CORONA VIRUS DISEASE – COVID 2019

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Introduction

Globally we are witnessing the COVID - 19 pandemic. WHO has declared pandemic due to Novel COVID - 19. Epidemics and pandemics of respiratory infection are a major medical concern frequently hatching considerable morbidity and mortality, typically over a relatively short time span.[1] Historically, Coronaviruses have caused two major pandemics in the past two decades - Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[2]

Origin of the pandemic

In the past 50 years, several veterinary and human coronaviruses (CoVs) that cause a wide array of diseases, have emerged periodically. CoVs are known to cause mild respiratory illness in humans until the SARS-CoV-1 outbreak in 2002-03. MERS-CoV emerged in 2012. The causative agent of the COVID-19 pandemics also a zoonotic virus similar to SARS and MERS CoV and is also known as SARS-CoV-2.The epicenter of this ongoing outbreak was in the city of Wuhan of Hubei Province of Central China and the Huanan seafood wholesale market was thought to be at least one of the places where SARS-CoV-2, from an unknown animal source, might have crossed the species barrier to infect humans (Spill-over).[4] Based on genome sequencing and analysis, the virus is suspected to have originated in bats and pangolins transmitted to humans via an unknown intermediate.[5]

Etiological agent- Brief microbiology

CoVs are enveloped viruses with a positive-sense single-stranded RNA genome. The replicase gene occupies two-thirds of the ~30 kb long genome and encodes the nonstructural proteins. The remaining third encodes the structural proteins namely the Spike (S), Membrane (M), Nucleocapsid (N) and Envelope (E) proteins.[6] The S protein is involved in the attachment and entry of the virus. Within the coronavirus genera namely Alphacoronavirus and Beta coronavirus, which mainly infect mammals, 7 out of 15 currently assigned viral species are exclusive to bats. It is proposed that bats play an important role as the gene source in the evolution of these two coronavirus genera. Among the coronaviruses harbored by bats, some have drawn particular research interests, as they have been found to be associated with two high profile human disease outbreaks, SARS and MERS.[7] The virus responsible for COVID-19 (SARS-CoV-2), is slightly larger than Influenza, SARS and MERS viruses. It is almost certainly a descendant from a bat corona virus of which there are many. The closest is a virus that originated from the Rhinolophus bat is > 96% homologous with the current SARS-CoV-2 virus and is only 79% homologous with original SARS CoV which caused SARS outbreak.[2]

World health organization (WHO)[8] and Centre for Diseases Control (CDC)[9] have given guidance about different terminologies describing the extent of the spread of disease. Sporadic refers to a disease that occurs infrequently and irregularly. Endemic refers to the constant presence and/or usual prevalence of a disease or infectious agent in a population within a geographic area, beyond sporadic numbers. Hyperendemic refers to persistent, high levels of disease occurrence. Occasionally, the amount of disease in a community rises above the expected level. Epidemic refers to an increase, often sudden, in the number of cases of a disease above what is normally expected in that population in that area. Outbreak carries the same definition of epidemic but is often used for a more limited geographic area. Cluster refers to an aggregation of cases grouped in place and time that are suspected to be greater than the number expected, even though the expected number may not be known. Pandemic refers to an epidemic that has spread over several countries or continents, usually affecting a large number of people.[8,9]

Clinical presentation and course of disease

The accepted clinical symptoms of COVID-19 are fever, dry cough, fatigue, nasal congestion, sore throat and diarrhea. A small number of patients can have headache, dyspnea or hemoptysis or may even remain relatively asymptomatic. Affected older patients with comorbidities are more likely to suffer from Acute Lung Injury (ALI) and respiratory failure due to severe alveolar damage or also known as Severe Acute Respiratory Injury (SARI). Disease onset may show rapid worsening to multi-system organ dysfunction (e.g., shock, acute respiratory distress syndrome [ARDS], acute cardiac injury, and acute kidney injury) and even death in severe cases. Patients may have normal or lower white blood cell counts (< 4000/cc), lymphopenia (<15%), or thrombocytopenia (<1.5 x 10^3), Serum Ferritin (150-300 ng/ml with extended activated thromboplastin time and increased C-reactive protein level.[10]

