Impact of COVID-19 Variants on the Second Wave in India and Subsequent Discretion of Possibilities of the Third Wave

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Review Article

ABSTRACT

Introduction: Epidemiological comprehension of the COVID-19 situation in India can be of great help in early prediction of any such indications in other countries and possibilities of the third wave in India as well. It is essential to understand the impact of variant strains in the perspective of the rise in daily cases during the second wave – Whether the rise in cases witnessed is due to the reinfections or the surge is dominated by emergence of mutants/variants and reasons for the same. Overall objective of this study is to predict early epidemiological indicators which can potentially lead to COVID-19 third wave in India.
Methodology: We analyzed both the first and second waves of COVID-19 in India and using the data of India's SARS-CoV-2 genomic sequencing, we segregated the impact of the Older Variant (OV) and the other major variants (VOI / VOC). Applying Kermack–McKendrick SIR model to the

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segregated data progression of the epidemic in India was plotted in the form of proportion of people infected. An equation to explain herd immunity thresholds was generated and further analyzed to predict the possibilities of the third wave.

Results: Considerable difference in ate of progression of the first and second wave was seen. The study also ascertains that the rate of infection spread is higher in Delta variant and is expected to have a higher threshold (>2 times) for herd immunity as compared to the OV.

Conclusion: Likelihood of the occurrence of the third wave seems unlikely based on the current analysis of the situation, however the possibilities cannot be ruled out. Understanding the epidemiological details of the first and second wave helped in understanding the focal points responsible for the surge in cases during the second wave and has given further insight into the future.

1. INTRODUCTION

Ever since India witnessed the second wave of COVID-19, various versions of descriptions have been put together to understand the reasons behind the sudden surge in the cases during the second quarter of the year 2021. Several arguments and counterarguments have been expressed regarding the Public health response in India [1,2]. However, an epidemiological comprehension of the situation can yield an overriding understanding of the complex causes leading to sudden surge of COVID-19 cases. Epidemiological analysis of the situation can be of great importance in early prediction of any such indications in other countries and possibilities of the third wave in India as well. As on June 20, 2021 there are four Variants of Concern (VOC) and seven Variants of Interest (VOI) in the world according to WHO's weekly Epidemiological update on COVID-19 [3]. Few of these variants have been found extensively in India as well. It is essential to understand the impact of these variants in the perspective of the rise in daily cases during the second wave. It is also important to understand the component of the ancestral variant (Old variant) of SARS-COV-2 during the second wave and how the old variant is behaving – Is it due to the reinfections of the older variant re-emerging after a dormant period of decline or is the older variant continuing along with its course as expected and the major impact is due the emergence of mutants/variants. Early prediction of epidemiological parameters of emerging variants can be very helpful in preventing recurrence of such waves and hence a thorough review of the epidemiological pattern of the second wave was carried out and is presented in this paper. While talking about VOC, there are majorly three epidemiological parameters / indicators that should drive us onto

enhancing our focus on a particular form of mutant namely – Increase in transmissibility / infectivity, Increase in severity / virulence and encountering resistance to countermeasures such as vaccines, natural immunity or drugs [4].

Secondly, a comparative analysis between first and second wave is important to know the differences and denounce second wave properties. With a historical understanding of the first wave which was dominated by the older variant, the impact of new variants can be predicted. Serological studies during the first wave have shown that the actual number of infections are largely underestimated [5]. Many victims of Covid-19 remain asymptomatic or pre-symptomatic, displaying mild symptoms, through the course of their infection. Generally, mildly affected, or asymptomatic individuals are not screened. As a result, the number of confirmed SARS–CoV-2 cases reported give low estimates of the actual infections. Serological studies give an indication of the actual estimates of people having antibodies against the virus. Since the old variant is circulating in the community for over one year, the impact is presumed to be lower in the second wave as good proportion of population is immune to the older variant. However, the duration of persistence of antibodies after infection is not yet clear, and hence it is essential to analyse the second wave by segregating the effect of different variants to have a clearer picture and see if the second wave has a good component of the older variant. Should the rise in cases be attributed to the reinfections due to older variant in the form of a cyclical trend? Well, the sudden increase in frequency and volume of cases indicate that the second wave is mostly composed of newer variants. Hence, with an aim to assess the components (impact of various newer variants) of

the second wave of COVID-19 from inputs of the first wave and to secondarily predict the future trajectory of the second wave, the current review was planned. Overall objective of this study is to predict early epidemiological indicators which can potentially lead to surge in COVID-19 cases in the future.

