although SARS-CoV-2 is already known to adapt to bind the ACE2 receptor more efficiently than SARS-CoV, currently available data including computational studies have identified additional mutations that might involve in functional changes of pathogenesis, infectivity or virulence of SARS-CoV-2 (Day et al. 2020)

The rapid spread of COVID-19 throughout the world in this pandemic has fueled the possibilities of enhancing abilities of asymptomatic transmission acquired by SARS-CoV-2. In a recent report, Saad-Roy et al. (2020) have mentioned that asymptomatic, less-symptomatic, or fully symptomatic first stages of COVID-19 are possible evolutionary outcome. A less symptomatic initial infection can persist longer due to reduced host immune response, but at the cost of reduced transmission (Saad-Roy et al. 2020).

As SARS-CoV-2 is assumed to evolve to an optimal balanced state of, the choice of which trade-off function to use (e.g. transmission – mortality or transmission – recovery) is thus critical to understand the evolution of virulence. In asymptomatic infections, host control will place a boundary on viral replication, which will tend to reduce the length of an infection (increasing recovery rate), and therefore limit transmission (Saad-Roy et al. 2020).

## HOW DO ASYMPTOMATIC INFECTIONS BE EXPLAINED?

There is no one set meaning of the term 'asymptomatic'. Some patients affected by the novel coronavirus may be infected but not exhibit any of the typical symptoms, including coughing, fever or breathing issues. These are what experts' term 'asymptomatic or atypical coronavirus positive' cases. China has reported that 300 asymptomatic carriers were found to be non-infectious. World Health Organization let out a statement recently, saying that COVID-19 transmission rate from asymptomatic patients is "rare". However, soon after, they retracted the statement, adding that the statement was misinterpreted, and much data remains unknown and there was a 40% chance of patients transmitting the illness onto others without being symptomatic. However, remaining 60% remain non-transmitters.

Recently the Indian Council for Medical Research (ICMR) has released the result of sero-survey conducted in the third week of May 2020 in 83 districts with sample size of 26,400. The serological survey results for positive IgG from general population have found a broad indication of low prevalence; 0.1% in rural populations and slightly higher in cities and COVID-19 containment zones.

(<http://164.100.117.97/WriteReadData/userfiles/PPT%20June%2011%20Media%20Briefing.pdf>). All these positives are asymptomatic in nature indicating their natural immunity might have overcome the viral infection and win the battle.

Zou et al. (2020) have reported recently that the viral load of respiratory tract samples in an asymptomatic patient are alike that in the symptomatic patients. However, a single sample is difficult to be representative and more data on asymptomatic viral load and viral shedding are essential to confirm. Thus, in the light of "Zero infection" for 60% case (WHO), it is safe to assume that the infective viral load of respiratory tract samples in the asymptomatic patient might not be high. Moreover, it was observed experimentally that in influenza A and B virus infections, the mean levels of viral RNA shedding in the asymptomatic case patients were approximately 1–2 log<sub>10</sub> copies lower than in symptomatic patients (Ip et al. 2017). Moreover, although pathogenic nucleic acids can be detected in respiratory tract samples from asymptomatic carriers, the opportunity of transmission is lower than that in symptomatic patient owing to the absence of the way expelling pathogen via cough and sneezing. Based on the foregoing discussion, we presume that the infectivity of some asymptomatic SARS-CoV-2 carriers might be weak. However, the question remains to be answered, why is so?

Here is how the natural immunity works in human. If someone is exposed to same or similar pathogen in the past, the battle begins by preventing the pathogen from binding to host cell receptors by neutralizing antibodies. This normally works only partially, not all attachment proteins are blocked and some pathogens will still attach to the receptors on host cell. Second line of defense immediately starts by engagement of killer T-cells, which can identify bind and kill cells where the virus is taken shelter to multiply. These virus incubating cells are in the host body and killed by the T-cells until all viruses are dead.

We hypothesized that the genetic markup and or acquired immunity in the past of the an asymptomatic is such that their immune system creates battery of neutralizing antibodies against a) spike protein and or b) some replicating proteins of the SARS-CoV-2. Spike protein is an essential viral element that helps in the attachment and virus internalization to the host cell. A vast amount of host cell receptors are targets for viruses, including the cell surface GRP78. Spike protein is also a major antigenic determinant that can induce immune response in the hosts. Inhibiting the interaction that occurs between the SARS-CoV-2 spike protein and the host cell receptor GRP78 would probably decrease the rate of viral infection. Binding of any neutralizing antibodies to the virus is expected to reduce the risk of virus transmission by producing a virus in attenuated form.

