

# RHYTHMOS



October 2020 • Volume 15 • No 4 (60)

ISSN: 1792-7919

e-ISSN: 1792-7927

URL: [www.rhythmoss.gr](http://www.rhythmoss.gr) / <http://rhythmoss.info.tm>

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### EDITORIAL

#### Asymptomatic Carriers/Patients with COVID-19 Infection: How is this Possible?

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#### Abstract

A sizeable proportion of individuals contracting the corona virus disease 2019 (COVID-19) infection remains asymptomatic, while some patients develop mild symptoms and others exhibit severe symptomatology becoming critically ill necessitating admission to intensive care unit exposed to a high mortality risk. The pathophysiological mechanisms underlying this diversity in the clinical picture of COVID-19 are poorly understood. A variety of reasons have been postulated, among which, viral load, age, gender, immune response, blood type, genotypes, polymorphisms, comorbidities and pre-existing immunity are actively explored. Thus, there is a dire need to further elucidate this phenomenon and find ways to identify and discern susceptible from resistant individuals with the ultimate goal to find a cure for the disease. These

issues are herein discussed and pertinent recent literature is reviewed. *Rhythmoss 2020;15(4):65-72.*

**Key words:** SARS-CoV-2; COVID-19; asymptomatic COVID-19; ACE2; immune response; immunity; transmissibility; polymorphism; genetics; children; blood type; vitamin D

**Abbreviations:** ACE = angiotensin converting enzyme; ARDS = acute respiratory distress syndrome; BCG = bacillus Calmette-Guerin (vaccine for tuberculosis); COVID-19 = coronavirus disease 2019; CT = computed tomography; ICU = intensive care unit; IL = interleukin; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

#### Introduction

Corona virus disease 2019 (COVID-19) infection can produce a wide range of symptoms, from mild to severe, or no symptoms, at all.<sup>1</sup> Symptoms develop 2-14 days after exposure to the virus. However, it remains a big mystery why some patients with COVID-19 infection, even in the absence of underlying diseases, become severely ill and/or succumb to their disease, while other individuals remain asymptomatic, even persons with high-risk factors. The majority of patients are either asymptomatic carriers who

though have the potential to be infectious and transmit the disease to others coming in close contact, or have a mild flu-like illness which cannot be differentiated from a simple common cold.<sup>2</sup> According to a recent seroprevalence study of a Greek medical school employees, one in three COVID-19 infections was asymptomatic.<sup>3</sup> A South Korean study indicated that one fifth of the COVID-19-positive individuals without severe symptoms were asymptomatic.<sup>4</sup> Furthermore, viral loads were comparable to those in symptomatic patients. According to a recent estimate made by Dr Anthony Fauci, Director of the National Institute of Allergy and Infectious Diseases of the US, ~40%-45% of COVID-19 infections are asymptomatic ([www.medscape.com/viewarticle/937297](http://www.medscape.com/viewarticle/937297)). A recent systematic review and meta-analysis of 79 studies comprising 6832 patients with COVID-19 infection indicated that the overall estimate of the proportion of people who become infected with COVID-19 and remain asymptomatic throughout the course of infection was 20% (95% CI 17%–25%, 79 studies), with a prediction interval of 3%–67%.<sup>5</sup> In studies that identified SARS-CoV-2 infection through screening of defined populations, the proportion of asymptomatic infections was 31% (95% CI 26%–37%, 7 studies).

Finally, a meta-analysis of 50,155 patients from 41 studies with confirmed COVID-19 showed that the pooled percentage of asymptomatic infection was 15.6% (95% CI, 10-23%); 27.7% (95% CI, 16.4%-42.7%) in children (11 studies, n=1152).<sup>6</sup> The pooled percentage of pre-symptomatic infection (initially asymptomatic then developing symptoms during follow-up) among 180 initially asymptomatic patients (10 studies) was 48.9% (95% CI, 31.6%-66.2%). Abnormal chest computed tomography (CT) features were common in asymptomatic patients; 15 (41.7%) of 36 patients (4 studies) had bilateral involvement and 14 (38.9%) had unilateral involvement. Reduced white blood cell count, increased lactate dehydrogenase, and increased C-reactive protein were also recorded.

