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How to Understand Herd Immunity in the Context of COVID-19

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Abstract

COVID-19 is an emerging rapidly evolving situation, which is widely disseminated all over the world. During this period, the concept of herd immunity is often mentioned, but it is easily misunderstood. In the context of COVID-19, this article comprehensively expounds the concept and purpose of herd immunity, the necessary conditions for realizing the herd immunity, the restrictive conditions for the application of herd immunity, and the challenges faced by the realization of herd immunity. Furthermore, starting from the ‘‘three elements,'' which refers to the characteristics of the pathogen and the population, as well as the behaviors taken by the population, the relationship between herd immunity and COVID-19 is deeply analyzed. Based on the aforementioned, the implementation of corresponding measures is expected to slow down the spread of the epidemic and even eliminate pathogens.

Keywords: herd immunity, COVID-19, pathogen, population, behaviors

Introduction

HERD IMMUNITY is an important concept in epidemiology, which explains how to evaluate the level of transmission of a pathogen in a population from the perspective of individual immunity. When a sufficient number of individuals in a population are immune to a pathogen, even if the disease is originally introduced by an infected individual, the outbreak cannot occur because the likelihood of effective contact between the diseased and susceptible individuals has been reduced, which means herd immunity is achieved (20).

To understand herd immunity, we need to consider the influence of various factors on the infectivity of the pathogen, the route of transmission, the immune status of the organism, and the behaviors in the population that may result in less-than-favorable outcomes (54). In general, the realization of herd immunity is closely related to the characteristics of the ‘‘pathogen'' and the ‘‘population,'' as well as the ‘‘behaviors'' taken by the population since herd immunity occurs when a sufficient proportion of the ‘‘population'' is sufficiently immune to prevent ongoing ‘‘behavior-dependent'' transmission of the ‘‘pathogen'' to susceptible individual. Understanding these ‘‘three elements'' and implementing actions accordingly can, therefore, play an important role in preventing epidemics and can be an important part of disease eradication or eradication programs.

In late December 2019, COVID-19 caused by SARS-COV-2 infection was first reported in Wuhan, China, and spread rapidly around the world. Countries have responded positively and taken a series of measures in accordance with their respective national conditions. The scientific basis behind many of these measures includes the concept of herd immunity, such as self-isolation at home for mild patients, evaluation and restriction of group activities, and teaching about hand hygiene. These measures have already paid off in many countries and regions. In terms of the general public, many people know or have heard of the term to some extent, but most people may not fully understand it or have some misunderstandings. Therefore, this article will systematically and comprehensively explain how to understand herd immunity in the context of COVID-19.

Concept and Purpose

Herd immunity is the resistance of a group or population to attack by a disease to which a large proportion of the group is immune, thus lessening the likelihood of an infectious individual to make effective contact with a susceptible individual (20). Herd immunity prevents an infected individual from introducing the pathogen into the population or minimizes the extent or speed of transmission once it has entered the population. As shown in the Figure 1, initially everyone is a

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susceptible population (white circle) and an infected individual (coil) is introduced. The infection spreads rapidly (arrow), but when a certain threshold is reached, new infected individuals cannot infect new susceptible individuals, because by then most of the population has recovered and acquired immunity (black circle), and the remaining nonimmune individuals, namely susceptible individuals, are indirectly protected.

At present, opinions are widely divided on the origin of novel coronavirus. The clinical characteristics of the first group of 41 patients transferred to designated hospitals for treatment due to SARS-COV-2 infection in Wuhan were analyzed, and it was found that the exposure history of the Huanan seafood market was a very important epidemiological indication for diagnosis in the early stage of the epidemic. But with more cases in the second and third generations, the proportion of patients with a history of seafood market exposure is gradually declining (27). That is, when an infected person, an animal, or a group of animals enter Huanan seafood market, almost all the people around them are susceptible individuals. These susceptible individuals then become infected persons or carriers and continue to spread the virus, resulting in the rapid spread of the epidemic and even the outbreak of the epidemic. On the contrary, if the infected person or animal enters another specific territory where a certain percentage of the population around it has acquired immunity to SARS-COV-2, then the remaining susceptible individuals will also be indirectly protected.

Therefore, the realization of herd immunity can effectively reduce the possibility of effective contact between infected individuals and susceptible individuals, thus greatly reducing the degree and speed of pathogen transmission, or even blocking its transmission.