2. METHODOLOGY

This study is a review article written by analysing the Epidemic curve of COVID-19 in India since the announcement of COVID-19 Pandemic on March 11, 2020 to early June 2021 [6]. We analysed both the first and second waves of COVID-19 in India and the impact of new variants in rise of incident cases during the second wave. Using the data of India's SARS-CoV-2 genomic sequencing from "GISAID" and epidemiological data from "Our World in Data", we segregated the impact of the Older Variant (OV) and the other major variants (VOI / VOC) namely B.1.617.2 - Delta, B.1.1.7- Alpha & B.1.617.1 - Kappa (which reported ≥5% of the total genomic sequencing for at least once throughout the course). [4,7,8] Post-segregation, we created a separate Epidemiological curve for the OV and was interpreted. Based on various serological studies across India during the year 2020, an Case Infection Ratio (CIR) of 50 was assumed for the OV during analysis [5,9]. Applying Kermack–McKendrick SIR (Susceptible – Infectious – Recovered) model to the segregated data of actual number of infections, we created a predictive model [10]. We plotted the progression of the epidemic in India in the form of proportion of people infected and an equation was generated against the best fit to the actual curve, following which projections were made along with predictions for herd immunity. Similar analysis was made against the Delta variant infections in India and Rate of progression of the epidemic between Old variant & Delta variant has been compared. Ethical committee permission was not taken for the study because the review used the data only available from public domain. The study did not include any animal or human experiments and no clinical or public health interventions have been carried out during the course of this review.

3. RESULTS

Daily reported COVID-19 cases in India from the start of this pandemic till early June 2021 was utilized to prepare an epi-curve (Fig. 1). The epi-curve has been segregated to show proportionate daily cases estimated, based on the proportion of various variants reported through genomic sequencing. First cases of Alpha variant, Delta variant and Kappa variant were reported on September 2 2020, September 7 2020 and December 1 2020 respectively in India. The epi-curve consists of two waves, *the first wave,* composed almost exclusively of the OV which attained its peak on September 17 2020 with 93,277 cases and *the second wave,* majorly dominated by the Delta variant which attained its peak on May 8 2021 with 3,92,331 cases. Number of cases reported during the peak of second wave was found to be 4.2 times the first. It was noticed that between February 20 2021 and May 20 2021, 6.6% belonged to the Alpha variant, 70% belonged to Delta variant, 10.7% belonged to the Kappa variant and 12.7% belonged to the OV (including other minor variants – Eg: Beta and Eta have an average prevalence of 2% each during the second wave). Analysis of the epi-curve indicates that the second wave contains less than 10% cases due to the OV.

Fig. 1 shows that the rise in cases during the second wave was mainly due to the new variants and not the older one. The OV remained more or less similar to the pre-second-wave pattern. Average daily cases of OV during the months April to June is same (around 18-20 thousand cases) as the daily incident cases in three prior months. This shows that the first wave is continuing its trend towards attainment of herd immunity and has hardly any impact on the second wave. So, in order to know the epidemiological dynamics of OV by unmasking the new variants from epi-curve, Kermack–McKendrick SIR model was used. Review of serological studies conducted in the year 2020, estimated according to the population of India projected for the year 2020 suggest that the CIR could be around 1:50 [5,9]. Assuming average Case Infection Ratio (CIR) during the first wave in India to be 1:50, the number of infections were projected accordingly as per the total number of cases reported (Fig. 2). Kermack–McKendrick SIR model, in a basic notion uses the following principle. At any point in time, Total population = Total people Susceptible for the disease (S) + Total people Infected (I) + Total people who have been Recovered & deceased (R).

Based on this, the "percentage of population susceptible" and "percentage of people recovered & Dead" have been plotted in the graph in the form of horizontal lines and the

"number (not the % age, for scaling) of infected people" have been plotted as epi-curve. The curve seems to follow the "Normal Gaussian distribution". It was noticed that 82.23% of the population was still susceptible when the wave reached its peak. The slight rise in numbers of OV infections reflected in the graph during the second wave of pandemic is seen because a uniform CIR was used to calculate infections throughout the course. Factors leading to the mild surge in the daily incidence of cases seen during the second wave could be explained by the following facts:

- The number also *includes other variants* such as Beta and Eta into its count since only three major variants have been separated.
- Serological studies have shown that the actual prevalence of Anti-SARS-CoV2 antibodies prevalence is much higher than the actual cases reported and detecting these cases can cause decrease in CIR and higher reporting of infections. As the other variants, especially Delta showed steep rise during the second wave, test positivity rate increased and increases detection of OV cases too happened as a secondary phenomenon due *to increase in number of tests*. However, it should be known that the CIR for the OV had considerably reduced during the second wave.

- Steep rise in number of cases also encourages prompt *contact tracing activity*, leading to increased detection of asymptomatic cases.
- The claim is also supported by the fact that the number of number of cases of the *old variant also showed decline as the total number of cases per day* (mainly composed by the Delta variant*) started declining* during the second wave.

Considering all these factors, the first wave is continuing itself towards the course of attaining herd immunity. In order to understand the phenomenon better, a curve representing cumulative infections was plotted against time.

