

Immune reactivity during SARS-CoV-2 infection and further mitigation measures for COVID-19

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Abstract: In the wake of the COVID-19 outbreak in 2019, particular attention has been paid to populations often considered immunocompromised -- the elderly, pregnant women, newborns, and children. Therefore, this review aims to study these populations. This study collected the immune characteristics of the above "suspected immunocompromised people" from various sources in the public domain, the body's reaction to being "attacked" by the virus, and the adverse physical effects of the virus on these people. According to the survey, the elderly is more vulnerable to the virus, more difficult to treat, the prognosis is relatively poor; As the immune stage of pregnant women is divided into three stages, each stage has different resistance to the virus, and the risk of infection is different at different stages. Unevenness of vaccines availability has been discussed in this review as it is one of the key factors impacting the trend of the pandemic control negatively. Public health and social measures (PHSM) have been reviewed and its significance in controlling the spread of the disease even after vaccination is discussed.

1. Introduction

In December 2019, a new infectious disease, now collectively known internationally as COVID-19, broke out in Wuhan, Hubei Province, China. The large-scale epidemic of virus or bacteria often causes high concern in various scientific fields, and causes widespread concern among the public, thinking that it is related to the health and safety of many people. This review provides an epidemiological and clinical analysis of the COVID-19 outbreak.

An epidemic would threaten the general population; However, certain groups of people, such as the elderly, pregnant women, newborns, and children, who are generally considered to have low immunity, may be more vulnerable to infectious diseases and may be at greater risk from an epidemic. Because these three groups are at different stages of human development, their immune systems differ from those of normal adults. As a result, this immune specificity makes it difficult to study the response of these populations in the current outbreak. The most representative questions are : (1) what are the immune characteristics of these populations? (2) What kind of reaction will these people have when they are infected by the virus? (3) What subsequent adverse effects will these people have after being infected?

It is generally assumed that these groups have low immune capacity and should theoretically have similar clinical manifestations, but surprisingly, the clinical manifestations of these three groups are completely different.

By comparing the performance of these different "immunocompromised" populations in the face of COVID-19 infection, we can initially discover the "propensity to attack" when the virus damages the body. At the same time, these comparison results can also prompt scientists to further study the mechanism of action of the virus, and to some extent, can improve citizens' awareness of prevention play a positive role.

Cooperation between countries seems difficult because of known economic and cultural differences. But we think it is time for countries to break down barriers and engage in positive cooperation in the face of our current "common enemy" -- COVID-19. In view of the current epidemic

situation, how to control the current situation is one of the issues we are very concerned about at present. Therefore, we are committed to studying the strategies that have been found to effectively control the epidemic, which will also play a good reference for the prevention and control of the epidemic in the future.

2. Immune responses in different populations

2.1. The immune response caused by COVID-19 in the elderly

Characteristics of the immune system in the elderly

Because older people are thought to have lower immunity, this review examines whether the virus could have serious adverse consequences for older people who contract COVID-19. In everyday life, older people seem to be more prone to illness and tend to have poorer outcomes [1, 2]. One of the reasons is the immune system of elders, which is used to protect the body from bacteria and viruses, has aged. This immune system aging can progress to a status called immune senescence. As aging continues, the body's ability to fight infection and the response to antigens have decreased. Consequently, the incidence of autoimmune and chronic diseases gradually increases. At the same time, with the growth of age after puberty, the thymus, which plays an important role in immunity, is gradually atrophied, and replaced by adipose tissue [3]. Thymus is mainly used as the production site of T cells in human body. With the atrophy of thymus structure, its function decreases. In contrast, some T cell subtypes increase, including CD8 T cells (CD8 and CD28) and replicating senescent T cells [4]. The increase of these cells contributes to the inflammatory state and affects B cells, producing an ineffective viral response [5] and reducing the body's immune response [6, 7].

In human important innate immune response, immune defect in T cell aging and the excessive activation of the inflammatory response, at the same time, the composition used to detect pathogens triggering host defense response of T cell expression abnormal, and neutrophils, dendritic cells, and NK cell's function is impaired, including neutrophils spontaneous apoptosis rate will increase [8, 9]. These effects will lead to the body's immune tilt to the pro-inflammatory state, so that local or even the whole produce excessive and even uncontrolled inflammatory response, and eventually even develop into cytokine storm [10]. The term "cytokine storm" has been applied to several clinical conditions, some of which are related to infectious diseases [11, 12].