On February 14th, Chinese CDC published the first details of 44,672 confirmed cases, in the biggest study since the outbreak began. The findings reveal COVID-19 manifestations were mild in around 81% of patients and had an overall case fatality rate (CFR) of 2.3%. Out of all the confirmed cases, 2.2% were under the age of 20 years. As compared to adults, children generally presented with milder clinical symptoms. It is likely that future serological studies may show much asymptomatic disease in children. As compared to H1N1, pregnant women do not appear to be at higher risk of severe disease. The severity of the disease appears to be associated with age, with the elderly at the higher risk; especially those above the age of 80 years had a CFR of 14.8%. The CFR augmented in patients with comorbidities like cardiovascular diseases, diabetes mellitus, chronic respiratory diseases, hypertension, cancers etc. The commonest cause of death is was respiratory failure, shock or/& multiple organ failure.[11]

COVID 19 in India

The COVID-19 pandemic quickly spread affecting most countries in the world. India reported the first confirmed case of the coronavirus infection on 30 January 2020 in the state of Kerala. The affected had a travel history from Wuhan, China. Soon it spread to other states like Maharashtra with Pune reporting first case. The patient was admitted on March 22nd and was later tested positive. The recent data suggest that India has now more than 40,000 active cases with more than 2500 COVID 19 related deaths.[12]

However, there are some striking differences in how COVID-19 has been behaving in different geographies. For instance, in Italy in spite of strong social curtails COVID-19 mortality is much higher, in contrast to few of the Asian countries like Japan or South Korea who recorded some of the earlier cases, but they reported much lower mortality in comparison to few of European countries despite of adopting much fewer social isolation measures.[13]

Despite of having huge population burden and geographical proximity to the center of origin of the COVID pandemic, India has so far witnessed fewer cases and deaths. Possible scientific explanation for this is not available yet but some postulations favor reasons as underdiagnosis or under screening, higher atmospheric temperature, possibility of less virulent strain of SARS-CoV2 or COVID 19. However, there are no robust clinical evidence to substantiate these yet.

One more unsubstantiated hypothesis could be protective effect of universal immunization of Indian population by BCG vaccination. Several vaccines including the BCG vaccination have been shown to produce positive "heterologous" or non-specific immune effects leading to improved response against other non-mycobacterial pathogens. A preclinical study has shown that BCG vaccinated mice infected with the vaccinia virus were protected by increased IFN-Y production from CD4+ cells. This phenomenon was named as 'trained immunity' and is proposed to be caused by metabolic and epigenetic changes leading to promotion of genetic regions encoding for pro-inflammatory cytokines. BCG vaccination has been also shown to significantly increase the secretion of pro-inflammatory cytokines like IL-1B, which plays a vital role in antiviral immunity.[13]

There could be many other causes for possible lower severity and cases of COVID19 in India compared to western countries. Certain habits and cultural practices which are prevalent in Indian population may actually prove to be beneficial in reducing the spread of this pandemic in the country. Indians have been practicing yoga, vegetarian diet and using Namaste for greeting each other instead of handshakes since ages which are some healthy habits providing protection against COVID19 spread. Indian habit of hand washing before & after food over fork & spoon culture – hand washing after use of toilet over tissue paper use may be advantageous. Indian diet is rich in spicy food ingredients like ginger, chilies, turmeric, fenugreek etc. which may probably have antioxidant and antiviral properties. Indian population is exposed to many viral infections like measles, influenza, mumps etc. which may play a role in development of antibodies and cross-immunity against other viral infections as well. Overcrowding, lack of cleanliness, poor hygiene, exposure to dirt and dust may lead to bacterial overgrowth leading to less decreased viral growth and subsequent infections. Certain religious practices like taking dip in holy rivers which may be a source of many infections and crowding at religious festivals may help in building immunity and cross-immunity against common viral and bacterial pathogens. Relatively lesser incidence of addiction to smoking, alcoholism compared to western countries can also be a factor favoring better relative immunity in Indians. Other factors which may play important role in lower cases could be low socioeconomic class of majority of population and daily physical labor for earning a living could actually help in enhancing immunity. Relatively younger aged Indian population in comparison to rest of the globe could also be a contributory factor for lower disease burden. Lastly, the diverse tropical and subtropical ecological and environment conditions in Indian subcontinent makes it difficult for temperature and humidity sensitive respiratory viruses to cause mass morbidity in a genetically heterogeneous population.