Cumulative percentage of people infected includes the current active infections, recovered infections and deceased. Since very few cases of reinfections from the OV has been reported, it can be assumed that there is a good rate of seroconversion among individuals recovered from the OV infections. Hence, it is an educated guess that, the "cumulative %age of people infected" at any point in time = (100 - %age of susceptible people). With this background, the cumulative infected percent of population curve (Fig3) was constructed by using the susceptible %age data from the above Kermack–McKendrick SIR model. Since the Cumulative Infections graph does not follow a linear pattern, a non-linear smoother curve was used as Y-Fit to predict the future course [11].
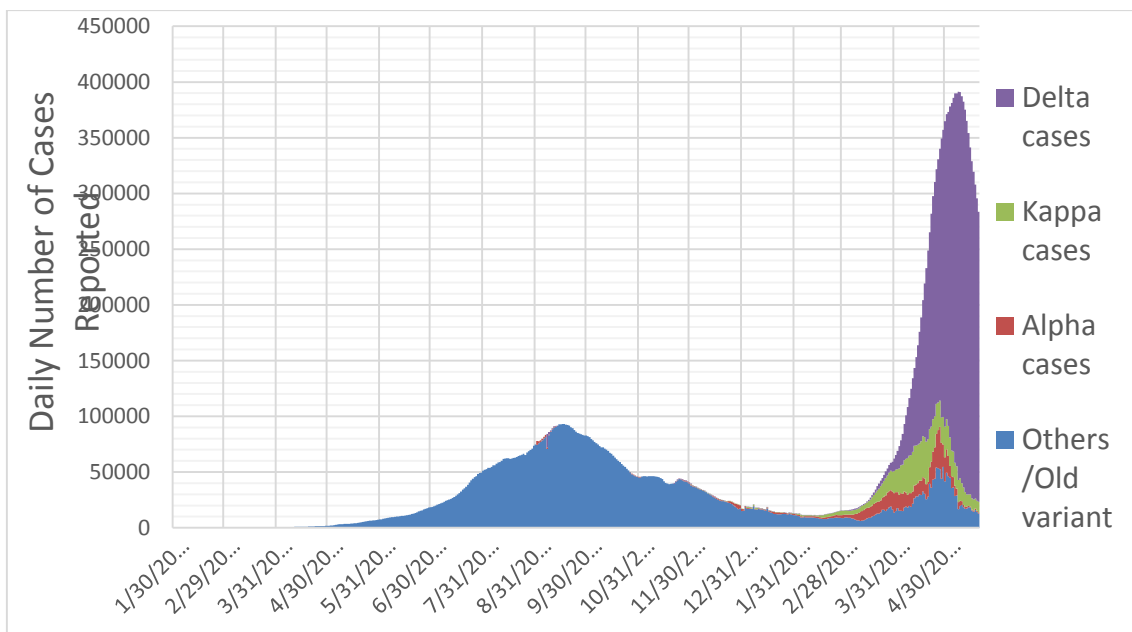

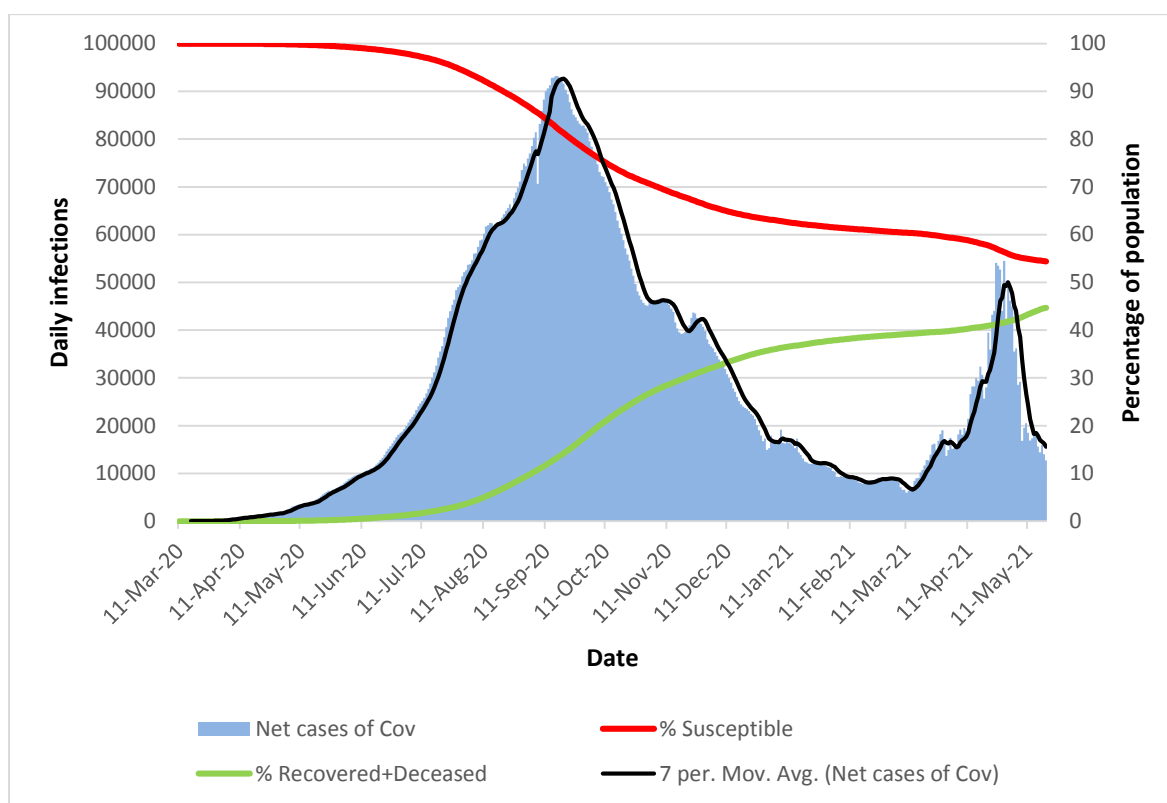**Fig. 1. Progression of COVID-19 (Initial Virus and Major variants) in India**

