

# Host factors influencing variable symptoms of COVID-19

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## Abstract

Similar to many other viruses, SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) causes various symptoms in individuals who have been exposed to the virus. Individuals exposed to the virus can be asymptomatic, mild, severe, and critical for mortality. Most hypotheses explaining the uncertainty of symptoms are based on innate immunity, which is unclear in explaining some issues. For example, 1. uncertain symptoms of SARS-CoV-2 infection, 2. failure to induce immunity for prevention by vaccines in some individuals, and 3. repeated infections in some individuals. With the ambition of explaining this clearly, this article proposed another perspective to explain the cause of uncertain symptoms in SARS-CoV-2-positive individuals. This could be influenced by host factors with a variety of cellular molecules (viral receptors/co-receptors) and major histocompatibility complex (MHC) polymorphisms, which are crucial factors in explaining this question. Hopefully, this perspective could encourage further research and pave the way for developing new public health policies to deal with COVID-19 and emergent viral epidemics in the future.

**Key words:** SARS-CoV-2, uncertain symptoms, cellular variants, viral receptor, MHC polymorphism, emergent viruses, viral immunology

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## Abbreviations:

APC	antigen-presenting cell
BCR	B cell receptor
HLA	Human leucocyte antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HSV	Herpes simplex virus
Ig	Immunoglobulin
MHC	Major histocompatibility complex
pMHC	MHC-peptide complex
RBD	Receptor binding domain
TCR	T cell receptor
Tc	Cytotoxic T cell
Th	Helper T cell

## Introduction

There have been reports that many people worldwide have been exposed to certain types of infectious viruses without symptoms or self-notice. Studies have found that various kinds of viral antibodies, such as dengue,<sup>1</sup> Japanese encephalitis,<sup>2</sup> Influenza,<sup>3</sup> and others<sup>4-6</sup> including SARS-CoV-2,<sup>7</sup> have been found in major populations who do not have history of the respective clinical/symptomatic infection. For COVID-19, 70–85% of people are asymptomatic or mildly symptomatic, 10–25% require hospitalization, and 1–2%, accounting for almost 7 million people, die as a result of the infection.<sup>8,9</sup> For those with severe symptoms, some can survive spontaneously without any specific treatment, whereas others do not, even though optimal treatment has been administered. To date, there has been no clear explanation for the varying symptoms of each individual. Age and underlying diseases have been observed to be the main factors causing severe symptoms and mortality.<sup>10,11</sup> However, there have been reports of survival among aging patients and those with underlying conditions. The severity and underlying diseases are not consistently correlated with virally exposed persons, as some individuals with underlying diseases might not have severity. However, individuals with no underlying diseases could also have severe symptoms. Accordingly, the key factors to explaining severity and mortality of the SARS-CoV-2 positive individuals, besides underlying and ageing, should be given more investigation.

Additionally, innate immunity has been proposed as a possible factor associated with uncertain symptoms. Based on the fact that the pathogenesis of COVID-19 is caused by pro-inflammatory cytokines which mainly originate from innate immunity.<sup>12</sup> There is no evidence that innate immunity can clear viral agents through its own pathway, but it requires adaptive immunity through the role of specific cytotoxic T cells (Tc). Innate immunity might be able to temporarily reduce viral agents but is not effective enough to clear the viral agents from the body as the specific Tc does. In addition, there is a report concerning the impairment of interferon (IFN) type I, especially IFN beta, in patients with severe and critical COVID-19-infected patients.<sup>13</sup> However, the clinical use of IFN type I for the treatment of COVID-19 remains unclear owing to its efficiency. Therefore, the association between IFN type I impairment and COVID-19 severity requires further investigation.<sup>14</sup> A clear explanation could be important for the public health care system in terms of prevention and treatment. In addition, new viral strains with genomic mutations have been widely suggested to explain the different symptoms and severities.<sup>15</sup> However, based on the WHO record, new viral strains of SARS-CoV-2, such as O-Micron and others, do not cause more serious pandemics to global public health than the original strain of SARS-CoV-2.<sup>9</sup> Viral mutations have been used as a guideline to explain the cause of pathogenicity and severity, with a mechanism to evade immunity from previous infections and vaccinations.<sup>15</sup> Besides the mechanism of immune evading which is based on the viral factor, this article proposes a concept to explain the uncertain symptoms, spontaneous recovery, and viral reinfection associated with variants of cellular molecules and the major histocompatibility complex (MHC) of individuals, which are host factors. Cellular molecules and viral receptors/co-receptors are associated with viral infections for viral attachment and penetration into the target cells. MHC molecules play a role in inducing an adaptive immune response that increases the efficiency of virus clearance. The details of different long existing viruses will be integrated to propose this concept concerning variants cellular molecule for viral susceptibility and MHC polymorphism for the immune responses. Hopefully, this perspective can contribute to fundamental guidelines for developing better global health systems for the prevention of emergent viruses.

