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Commentary

Case fatalities due to COVID-19: Why there is a difference between the East and West?

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Abstract: COVID-19 has caused significant morbidity and mortality around the world. However, it has been noticed that case-fatality rates have been significantly higher in Europe and North America compared to the Asia, Middle East and Africa. This could be due to several factors which include average age of the population, testing and tracing facilities, social distancing measures and difference in immunogenic response to SARS-COV-2. In this report, we have discussed the factors which may affect a population to develop herd immunity against COVID-19. We have hypothesized here that frequent prior exposure to other coronaviruses in Asian population might impart partial immunity to COVID-19. This may be the reason for significant lower number of case fatalities seen in this region compared to the west. We, therefore, propose molecular immunological studies to correlate prior exposure to coronaviruses with disease severity. This will help us to develop therapeutic targets to treat severe infection with COVID-19.

Keywords: case fatalities; COVID-19; immune response; herd immunity

1. Introduction

Herd immunity refers to the indirect protection from a pathogen that is established at the level of the population when a proportionally large number of individuals acquire immunity through natural infection or vaccination. Herd immunity depends heavily on the degree of communicability of a pathogen and the population characteristics [1]. It is explained by the parameter R_0 (basic reproduction number) which refers to the average number of individuals who obtain the infection as a result of the presence of one infected individual in a susceptible population or the equivalent Rt which is extracted using real-life data [1]. The more communicable the pathogen is the larger the number of immune individuals needed to achieve the herd immunity threshold. The population characteristics and geographic factors also have an important role on herd immunity making it theoretically hard to establish a certain R_0 of the ongoing COVID-19 pandemic since it varies between populations [2]. Sarmadi et al. has observed that the highest number of confirmed COVID-19 cases were in the northern hemisphere including Asia, Europe, and parts of North America which, interestingly, are known to have better socioeconomic state and colder climate [3].

2. The geographical and temporal spread in the East and West and hypothesis on differences in the pandemic course

The first COVID-19 cases can be traced back to 8th December 2020 in Wuhan and surrounding Hubei province in China. On 11th February, 2020, there were 44672 cases in all thirty one provinces of Chinese mainland, after which the number of cases peaked the very next day. On 30th January, 2020, the first case was reported in Tibet. Most patients were found to be on the thirty to eighty years range, with an almost equal male to female distribution. The case fatality during this time was 2.3%, compared to 9.6% in SARS and 34% in MERS. The case-fatality for cases outside China had been higher at 4.5%, with countries such as Italy, the United States, Spain, Germany and Iran having shown uncontrollable spread during the same period [4]. On January 12, the WHO coined 2019-nCoV or Novel Coronavirus as the pathogen causing the outbreak; On January 23, Wuhan was closed off to prevent the spread; On January 30, the WHO named the 2019-nCoV as the 6th “public health emergency of international concern”. 2019-nCoV was renamed as the coronavirus disease (COVID-19) on 12th February 2020 by the International Committee in Taxonomy of Viruses. On 13th January 2020, Thailand recorded a Chinese visitor infected with SARS-CoV-2. While initially transmitted from bats to humans, SARS-CoV-2 has been currently transmitted from human-to-human; among them, asymptomatic carriers are more unidentifiable, and therefore unpredictable. The epidemiological data noted that vulnerable groups such as pregnant women, children, healthcare workers, the elderly, and individuals with pre-existing co-morbid conditions such as immunodeficiency, heart disease and diabetes conferred increased susceptibility to contracting COVID-19, for whom improved protective measures were required [5,6]. China has also shown swift response to the outbreak through never seen before lockdown of cities and districts, shutdown of public places and transportation and building new hospitals to accommodate specifically COVID-19 patients at a break-neck speed had all contributed to its effective pandemic control [7].