How do we control this Pandemic?

Many countries are using a combination of containment and mitigation activities to respond to COVID-19, with the intention of delaying major surges of patients levelling the demand for hospital beds. At the same time, trying to protect the most vulnerable population from infection. The measures to accomplish these goals may vary and are based on national risk assessments that many times include estimated numbers of patients requiring hospitalization, availability of hospital beds and critical care support. The response strategies of most countries include varying levels of contact tracing and self-isolation or quarantine. One important part of the strategy also includes promotion of public health measures, including hand-hygiene and sanitization, respiratory etiquettes, and social distancing. Strengthening of health systems for a surge of severely ill patients; strengthening health facilities for infection prevention and control, with special attention to nursing home facilities; and postponement or cancellation of large-scale public gatherings.[14]

Social distancing and science behind it:

In the absence of scientifically proved medical therapies and vaccine, social distancing has emerged as one of the most widely adopted strategy for COVID 19 mitigation and control. The suppression of social contact at workplaces, schools and other public gatherings is the target of such measures. Since social contacts have a strong assortative structure in age, the efficacy of these measures is dependent on both the age structure of the population and the frequency of contacts between age groups across the population.[15]

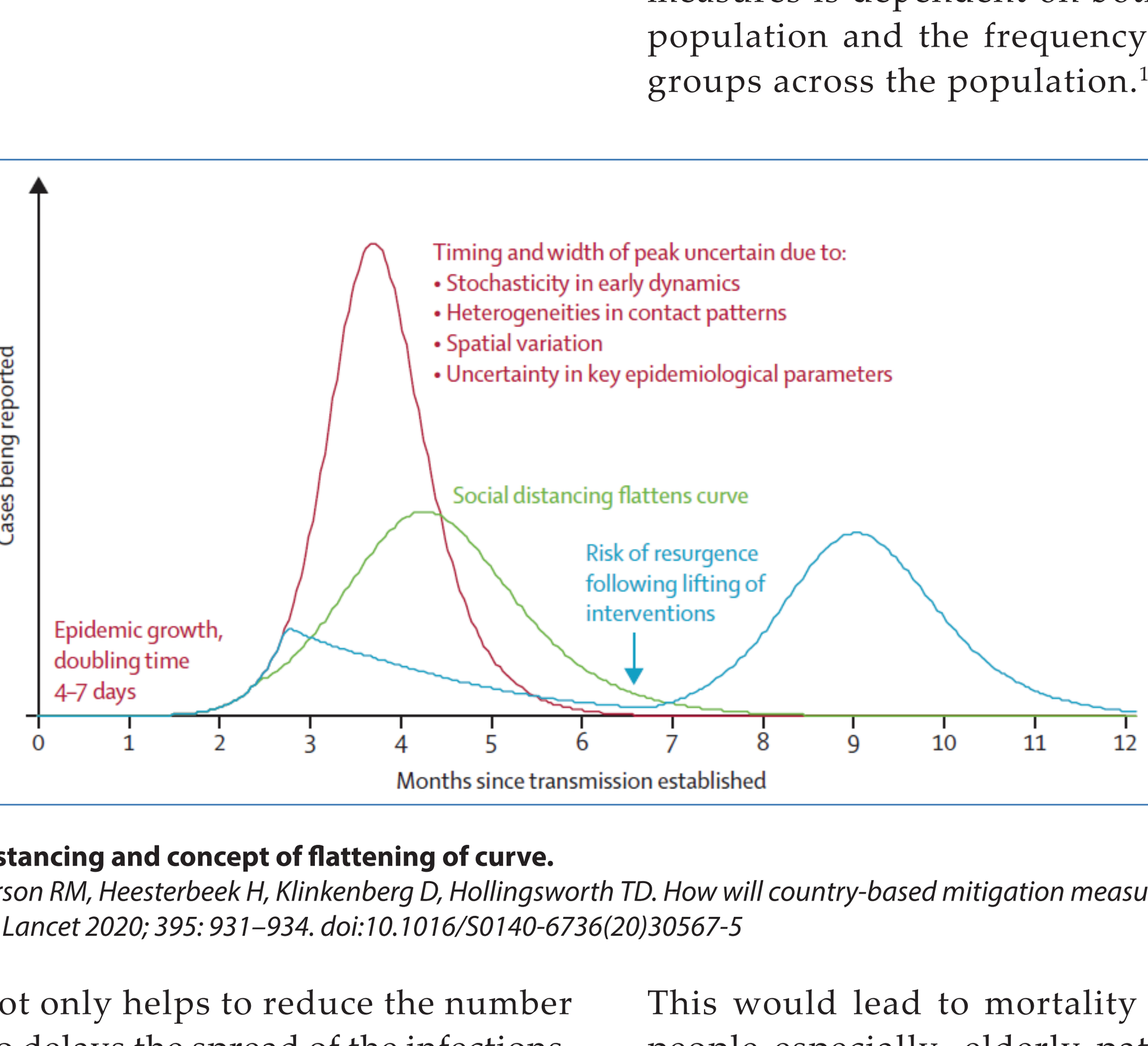

Fig. 2: Impact of social distancing and concept of flattening of curve.
Adapted from: Anderson RM, Heesterbeek H, Klinkenberg D, Hollingsworth TD. How will country-based mitigation measures influence the course of the COVID-19 epidemic? Lancet 2020; 395: 931–934. doi:10.1016/S0140-6736(20)30567-5