The body's reaction to COVID-19 infection

The immune response of the body is divided into innate immune response and adaptive immune response. Innate immune response is the first reaction system that virus and bacteria enter the body to play a defensive role. Activation of the innate immune system leads to rapid production of inflammation-stimulating molecules, a response that induces cytokine storms in older adults. According to previous studies, it is generally believed that the main reason for many adverse reactions caused by COVID-19 in humans is that the virus can promote the production of cytokine storm in human body. ¹⁰The cytokine storm, the host's overactive immune response to the virus, triggers an overactive inflammatory response, and these overactive inflammatory responses lead to damage [13]. Several factors have played important roles in the cytokine storm in the elderly. IL-6, IL-8, IL-1 β and TNF- α have been detected and identified as key components of the cytokine storm in the early immune response to the entry of COVID-19 into the body [14-16]. In addition, with the gradual damage of cytokine storm to tissue cells, infection sites, newly generated cytokine fragments and coronavirus will further damage healthy cells and promote the sustainable development of cytokine storm [17]. It's a vicious cycle that continues to damage the body and gets worse over time. Moreover, a new paper recently suggested that damage in type 1 INF responses is also associated with reduced viral clearance [18].

Complications of COVID-19 in older adults

When COVID-19 invades the elderly, it can cause serious complications involving many organs and systems. As the cytokine storm continues to amplify, many pathophysiological consequences, adverse reactions, and mortality in tissues are also increasing. For example, pneumonia, a common

complication in the Novel Coronavirus process. The disease is due to the cytokine damage to endothelial cells, fluid leakage into the alveolar space, resulting in the gradual amplification of lung injury and the enhancement of local inflammatory signals [19]. Other adverse reactions, such as local or diffuse DIC, tissue hypoxia, and even systemic adverse symptoms, including headache and delirium, anorexia, lack of thirst etc [20-26].

2.2. The immune response caused by COVID-19 in pregnant women

Characteristics of the immune system in pregnant women

It is often thought that women are immune weakened during pregnancy and that pregnant women are often more susceptible to infectious diseases. It is true that immune weakness is a problem in pregnant women at some stage, but it cannot be generalized. If, as is commonly believed, pregnancy is an "anti-inflammatory state," fetuses can also be aborted by cytokines, but there is not much evidence supporting this state that neither hypothesis can prevail over the other alone [27-31]. Of the 65 pregnant women counted with COVID-19 viruses' infection, we found that two of them contracted the virus at 25 to 27 weeks of gestation, while the remaining pregnant women contracted the virus in the third trimester of pregnancy [32-41]. From this we can infer that pregnancy is actually a long process, and its immune efficacy can be divided into different stages.

The first stage is the early stages of pregnancy. Because the blastocyst breaks through the uterine epithelium and implants into the mother, the endometrial tissue is damaged. The need to connect the mother to the implanted fetus to ensure blood supply between the fetus and placenta also damages the mother. The implantation of the fetus creates a huge wound in the mother, which leads to a violent inflammatory response [42].

The second stage is the stage of rapid growth and development of the fetus. The main immune feature of this stage is the induction of an anti-inflammatory state. Currently, the mother, placenta and fetus are symbiotic, and the overall immune ability is relatively strong.

The third stage is when the fetus completes its development to delivery. This stage is characterized by the reactivation of immune cells and the recurrence of inflammatory responses that promote uterine contractions, infant exclusion, and placental rejection [43, 44].

According to the above, it is not difficult to see that the anti-inflammatory state or pro-inflammatory state of pregnant women depends on which immune stage they are in [45, 46], and different stages have different infectivity to different viruses. Similarly, malaria infections usually occur in the first half of pregnancy, and the incidence declines in the second half of pregnancy [47]; Lassa fever is especially contagious in the third trimester of pregnancy [48]. If these two examples can be accidental, then we can be sure that pregnant women during pregnancy have a significant resistance to HIV.