## Viral infection

Unlike extracellular organisms, a virus requires a susceptible target cell for replication, because it is an obligate intracellular organism. A virus uses its receptor-binding domain (RBD) to attach to a specific receptor, which is a cellular molecule of the target cell. The virus also requires a different cellular molecule as a co-receptor to enter the target cell. Some viruses have been found to use more than one cellular molecule as their receptor or co-receptor. For SARS-CoV-2, the original receptor molecule is angiotensin-converting enzyme 2 (ACE2) with transmembrane protease serine 2 (TMPRSS2) and furin as its co-receptors.<sup>16-18</sup> Variants of these cellular molecules are associated with susceptibility to viruses.

Previous reports have shown that variants of individual cellular molecules influence susceptibility to virus attachment and entry. Although individuals are exposed to a virus, the virus is unable to enter target cells for replication, including SARS-CoV2.<sup>18-21</sup> In addition, the variants of the ACE-2 associated with the severity of SARS-CoV-2 infected individuals have been reported.<sup>20,21</sup> For most viruses, pathogenesis is related to the host's response to foreign substances, which is known as an immune-pathogenic syndrome.<sup>22-23</sup> This includes COVID-19, which is caused by the release of pro-inflammatory cytokines.<sup>18-23</sup> If individuals do not have susceptible variants of cellular molecules that enable the virus to attach and enter, they would be asymptomatic or mildly affected. Although the virus does not enter susceptible target cells, it can enter antigen-presenting cells (APCs) such as macrophages and dendritic cells. During this period, viral-exposed individuals may show symptoms, such as the effect of pro-inflammatory cytokines by APCs.<sup>22,23</sup> APCs play a role in presenting viral particles to induce adaptive immune cells such as cytotoxic T cells (Tc) and helper T cells (Th) in secondary lymphoid organs.<sup>23,24</sup> During this period, viral-exposed individuals may show symptoms owing to the effects of pro-inflammatory cytokines.<sup>17</sup> This is unlike in those who are truly infected with the virus, where the target cell becomes a comfortable source in which the virus can replicate excessively, causing uncontrolled release of inflammatory cytokines and severe symptoms in those who are genetically susceptible to viral infection.

## Viral immunity

To eradicate and clear infected viral agents in those who are truly infected with a virus, the body must be able to activate effective Tc. After invasion into the body, the viral agent is captured by APCs, which subsequently digest and present viral epitopes to induce adaptive immune cells.<sup>24,25</sup> APCs randomly cleave viral peptides into oligopeptides of 8–20 amino acid residues, which are called T-cell epitopes. T cell epitopes then combine with the major histocompatibility complex (MHC) molecule to form the MHC-peptide complex (pMHC), which eventually plays a significant role in the activation of a specific T cell clone on its T-cell receptor (TCR). There are two classes of MHC: classes I and II. MHC class I combines with a viral epitope to form pMHC-I, which subsequently activates Tc cell clones.<sup>26</sup> MHC class II forms pMHC II to induce Th cell clones, which then play a role in inducing activated Tc to become effective and memory Tc.<sup>27</sup> Eventually, the effective Tc can clear the virus-infected cells.