Social distancing not only helps to reduce the number of active cases but also delays the spread of the infections. It follows a simple mathematical principle which can be explained by the example. A single case of COVID 19 may infect around 2.5 other person in just 5 days and around 406 people in a month. By exercising social distancing, we can reduce the percentage exposure by 50% which will reduce the number of people infected by a single case to 1.25 in 5 days and to 15 cases in a month. This can further be reduced by decreasing percentage exposure by 75% thereby reducing the number of people infected in a month will be approximately 2.5 in a month as number of people infected by single person will be as low as 0.625. Thus, social distancing reduces the number of infected patients drastically and allows the much-needed respite and time to strengthen burdened healthcare system.

Is heard immunity a possible solution?

There have been serious debates about how to react to the spread of this disease, particularly in European countries, such as Italy, Spain, Germany, France and the UK. From closing schools and universities to locking down entire cities and countries. An alternative strategy would be to allow the causal virus (SARS-CoV-2) to spread to increase the population herd immunity, but at the same time protecting the elderly and those with multiple comorbidities, who are the most vulnerable to this virus. Before contemplating and initiating either of these strategies, we need to estimate the *basic* reproductive number (R_0), or the more 'real-life' *effective* reproductive number (R_t) for a given population. R_0 is the number of secondary cases generated by the presence of one infected individual in an otherwise fully susceptible, well-mixed population. R_t is a more practical real-life version of this, which uses real-life data (from diagnostic testing and/or clinical surveillance) to estimate the reproductive number for an ongoing epidemic or pandemic. Using these parameters, we can then calculate the minimum ('critical') level of population immunity also called as $P_{crit.}$[16]