Pregnant women's reactions to COVID-19

Because pregnant women have special immunity, this review also examines whether the virus has different or more severe adverse consequences for pregnant women after they become infected with COVID-19. In one study, 65 pregnant women who were infected with coronavirus during pregnancy were surveyed, 12% (8) of them appeared premature rupture of membranes, (2) 3% of preeclampsia, gestational hypertension 6% (four), 5% (3) in gestational diabetes, 3% (2) in hypothyroidism, 2% (1) a tachycardia, Three percent had abnormal umbilical cords, and two were admitted to intensive care requiring mechanical ventilation, one of whom had developed multiple organ failure [32-41]. Although there are only a few specimens observed at present, we can still preliminarily infer from the above data that novel Coronavirus will cause different degrees of serious complications in pregnant women and have a certain degree of adverse impact on their physical health.

However, we also found that three of the mothers were infected with COVID-19 virus 23 days before delivery, and their newborns were born with immunoglobulin G and M carrying novel coronavirus [49, 50]. Based on this finding, we cannot infer that the fetus has not been affected in any way, for better or worse, by the virus in the mother. Similarly, we cannot completely rule out the possibility of vertical transmission of novel Coronavirus.

2.3. Novel Coronavirus effects on children

Newborns and children are the future of a country, the new generation, the dependence of human sustainable development, and a very important part of human composition. Because the growth and development of this part of the population is not complete, it is generally believed that the function of each tissue and organ system of this population is not perfect, especially the function of the immune system is very weak, and this population should have lower immunity compared with adults. We believe this group is likely to be harder hit in the current pandemic. So, the health of newborns and children is also being closely watched in this COVID-19 outbreak. Instead, young people, especially children, are doing well in the COVID-19 pandemic. Although their infection rates are now consistent with those of adults, this group has fewer symptoms, milder disease, lower case fatality and better prognosis [51].

Potential dangers to newborns.

Because a newborn is born from the mother, the fetus is completely dependent on the mother for growth and development before birth. Every aspect of a fetus's body is closely linked to its mother, and the experiments included in this article included a group of pregnant women infected with THE COVID-19 virus [49, 50]. So, it was reasonable to suspect that the virus might have traveled through the placenta to the fetus, leading to fetal death or congenital abnormalities. Even if the virus is not transmitted through the placenta, the fetus may be adversely affected by a reaction to the mother's infection.

This review includes a survey of 67 newborns whose mothers were infected with the virus, 18% (12) developed respiratory distress or pneumonia, 13% (9) underweight, 3% (2) rash, 3% (2) disseminated vascular coagulation, 2% (1) asphyxia, and 3% (2) perinatal death [52, 53]. It can be inferred that the virus has a certain impact on the newborn, especially the adverse effects of the virus on the respiratory tract and lungs.

Response of other non-newborn groups of children to the COVID-19 virus

This article contains an experiment on children infected with COVID-19 virus. Of 333 sick children, 35% were asymptomatic, 48% had cough, 42% had fever, 30% had pharyngitis but 0% progressed to shortness of breath. Laboratory tests showed slight changes in white blood cell numbers and slight increases in inflammatory markers, but no significant changes in either. These tests showed mild symptoms and fewer laboratory abnormalities [54]. In Cao's study, 398 children were treated for the disease. Most of them recovered in 1-2 weeks [55].

3. Importance of international cooperation in combatting COVID-19

The expectation to end COVID-19 pandemic soon calls for global cooperation, rather than competition and confrontation. The COVID-19 virus, as the "common enemy" for all countries all over the world, longer it is spreading among people, there is higher chance for it to mutate and wreaks havoc in human life. Despite differences in economic status and culture, it is paramount for all countries to realize that harms to one means harms to all. Therefore, working together is the only way to defeat the COVID-19 which has highly infectious and destructive feature. Major effective strategies in controlling the COVID-19 pandemic include vaccination and mitigation measures. This review examines important factors that affect the efficiency in controlling the COVID-19 outbreak, including economic status, induced variety of vaccination coverage in different countries and implementation status of public health and social measures.

3.1. The inability of the covid-19 vaccine to be fair is a public health tragedy

Unequal distribution of vaccines

The mutated virus has been competing against the COVID-19 vaccine due to fast mutation rate. Initial studies have shown that vaccines are sufficient to reduce the number of confirmed cases and deaths [56]. However, the uneven production and distribution of the vaccine has delayed the elimination further. The enormous gap in accessing to vaccines in developing countries continues to

be one of the biggest hurdles to end the pandemic. Lower vaccination rate in countries with unmet vaccine need provides the chance of further virus spreading. Consequently, the global economy will continue to suffer. Therefore, from an ethical, epidemiological or economic standpoint, it is a critical moment for global solidarity in controlling the pandemic.