Necessary Conditions

The realization of herd immunity is not easy. Only when ''sufficient proportion'' of the population have ''sufficient immunity'' can the pathogen be prevented to spread to susceptible individuals.

Sufficient proportion of the population

The micro-organisms that cause disease all have different characteristics of infection, and some diseases (such as measles and influenza) are more easily transmitted from person to person than others. Many of the characteristics, especially infectivity, affect the herd immunity threshold for an infectious disease, which is the minimum percentage of individuals that a population needs to be immunized against an outbreak of an infectious disease.

To set such a threshold, epidemiologists use a value called the ''base reproduction number,'' often referred to as ''R_0,'' which represents how many people in a fully susceptible population an infected person can pass the disease on to. For example, R_0 for measles is between 12 and 18. R_0 can be used to roughly estimate the percentage of immune individuals needed to reach the herd immunity threshold (P_C): $P_C > 1 - 1/R_0$ (54). In other words, the higher the value of R_0, the higher the threshold of herd immunity must be to protect the community. For example, because measles is highly contagious and can be spread through aerosols, the immune threshold needed to protect a population is as high as 95% (18). In China, the R_0 of COVID-19 in the early stage of the epidemic is about 2.5 (37,70); therefore, the proportion of immunized individuals required to reach the herd immunity threshold is about 60%.

R_0 is a function of biological, behavioral, and environmental factors that influence the rate of transmission. It is a dimensionless statistic, not a measure of the rate of change over time or the severity of the disease. Another concept compared with R_0 is ''effective reproduction number,'' often referred to as ''R_t,'' which refers to the average number of infections that actually spread. Compared with R_0 (transmission in a fully susceptible population), R_t can vary over

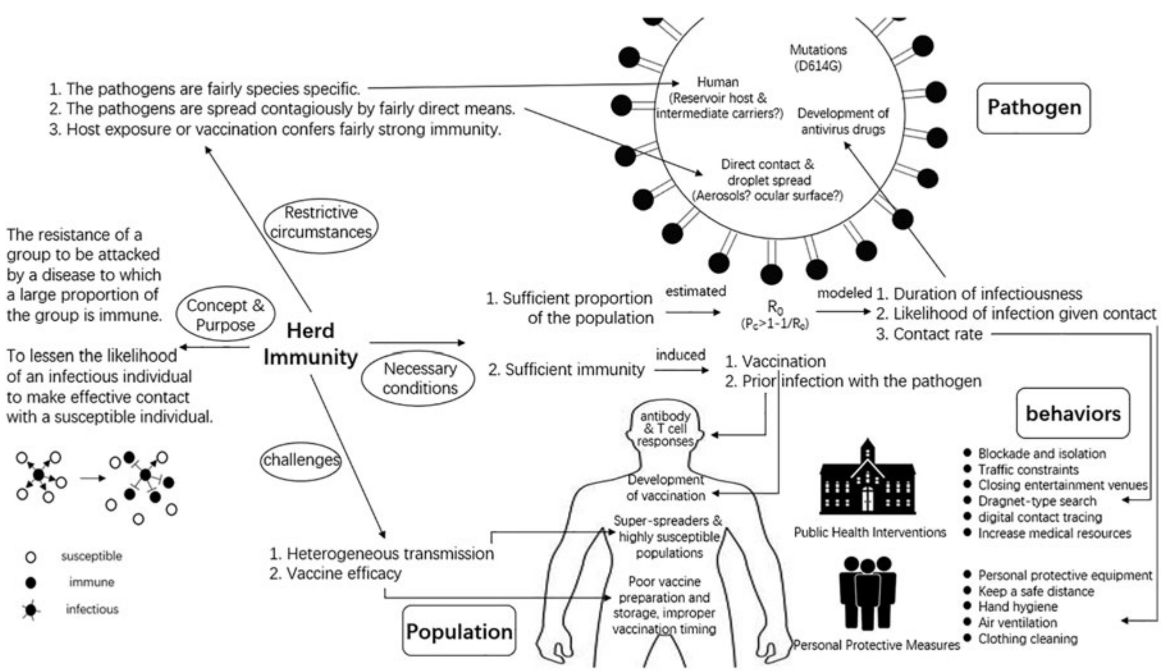

FIG. 1. Herd immunity and COVID-19.

time with changes in immunity in the population and can sometimes be estimated based on population data (12). If R_t is >1, transmission continues and a pandemic occurs. Until the proportion of exposed susceptible people drops to a point where R_t is <1, the infectivity is reduced or the pathogen cannot transmit (12).

