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COVID-19 Outbreak: Reviewing Various Factors Affecting its Fate

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ABSTRACT

With a total of 5,370,375 cases worldwide and a death toll of 344,454, as on the 26th of May 2020, the COVID-19 pandemic has affected humankind in profound ways. Originating from the city of Wuhan, the disease has gripped, till now, 216 countries and territories.[1] The mode of transmission is most evidently via aerosols and affects different people in different ways. However, the disease presents most commonly with fever, fatigue, and dry cough. The ongoing battle against it has compelled global healthcare to reawaken and re-evaluate to meet the needs of providing appropriate strategies, which in turn abet the pandemic. To realize this, a need to speculate and understand specific factors that can impact the disease occurrence, transmission, course, and outcome is the utmost need. COVID-19, with an R_0 of more than one, has proved to be more transmissible than its previous counterpart outbreaks viz. Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). However, SARS and MERS had observed higher case fatality rates. The bionomics of the SARS-CoV-2 virus, the associated epidemiological factors, and the immune responses in the human after being infected body seem to determine the fate of the present disease, COVID-19.

Keywords: COVID-19 pandemic, SARS-CoV-2, herd immunity

INTRODUCTION

A pandemic is almost always unpredictable, and COVID-19 has proved to be quite an unpredictable one. The present outbreak of novel coronavirus disease, now officially named coronavirus disease-2019 (COVID-19), is an infectious disease caused by a newly discovered strain of coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[2] It reminds us of the previous two threatening global pandemics caused by coronavirus infection; namely, Severe Acute Respiratory Syndrome (SARS) during 2002-2003 that originated in China and the Middle East Respiratory Syndrome (MERS) during 2012-2013 which had its origin in Saudi Arabia. [3]

The outbreak of COVID-19 was initially noticed in mid-December 2019 from a seafood market in Wuhan City, the capital of the Hubei province of China.[4] As the presentation of illness in the cases was similar to that seen in the flu, it remained neglected in its initial phase. Gradually development of shortness of breath and progression to viral pneumonia and multi-organ failure in some cases raised the whistle. On the 31st of December 2019, the WHO China country office was informed about pneumonia cases

of unknown causes in Wuhan city. Subsequently, on the 7th of January 2020, a novel coronavirus was isolated and identified as the causative virus by Chinese authorities. On the 12th of January 2020, the World Health Organization (WHO) confirmed that a novel coronavirus (SARS-CoV-2) was the cause of the respiratory illness in a cluster of people in Wuhan.[5] Since then, it has spread exponentially to more than 213 countries/territories and 18 international conveyances worldwide including India. On the 30th of January 2020, the World Health Organization (WHO) declared the 2019-20 novel coronavirus outbreak a Public Health Emergency of International Concern (PHEIC) and finally a pandemic on the 11th of March 2020.[6,7,8]

Though COVID-19 has spread to most of the countries of the World, but puzzlingly, the impact of the disease varies from nation to nation. This article aims at reviewing the various epidemiological and immunological factors which are directly or indirectly related to the current pandemic of coronavirus disease and are speculated to govern the fate of this dreaded threat to human civilization.

The burden of disease: How big is the problem?

There are three parameters that need to be understood in order to assess the magnitude of the risk posed by this novel coronavirus, namely, Basic Reproduction Number or Transmission Rate (R_o), Case Fatality Rate (CFR) and determining whether an asymptomatic transmission is possible. The R_0 (pronounced R-nought or R-zero) denotes the attack rate or the transmissibility of an infectious agent, which represents the average number of people to which the agent will be transmitted by a single infected person. WHO has estimated R_o for SARS-CoV-2 to be between 1.4 and 2.5 while other studies have estimated a R_o between 3.6 to 4.0, and between 2.24 to 3.58. [9,10] Commonly, when $R_0 > 1$, the infection is able to start spreading in a population, but not if $R_0 < 1$. An outbreak with a reproductive number of below 1 will gradually disappear. For comparison, the R_o for the common flu is 1.3, and for SARS, it was 2.0. Hence, COVID-19 with $R_0 > 1$ is declared as a pandemic.