As alluded to, perhaps the higher percentages of asymptomatic patients reported by various studies may be due to the inclusion of pre-symptomatic patients who are initially asymptomatic, but a proportion of them will go on to develop symptoms at a later time.

The reason why some patients remain unaffected by the virus or have mild symptoms has not been unraveled yet; many ongoing studies are exploring this issue, which is of utmost importance in identifying and discerning susceptible from resistant individuals with the ultimate goal to find a cure for the disease.

Only some hypotheses have been formulated to explain why some people remain unaffected by the disease, while others may have a fatal course. It has been proposed that the severity of COVID-19 infection may be commensurate with the amount of the virus an individual is exposed to, with a higher exposure and viral load leading to a much more severe form of COVID-19 infection. Others have suggested that prior infection with other coronaviruses may provide a degree of immunity, or that the severity of the disease is linked to the immune response of the patient. In particular, there is need for anti-viral immune response to eliminate the invading virus; however, a strong and persistent anti-viral immune response might also cause massive production of inflammatory cytokines and damage to host tissues.<sup>7</sup> A hyperinflammatory response with overproduction of cytokines caused by aberrant immune activation is known as a *cytokine storm*, which may cause acute respiratory distress syndrome (ARDS) and other organ damage.<sup>8</sup> Therefore, an effective targeted anti-viral response that clears the virus without an exaggerated generalized immune response might be the reason for limited or absent symptomatology. In a similar context, there have been suggestions that heterologous vaccinations (BCG and oral poliovirus vaccine) performed in the past might have conferred nonspecific protection (trained immunity) against COVID-19 infection accounting for a less manifest course of the viral disease.<sup>9</sup> A multivariable analysis covering 55 countries has suggested that BCG immunization coverage, especially among the most recently vaccinated population, has contributed to attenuation of the spread and severity of the COVID-19 pandemic.<sup>10</sup> Individual studies have also suggested the potential of BCG in preventing more severe COVID-19.<sup>11</sup>

Nevertheless, there is little evidence, with some exceptions, to strongly support any of the proposed theories. A recently published study from China suggests that patients who are asymptomatic have a much weaker immune response to the SARS-CoV-2 virus.<sup>12</sup> The study involved an in-depth clinical and immunological analysis of 37 patients diagnosed as having been infected with SARS-CoV-2 and were asymptomatic and of 37 symptomatic patients. Each of the patients in the asymptomatic group reported no relevant symptoms in the 14 days prior to testing, nor during the period of hospitalization after diagnosis.

According to a study from Wuhan, China, there was less consumption of CD4<sup>+</sup>T lymphocyte in asymptomatic infections suggesting that damage to the immune system is milder in asymptomatic vs symptomatic patients.<sup>13</sup> Specifically, among 78 close contacts with confirmed

SARS-CoV-2 infection, 33 patients (42.3%) were asymptomatic, who, compared with symptomatic patients, were younger (median age, 37 vs 56 years;  $P < 0.001$ ), and had a higher proportion of women (66.7%;  $P = 0.002$ ), lower proportion of liver injuries (3% vs 9.20%;  $P = 0.03$ ), less consumption of CD4<sup>+</sup>T lymphocytes (median maximum difference of CD4 lymphocytes during treatment, 203 per  $\mu\text{L}$  vs 328 per  $\mu\text{L}$ ;  $P < 0.001$ ), faster lung recovery in CT scans (median duration, 9 vs 15 days;  $P = 0.003$ ), and shorter duration of viral shedding from nasopharynx swabs (median duration, 8 vs 19 days;  $P = 0.001$ ).

There is, of course, a higher risk for transmission of the virus by asymptomatic patients with the only consolation being that asymptomatic patients appear to have a shorter duration of viral shedding from nasopharyngeal swabs and lower risk of a recurrence. Nevertheless, identifying and isolating patients with asymptomatic COVID-19 as early as possible is critical to control the transmission of COVID-19.

Emerging evidence suggests that a mixture of genetics, age, and individuality in people's immune systems might play a role in determining the clinical manifestations of COVID-19 infection (Table 1).