In addition, B lymphocytes block viral re-entry into new target cells by secreting antibodies. The best strategy for neutralizing viral agents is to bind to the viral RBD. This is the primary approach for manufacturing viral vaccines. The B-cell receptor (BCR) recognizes B-cell epitopes based on the native form of the antigen; thus, it does not require APC and MHC molecules.<sup>28</sup> Initially, activated B cells synthesize IgM antibodies. To synthesize other classes of immunoglobulins, such as IgG, IgA, and IgE,

the B-lymphocyte clone requires the cognate Th clone to be promoted. During this period, B and Th cells play reciprocal roles in supporting each other.<sup>29,30</sup>

B cells, which also express MHC II molecules, play an antigen-presenting role in cognate Th cells, which also send signals to promote the differentiation of B lymphocytes into plasma cells to synthesize various classes of immunoglobulins. Without Th cells, B cells cannot produce other classes of immunoglobulins except IgM. More importantly, these cells cannot differentiate into memory B-cells. In addition to its short half-life, IgM also has a low affinity for viral antigens and a limited ability to combat the virus during extracellular existence. IgG has the highest capacity to bind to viruses with strong affinity. The affinity of IgA is second to that of IgG, but it plays a significant role in mucosal organs, which are the main route of many viral transmissions,<sup>27,28</sup> including SARS-CoV-2. Accordingly, Th cells play a central role in maturing B and Tc lymphocytes, including memory cells, for long-term protection from secondary viral infections.<sup>27-30</sup>

### Immunodominant epitope

Human MHC molecules are called human leukocyte antigens (HLA), which are classified into classical and non-classical loci. HLA molecules are predominantly inherited from the parents. Thus, each locus of the MHC genome in an individual can be either heterozygous or homozygous. For classical loci, each class of human MHC had three loci. Accordingly, the number of MHC class I gene alleles in any individual is limited to 3–6 alleles.<sup>26,27</sup> For example, an individual who was homozygous for all three loci had only three alleles, whereas those who had all heterozygous loci had six alleles. As HLA gene alleles are highly polymorphic, the possibility of two individuals having the same set of gene alleles is at least one in a million (mostly observed in identical twins).

MHC molecules have a pocket that allows some amino acids of the peptide to fit inside. Studies have shown that each MHC variant can bind to many different peptides.<sup>31,32</sup> This means that MHC molecules have broad specificity for T cell epitopes presented by APCs. However, each MHC molecule can bind to only one peptide at a time, because there is only one cleft on each MHC molecule. To form pMHC, the MHC molecule requires only a few amino acids of the T-cell epitope, the so-called anchor residue, for interaction.<sup>31,33,34</sup> This allowed each MHC allele to bind to different peptides. Any peptides derived from foreign substances processed by APCs must contain amino acids that can fit the MHC allele cleft to form pMHC.<sup>35,36</sup> pMHC is a crucial molecule for inducing a specific TCR in T cell clones. TCR requires interaction with both peptides and MHC molecules.<sup>35,37</sup> This conforms to the development of T-cell clones in the thymus, which requires positive selection and the ability to work with the self-MHC alleles of individuals.<sup>38</sup> Notably, studies have shown that the interactions between each MHC allele and different peptides have different affinities. Each MHC allele has a limited ability to bind peptides.<sup>39,40</sup> It is unlikely that all epitopes of foreign peptides can form pMHC with a single MHC allelic molecule.<sup>39-41</sup> Accordingly, the MHC allelic molecules of each person

have the ability to form pMHC with some of the peptides if they do not contain anchor residues that are compatible with the MHC alleles of individuals. It has been reported that individuals who are MHC homozygous are more susceptible to pathogens than those who are heterozygous.<sup>42,43</sup> This explains why people with fewer MHC alleles may have limitations in binding with an immunodominant epitope to form pMHC molecules. Interaction of the peptides, immunodominant epitope, and peptide-binding groove of the MHC molecule is crucial for the induction of immunodominant T-cell clones. Besides the possibility of viral variants, the lack of available MHC alleles and antigens might explain why some individuals become infected and do not respond efficiently to gain seroprotection after viral vaccination.<sup>44,45</sup> Therefore, the invasion of any particular antigen of a virus into different individuals does not guarantee the induction of the same level of immunity because of the limited variety of MHC alleles in each person. Thus, viral infections have been reported in vaccinated individuals.