The case fatality rate gives us the percentage of deaths among infected people within a certain time after the disease was diagnosed. It is ideally suited to express the prognosis in infectious or acute diseases. The novel coronavirus's case fatality rate was estimated at around 2% by WHO and declared in the WHO press conference held on the 29th of January, 2020, while another study estimated it to be 3%.[11] There is huge variability in the case fatality rate due to COVID-19 across countries, ranging from as high as 10-12 % in Spain, Italy, France, the United Kingdom, and less than 1% in a majority of the nations. The case fatality rate for COVID-19 (global average 6.9%) has been till now lower than SARS (9.6%), and MERS (34.4%), but the transmission has been significantly higher, with a significant total death toll.[12,13] The fatality rate can change as a virus can mutate, according to epidemiologists. It is too early to declare the exact case fatality rate for COVID-19 as the cases are added daily. It would be possible once the present pandemic is contained.

As on the 26th of May 2020, more than 5 million cases have been reported, with 344,454 deaths globally.[1] In India, the first case of the 2019–20 coronavirus outbreak was reported on the 31st of January 2020, from Kerala among students who returned from Wuhan, China. As of the 26th of May 2020, the Ministry of Health and Family Welfare, Government of India have confirmed a total of 145,379 infected cases with 60,490 recoveries (including one migration) and 4167 deaths in the country.[14] Experts suggest that the number of infected persons could be much higher since the screening rates in India are among the lowest in the World.[15] The countrywide lockdown has slowed the growth rate of the pandemic from a rate of doubling every three days to a rate of doubling every thirteen days.[16] Despite a bundle of efforts to control the pandemic at various levels, the number of cases is continuously on the rise both in India as well as globally.

Bionomics of Coronaviruses: SARS-CoV-2

Coronavirus is a large family of viruses. Some strains are responsible for illness in people, and others circulate among animals, including camels, cats, and bats. Sometimes coronaviruses that infect animals can evolve into a new human coronavirus by antigenic shift and antigenic drift mechanism and make people sick, as has been seen in pandemics of the past, for instance, SARS-CoV which emerged during 2002 in Southern China, MERS-CoV during

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2012 in Saudi Arabia and SARS-CoV-2 which has recently emerged in December 2019 in Wuhan city of Republic of China.

Coronavirus got its name derived from the Latin word 'corona' which means a crown.[17] It refers to the characteristic appearance of a fringe of large, bulbous surface projections on the virions (the infective form of the virus), creating an image evocative of a crown or a solar corona on electron microscopy. The viral spike peplomers, which are proteins on the surface of the virus, create this morphology.[18,19] The viruses display a characteristic fringe of large, distinctive, petal-shaped peplomers or spikes which resembles a crown, like the corona spinarum (crown of thorns) in religious art; hence the name coronaviruses.

The Coronaviruses are large pleomorphic spherical particles with bulbous surface projections with an average diameter of around 120 nm (0.12 μm).[20,21] The viral envelope constitutes of a lipid bilayer wherein the membrane (M), envelope (E), and spike (S) structural proteins are anchored.[22] Within the envelope, the positive-sense single-stranded RNA genome is bound to the nucleocapsid in a continuous beads-on-a-string type conformation. The nucleocapsid is derived from multiple copies of the nucleocapsid protien[23,24] The lipid bilayer envelope, membrane proteins, and nucleocapsid protect the virus when it is outside the host cell.[25]

The SARS-CoV-2 is a single-stranded positive-sense RNA virus that is closely related to the severe acute respiratory syndrome coronavirus (SARS-CoV).[20] It was first isolated from three people diagnosed with pneumonia connected to the cluster of acute respiratory illness cases in Wuhan.[26] All genetic features of the novel SARS-CoV-2 virus occur in other related coronaviruses in nature.[27] It is postulated to have a zoonotic origin. The genetic analysis revealed that the coronavirus genetically clusters with the genus Beta coronavirus, in subgenus Sarbecovirus (lineage B) with two bat-derived strains. At the whole genome level, it is 96% identical to bat coronavirus samples (BatCov RaTG13).[28]

The newly identified SARS-CoV-2 has a zoonotic transmission, that is, it spreads from animals to humans and subsequently human to human transmission. The suspicion on the intermediate host persists, even though it was found that there is only a difference of one amino acid in certain parts of the genome sequences between the viruses from pangolins and those from humans reported in a research conducted by Chinese researchers in February 2020. These findings of whole-genome comparison are insufficient to prove pangolins to be the intermediate host.[29]