## Transmissibility

The US Center for Disease Control (CDC) estimates the percent of asymptomatic infections to hover around 40%, the infectiousness of asymptomatic cases ~75% compared to symptomatic patients, and percentage of transmission occurring prior to symptom onset at ~50%, but the agency cautions that this assumption is based on an unclear understanding of what's known as "viral shedding," in which people unknowingly release contagious virus into the atmosphere ([www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html](http://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html)). A retrospective study of 79 asymptomatic COVID-19 patients at admission reported lower levels of alanine aminotransferase and C-reactive protein in these patients compared with symptomatic patients indicating that these patients had less liver damage and inflammation.<sup>14</sup> However, 43% of these patients developed symptoms during hospitalization, which assigns them to the pre-symptomatic rather than asymptomatic group of patients. The viral shedding duration of the completely asymptomatic patients is reported at 12 days (median), which is comparable to that in the presymptomatic patients. The viral shedding duration of the asymptomatic patients is shorter than that of the symptomatic patients, which is reported at 17 days or even longer (19-22). However, recent papers reported a median

duration of viral shedding in the asymptomatic group as long as 19 days (15-28).<sup>12, 15</sup> Presymptomatic transmission has been reported in about 40-50%.<sup>16</sup>

**Table 1.** Possible reasons and potential mechanisms leading to asymptomatic status of COVID-19 infection

More active and targeted anti-viral innate immune response \*  
Weaker generalized immune response \*  
Healthier respiratory tracts  
Upregulated ACE2 in the lower airway  
Protective ACE2 polymorphisms  
Lower viral load  
? Nonspecific protection conferred by heterologous vaccination (BCG and oral poliovirus vaccine)  
Genetics

\*The anti-viral immune response is essential to eliminate the invading virus, but an exaggerated, generalized and persistent (aberrant) anti-viral immune response might cause massive production of inflammatory cytokines and damage to host tissues (hyperinflammatory status).<sup>7</sup> The overproduction of cytokines caused by such aberrant immune activation is known as a cytokine storm.

## Preexisting Immunity / Seroprevalence

Immune memory derived in part from prior infections with common cold corona viruses has been suggested as a mechanism for pre-existing immunity for COVID-19 infection in some individuals.<sup>17</sup>

A New York State-wide seroprevalence study, based on 1887 of 15,101 (12.5%) reactive results, estimated a cumulative incidence of 14% through late March 2020, corresponding to 2,139,300 COVID-19 infection-affected adults; cumulative incidence was highest in New York City at ~23%.<sup>18</sup> An estimated 8.9% of infections were diagnosed, with diagnosis being highest among adults aged  $\geq 55$  years (11.3%). A UK analysis of sero-surveillance of COVID-19 indicated a highest SARS-CoV-2 antibody seroprevalence in blood donors of 17.5% in London in week 18 ([www.gov.uk/government/publications/national-covid-19-surveillance-reports/sero-surveillance-of-covid-19](http://www.gov.uk/government/publications/national-covid-19-surveillance-reports/sero-surveillance-of-covid-19)). The highest adjusted prevalence in all UK regions was found among adolescents and young adults aged 17-29 years; however, in the most recent data from London, the increase was more marked in older age groups suggesting that this population had been affected later.

A survey in Spain indicated that seroprevalence was ~5%; lower seroprevalence was recorded in children younger than 10 years (<3%).<sup>19</sup> There was substantial geographical variability, with higher prevalence around

Madrid (>10%). Seroprevalence among 195 participants with positive PCR more than 14 days before the study visit ranged from 87.6% (81.1-92.1; both tests positive) to 91.8% (86.3-95.3; either test positive). In 7273 individuals with anosmia or at least three symptoms, seroprevalence ranged from 15.3% (13.8-16.8) to 19.3% (17.7-21.0). Around a third of seropositive participants were asymptomatic, ranging from 21.9% (19.1-24.9) to 35.8% (33.1-38.5). Only 19.5% (16.3-23.2) of symptomatic participants who were seropositive by both the point-of-care test and immunoassay reported a previous PCR test. In countries, like Greece, with low number of COVID-19 infections, seroprevalence has been reported as low as 1%, with one in three infections being asymptomatic.<sup>3</sup>