### Fact concerning immune evasion as in the case of latent infection of Herpesviruses

As mentioned, one of the previous aspects explaining the severity of the COVID-19 epidemic is immune evasion, which is related to viral mutations. If the mutated virus can evade the host's immunity, it should happen to everyone, not just some individuals. Therefore, the definition of immune evasion needs to be discussed. Usually, virally infected patients can recover from acute viral infections within a specific period of approximately one–two weeks, through effective immunity. Most viruses cause both acute and chronic infections. Chronic viral infection is defined as an infection that persists within a host for a longer period, usually longer than six months. During this time, most infected individuals who look normal are unaware of transmission to others. Chronic viral infections can be divided into two types: latent and persistent. Latent infections are common in the Herpesviridae family, including herpes simplex virus (HSV) and varicella-zoster virus (HZV). Herpesviruses can produce latency-associated transcripts (LAT) to inhibit cellular apoptosis and avoid host immunity after causing symptoms during primary infection.<sup>46</sup> During latent infection, viruses remain dormant in the host without any clinical symptoms.<sup>46,47</sup> Studies have shown that herpesviruses downregulate MHC class I expression in host cells.<sup>48</sup> This interferes with the ability of cytotoxic T cells (Tc) to recognize and eliminate virus-infected cells.<sup>49</sup> The virus can remain latently infected in all individuals who have not been treated properly during primary acute infection. The virus migrates to nerve cells, which are immune-privileged organs in which adaptive immunity, including Tc, cannot invade normally. Thus, this is a mechanism to evade the host's immunity to herpesviruses, which can occur in the same manner as in all virally infected patients. Acyclovir is an effective antiviral drug for the treatment of acute HSV infection to avoid chronic latent infection. Accordingly, the virus usually remains latently infected unless the patient is properly treated during primary acute infection

to eliminate all the herpesvirus agents before they can migrate to nerve cells, which are immune-privileged organs.<sup>50</sup> Thus, herpesviruses should be considered infecting agents that can naturally evade immunity in all infected individuals. This can be explained for all individuals, not the case in which some do but others do not.

Another type of chronic viral infection is viral persistence, which can be observed in both DNA and RNA viruses. RNA viruses have much higher genomic mutations than DNA viruses because of the low efficacy of RNA polymerase in proofreading their genomic replication.<sup>51</sup> The hepatitis C virus (HCV) has the highest prevalence of persistent chronic infections. The WHO reported that only approximately 30% (15-45%) of HCV-infected individuals have immune clearance within 6 months without any treatment. Of the remaining HCV-infected individuals, approximately 70% (55-85%) develop chronic infections.<sup>52</sup> Previously, viral mutations have been suspected to be the cause of chronic HCV infection. However, there are reports showing that HCV mutations might not be the only cause of viral persistence.<sup>53</sup> In the meantime, Hepatitis B virus (HBV), a DNA virus, can also cause chronic liver infection in lower-rated than HCV with approximately 10-12% of HBV-infected patients.<sup>54</sup> Individuals chronically infected with HBV and HCV tend to develop liver cirrhosis and hepatocellular carcinoma.<sup>55</sup> Regarding herpes viruses, HBV and HCV also downregulate MHC class I expression, which is claimed to be the cause of their persistence.<sup>56</sup> Questionably, why do not all HBV- and HCV-infected individuals become chronically infected? Reports showed that 85-90% of HBV-infected and 15-45% of HCV-infected patients spontaneously clear the viral agent. Thus, chronic HBV and HCV infections should not be explained just by the viral factor as it does for herpes viruses. In contrast to latent viral infection, chronically persistent viral infections are not consistent but vary by individual.<sup>57,58</sup> It should be noted here that many other RNA viruses, which have low efficacy in proofreading their genomic mutations, have been reported to have a different ratio of chronic infections, such as Ebola,<sup>59</sup> Influenza,<sup>60</sup> measles,<sup>61</sup> and SARS-CoV-2.<sup>7,62</sup> Thus, the cause of chronic persistent viral infections requires a different explanation from that of chronic latent infections.