According to current evidence, SARS-CoV-2 is primarily spread between people during close contact. Once in humans, the main route of transmission is via inhalation of aerosol (suspended, fine particles in the air) or small droplets produced during coughing, sneezing, or talking by infected individuals.[30,31] SARS-CoV-2 also gets transmitted via fomites, i.e., when a person touches his/her mouth, nose, or possibly their eyes after direct contact with a contaminated surface or an object.[32]

SARS-CoV-2 is highly contagious due to the production of high viral load and efficient shedding of virus from the upper respiratory tract. Rather than traveling over large distances, small droplets produced during coughing, sneezing, talking, or when breathing out, tend to fall to the ground. Since they are too heavy to hang in the air, they quickly fall on the floors or surfaces.[33,34] These droplets are highly infectious within the range of one meter. They typically do not travel more than 6 feet (about 2 meters) from the infected individuals but can remain viable for up to 3 hours under optimum conditions. It is being noted that the virus can survive on surfaces for up to 72 hours.[35] Specifically, it is found to be detectable for one day on cardboard, up to four hours on copper utensils and for up to three days on plastic and stainless steel .[36] However, studies have reported a variable effect of temperature and humidity of the environment on the stability and transmissibility of the respiratory virus.[37] Outside the human body, the household soap kills the virus by bursting its protective bubble.[38]

Infectious droplets and body fluids can easily contaminate the human conjunctival epithelium.[39] Respiratory viruses can induce ocular complications in infected patients, which then leads to respiratory infection. The fact that exposed mucous membranes and unprotected eyes increase the risk of SARS-CoV transmission suggests that exposure of unprotected

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eyes to SARS-CoV-2 could cause acute respiratory infection. [40]

Feco-oral route of transmission has also been suspected because of the presence of viral nucleic acids in the stool samples of the diseased persons, but it remains unconfirmed in the absence of authentic conclusive studies.

Various global epidemiological data related to COVID-19 indicates that disease transmissibility also depends on various variables such as density of population, local hygiene practices, and infection control standards prevalent in the concerned region of the World. Low standards certainly account for the higher prevalence of the disease.

Clinical and preventive aspects of COVID-19

Who is a suspected case of COVID-19?

A patient is suspected of COVID-19 when presented with fever and at least one sign/symptom of respiratory disease (cough, shortness of breath) along with a history of travel to or residence in a country/area or territory where local transmission of COVID-19 disease has been reported 14 days prior to symptom onset; or a healthcare worker/patient with an acute respiratory illness has been in contact with a COVID-19 case confirmed in the last 14 days prior to the onset of symptoms; or a patient with a severe acute respiratory infection, fever and at least one sign/symptom of respiratory disease (shortness of breath) requiring hospitalization, with no other etiology that fully explains the clinical presentation.

Symptoms of COVID-19 may emerge in, as few as, two days or as long as 14, with a median of about 5-6 days based on the available data during which the virus is contagious, without the patient displaying any symptom (asymptomatic transmission) referred as the incubation period. [41] Although coronavirus is most infectious during the first three days after symptoms appear, the spread may occur before symptoms onset and in the later stages of the disease.[42] Symptoms seem to start with fever, cough, and then followed by shortness of breath and some other respiratory symptoms like stuffy nose, weakness or malaise, nausea, vomiting, diarrhoea, or headaches. Emergency warning signs of COVID-19 demand immediate medical attention, which includes trouble in breathing, persistent chest pain or pressure, new confusion or inability to arouse, bluish lips or face, and other symptoms that are severe or concurrent.

Most people (85%) experience mild to moderate respiratory illness and recover without requiring special treatment. On the other hand, people of older age-group and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, cancer, and immunocompromised conditions are more likely to develop serious illness and higher chances of mortality. Healthcare-associated infection by the SARS-CoV-2 virus has been documented among healthcare workers in many countries. Those who are in close contact with the suspects or confirmed COVID-19 patients or involved in the care of such patients are the people most at risk of COVID-19 infection.

The current testing strategy includes:

1. All symptomatic individuals with history of international travel in the last 14 days.
2. All symptomatic contacts of laboratory confirmed cases.
3. All symptomatic health care workers/ frontline workers involved in containment and mitigation of COVID-19.
4. All patients of Severe Acute Respiratory Infection (SARI).
5. Asymptomatic direct and high-risk contacts of a confirmed case to be tested once between day five and day 10 of coming into contact
6. All symptomatic individuals within hotspots/containment zones.
7. All hospitalised patients who develop symptoms.
8. All symptomatic among returnee and migrants within 7 days of illness.[43]

All contacts of a confirmed case, if asymptomatic, should be put under home quarantine for at least 28 days, and if symptomatic, they should be lab tested for COVID-19.