Studies have estimated the R_t value of COVID-19 in Wuhan, China, at different stages: in the early stage of the epidemic, due to large population movements and limited intervention measures, the R_t value continued to increase and reached a peak of 3.82 on January 24; Later, with the implementation of public health interventions such as city closure, traffic control, and home quarantine, R_t value effectively dropped and fell <1 on March 1 (50). It can be seen that effective measures to reduce the proportion of exposed susceptible population can delay or even stop transmission to a certain extent.

Similarly, we can consider how to slow or stop the epidemic from the perspective of R_0. In general, R_0 can be estimated from the following three aspects: duration of infectiousness, the likelihood of infection given contact between an infectious and susceptible host, and the contact rate (13). Therefore, we can start from these three aspects and reduce the proportion of immune individuals required to reach the herd immunity threshold by taking corresponding measures to reduce R_0.

First, antiviral drugs can be developed to reduce the duration of an individual's infectivity after infection. Currently, no antiviral drug has been approved for SARS-COV-2 infection, but based on its viral structure, antiviral drugs that target the spike S protein (62), the key receptor of the spike protein ACE2 (45), and the protease that cuts the S protein such as TMPRSS2/Mpro (9,26), are being synthesized and developed.

Second, a range of measures can be taken to reduce the likelihood of infection in susceptible individuals after contact with an infected person, including preparation and use of personal protective equipment such as gloves, masks, air purifying respirators, goggles, masks, respirators, and protective clothing (39); keeping a safe distance from others all the time (67); reminding hand hygiene (14); ventilating the room to reduce the potential viral load (38); and timely cleaning and drying out clothes (38).

Third, methods to reduce the frequency of exposure in groups are mainly reflected in public health interventions, such as blockade and isolation (43,50); traffic constraints (50,58); closing entertainment venues (50,58); dragnet-type searching (50); digital contact tracing (e.g., health codes) (17); and increasing medical resources, especially in intensive care beds (32).

Through the implementation of the aforementioned measures, R_0 can be reduced in theory, so that the population can achieve herd immunity at a lower proportion of immune individuals, thus delaying or blocking the outbreak and epidemic of the disease.

Sufficient immunity

The realization of herd immunity depends on the aforementioned sufficient proportion of the population having sufficient immunity, which is generally acquired through two ways: vaccination and pathogen primary infection.

Vaccines are the most effective strategy for preventing infectious diseases, because vaccines are more cost-effective than drugs, and can reduce incidence rate and mortality rate, without long-term impact (2). At present, the development of SARS-COV-2 vaccine is under intense development. Spike S protein is an important target because it mediates infection mechanism by binding with receptor of host cell (8,16).

In general, vaccine platforms can be divided into six categories: live attenuated viruses, recombinant viral vector vaccines that have been bioengineered to express target pathogen antigens *in vivo*, inactivated virus vaccines, protein subunit vaccines, virus-like particles and nucleic acid-based (DNA or mRNA) vaccines. As of October 5, four adenovirus vector vaccines (ChAdOx1nCoV-19/Ad5-nCoV/Gam-COVID-VacLyo/Ad26.Cov2-S), two inactivated virus vaccines (BBIBP-Corv/PiCoVacc), two mRNA vaccines (mRNA-1273/BNT162b2), and one recombinant protein subunit vaccine (SARS-COV-2rS) have entered phase III clinical trials, and more other vaccines are in phase I/II clinical trials.

Based on these, the effectiveness and safety of various types of vaccines, the need for immune adjuvants, the possibility of protective immunity induced from immunogenicity, the applicability to specific vaccination routes, and the need to use primary immunization-enhanced vaccination regimens to improve vaccine-mediated protective immunity and its durability need to be tested (28). Published data showed that ChAdOx1nCoV-19 vaccines represent safety, good neutralizing antibody induction, and T cell activation in >90% of vaccinated people (19,60); Ad5-nCoV vaccines were unsafe in high doses, but neutralizing antibodies could be produced in about 50–60% of vaccinated people at low and medium doses (72). mRNA-1273 vaccine could induce neutralizing antibody of 100% of vaccinated people and $CD4^+$T cell response of some vaccinated people, but it could cause serious adverse reactions of 20% of vaccinated people at high dose (7,49). BBIBP-Corv (22), PiCoVacc (65), and BNT162b2 (63) vaccines also showed good immunogenicity and safety.