### **Crucial role of MHC molecule for viral clearance to prevent persistent viral infection**

In fact, persistent viral infections can normally be found in low-evolved immune animals. Insects do not elicit adaptive immune responses. They only possess innate immunity. Insects are a great source of carriers for important medical arboviruses, such as dengue hemorrhagic fever, Japanese encephalitis virus, and West Nile virus.<sup>63</sup> Penaeid shrimp, a vital farming commodity in many countries, is another example of a persistent viral infection in low-evolved immune animals. As an important economic commodity, there are many studies concerning viral epidemics in penaeid shrimp, leading to information concerning the association between shrimp viruses and innate immunity in low-evolved immune animals for further discussion.

The viruses of penaeid shrimp, yellow head virus (YHV), and white spot virus (WSV), each caused disaster to the industry when they first emerged almost three decades ago.<sup>64-66</sup> Notably, there is evidence of persistent viral infection in shrimp, and mortality declined sharply after several epidemic years once pond management systems were optimized for water quality, feeding systems, temperature, and rearing population size. However, high mortality still exists in poorly managed farms.<sup>64,66</sup> This could explain why shrimp perform an unknown mechanism to tolerate infectious viruses. There is a question of whether genomic mutations in these viruses might be the cause of their lower pathogenesis and mortality. However, a study that challenged naïve shrimp with a virus isolated from occluded, persistently infected shrimp showed acute infection and high mortality.<sup>64,66</sup> Accordingly, viral genomic mutations should be excluded from the explanation of the cause of persistent shrimp infections. Naturally, innate immunity is not as effective in clearing the virus and virus-infected cells as adaptive Tc. Therefore, viruses can persist in animals that lack adaptive immunity as in the cases of penaeid shrimp. Interestingly, persistently virally infected animals can live normally if the suitable environment and conditions are optimized. However, the balanced interaction of the pathogen and host to accommodate together should be interesting for further study.

Concerning chronic persistent viral infections in humans, many studies have shown associations between HLA variants and chronic persistent HBV<sup>67</sup> and HCV.<sup>68</sup> More interestingly, Bhaskaran et al. showed more details regarding the association of HLA alleles with persistent/cancer and the protection of human papillomavirus (HPV). The study found that HLA-B\*44 and DRB1\*07 were significantly associated with persistent HPV-16 infection [odds ratio,  $p = 26.3, 0.03$ , and  $4.7, 0.01$ , respectively]. HLA-B\*27 and DRB1\*12 were significantly associated with both HPV-16<sup>+</sup> cervical cancer (CaCx) and persistent HPV-16 infection [23.8, 0.03, 52.9, 0.01, 9.8, 0.0009, and 13.8, 0.009, respectively]. HLA-B\*15 showed a negative association with HPV-16-positive CaCx (0.1, 0.01), whereas DRB1\*04 exhibited protection against both HPV-16-positive CaCx and persistent HPV-16 infection [0.3, 0.0001, and 0.1, 0.0002, respectively].<sup>69</sup> This could be associated with adaptive immune cells through the role of Tc cells in recognizing and clearing the infected virus to prevent chronic persistent infection in each individual. These studies support the association between HLA variants and the cause of persistent viral infection in some individuals, which should be intended to evaluate the crucial role of MHC molecules in viral epidemics from persistent viral carriers who cannot induce an effective Tc cell clone to clear the viral agent.

### **Perspective to explain various symptoms after viral exposure to SARS CoV-2**

There was a report concerning the association between the HLA allele and asymptomatic COVID-19.<sup>70</sup> However, the clear explanation to demonstrate the relationship between HLA and asymptomatic has not been discussed yet as it could be a co-incidence of some other factors.