## Immune response

An important feature of COVID-19 in hospitalized patients is heterogeneity of the immune response.<sup>20</sup> Exuberant immune response (immunotype 1) with robust CD4 T cell activation has been blamed for the development of the cytokine storm and its detrimental effect on the clinical course of COVID-19 infection. On the other hand, a weaker or intermediate immune response (immunotype 2) has been associated with less severe disease, including an asymptomatic or oligosymptomatic or benign course. However, a very weak response (immunotype 3) with minimal lymphocyte activation (considered to represent ~20% of COVID-19 patients) may be responsible for a poor clinical course. A recent study of 58 COVID-19 patients (median age of 43, range 22-81 years; 50% male), divided into three groups according to disease severity: asymptomatic (n = 20), mild pneumonia group (n = 27) and a severe group (n = 11), showed that during follow up, 9 (15.5%) patients required ICU admission and 3 of them succumbed to the disease.<sup>21</sup> Levels of serum interleukin (IL)-18 were correlated with other inflammatory markers and biochemical markers of organ injury, creatinine, liver enzymes and troponin; levels were remarkably higher in COVID-19 patients compared to healthy subjects (n=20) with highest levels found in patients with severe pneumonia (p<0.001); IL-18 levels were almost 4-fold higher in patients with worse outcome compared to favorable outcome (p < 0.001). Asymptomatic patients (n=20) had the lowest median concentration of IL-18 (84 pg/ml) (similar to that of healthy subjects: 103 pg/ml) compared to patients with mild symptoms (401 pg/ml) and those with severe symptoms (800 pg/ml) (p<0.001).

As mentioned, another study from China of 37 asymptomatic individuals with confirmed COVID-19 infection showed that asymptomatic individuals had a

weaker immune response to SARS-CoV-2 infection and exhibited lower levels of 18 pro- and anti-inflammatory cytokines.<sup>12</sup> On the other hand, other studies show that a maladapted immune response profile seems to be associated with severe COVID-19 and poor clinical outcome.<sup>22</sup>

## Trained Immunity

As mentioned, data from countries where heterologous vaccinations (BCG and oral poliovirus vaccine) had systematically been performed suggest a nonspecific protection (trained immunity) conferred against COVID-19 infection accounting for a less manifest and less severe course of the COVID-19 infection.<sup>10</sup>

## Blood Type

A preliminary report from China indicated that blood group A was associated with a higher risk for acquiring COVID-19 compared with non-A blood groups, whereas blood group O conferred a lower risk for the infection compared with non-O blood groups.<sup>23</sup> A small Swedish study of 64 COVID-19 patients indicated that blood type A or AB was associated with an increased risk of requiring critical care or dying of COVID-19, but there was no comparison between patients suffering from severe COVID-19 disease versus those only mildly affected as a control group.<sup>24</sup> However, subsequent studies have not confirmed such a claim.<sup>25, 26</sup> A study of 428 COVID-19 patients showed that the blood types were not associated with hospitalization or admission to intensive care unit or death in COVID-19.<sup>25</sup> Another study of 1289 individuals tested positive for COVID-19 with a known blood type, indicated that after multivariable analysis, blood type was not independently associated with risk of intubation or death.<sup>26</sup>

Nevertheless, a recent genome-wide association study (GWAS) claimed that a potential involvement of the ABO blood-group system was identified in patients with COVID-19 with severe disease complicated by respiratory failure, with a higher risk in blood group A compared to other blood groups (odds ratio, 1.45) and a protective effect in blood group O than in other blood groups (odds ratio, 0.65).<sup>27</sup>

## Vitamin D sufficiency

A systematic review and meta-analysis of 25 randomized controlled trials (RCTs) comprising 11,321 individuals indicated that vitamin D supplementation reduced the risk of acute respiratory tract infection among all participants (adjusted odds ratio 0.88; P for heterogeneity <0.001); individuals who were very

deficient in vitamin D and those receiving daily or weekly supplementation without additional bolus doses experienced particular benefit.<sup>28</sup> These data raise consideration that adequacy of vitamin D status in COVID-19 patients might be protective against manifestation of acute respiratory tract symptoms. A recent retrospective cohort study of 489 patients indicated that likely deficient vitamin D status was associated with increased COVID-19 risk.<sup>29</sup>