Another way for people to gain immunity to a pathogen is to have been previously infected with it. One study of severe acute respiratory syndrome (SARS) patients showed that about 90% of them had functional virus-neutralizing antibodies, and about 50% had a strong T-lymphocyte response (36). Similar to the results of SARS, serological analysis of COVID-19 patients showed that most of them could detect the specific IgM to the spike receptor-binding domain about 12 days after the onset of symptoms, and the IgG against nucleoprotein in about 14 days, among which the titer of antibodies in the serum of severe patients was significantly higher than that of mild patients (69). Several other large studies have found similar results (40,41), which suggests that most COVID-19 patients can produce protective antibodies within 10–14 days of the onset of symptoms.

There is currently insufficient evidence to support the question of how long immunity to COVID-19 may last, and more accurate estimates can be derived from studies of other coronaviruses. Research data on SARS and Middle East respiratory syndrome (MERS) showed that in people with antibody responses, the titer and protective effect of the antibody decrease over time, but could still be detected after 2–3 years (5,56). Although the time-dependent attenuation of this neutralizing antibody titer theoretically implies a loss

of protection against CoVs reinfection, since both SARS and MERS have lacked an epidemic transmission that allows reinfection, no definitive conclusion can be drawn as to whether and when COVID-19 will recur (30).

The understanding of these two ways of acquiring immunity is prone to a certain deviation. Herd immunity is not about letting every susceptible individual or every life be immunized by exposure, but rather about relying on a well-developed and effective vaccination program. In other words, we should implement a series of measures to contain outbreaks until a safe and effective vaccine is developed. Once the vaccine is available, we can achieve herd immunity through vaccination, thereby blocking transmission and even eliminating pathogens. So far, as the SARS-COV-2 vaccine is still in the process of development, active public health interventions and effective personal protection measures should be taken to curb the further development of COVID-19.

Sufficient immunity in a sufficient proportion of the population are two necessary conditions for achieving herd immunity. However, currently, the concept of antibody dependent enhancement (ADE) has also been gradually focused, that is, virus-specific antibodies promote the virus to enter host cells through the fc receptor pathway, leading to the phenomenon of enhanced viral infection (59), which means antibodies produced by vaccination or primary infection can possibly increase the infectivity of the virus. The presence of ADE in SARS-COV-2 infection is still controversial (53,64), which is of great significance to the development of vaccine and the diagnosis and treatment of the disease.

Restrictive Circumstances

It is impossible for a population to achieve herd immunity against all pathogens, which is limited by the following three conditions:

1. The pathogens are fairly species specific.
2. The pathogens are spread contagiously by fairly direct means.
3. Host exposure or vaccination confers fairly strong immunity (20).

First, if a pathogen can infect multiple hosts, it removes the indirect protection of an immune individual against a susceptible one. For example, although effective immunity can be obtained after infection with the malaria parasite, the mosquito as its definitive host can transmit the malaria parasite to new susceptible individuals and, therefore, herd immunity cannot be achieved. As for SARS-COV-2, the current confirmed host is human, but there is no conclusive evidence for its reservoir and definitive host. Related research found that bat coronavirus RaTG13 is the most closely related coronavirus to SARS-COV-2, and genetic sequence of a coronavirus isolated from pangolin in Malaysia has 91% homology with SARS-COV-2. Therefore, it is likely that for the moment, bats are probably the origin of new coronavirus, whereas pangolin is the intermediate host (34,71). Since these wild animals are not closely related to humans in the same way as mosquitoes, SARS-COV-2 could roughly be considered to meet this restriction.

Second, the spread of tetanus or bacillus anthracis is mediated by exposure to specific environments, so the immune individual cannot indirectly protect the susceptible individual. With regard to the mode of transmission of SARS-COV-2, an analysis of a family with a family cluster in Shenzhen confirmed the characteristics of the person to person transmission (4). It has been confirmed that SARS-COV-2 is spread mainly by close contact and droplet (4), whereas whether it can be transmitted through the ocular surface or aerosols still needs further study (42,44).

Finally, the ability to achieve stable and lasting immunity after exposure or vaccination is the basis of herd immunity. Only when these three constraints are met can herd immunity be achieved.

Challenges

Even though the aforementioned two necessary conditions and three limitations are met, the ability to achieve herd immunity still faces the challenge of heterogeneous transmission and vaccine efficacy.