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Fig. 2. Net Infections of the Old variant (CIR 1:50) and Kermack–McKendrick SIR model

Fitting the line: Consider a scenario when 0% of the population is infected, then 100% of the population is susceptible, the virus has higher chances of infecting a new person. However, as the number of previously infected persons increase (the proportion of people having antibodies against the virus increase), the chances for the virus to infect a susceptible host decreases (decrease in degrees of freedom). Standard exponential equation representing such type of scenario is Y=1-exp(-x) where "Y" is the proportion of population infected and "x" is the time [12]. However, several other factors play a role in defining susceptibility of host from time to time including public health measures taken and susceptibility risk based on geographic location (E.g. The virus spread was rapid in Metro cities but took longer to reach semi-urban and rural areas/periphery). Hence, a non-linear curve with time X is expected to follow the path as shown in the graph (Figure 3, Yellow line). The best smoothened curve (Y-fit) for the non-linear curve follows the equation Y=f(x)= (1- exp(-kxn)) [11,13].

In the above equation, "k" and "n" are the constants (linear and exponential, respectively) influencing the values of Y = f(x) for different

trajectories and the value of Y ranges between 1 & 0. Since we are looking for percentages, a modification of the above equation by multiplying with a constant "A" is done to arrive at a best fit for the observed curve, in the following form

$$Y=f(x)= A*(1- exp(-kx^n)) \text{ [11,13]}$$

Where,

The value of "A" ranges between 0 and 100,

By using the Sum of Squares of Residuals (SSR), for the observed curve, the best fit of Y=f(x) was obtained (Fig. 3, Blue line). Least SSR for Y-fit was seen at A = 44.37497, k = 1.15098E-06 & n = 2.469263. Since, A = 44.37497, that is the maximum attainable value for Y=f(x). Hence, our model predicts that the herd immunity threshold for the first wave to be 44.4%. Table 1 gives projected values of some important nodal points in the curve based on this model.

From the experience of the first wave, a relative prediction of CIR for the Delta wave was done. It is noticed that 82.23% of the population was still susceptible / 17.77% (100-82.23) of the

population were infected when the first wave reached its peak. Assuming the same proportion of population to be infected while Delta variant reached its peak, CIR of 1:38.4 was estimated using the cumulative number of Delta cases reported during its peak. Based on the CIR of

1:38.4, an epi-curve was plotted separately for the Delta variant and Kermack–McKendrick SIR model was applied to understand the trajectory of the proportion of population infected due to the Delta variant (Fig. 4).
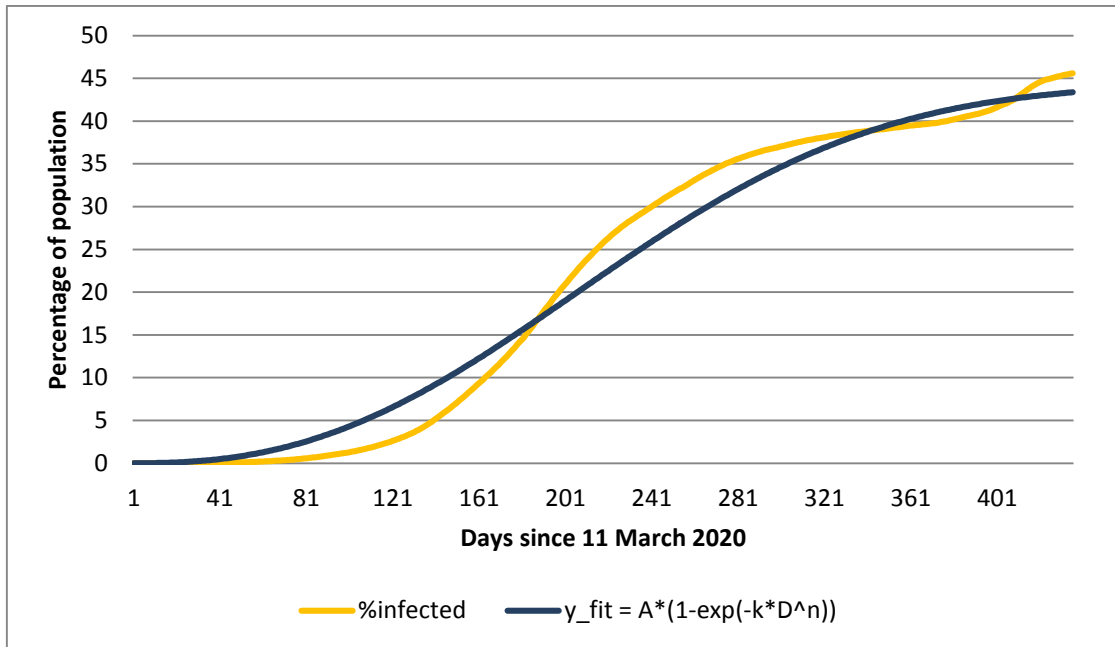