By the end of the year, more countries are likely to reach the target of 40% vaccination rate. However, Burundi, Eritrea, and North Korea are still far from this goal. Many countries are short of vaccine supply. By the end of September 2021, 56 countries had failed to meet the target of vaccination corresponding for at least 10% of the world's population. Africa and the Middle East have suffered most from the vaccine shortage [56].

By 2020 the debt of low-income countries will grow by 12 % to a record of \$860 billion according to statistics

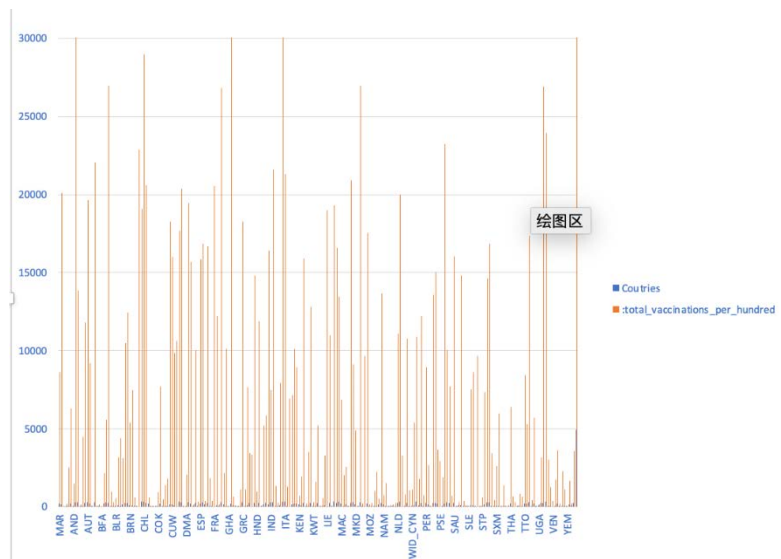


Figure 1. Visualization of the world distribution of total vaccinations per hundred people for different countries. Cite from <https://covid19.who.int>

released by the World Bank [58]. By October 2021, the current outbreak had plunged nearly 100 million people into extreme poverty and exacerbated inequalities between countries with income expected to grow by nearly 5% per capita in advanced economies and 0.5% in low-income economies by 2021. According to the World Bank's Autumn 2021 East Asia and Pacific Economic Update, the growth forecasts for most countries in the region have been revised downwards, despite China's growth has been projected as 8.5% and the rest of the world has forecast of only 2.5%, 2% lower than the April forecast [58]. The relationship between health and the economy is bidirectional, whereby economic growth enables funding in investigations that improve health; and a healthy population contributes to enhanced economy. Therefore, the spread of the mutated virus poses a serious threat to the global economic recovery.

Of the 1.6 billion vaccines distributed globally until May 2021, 83% had been used by high- and middle-income countries. Low-income countries receive less than 0.5% of the global vaccines. Less than 5% of Africa's population is fully vaccinated, and the vaccine gap remains huge [60]. Key reasons behind these phenomena are lack of financial support, healthcare researchers and funding for research, which reflects the root cause of the uneven vaccine distribution as economic inequality.

Although the root cause of vaccine shortage is not easy to cope, this acute challenge of pandemic is calling for financial support and equal distribution of vaccines as it is the most economic approach to revive the whole world.

Public health and social measures (PHSM) Severity Index is a composite measurement of the severity of SMSP based on an average of the following six measurements: masks facial coverings and/or mask wearing, schools adaptation or closure of schools, businesses adaptation or closure of businesses, restrictions on public and private gatherings, domestic movements restrictions, public transport and stay at home orders and international travel restrictions. Currently, the trend of COVID-

19 infection is still largely unstable. With the expectation to eliminate COVID-19 epidemic, it is still necessary for every country to adhere to PHSM. Although vaccination has shown effectiveness in virus containment, it is alone is not sufficient to end the pandemic. Main reasons include the unmet vaccination rate and breakthrough infection among vaccinated populations. Therefore, PHSM measures have to be tighten up while people are immunized. At present, we have made a small step toward the direction of controlling the COVID-19, but there is still long way to go. It is still too early for us to relieve our guard for the fight against the COVID-19 epidemic.

South Africa functions better on following the PHSM measures even though they are lacking vaccine supply. The number of confirmed cases has declined after restricted control implementation which indicate that well implemented PHSM such as shutdown of companies and restrictions of public and private gatherings have high efficiency in mitigating virus spreading [61].