COVID-19 was first reported to be transmitted between humans in the United States in February 2020 according to the Center of Disease Control (CDC). As of December 19, 2020, the case fatality rates had reached 320000, with the number of COVID-19 cases 17 million in United States (US). The differences in cases between jurisdictions was described as a difference in the ages of the population, with older ages being more susceptible to infection, in addition to those having under lying medical conditions. A lack of testing, differences in public health reporting, population density, COVID-19 mitigation strategies and time of introduction of COVID-19 were also correlated with more case fatalities [8]. By May 13th, 2020, 4170424 cases of COVID-19 with a total death count of 287399 was reported worldwide of 20 countries. According to the WHO, there was a wide difference in number of cases between the US and the rest of the world. While the cases in the US steeply increased to 1322054 around this time, the cases in the Eastern Mediterranean (284270), South-East Asia (110932), and African regions (49229) were only fractional compared to the total number of cases in the US and Europe. The reproduction number (R_0) had been estimated to be 3.28, a measure of its transmissibility [9]. According to a study in Columbia, infection cases grew in an exponential model as in Europe, with a one-week difference making an increase to 40535 cases from 2581 cases in early April. The case fatality in Columbia, however, was 0.6% compared to the case fatality of Europe, notably Italy, with more than 8% and Mediterranean European countries (9% to 11%) by March 18, 2020. An interesting observation made in this study was that the differences in case fatalities between Columbia and Europe could be explained due to the lesser percentage of aging populating (13% vs 29% in Italy), tropical climate and earlier preventive measures taken [10]. East Asian countries have been successful in limiting the spread of the pandemic, with South Korea being the most important example in which, with the aid of aggressive diagnostic tests and screening; contact tracing and isolation; and high technologies and rapid dissemination of information had terrific results in controlling the pandemic. Vietnam, with case identification, isolation, contact tracing and mass mask wearing policies, along with the use of mobile applications to report COVID-19 cases, controlled its cases despite not being able to afford country-wide testing. Taiwan and Hong Kong have also adopted similar strategies. In comparison, the West, although enacting border control and social distancing protocols, has shown delayed response and even case-by-case management, rather than nationwide policies. Countries such as Italy, France, Spain, Belgium, and the United Kingdom have not shown to be as successful at handling the pandemic when compared to Eastern countries and Germany (a special exception), due to late response, lack of initial mass testing, political deterrents to initiating lockdowns and testing. Sweden took a population approach of social distancing and recommended against large gatherings, working from home, and performing not optimal testing. The main differences in strategies have been the timely coordinated response, a community-based approach and screening asymptomatic patients. Symptomatic patient treatment had been ineffective in curbing the case fatality rates when a lot of asymptomatic people were already a hornet nest for disease transmission [11]. A higher number of cases in the west can also be explained by the availability of diagnostic kits and crowdedness of the large industrial cities located in the region. Another possible contributing factor is air pollution as it is positively linked with the number of confirmed cases in comparison with cleaner air [12].

The African scenario in light of COVID-19 provides some interesting perspectives. With an armamentarium limited in human resources and personal protective equipment (PPE), the infrastructural model of the continent is not likely to offset the use of telemedicine and digital services in lieu of a short, yet indispensable supply of PPE. Although Africa had been introduced to the SARS-CoV-2 virus after Europe and Asia by weeks, the number of cases and case fatality had increased rapidly, with geographical variations across the continent due to differences in SARS-CoV-2 testing and air-travel volume. A regional difference in supply and demand also significantly affects the COVID-19 trajectory in different countries. Where Mozambique may have 6 nurses or midwives per 10000 people, Kenya has 11. Other countries in Africa have fewer than 30 critical beds in the entire country. The limited PPE resources in high-income countries made it even more difficult to allocate resources to Africa. Moreover, the large scale of distances makes it harder to transfer critical patients [13]. COVID-19 is not the first epidemic in this continent; smallpox, malaria, African sleeping sickness, HIV infection, the Ebola virus have all been experienced in the region. The first case was confirmed in Egypt on 14th February 2020, followed by Algeria the next day. In April, almost every country in Africa had been introduced to COVID-19, ranging from hundred to a thousand of cases. Establishments such as Africa Taskforce for Coronavirus Preparedness and Response by the African Union Commission, the Africa CDC, and the WHO Regional Office for Africa (AFRO) were mobilized, starting as early as February. The African Taskforce oversaw the smooth operation of laboratory diagnosis, surveillance, infection control, clinical management of severe COVID-19, risk communication and supply chain management [14].