Fig. 3. Cumulative Infections and fit (Old variant) – Since 11 March 2020
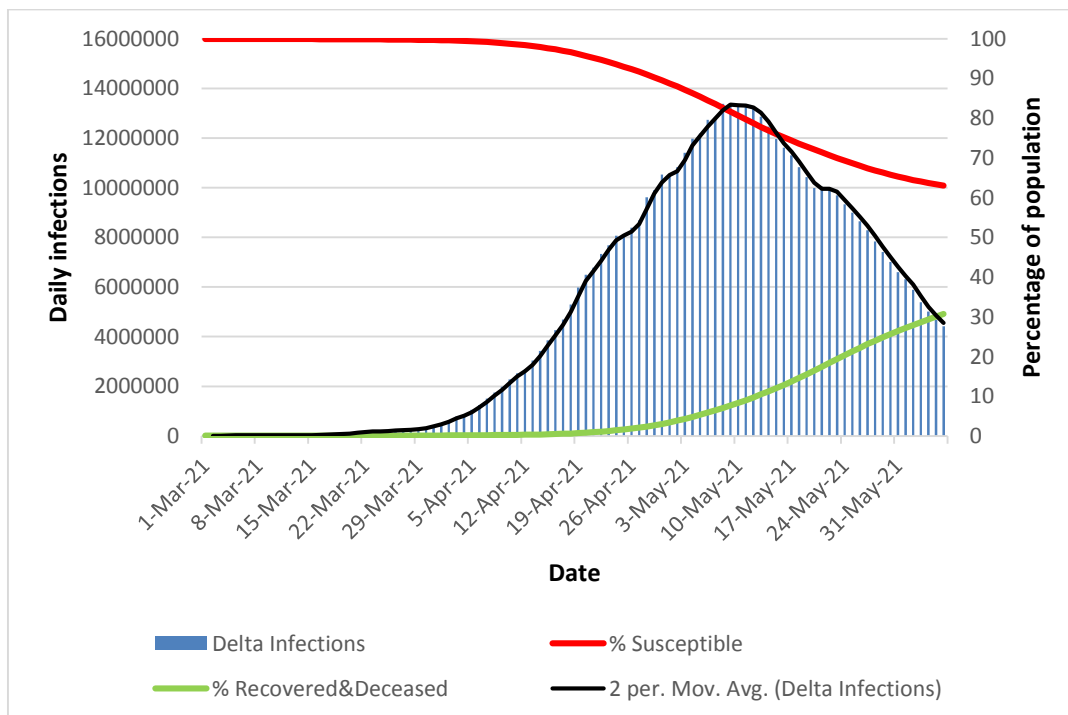*Footnote: A = 44.37497, k = 1.15098E-06 & n = 2.469263*

Fig. 4. Net Infections of the Delta variant (ICR 1:38.4) and Kermack–McKendrick SIR model

Table 1. Projections for the old variant

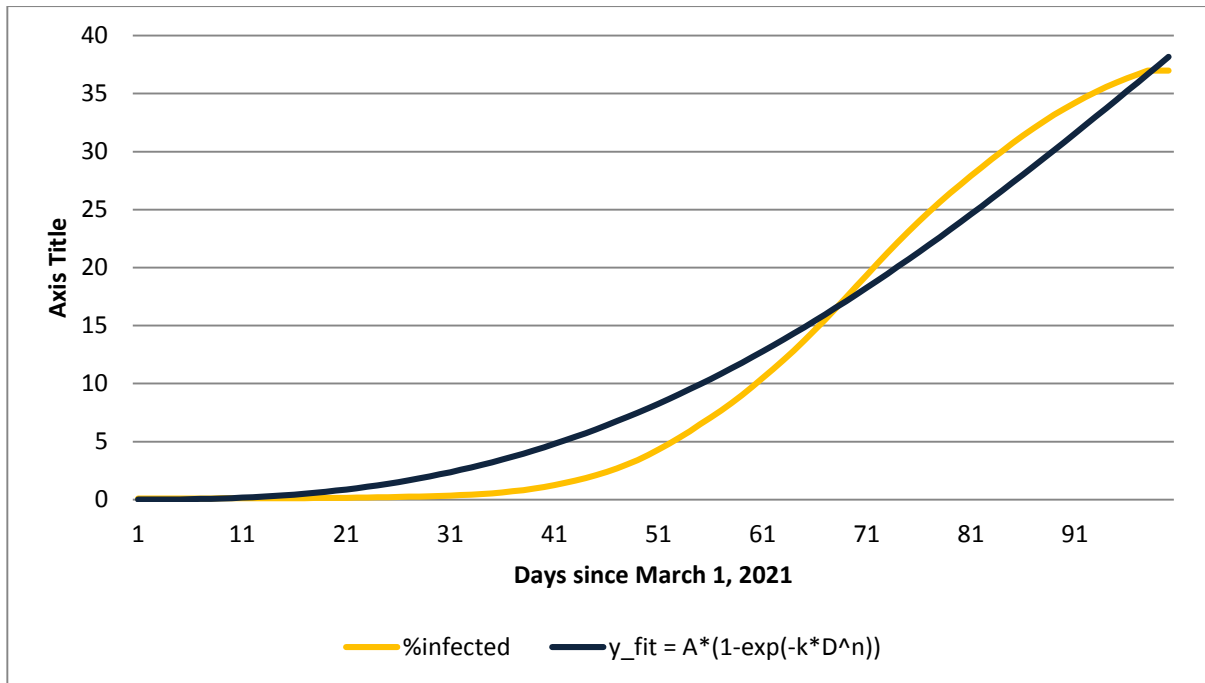| Date	Days since March 11, 2021	Value of % of infected population predicted by Y-fit
3-Mar-21	358	40.06
2-Jul-21	479	44.00
7-Mar-22	727	44.37 (HI threshold)