Vital preventive measures for COVID-19

Everyone, irrespective of their age, needs to protect themselves from infection, not just to keep themselves healthy but also to break the chain of transmission of the virus. The key revolves around social distancing, regular hand washing, avoiding touching of eyes, nose, and mouth, and self-isolation.

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The standard precautions are designed to mitigate the risk of transmission of bloodborne and other pathogens from both recognized and unrecognized sources. These precautions, the basic level of infection control, should be used as a minimum in the care of all patients. It includes hand hygiene, personal protective equipment, respiratory hygiene, and cough etiquette. Persons with respiratory symptoms should follow source control measures, i.e., cover their nose and mouth when coughing /sneezing with tissue or mask, dispose-off used tissues and masks, perform hand hygiene after contact with respiratory patients, healthcare facilities should place acute febrile respiratory symptomatic patients at least one meter from others in common waiting areas, host visual alerts at the entrance to healthcare facilities instructing persons with respiratory symptoms to practice respiratory hygiene/etiquettes, make face masks and hand hygiene resources available in common waiting areas and areas used for the evaluation of patients with respiratory diseases.

Presently, no specific vaccines or treatments are available for COVID-19. However, vaccine development is underway, and there are many ongoing clinical trials evaluating potential treatments. According to present-day estimates, more than 80% of COVID-19 cases have a mild-to-moderate illness, and so, a comprehension of the immune response in such mild cases depict a key research area.

Role of herd immunity

Countless articles on the COVID-19 are making the argument that, albeit potentially risky, achieving herd immunity could be one response to our crisis. Many of them are predicting that herd immunity as a preventive strategy that may impede the tidal wave of disease, but herd immunity without a vaccine is, by definition, not a preventative measure. Herd immunity, in epidemiological concept, describes the state where a population is sufficiently immune, either through vaccination or natural immunity, to a disease that the infection will not spread within that group. If ample people become immune to the disease, the virus will stop spreading in the population. Anyone considering herd immunity as the strategy for prevention until a vaccine is available is simply mistaken.

Generally, the larger the value of the basic reproduction number (R_0), the more difficult it is to control the epidemic. For simple models, to prevent the sustained spread of the infection, the proportion of the population that is required to be effectively immunized (meaning not susceptible to infection) has to be larger than $1 - 1/R_0$.[44] Hence, approximately two-thirds of the population needs to be immunized either by sub-clinical infection of the virus or by effective vaccination of the community to acquire adequate herd immunity against SARS-CoV-19 virus. In contrast, the proportion of the population that remains susceptible to infection in the endemic equilibrium is denoted by $1/R_0$. The basic reproduction number (R_o) is affected by several factors, such as the duration of infectivity of affected patients, the infectiousness of the agent, and the number of susceptible people in the population that are in contact with the affected patients.

The rapidly spreading COVID-19 pandemic is taking a particularly harsh toll on older people. Although all age-groups are susceptible to COVID-19 infection, the elderly cases with co-morbid conditions like diabetes mellitus, hypertension, chronic cardiovascular or respiratory illness, tumor, etc. are prone to severe illness and complications leading to higher mortality in older age-groups.[45,46] On analysis of death cases from the data available till-date, it has emerged that the demographic profile is mainly male, accounting for 2/3rd and females accounting for 1/3rd of total. Those who have succumbed to death are mainly elderly; more than 80% are aged over 60 years, and more than 75% had a presence of underlying diseases. Country-wise highest mortality among an older section of the society has been reported from the United States, Italy, Spain, France, the United Kingdom, and other European countries. On the other hand, young children do not appear to be at increased risk of serious COVID-19 complications, as has been previously observed with other viral infections like the seasonal flu.

A valid question arises in everyone's mind; what puts the older people at increased risk from viruses like this? Primarily, the changes in the human immune system with advancing age are the culprit. To understand this, first, we should understand our immune system. The human body has two types of immune response; one is adaptive and the other being innate. The adaptive and innate immune systems act together like a fine-tuned machine to detect and clear out pathogens.