Heterogeneous transmission

The proportion of immune individuals in a population required to reach the herd immunity threshold is based on the assumption that the contact between infected and susceptible individuals is random. However, heterogeneous transmission is common in most human and animal populations. Specifically, the presence of super-spreaders and highly susceptible populations makes it difficult to estimate the proportion of individuals who need to be immunized to reach the herd immunity threshold so as to destroy and eliminate the corresponding pathogens (18,20).

Super-spreader is an epidemiological term that refers to a highly contagious person who is more likely to infect others than a normal person, resulting in a large-scale outbreak. One study found that SARS-COV-2 super-spreaders exhaled droplets with higher viral loads and produced more aerosols (44), which somewhat increased the likelihood that susceptible individuals would be infected at the same exposure. At present, the primary focus is to identify these super-spreaders and analyze their biological and social behavior characteristics, but there has been no extensive research to determine their identity and the environment in which they spread. Therefore, without knowing who the next super-spreader will be, we should try our best to stay at home, wash our hands frequently, and wear masks when going out, so as to make ourselves safer and avoid the further spread of the epidemic.

In contrast, the current analysis of the clinical characteristics of COVID-19 patients shows that old age (25,67), no history of coronavirus infection (23,35), combination of other underlying diseases (25), and smoking (24,61) may be susceptibility factors, whereas the conclusions of gender factors vary from study to study (6,57). Similarly, highly susceptible populations with these susceptibility factors may have a higher risk of infection at the same exposure.

Understanding the role of age in COVID-19 transmission and disease severity is critical to determining the impact of social distancing measures and to accurately estimating the global number of cases. It was found that the susceptibility to SARS-COV-2 infection increased with age (67). Another study utilizing age-based transmission models indicated cities with a higher population age have more estimated

clinical cases, whereas cities with a lower population age lead to more asymptomatic (or mild) infections (11). Seniors may be particularly more likely to suffer from COVID-19 owing to immunosenescence and their tendency to mount exaggerated inflammatory responses (21,55). There are also significant differences in transmission status and case fatality rates among aging countries. Most notable is Italy, where intergenerational interaction patterns, housing arrangements, and commuting patterns may have accelerated the outbreak by increasing older people's access to infected people excluding the impact of the run on medical resources (15).

Nursing homes and other long-term care facilities also contribute significantly to COVID-19 mortality, which account for 11% of cases but 35% of all deaths (31). Issues such as lack of protective materials, limited detection capacity, market-oriented pension system, and policies and propositions of leaving nursing homes to operate have increased the possibility of elderly people being infected after contact with infected people. Stricter measures are, therefore, needed to avoid overloading the health system, with special attention to those at higher risk as well as intergenerational patterns of interaction.

So far, seven coronaviruses have been found to infect people and cause disease. In addition to SARS-COV, MERS-CoV, and SARS-COV-2, there are HCOV-229E, HCOV-OC43, HCOV-NL63, and HCOV-HKU1, which can cause the common cold. It was shown that individuals that have immunity to hCovs couples cross-reactive T cell immunity to SARS-COV-2 (23,35). Grifoni *et al.* analyzed individuals who had not been infected with SARS-COV-2, helper T cells could also be detected in 40–60% of the blood samples (23). Le Bert *et al.* presented similar results that 19 of 37 healthy individuals had immune T cells specific to SARS-COV-2 (35).

Such a finding is encouraging, but it may not mean that these populations are COVID-19 protected, because T cells recognize peptides consisting of a few amino acids, and such peptides are easy to find in highly conserved regions of the coronaviruses. But these studies still convey three important messages. One is that T cells (not just antibodies) are an important part of anti-SARS-COV-2 immunity. Second, coronavirus infection induces persistent cross-reactive T cell immunity. Third, SARS-COV-2 appears to have preexisting immunity in the common population. These three pieces of information also support the theory of herd immunity, which makes it easier for the proportion of immune individuals in the population to reach the threshold of herd immunity. However, such prestored immunity does not guarantee the existence of protection, and people need to establish a higher level of protection.

Vaccine efficacy

Another important challenge in achieving herd immunity is that vaccination may not yield the desired results. Even in the standardized large-scale vaccination plan, only 70% of the single vaccinated individuals can achieve the effect, and only 90% of the data after two vaccinations (52). Poor vaccine preparation and storage, improper vaccination timing, and so on may lead to population immunity lower than expected. This low level of immunity may even promote the further spread of the pathogen, as it may make patients' clinical symptoms less obvious, and policy-makers relax their vigilance.

The design of vaccine includes the choice of antigen, vaccine platform, and vaccination route and scheme.