Fig. 5. Cumulative Infections and fit (Delta Variant) – Since March 1, 2021
Footnote: A=92.13055, k=3.67E-06 & n=2.581834

Studies have shown that neutralization ability of monoclonal antibodies, convalescent and vaccine sera to neutralize Delta and Kappa variants is reduced as compared with ancestral related strains [14]. In fact, B.1.351 (Alpha) and P.1 (Gamma) sera is reported to show markedly more reduction in neutralization of Delta variant suggesting that individuals previously infected by these variants may be more susceptible to reinfection by the Delta variant [14]. Hence, for a conservative estimate, the whole population is considered susceptible for the Delta variant while projections were made in the model during this study. Similar to that of the OV, a curve showing the proportion of population infected with progression (time) of the epidemic is plotted along with a Y-fit curve (Fig. 5).

Least SSR for Y-fit was seen at A = 92.13055, k = 3.67E-06 & n = 2.581834. Since, A = 92.13055, that is the maximum attainable value for Y=f(x). Hence, our model predicts that the herd immunity threshold for the second wave to be 92.13%. Table 2 gives projected values of

some important nodal points in the curve based on this model. The percentage of infected population predicted by the model should be considered as the overall seropositivity, which may not be reflected in the daily number of cases as the days progress. Cross-immunity between the OV and the Delta variant can lead to lesser number of daily infections. Nevertheless, progression of the overall seropositivity is expected to take a similar course as predicted by the model.

Several differences between the OV and the Delta variant have been deduced from the current review showing why the Delta variant is a Variant of Concern. Eg:

- Delta variant showed increased *transmissibility* which can be noticed by the duration required to attain its peak (2-3 months) which is way less comparatively to the OV which attained peak in around 6 months.

- Delta variant showed increased *severity* which can be noticed by the difference in CIR between the two variants. Delta variant showed 30% [ie., $\frac{(50-38.4)}{38.4} * 100$] higher chance of chance for an asymptomatic infection to be converted into a symptomatic case / getting counted as a case of COVID-19.
- Difference in Herd immunity threshold. Delta variant has a possibility to infect as many as 92% of the population before attaining herd immunity and keep propagating since it attains the threshold. This is also an indication for increased *transmissibility.*
- Fact that the Delta variant was able to cause such a sudden rise in cases in a population having >40% seropositivity against the previously infected strain of

the OV definitely indicate certain amount of *resistance to neutralization / immune escape mechanism* against previously generated natural antibodies.

Further, a comparative graph depicting the difference in progression of the epidemic between the two variants is shown in Fig. 6, using the projections of the respective Y-fit trajectories.

4. DISCUSSION

Our review concludes that the second wave of COVID-19 is majorly composed of the Delta variant and the OV has a minimal impact, in fact the analysis shows that the OV is following the usual SIR model of the epidemics so far and is reaching its level of herd immunity.