Herein, this article proposes a perspective to explain the causes of the uncertain symptoms of SARS-CoV-2-positive individuals based on the variants of susceptible viral receptor molecule(s) and compatible MHC variants for the immune response. As described in the previous sections, the variants of susceptible viral receptor molecules distinguish individuals as the truly infected out of the viral exposed individuals. MHC polymorphism explains how individuals can raise their immunity to prevent and clear viral agents through the role of adaptive immune cells. Accordingly, individuals are classified into eight groups as shown in **Table 1**. After exposure to the virus, there are those who are actually infected and those who are not truly infected (just invaded). Groups 1–4 were individuals who did not have a susceptible viral receptor/co-receptor and were not truly infected. They are asymptomatic or have mild symptoms since the virus does not replicate greatly in the target cell. Their immunity depends on the presence of major histocompatibility complex (MHC) alleles (**Table 1**). Groups 5–8 have susceptible viral receptors and can be truly infected. Viral multiplication in target cells can continuously induce the production of pathogenic cytokines, thereby causing severe symptoms. Group 5 contains individuals who are MHC classes I and II, compatible with the immunodominant viral epitope. They can activate specific Tc and B cell clones to develop an effective Tc to cure and produce memory B cells for further protection. These individuals should be able to survive spontaneously if they do not have any related underlying diseases that can cause additional critical symptoms, particularly during the first couple of weeks of infection. Individuals in Group 6 might be able to activate a specific Tc clone, but cannot develop an effective and memory Tc clone because a particular Th cell is not produced.

To clear the viral-infected cell, the body needs an effective Tc, not just a primary-activated Tc. However, with some medicines preventing the virus from entering the target cell, such as neutralizing antibodies, this might be helpful. In addition, the individuals in Group 6 were not effectively protected by vaccination for the development of memory B cells. Therefore, it is difficult to provide prognosis for individuals in this group. It is possible that they can survive but will have chronic symptoms that depend on their living conditions and behaviors, such as penaeid shrimp. Therefore, it would be interesting to conduct this study further in this individuals. Groups 7 and 8 might be more or less the same, having severe symptoms, because an effective Tc clone cannot be developed. Therefore, these patients do not recover spontaneously. Group 7 may find it more likely to be cured than Group 8. Memory B cells may be sufficient to cure viral infections if there is some cooperation between natural killer cells (NKs) and a specific antiviral IgG to eradicate the infected virus. This approach requires further investigation.

From this perspective, it could explain the repeated infection in some people and the cause of infection in some vaccinated individuals. For repeated infections, these people are SARS-CoV-2 positive, but are mild (Flu-like) or asymptomatic. These individuals do not have susceptible receptors/co-receptors for viral infections. However, they can be exposed to the virus and test positive in laboratory tests. They should be considered as viral-invaded individuals rather than viral-infected patients. In the case of viral infections in vaccinated individuals, this should be divided into two categories. The first is virally invaded individuals (groups 1-4) as mentioned above. The other was truly infected patients with severe symptoms. These individuals are classified into Groups 5-8 which contain cellular molecules

**Table 1. Classification of individuals based on their susceptibility to viral infection (viral receptor variants) and immune compatibility (MHC class I and II) to fight against the viral agent.**

Individual group	Viral receptor variant	MHC I allele	MHC II allele	Prediction on viral exposure
1	Non-susceptible	Compatible	Compatible	No or mild symptoms with the production of an effective Tc cell clone including all of the memory cells of adaptive immune cells
2	Non-susceptible	Compatible	Non-Compatible	No or mild symptoms with the production of a specific Tc cell clone, which can produce only IgM and no memory B or Tc cells
3	Non-susceptible	Non-Compatible	Compatible	No or mild symptoms without the production of an effective Tc cell clone, but which can produce memory B cells
4	Non-susceptible	Non-Compatible	Non-Compatible	No or mild symptoms without the production of effective Tc cell and memory B cell clones
5	Susceptible	Compatible	Compatible	Severe symptoms but can recover completely due to the role of effective Tc. These individuals could be protected if vaccinated
6	Susceptible	Compatible	Non-Compatible	Severe symptoms. Can activate the specific Tc clone but cannot develop an effective and memory Tc. These individuals could not produce memory B cells.
7	Susceptible	Non-Compatible	Compatible	Severe symptoms. Cannot activate the specific Tc clone but can earn protection via viral vaccine. These individuals should be protected if vaccinated
8	Susceptible	Non-Compatible	Non-compatible	Severe symptoms. Cannot produce any effective or memory immune cells. These individuals should be vaccinated frequently. Probably, all will die if they become infected.

that are susceptible to viral attachment and penetration into the target organs. In addition, if their MHC alleles, as in Groups 6 and 8, are not compatible with the vaccine epitope to create the proper pMHC-II to activate specific Th cell clones. These individuals do not have the potential to produce memory B cells that produce an effective antibody to prevent viral infection. Therefore, they are vulnerable to infections. In addition, this perspective could explain why companion animals that are SARS-CoV-2 positive have never been reported to have severe symptoms. This could be explained by the unsusceptible cellular molecules for viral replication that cause severe symptoms, similar to individuals in groups 1-4 as described.