The Middle-East respiratory syndrome (MERS) epidemic in 2012 in Saudi Arabia better prepared the country for response measures to the COVID-19 outbreak. The first case of COVID-19 was reported on 2nd March 2020, in a returning passenger from Iran. By 18th of April, there were 8200 cases and 92 case fatalities. The majority of Saudi population is made of younger individuals; 32.4% of its citizens are in the 0–14 age group, whereas 2.8% are more than 65 years. Not only does [7] the holy muslim pilgrimage, Umrah, was suspended since 4th March 2020; On 12th March all public gatherings were suspended, including the Saudi-African and Arab-African summits, domestic and international flights, sport events, daily public prayers in mosques. Digital health apps such as “My Health” app were utilized to offer medical advice to the population. A late introduction of COVID-19 in Saudi Arabia and taking swift responses when the cases had started to reach 300 in a population of 34 million had significantly limited the spread of the virus [7]. The first COVID-19 case in the Arab world was seen in the United Arab Emirates (UAE); By February, the number of cases were highest in Kuwait, followed by Bahrain, UAE and Iraq. Iran had been one of the most severely afflicted countries by May 18. Iran, along with Saudi Arabia, is considered as a religiously important geographical location, which is one theory why it had faced a tumultuous course of COVID-19. By 31st May 2020, the number of cases in all Arab countries had been 290428 with 3696 case fatalities. The highest number of reported cases was seen in Saudi Arabia at 85261, with 0.59% mortality. Qatar, the UAE, Kuwait and Egypt have followed in cases. The highest case fatalities were present in areas afflicted with civil wars in Syria (23.77%) and Yemen (24.84%). In conclusion, the younger average in the Arab world (26.77 years) has painted a less aggressive picture of the pandemic, compared to the rest of the world. Ranking fourth after USA, Brazil and Russia, Arab countries have noted the lowest rate of deaths at 8 per million, similar to India, whose average age is 28 (and death rate at 4 per million). Alternatively, China, USA and Italy have seen more deaths in the older subpopulation group [15].

3. Factors affecting herd immunity

Statistical studies observe that a lack of herd immunity can lead to 40–70% transmission of SARS-CoV-2 in the population, if no mitigating strategies exist in place. Important steps involved for containing the infection include identification, contact tracing and quarantine. Other public health measures that have been taken hold in the public health response model is the closure of public spaces, lockdown, social distancing and temperature check in public places (which is not the most effective method as it misses 46% of asymptomatic patients). Measures like use of alcohol-based sanitizers containing 70% isopropyl alcohol, use of personal protective equipment (PPE) such as the three-layered mask or N95 mask and its proper disposal are also important scientific measures taken to reduce the spread of the pandemic. The timeliness and adherence of these measures are also important variables [16].

Herd immunity is a concept in epidemiological theory whereby enough members of a population affected by an infection makes the probability of an non-sensitized person to contract it lesser by decreasing the chances of contact between diseased and susceptible persons. It is an important concept for disease eradication and epidemic prevention [17]. Herd immunity follows a threshold theorem, where if in a population mixing freely, the disease was transmitted from each individual to R_0 individuals, and immunity, like vaccination was also provided at random, then the number of infected individuals would decline by the Eq 1. This is the herd immunity threshold a level of immunity maintained by the population that protects susceptible individuals from the disease. Selective vaccination in individuals that are more important in infection spread can stop the spread of disease. Smallpox has been completely eradicated due to vaccination. The vaccine effectiveness also in turn depends on transmission, immunity conferred by the vaccine, mixing population models, and vaccine distribution. Vaccine effectiveness against disease (E) is also important for measuring critical vaccine level, Eq 2 [18]. The strength of transmission is measured through R_0, an $R_0 > 1$ is indicative of a self-sustaining infection; whereas an $R_0 < 1$ indicates a decreasing number of cases with time. The R_0 of HINI was 1.25; SARS-Co (2.2–3.6); and SARS-CoV-2 was estimated to be various numbers at 2.2, 3.11, and 2.68. This number ($R_0 > 1$) indicated a high and self-sustaining transmissibility [5].