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The adaptive immune system is a subset of the immune system which comprises of specialized cells, namely the B-cells and T-cells. They recognize the pathogens and curb their growth in the body. During an infection, the B-cells proliferate and produce antibodies that grab onto pathogens and block their ability to spread within the body while T-cells work by recognizing infected cells and killing them. The human body has another layer of defense mechanism in the form of the innate immune response. In this, human cells mainly monocytes detect these invader molecules, trigger the production of antiviral interferon protein, which imposes the infected cells to die, thereby limiting the infection. As age advances, monocytes produce less interferon in response to viral infection. Also, the presence of low-grade chronic inflammation in individuals reduces the ability of the innate and adaptive immune response to react to pathogens and thereby resulting in serious disease and death.[47]

Another study published recently tried to explain a hypothesis based on epidemiological evidence indicating that some of the differences observed in morbidity and mortality produced by COVID-19 across countries might be due to differences in the Bacillus Calmette Guerin (BCG) vaccination policy. They observed a significant positive correlation between the year of the establishment of universal BCG vaccination and the mortality rate due to COVID-19. Countries like the United States, the Netherlands, and Italy who have not adopted universal vaccination policy and nations like Spain, France, and Switzerland who have discontinued their universal vaccination policies, have experienced heavy mortality as a result of SARS-CoV-2 infection.[48]

BCG vaccination, along with other vaccines, has been known to confer nonspecific immunity against other non-mycobacterial pathogens. This is based on two mechanisms. The first is heterologous immunity, which refers to cross-protection mediated by memory T-cells. The second phenomenon is based on epigenetic reprogramming, wherein non-specific immune memory is conferred to innate immune responses. This is explained on the basis of the 'trained immunity' phenomenon observed in BCG vaccinated mice, which were protected against vaccinia virus infection as a result of increased interferon gamma (IFN-γ) production from CD4+ and CD8 T cells.[49] BCG vaccination plays a vital role in antiviral immunity as it has been seen to significantly increase the secretion of pro-inflammatory cytokines, specifically Interleukin 1 beta (IL-1β).[50] Additionally, lower infectivity and mortality among children observed globally in the present pandemic may be explained by the findings of a study conducted in Guinea-Bissau, West Africa, which reported that children vaccinated with BCG had a 50% reduction in overall mortality. This finding was attributed to the vaccine's effect on reducing other respiratory infections and sepsis.[51,52]

The role of immune parameters to predict disease outcome was strengthened by evidence of recruitment of large populations of immune cells (antigen secreting cells (ASC), activated CD4+ and CD8+, and T helper cells) together with certain antibodies in the blood prior to symptom resolution in non-severe COVID-19 cases in Australia.[53]

In the present scenario, when everyone is experimenting with various treatment options, some health facilities have performed convalescent plasma therapy to severe COVID-19 patients with results to be observed and approved by competent authorities. The Ministry of Health, along with Indian Council of Medical Research (ICMR), has not recommended it as a treatment modality until appropriate scientific research is documented on record with the pros and cons of the therapy. We need to keep our fingers crossed that soon, the scientists can come up with some authentic therapy to be followed universally as the therapeutic option.

Conclusion

This deadly pandemic sweeping across the World is continuing to take a heavy toll in terms of human lives and is threatening the global economy. It is currently raging unabated across several continents, and the peak is yet to come. The whole world is looking at India on the progression of COVID-19, as well as the political commitment and initiatives of the concerned authorities in handling the present pandemic. We have been lucky enough till now in curtailing the menace of this deadly disease. The chief executive director of the health emergency program of World Health Organisation, Michael Ryan, remarked that India, the second-most populous country, has a tremendous capacity to deal with the

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coronavirus outbreak and so will have an enormous impact on the World's ability to deal with it.[54]

For health authorities to plan and implement a more effective quarantine system for people suspected of carrying the virus, understanding the incubation period, as well as local governing factors, is crucial since an effective system will assist in controlling and, hopefully, preventing the transmission of the virus. On evaluating data from certain countries, BCG vaccination appears to significantly reduce mortality associated with COVID-19. This correlation might suggest long-lasting protection against the virus based on the two proposed mechanisms of immune responses, namely, the heterologous and the trained immunity phenomena of BCG vaccination. Further researches, including randomized clinical trials, are required to determine the correlation.

We recommend a further elaborative study on the role of body's immune response to the viral infection which would help understand why some people have higher chances of mortality from COVID-19 and to build additional knowledge to assist in the rapid response to present and subsequent episodes of COVID-19 and future emerging and re-emerging viruses.

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