Table 2. Projections for the delta variant

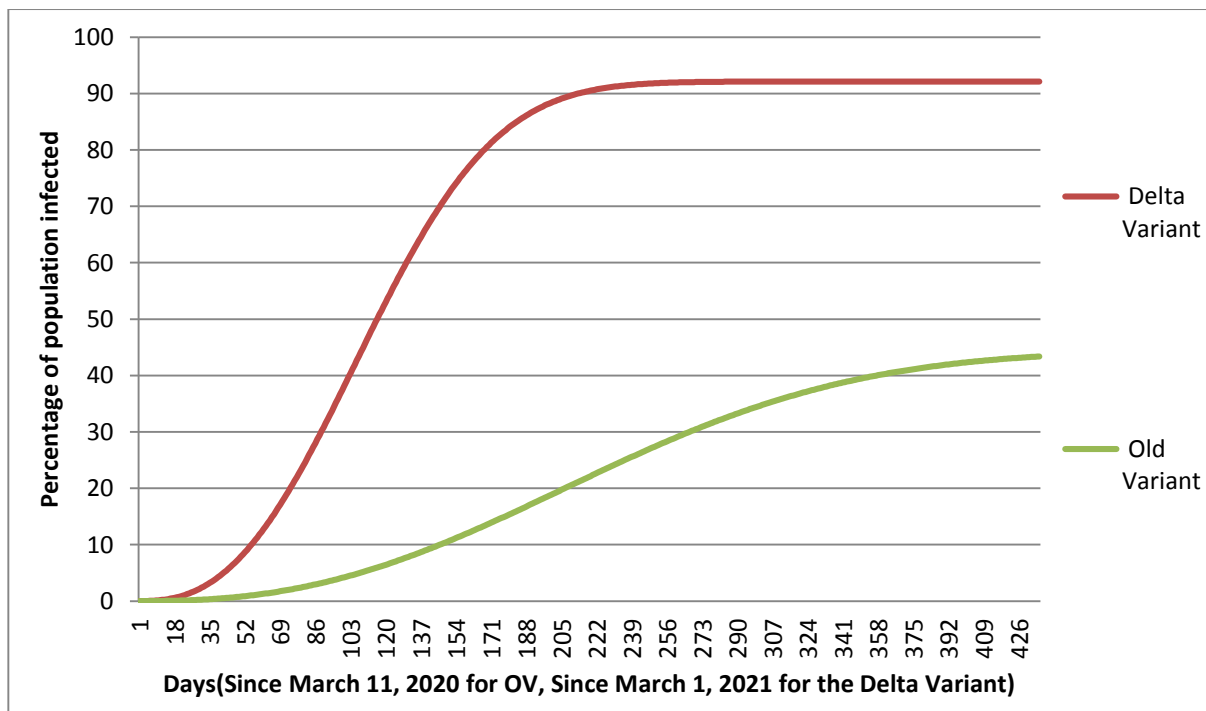| Date	Days since March 1, 2021	Value of % of infected population predicted by Y-fit
8-Jun-21	100	38.17
24-Jun-21	116	50.1
9-Jul-21	131	60.7
25-Jul-21	147	70.44
15-Aug-21	168	80.17
29-Sep-21	213	90.0
3-Apr-22	399	92.13 (HI threshold)

Fig. 6. Rate of Progression of the Old variant vs the Delta variant

The study also ascertains that the rate of infection spread is higher in Delta variant and is expected to have a higher threshold (>2 times) as compared to the OV. The other two major variants seen currently are the Kappa and Alpha. Although different variants were existing during the second wave, it was noticed that the Delta variant occupied a great chunk and the rest did not. In quest of the reason behind this, an explanation is proposed as follows. As discussed earlier, epidemiological indicators that can lead to a new wave by a new variant are primarily of three types - increased *transmissibility*, increased *severity,* and emergence of *resistance to neutralization / immune escape mechanism* against previously generated natural antibodies. In a country with high seroprevalence of the Anti-SARS-CoV2 antibodies, a sudden surge in cases as see during the second wave can be majorly attributed to the immune escape mechanism. Eg: Repeated seroprevalence studies in Delhi have estimated that seropositivity against COVID-19 can range from around 25% to as high as 56%. [15,16]. Yet, the City witnessed more daily incident cases in two months of second wave (April and May) as compared to the cumulative cases since the beginning up to March 31, 2021. Immune escape mechanism / resistance to neutralization of antibodies in the Delta variant is further justified by the summary of phenotypic impacts of Variants of Concern published as COVID-19 Weekly Epidemiological Update by WHO [3]. Reduction in neutralizing activity has been reported in Delta variant and in the Beta variant, moderate reduction in Gamma variant and not reported so far in the Alpha variant or the Kappa variant. Studies have reported 6-fold decrease in neutralization property to sera from convalescent individuals in Delta variant as compared to the Alpha variant [17]. The Delta variant is also known to show different efficacy against different vaccines [17]. It is well-established that E484K mutation of the Receptor Binding Domain (RBD) present in few variants (Beta and Gamma) is responsible for reduced neutralization of Anti-SARS-CoV2 antibodies. However, the Delta variant which do not have this mutation too is showing immune escape and is currently suspected to be due to mutations in N-Terminal Domain (NTD) and also some in RBD [18]. All these factors have led to increased population susceptibility to the Delta variant. Hence, immune escape / reduction in antibody neutralization is the most important factor that determine the occurrence of a more severe new wave. It is recommended that the identification of mutations and establishment of further evidence is very important along with regular genomic sequencing for early diagnosis of any potential public health concern due to COVID-19. It is also important for India to look at more potential mutations which can show immune escape mechanism to the convalescent serum of Delta infected individuals as well.