$$1/R_0 \tag{1}$$

$$V_c = (1 - 1/R_0)/E \tag{2}$$

A possible source of partial immunity is antibody cross-reactivity that is obtained from previous coronaviruses infections including OC43, 229E, NL63 and HKU1 which was observed in SARS-CoV [19]. Although SARS-CoV-2 is a new virus, several coronaviruses were circulating in the previous decade and were especially prevalent in Asian countries which could enhance their susceptibility to achieving herd immunity. As per observing asymptomatic COVID-19 cases, Hu, Z suggested that recovering from seasonal coronaviruses might lead to a milder or asymptomatic disease course [20]. Additionally, pre-existing cross-reactive $CD4^+$ memory T cells to SARS-CoV-2 were explained by several hypothetical immunological scenarios. A great deal of research has been studying the possibility of cross-reactive memory T cells to provide some form of immunity against COVID-19 and the implication of this phenomenon on herd immunity [21]. Cross-reactive T-cell immunity against SARS-CoV-2 associated with other circulating coronaviruses have been found in 30–80% of uninfected cases suggesting cross-reactive T cell recognition between “common cold” coronaviruses and SARS-CoV-2 [22,23].

A recent study by Shrock et al. assessed the antibody profiles of 232 COVID-19 patients and 190 pre-COVID-19 era controls. Strikingly, they identified several antibody epitopes which were shared between other coronaviruses and SARS-COV-2 [24]. COVID-19 infected patients requiring hospitalization showed much greater antibody response to infection but weaker response to prior other coronavirus infections compared to those who did not need hospitalization [24]. This shows that prior other coronavirus infection provides partial immunity and affects severity of disease. Indeed, this study further demonstrated that a significantly lower level of antibodies targeting enteroviruses, rhinoviruses and influenza in patients hospitalized with COVID-19 compared to non-hospitalized patients [24]. However, strikingly, Shrock et al showed higher seroprevalence for Herpes simplex virus 1 and cytomegalovirus in hospitalized COVID-19 patients. Taken together these finding suggest that prior exposure to non-coronaviruses does mount an immune response but it’s not enough to prevent hospitalization [24].

R_0 and the herd immunity threshold can be variable between populations depending on the prevalence of cross-reactive immunity among individuals. As COVID-19 has shown wide variation in disease outcomes and symptoms severity, cross-reactive T cell memory can explain this observation through tracking the confirmed cases clinical outcomes and epidemiology [25]. Although further functional applications of cross-reactive T cells have not been proven, $CD4^+$ T cells can critically limit the disease severity, infectiousness and duration rather than preventing infection [21]. It was proposed that the low morbidity rate observed in Asian countries could be explained by the multiple rounds of coronaviruses and the resultant partial acquired immunity in certain individuals [26]. It seems reasonable to assume that the multiple previous coronavirus infections and endemics encountered in Asia and the Middle East may have generated partial immunity against SARS-CoV-2 and subsequently lowered the herd immunity threshold. Moreover, the presence of different types of heterogeneities, such as age, special and social activity may influence disease-induced herd immunity [27]. This can be explained by the increased contact rate and activity levels in the younger population. Similarly, contact-rich environments and large crowded households may lead to an increase in the disease spread and concentration of immunity among contacted population. Herd immunity threshold is also influenced by variation in susceptibility and exposure to infection [28]. Therefore, individuals with high susceptibility and exposure rate are more likely to be infected and immune which lowers the herd immunity threshold.

4. Conclusions

Above discussion on molecular epidemiological studies, achieving herd immunity and pandemic response, we believe that molecular epidemiological studies must be done to study the differences in the geographical spread between the East and West. Public health studies studying the responses at an immunological and molecular level can aid in understanding how different interventions/treatments can create and alter the path of this pandemic. Finally, we also maintain that differences in immune response to different SARS-COV-2 antigens make western populations more susceptible to the family of *coronaviridae*. Thus, molecular immunological studies are key to control this pandemic and develop effective response.

Conflict of interest

All authors declare no conflicts of interest in this paper.

Authors contribution

AY: conceptualization, literature review, writing, review; AA: literature review, writing; TE: literature review, writing.

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