### **Proposed revision of public policy for emergent viral epidemic**

With controversy regarding the necessity of vaccination, many people have refused to be vaccinated, stating that some SARS-CoV-2-positive individuals survive without vaccination. These individuals feel that vaccination may not be necessary in such cases. This perspective explains the uncertain symptoms that depend on the genetics of individuals concerning their viral susceptibility and immune response. Based on this aspect, everyone should be vaccinated because we do not know who does (or does not) have susceptibility to viral receptors/co-receptors, and it is too complicated to identify the cellular variants for every individual. However, a campaign to ask people to vaccinate regularly should be reconsidered, especially for individuals who are positive for SARS-CoV-2, but are asymptomatic or demonstrate mild symptoms. In case of COVID-19, these individuals might account for 70–85% of the total and were classified into Groups 1–4, in which they were protected based on their genetic insusceptibility to viral infection. Individuals in these groups should survive regardless of their vaccination status. Most of the global population could be safe if effective vaccines have been administered in two or three doses, not once a year, as in campaigns in many countries.

Perhaps, vaccination should include a package to follow up seroconversion to detect IgG and IgA. Therefore, individuals with high IgG and IgA levels should be protected and safe from viral infection. Hence, these individuals may not need to be vaccinated regularly, because memory B cells have been created. Only individuals from Groups 6 and 8 may need to be vaccinated frequently to induce IgM, which has a short half-life. It will be great if we can develop the identification technology of HLA alleles as a medical routine and acceptable cost to record individuals' data in addition to the ABO, Rh blood group. This might also allow us to study and predict individuals for immune-related diseases which is not only infectious diseases but might also be beneficial for other diseases and health problem such as allergy, autoimmune diseases, and, of course, organ transplantation. HLA identification for every individual could be a great indicator for public health management to focus on prevention rather than waiting for the number of hospitalized required cases to occur beyond the capacity of medical personnel to cope.

Individual HLA data might help us to understand how to develop viral vaccines to be effective for every individual.

Based on this perspective, it should be considered setting up the study to prove the efficiency of any anti-viral medicine in the process of sample collections. The study concerning clinical treatment that includes patients in groups 1-4, and group 5 could cause false-positive results since the individuals of groups 1-4 are not truly infected, while the individuals of group 5 could be recovered by their own immunity despite having severe symptoms. Symptomatic treatment should be sufficient for these individuals, which relates to their MHC alleles, to process Tc to clear virus-infected cells, rather than by the antiviral medicine in the individuals in this group. The study of viral treatment should be more appropriate to include just individuals who are in groups 6-8 which might be identified based on the viral loads and elevated inflammatory cytokines. Thus, the efficiency of any antiviral medicines should be carefully evaluated for the discovery of the genuine antiviral medicines and let us reach the target to fight against any emergent viral epidemics for which we should stay alert within the proper direction.

### **Conclusion**

Based on a variety of cellular molecules (viral receptors/co-receptors) and MHC polymorphisms, this perspective of host factor variants explains the uncertain symptoms, infection, and reinfection of SARS-CoV-2 of individuals. The polymorphism of MHC alleles could also explain how the virus generally persists as a chronic infection in both animals and humans. It could be a way to understand how to prevent viral epidemics from the viral carriers. The understanding of this fundamental should provide a positive result, a more economical approach, and an optimal way to handle any emergent viruses, which is also applicable to other active viruses, not just COVID-19. Hopefully, this proposal could serve as a guideline for further study and development of more appropriate public health systems to handle any emerging viruses that might come again in the future.

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