Secondly, since the viral infectivity refers to infective virus load in samples and it is not very infective till it reaches a certain limit, therefore infectivity mainly depends on whether the virus is in a reproductive state or not. Therefore, because of presence of neutralizing antibodies, sometimes, despite having detectable viral nucleic acid, no active virus can be detected or culturable in cell lines. Therefore, detection of viral nucleic acid positivity in some cases may not indicate infective viral load, thus infectivity. This finding implicates that asymptomatic patients cannot be defined as same class of patients with pre-symptomatic patients. They can be categorized in three categories.

In first category, an individual asymptomatic patient can result the infectivity and virulence in a specific way. The patient can attenuate the virus in a way that the infectivity almost goes as the attenuation had happened in spike protein and thereby these patients cannot infect others. In the second category there could be attenuation in other part of the virus to make it less virulent but not less infectious as the spike is intact. In that case they infect but the symptom is not severe with the secondary patient. The third category (WHO indicated 40% Group) could be the release of virus without any significant attenuation and thereby both infectivity and virulence prevail.

Now similar individuals can form a "class" or group depending on the geography, age group, sex, living style, social status, determining their natural immunity, and previous similar disease prevalence in that area. Hence, the study of a group of asymptomatic patients may not be similar to another group. Asymptomatic patients of China, Italy, or India might be different due to their ethnicity and varied exposure of different microbiome in the environment.

## HOST DERIVED MUTATIONS MAY IMPACT THE PATHOGENICITY OF SARS-CoV-2

As discussed above there could be a continuous host-pathogen interaction exist resulting from host immune responses against the novel SARS-CoV-2. As a result, due to a host sift, SARS-CoV-2 is undergoing evolutionary changes in order to adapt in to the new human host by adapting to an optimal balanced state in order to avoid the host's antiviral immune responses (Saad-Roy et al. 2020, Day et al. 2020). The remarkable capacity of RNA viruses to adapt to new host and environment is highly dependent on their ability to *de novo* diversity in a short period of time (Sanjuan & Domingo-Calap 2016). Viral mutation rates indicate that viral genetic diversity is determined by multiple virus- and host-dependent process, and that viral mutation rates can evolve in response to host specific selective immune pressure (Sanjuan & Domingo-Calap 2016). The process underlying has important implications in managing pathogenesis, immune escape, drug resistance, and vaccination.

RNA viruses, like SARS-CoVs can mutate faster, while the rate of mutations is modulated at different levels, including polymerase fidelity, sequence context, cellular microenvironment, replication mechanisms, proofreading, secondary structure, and access to post-replicative repair (Sanjuan & Domingo-Calap 2016). Additionally, massive numbers of mutations can be introduced by some virus-encoded diversity-generating elements, as well as by host-encoded cytidine/adenine deaminase (Sanjuan & Domingo-Calap 2016).

There is no doubt that SARS-CoV-2 is also mutating and thus has the potential to adapt during the current pandemic (Day et al. 2020, Pachetti et al. 2020). However, at this moment it is not clear or merely speculative, whether these mutations will lead the virus to changes in infectivity or transmission, severity, or the duration. It is speculative that SARS-CoV-2 is undergoing specific mutations to attenuate its pathogenicity as a survival advantage, resulting asymptomatic carrier (Day et al. 2020). Asymptomatic carriers of other human CoVs including 229E, OC43, NL63 and HKU1 have been well documented (Fung et al. 2020). However, at present our knowledge about the scope for the functional significance of the existing genetic variants is extremely limited. This knowledge gap is exacerbated by the lack of accessible data linking disease outcomes with genetic variants.

## CONCLUSION

The prevalence of SARS-CoV-2 asymptomatic infections in this current pandemic have been reported worldwide. However, the epidemiological significance of such asymptomatic infection, including its role in disease transmission and the possible outcome is not clearly understood. Here we presumed that asymptomatic carrier might be the result due to an evolutionary process. The resulting “asymptomatic carrier” might also be the outcome of an efficient host antiviral defense that effectively limits but could not block SARS-CoV-2 replication, and asymptomatic shedding might occur. In such scenario, the risk of transmitting the disease is relatively low due to a low viral load. Alternatively, the host antiviral immune response against SARS-CoV-2 is decoupled from viral replication, the viral load would be higher, posing a higher risk for transmission. However, a careful quantitative analysis of the replication dynamics of SARS-CoV-2 in asymptomatic carriers over time would be essential to clarify the validity of the hypotheses.

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