Vitamin D boosts innate immunity; its effects on dendritic and T cells may promote clearance of the virus and decrease inflammatory responses that produce symptoms by regulating the production of inflammatory cytokines and inhibiting the proliferation of proinflammatory cells;<sup>30</sup> increased vitamin D levels are associated with lower interleukin (IL) 6 levels, which are a major target for controlling cytokine storm in COVID-19; vitamin D is thus expected to decrease COVID-19 infection, transmission and severity.<sup>29, 31</sup> Vitamin D also affects metabolism of zinc,<sup>29</sup> which reduces replication of coronaviruses,<sup>32</sup> and may promote viral clearance and reduce inflammatory responses that produce symptoms. Higher vitamin D levels correlate with lower IL 6 levels, which are a major target for controlling cytokine storm in COVID-19.<sup>33, 34</sup> Thus, if vitamin D reduces inflammation and symptomatic presentation of COVID-10, it also increases asymptomatic carriage, making it hard to predict its effect on viral spread.

### Children and Young People

COVID-19 infection causes a severe respiratory syndrome that is different from all other known respiratory viral infections. Nevertheless, children have been consistently shown to be relatively spared from severe or any clinical manifestations of COVID-19.<sup>35, 36</sup> It is estimated that susceptibility to COVID-19 infection in persons younger than 20 years is about half that of adults, while clinical symptoms manifest in only 21% of infections in 10- to 19-year-olds, rising to 69% of infections in people aged >70 years.<sup>37</sup> Severe acute forms of COVID-19 infection are rare in children.<sup>38</sup> One such form of the disease is the newly described pediatric multisystem inflammatory syndrome with Kawasaki-like features which is also rare.<sup>39</sup> However, there is considerable uncertainty about children and young people's ability to contract, transmit, and spread COVID-19 infection. It appears though that children overall are relatively less susceptible to getting infected as well having less severe infection.<sup>38</sup>

A recent meta-analysis of 32 studies comprising 41,640 children and adolescents and 268,945 adults

showed that the pooled odds ratio of being an infected contact in children compared with adults was 0.56, albeit with substantial heterogeneity ( $I^2 = 94.6\%$ ).<sup>40</sup> The authors concluded that children and adolescents appear to have lower susceptibility to SARS-CoV-2 (odds ratio 0.56) compared with adults, while there is weak evidence that children and adolescents play a lesser role than adults in transmission of SARS-CoV-2 at a population level. It also appears that asymptomatic or oligosymptomatic younger individuals may have active infection in the upper airway without necessarily involving the lower airway.<sup>41</sup>

The reasons and mechanisms of an apparent relative resistance of children to COVID-19 and other infectious diseases remain obscure. It has been suggested that children, having a more active innate immune response, healthier respiratory tracts for not having been exposed to as much cigarette smoke and air pollution as adults, and having fewer underlying diseases, might be in a position to resist COVID-19 infection with its attendant consequences better than adults.<sup>42</sup> However, a more vigorous immune response in adults may account for a deleterious immune response that is associated with acute respiratory distress syndrome (ARDS).<sup>43</sup>

Other investigators have proposed that decreased expression of proteins, like angiotensin-converting enzyme 2 (*ACE2*) and transmembrane serine protease 2 (*TMPRSS2*) in the airway epithelium of children may block viral entry.<sup>44</sup> Furthermore, immune system differences in children compared to adults relating to relative preponderance of CD4<sup>+</sup> T cells, reduced infiltration with neutrophils, lower production of proinflammatory cytokines, and higher production of immunomodulatory cytokines and enhanced capacity of the developing lung in children to recover and repair after viral infection, might account for the apparent resistance of children to COVID-19.

As mentioned, a difference in viral receptors, like the *ACE2*, is often mentioned as a possible reason of the age-related difference in the incidence and severity of COVID-19 infection.<sup>41</sup> Upregulated lower airway *ACE2* has been suggested to offer protection from lung injury in children accounting for their relative resistance to COVID-19. *ACE2* may indeed protect against severe lung injury as shown in experimental animal models and in pediatric patients.<sup>45</sup> On the other hand, individuals that present already lower *ACE2* levels are particularly more susceptible to severe forms of the disease.<sup>46</sup>