In contrast, Europe has reported the largest number of newly confirmed cases recently even with higher vaccinate rate than Africa. Besides, United Kingdom has encountered the most severe increase of confirmed cases. These regions start to relieve all control measures with the expectation to go back to normal life without following PHSM. The sharp fact has shown that, facing the virus with high mutation rate and high breakthrough infection rate, lifting restrictions too quickly can be catastrophic for the whole society, especially when the vaccination rate is far from 100% [60].

Up to the report date (October 2021), according to the WHO data, the total number of confirmed cases and deaths associated with COVID-19 continues to decline every week. This is a promising trend observed since August 2021. In the week from 27 September to 3 October 2021, more than 3.1 million new cases and over 54,000 new deaths were reported [56]. This week's cases are 9% less compared to the previous week with a similar fatalities rate. However, the distribution of new cases has shown that most regions in the world has experienced decreased new infection for Europe. The African region (43%) reported the largest reduction of weekly new cases, followed by the Eastern Mediterranean (21%), South-East Asia (19%), the Americas (12%) and the Western Pacific (12%). This means that even in the vaccine-rich region such as Europe and UK, it is still paramount to make efforts on keeping PHSM as the control of the epidemic requires multi-faceted cooperation including vaccine, prevention measures, national policies and economic support.

4. Discussions

Epidemiological studies have shown an association between viral infection and preterm birth as well as congenital fetal abnormalities, but there are also evidences that most viral infections do not cause congenital fetal infections. Therefore, the cause of disease or adverse reactions in newborns remains to be investigated.

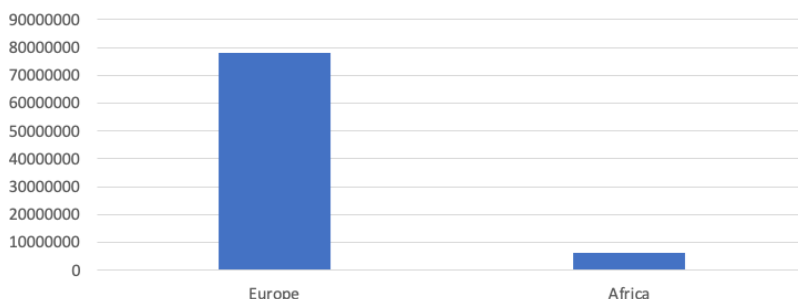


Figure 2. Comparison of confirmed COVID-19 cases in Europe and Africa.

The representation of the child population in this outbreak is consistent with that of the population in SARAS and MERS outbreaks years ago, with mild symptoms and little variation in laboratory tests; But this was not the case with other respiratory diseases in the group. This difference, I suspect, may be due to the nature of the pathogens that have targeted the respiratory system in these pandemics and the other pathogens that cause respiratory damage in our lives.

Although we often think of older adults and children as having similar immune characteristics, that is, low immune function, the two populations show very different responses to COVID-19. This may be because the immune response of the elderly mainly plays a role through CD4 and CD8 T cells and antibodies to resist the attack of the virus, while the innate immune response of children is relatively vigorous at the early stage of development, and the proportion of T cells, B cells and NK cells is relatively high, which can help the body to resist the virus. The two immune systems and their responses and functions in response to the COVID-19 virus are significantly different, which may be the key to the different outcomes of infection.

As COVID-19 emerges as a new pathogen, it is difficult to determine whether the pathogen will cause harm to the mother and the fetus. The virus may affect the course of pregnancy, and even if it does not, it may cause adverse effects in both mother and fetus, and even increase their sensitivity to other pathogens, leading to other serious illnesses. Under this concern, I suggest that prevention should be carried out as soon as possible based on ensuring the health and safety of mother and child and avoiding injury. The best means of prevention is to vaccinate the mother, but it needs to be paid special attention to, due to the particularity of the constitution of pregnant women, before deciding to vaccinate the safety of the vaccine, and rigorous risk assessment should be carried out to maximize the benefit of the vaccine.

From the perspective to control pandemic such as COVID-19 and prevent the delay of containment in future, from the long run, it is essential to enhance the overall strength of each country, including its financial, medical and educational capability. In terms of coping with current acute problem of uneven distribution of vaccines, collaboration among countries combined with donation of vaccines and financial support are necessary.

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