The infectivity in COVID19 is one of the highest amongst those infections known to mankind ever, therefore it is likely to have a very high R_0. Higher the R_0, higher is the HIT (Herd immunity threshold). In polio & smallpox with R_0 between 5 &7, 80 to 85% of population must get naturally infected or vaccinated to generate herd immunity in community. Despite having effective vaccines for these diseases & it took many (approximately 100) years to eradicate them by herd immunity. However, considering the lower mortality rate in these diseases it was still a potential option. Ebola and Influenza viral infections had R_0 between 1 & 2 with HIT between 30 & 50%. It means, if 30 to 50% of population gets infected, herd immunity will develop in the community. They have fairly high case fatality rate too. But with so high infectivity, 10 times higher mortality than flu, with no drug or vaccine at least for next 18 months, COVID 19 is likely to have high HIT, may be ranging from 85-100%, implying that large population must get infected, before herd immunity develops.

The concept of enhancing herd immunity to control the COVID-19 epidemic, given that the case fatality rate (CFR) of COVID-19 can be anything between 0.25–5.0% of a country's population, the estimated number of people who could potentially die from COVID-19 would be huge, whilst the population reaches the P_{crit} herd immunity level, which could very well be unacceptable.[17]

This would lead to mortality of significant number of people especially, elderly patients with comorbidities like diabetes, hypertension, cardiovascular diseases or immunocompromised states. It would be barbaric to let people die in an attempt to develop herd immunity.

Breaking the chain by prolonged lockdown, targeting, tracing, testing, isolating and treating positive cases, following all hand hygiene steps, wearing mask by all could be a better alternative strategy. COVID 19 virus is a large sized virus that may not enter through double layered cloth mask (majority of people don't need N95 masks for community, except frontline healthcare workers). Physical distancing with social closeness through phone/ social media, classes, cough/ sneeze/ no spitting etiquette can save many lives. Lifting lockdown prematurely would be a shortsighted approach considering some countries like Singapore has witnessed resurgence of infection after 2 weeks of lifting a short lockdown while others like Vietnam controlled the spread of infection well by strict lockdown measures. Economy may get ravaged due to lockdown temporarily but not irreversibly. On the other hand, strict lockdown along with testing and isolation may save many lives. One feels that it is always wise to choose lives over economic stability as a short-term control strategy.

Overall, in countries like India where mortality due to diseases like Tuberculosis, Diabetes, cardiovascular diseases is high, this viral pandemic may not prove to be as devastating or fatal for relatively large population. The incidence of other communicable and infectious disease conditions in India may actually be a bigger problem than current pandemic. So, we should not fear for the same. However, this may have significant impact on already overburdened healthcare system of the country; hence situation demands a degree of preparedness and caution to tackle it smoothly. The key epidemiological issues that determine the impact of social distancing measures are what proportion of infected individuals have mild symptoms and whether these individuals will self-isolate effectively. It will also depend upon time taken by symptomatic individuals to isolate themselves after the onset of symptoms; and the duration of any non-symptomatic infectious period before clear symptoms occur. Individual behavior will be crucial to control the spread of COVID-19. Personal, rather than government action, in countries like India, might be the most crucially important issue. Early self-isolation, seeking timely medical advice and social distancing are key to combat this pandemic.

There are many mysteries that are still surrounding this pandemic. We are not yet sure about the intermediate host which was responsible for transmission of SARS-CoV 2 from bat to human. There are hypotheses about possible role of mutations in virus leading to human transmission. The data is also limited regarding role of vectors in the transmission, feco-oral route of transmission and role of other domestic animals. Many researchers are also working hard for development of vaccine as well as exploring the efficacy of antibody treatment or plasma therapy. The answer to a million-dollar question of when we will be successful in developing the vaccine against this SARS-CoV 2 is most awaited. With every passing day we are getting richer in terms of knowledge and experience about this novel coronavirus and the day is not far when we will be able to tackle this pandemic effectively with minimum damage.

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