### Renin-Angiotensin System (RAS) / Endotypes

Data regarding age, gender, genotypes, polymorphisms, comorbidities and symptoms of disease



suggest the existence of different endotypes, with a probable central role of the RAS involved in severe cases.<sup>46</sup> The role of RAS seems pivotal; as mentioned, upregulated lower airway ACE2 has been suggested to offer protection from lung injury, while downregulated ACE2 may confer harm.<sup>41</sup> Furthermore, some of the asymptomatic COVID-19 cases may be ascribed to protective single nucleotide polymorphism (SNP) present in ACE2, while other SNPs may turn out to be harmful, depending on their effect on the binding affinity of the viral spike (S) protein/ACE2 complex.<sup>47</sup>

There appear to exist multiple and different pathophysiological mechanisms and bases of COVID-19 disease (endotypes) responsible for a wide spectrum of disease manifestations, ranging from asymptomatic to severely symptomatic cases.<sup>46</sup> Further exploration and identification of such specific endotypes could enhance our understanding of disease susceptibility or resistance and disease prognosis and facilitate and direct our therapeutic strategies.

## Genetics

A possible link between severity and genetic variations in chemokine receptors and blood group loci has been suggested.<sup>27</sup> In particular, a recent genome-wide association study (GWAS) involving 1610 patients with COVID-19 and severe disease (with respiratory failure) and 1255 control participants from Italy and 775 patients and 2205 control participants, analyzed 8,582,968 single-nucleotide polymorphisms (SNPs) and conducted a meta-analysis of two case-control panels. The investigators identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with COVID-19 with respiratory failure and claim, as mentioned, that they confirmed a potential involvement of the ABO blood-group system.

Also, as mentioned, ACE genotypes may affect the COVID-19/RAS interplay. A critical ACE polymorphism consists of the presence (insertion, I) or absence (deletion, D) of a 287-bp *Alu* sequence in intron 16; the D allele (DD genotype) seems to be associated with increased susceptibility and disease activity and severity.<sup>46</sup> On the other hand, the ACE I/D allele may confer some protection; where the I/D allele frequency ratio increases, the COVID-19 recovery rate in each country also increases.<sup>48</sup>

Other investigators have suggested 3 potentially important genetic gateways to COVID-19 infection that could explain at least in part the discrepancies of its spread, severity, and mortality.<sup>49</sup> The first gateway relates to variations within the ACE2 gene as mentioned. The human leukocyte antigen (HLA) locus, a key regulator of

immunity against infection, crucial in influencing susceptibility and severity of COVID-19 has been proposed as the second genetic gateway. Finally, the genes regulating Toll-like receptor and complement pathways and the ensuing cytokine storm that underlies severe COVID-19 infection, has been suggested as the third genetic gateway. Genetic variations in these pathways could also explain geographical discrepancies of COVID-19.

## Conclusion

A considerable, albeit variable (20-45%), percentage of patients who have contracted COVID-19 infection may remain asymptomatic, while others may be oligosymptomatic and have a favorable course of this viral pandemic, and other, less fortunate, individuals may have a severe course and a sizable portion may succumb to this dreadful disease (case fatality rates vary widely among countries from 0.2% in Germany to 7.7% in Italy, with the caveat of the unknown number of asymptomatic cases and varying criteria for testing; these rates are also age-dependent reaching 5-20% for ages >70-80 years) (<https://ourworldindata.org/mortality-risk-covid#the-current-case-fatality-rate-of-covid-19>). The reason and mechanisms for this discrepancy that lie behind the absent or minimal symptoms remain elusive. Emerging evidence suggests a mixture of genetics, age, and individuality in one's own immune system as playing a role in determining the clinical manifestations of COVID-19 infection. Postulations include a weaker immune response abating the cytokine storm and multiorgan failure, a lower viral load an individual is exposed to, preexisting immunity provided by prior infection with other coronaviruses, or an innate resistance to COVID-19 infection conferred by upregulated ACE2 in the lower airway, stronger innate immune protection, healthier general status, vitamin D sufficiency, and so on. Nevertheless, despite a fortunate course of asymptomatic or oligosymptomatic individuals, infectivity remains the biggest problem, either at the same rate as with the symptomatic individuals or at 75% rate of the symptomatic cohort, as the asymptomatic status makes difficult the application and conformance with the preventive measures to combat transmissibility. On the other hand, an opportunity appears to further study this phenomenon and avail from the emerging evidence by identifying and discerning susceptible from resistant individuals with the ultimate goal to find a cure for the disease.

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