For SARS-COV, it has been shown that only antibodies against S protein can neutralize the virus and prevent infection (3). Therefore, all SARS-COV-2 vaccines under development contain at least part of the S protein. As mentioned earlier, the choice of different vaccine platforms will show different effectiveness and safety. In addition, nonviral vaccine platforms can provide antigens, but usually need to manually provide signals to alert the immune system, called adjuvants, whereas live attenuated vaccines can naturally provide these two ingredients. One of the biggest challenges in adjuvant development is to regulate the inflammatory response while maintaining immune activation and protection. Some studies have reported one of the methods to enhance the protective response and limit inflammation, in which partial selective nuclear factor kappa B (NF-kB) inhibitors are used in combination with several current adjuvants to reduce systemic inflammation and enhance the protective response (47).

In addition to the careful selection of vaccine antigens and platforms, vaccination routes are also an important part of vaccine design. Protective IgG antibodies induced by parenteral immunization are easily present in respiratory mucosa, which is the main mechanism by which intramuscular measles or influenza vaccines provide protection to humans. However, this inoculation route does not effectively induce mucosal IgA antibodies or T_{RM} cells in the lungs (29). In contrast, the respiratory mucosal immune pathway is more conducive to the induction of antibodies and T_{RM} cells in respiratory mucosa, as well as macrophage-mediated trained immunity (46,48,66). Most of the current COVID-19 vaccine strategies are also focusing on the parenteral route of vaccination. Yet, the respiratory mucosal vaccine strategy that can directly induce these responses in the respiratory mucosa may be the most effective way to control or eliminate SARS-COV-2 in the early stage, which is also particularly critical for group of the elderly.

On the other hand, SARS-COV-2 is an RNA virus. Up to now, >10,000 mutations at different sites have been found in its genome sequence, among which the D614G mutant strain has attracted extensive attention. Studies have confirmed that the D614G mutant strain has become the most common form in the global pandemic, and it has been found that the D614G mutant strain has a higher viral load *in vitro* infection experiments (33). Similar results were obtained in other studies. Several teams found that the infection capacity of D614G mutant strain was enhanced in human lung epithelial cells (10) and hACE2 cells (68). However, viral load is not an adequate measure of disease status, as high titers may also be present in asymptomatic infected persons and more clinical data will be needed in the future.

Another concern is whether the D614G mutation will affect vaccine development. Fortunately, D614G is not located in the RNA binding domain (RBD) region, which is the target of many vaccines and therapies at present. At the same time, antibodies produced by naturally infected viruses containing D614 or G614 can be cross-neutralized, so for now, the D614G mutation is unlikely to have a significant impact on the efficacy of vaccines currently under development, but more experiments are needed.

Currently, no suitable vaccine has been approved for human coronavirus (1), and all types of vaccines against SARS-COV and MERS-COV are more or less limited (51). However, with the further understanding of the structure of coronavirus and the maturity of molecular targeting technologies, it is believed that the development of coronavirus vaccine has a good prospect.

Summary

The realization of herd immunity depends on the sufficient proportion of population in the population to obtain sufficient immunity, whereas the acquisition of immunity mainly depends on the mature and effective vaccination program. With the relentless spread of COVID-19, we need to correctly understand the relationship between herd immunity and COVID-19 from the aspects of pathogen, population, and the behavior taken by the population.

From the perspective of pathogen, it is crucial to determine its host and means of transmission in a timely manner, which determines the applicability of herd immunity and the way of prevention. In addition, the research on genetic material, structure, variability, as well as the exploration of vaccines and drugs based on it, are of great significance to block the transmission of pathogens and the realization of herd immunity.

As for population characteristics, early identification and corresponding disposal of super-spreaders and susceptible populations is one of the necessary contents to curb the rapid spread of the epidemic. In contrast, the immune response of primary infection and the immune effect of the vaccines in the population is one of the key points to block the transmission of pathogens and even achieve herd immunity.

From the aspect of population behavior, effective and practical public health interventions and personal protective measures can prevent the further spread of the epidemic or even eliminate pathogens, while enabling the population to achieve herd immunity with a lower proportion of immunized individuals.

Only with a deep understanding of the aforementioned contents, can we better deal with the COVID-19 epidemic as well as other public health emergencies that may occur in the future.

Authors' Contributions

M.D. was in charge of conceptualization, writing—original draft preparation, writing—reviewing and editing; F.H. was in charge of data curation, visualization, and investigation; Y.D. was in charge of conceptualization, and writing—original draft preparation.

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