Analysis of the OV progression in India through the lens of Kermack–McKendrick SIR model indicates that the OV is not the cause of sudden surge in cases during the second wave but is moving towards attaining herd immunity in near future. However, the potential impact of Delta wave is far from over since the herd immunity threshold predicted is as high as 92%. Our model predicts that currently (end of June 2021), around half of the population is still susceptible. It is important to address the satiation more cautiously than it might seem. Increasing the rate of reduction in susceptible population (dS/dT) is key to attain herd immunity earlier than expected as a preventive strategy to reduce the impact in the coming days. This can be attained by the following public health measures – Accelerating the vaccination process, coupled with reemphasizing the importance of basic COVID-19 appropriate preventive measures (Physical distancing, wearing masks, maintenance of respiratory etiquette, hand sanitization, consumption of nutritious food, prevention of non-communicable diseases through lifestyle modification and medication adherence) and counter the risk-communication fatigue in the community by stirring up application of innovative methods in Risk Communication and Community engagement [19]. Recognizing the fact that the vaccines can show different efficacy against different types of convalescent plasma (due to different variants), it is essential to vaccinate all age groups and the entire population as soon as possible. It is advised to release public restrictions in a controlled manner under scientific expert guidance.

What about the third wave? Few possibilities can be enlisted at this point through the inputs from the current review. In predicting the third or future waves of COVID-19, everything revolves around the principle of SIR model, if the susceptible population increase, there is a high possibility of witnessing the next wave. Reasons are described as follows:

- *Encountering a mutant (existing or new) which is resistant to either the OV or the Delta variant or the Vaccine.* Currently it is

known that few variants such as Beta and Gamma are having immune escape properties against the OV and few vaccines. Rising cases of these mutants should be detected early and counter measures must be taken. However, there is also a possibility that Anti-Delta-Variant antibodies can show a cross immunity response against these strains. This aspect needs further research to establish evidences. The situation can be vice versa, the countries having high prevalence of other variants can look for cross resistance for Delta variant [14].

- *Change in virulence or rate of transmission* can increase the number of daily incidence and/or hospitalization and/or mortality rates. Early identification of mutations leading to these changes and sharing with the world can prevent the possibility of a third wave.

- *Waning of antibodies among the general population after a period of time.* Our study has shown that the OV has not shown any major public health impact due to rise in cases post first wave indicating the prospects of reaching the herd immunity threshold. However, one should not rule out the possibility of antibody waning which can lead to increase in susceptible population again and can lead to a new surge in cases. The timing of second wave is such that the cross-protective effect of Anti-Delta variant antibodies against the OV might have masked the possibility of second wave of OV cases secondary to antibody waning. Hence, in absence of the third wave due to a new variant, antibody waning can be a major reason for its occurrence in future. Repeated serological surveys are thus needed to constantly monitor the situation. If possible, technologies can be developed, and surveillance can be conducted in the lines of obtaining serological prevalence for different major prevalent variants. Also, persistence of antibodies post-vaccination needs attention and monitoring.

- *Mass exposure to the virus of the protected cohort (Eg: Children).* Ever since the pandemic has occurred, children have stayed home and thus have lesser probability of getting exposed to the virus as compared to young adults. Sudden reopening of schools can lead to mass exposure to the virus and can cause sudden surge in number of cases.

- *Biological warfare.* Technology is a double-edged sword. Malicious intent associated with organized, concurrent, and coordinated efforts can be a potential threat. Historical experiences suggest that the possibility of use of biological weapons cannot be ignored [20]. Ensuring and strengthening biosafety and biosecurity mechanisms across the country as a part of preparedness and preventive plan against health emergencies, is recommended.

- *Antibody-dependent enhancement.* It is a phenomenon in which binding of a virus to suboptimal antibodies enhances its entry into host cells, followed by its replication. This leads to increased susceptibility of individuals having history of seroconversion to get infected. It has been previously reported in the case of Dengue virus and HIV where non-neutralizing level of antibodies have been found to enhance the viral infection through interactions of the complement system and receptors [21,22]. Mutations in the wild virus with such properties of recognizing the existing Anti- SARS-COV-2 antibodies sub-optimally leading to enhanced entry and higher susceptibility to infection can be a serious cause of concern for epidemiology, vaccine development, and antibody-based drug therapy [23]. No such cases for vaccine sera has been reported so far and the vaccine companies are closely monitoring through post-marketing surveillance, hence vaccines carrying the risk of potential public health concern through ADE is very minimal. Nevertheless, it is noteworthy to not rule out the possibility due to mutations in the wild virus and hence any increase in rate of reinfection due to new mutants should be given paramount importance expecting a possibility of ADE and immediate measures need to be taken. Maintaining transparency and immediate information dissemination process holds the key in alerting the rest of the world in these tough times of COVID-19 pandemic.

5. CONCLUSION

Understanding the epidemiological details of the first and second wave of COVID-19 in India helps us in understanding the prime / core nodal points responsible for the surge in cases during the second wave. It brings clarity into what measures

must be taken in public health point of view under short and long terms. It has aided in establishing a comprehensive discernment on the possibilities of the third wave and deeper insight into respective preventive measures supposed to be taken.

6. LIMITATIONS

- Recognizing the need for reach in the medical community, too complex mathematical explanations are either avoided or simplified as necessary
- CIR value has been assumed as 50 for the first wave (OV) as constant for the simulated period even though it is possible that the value varies as per the daily testing and contact tracing of cases. It has been assumed for whole of India, although geographical variations can be seen.

DISCLAIMER

The views and opinions expressed in this article are those of the author/s and do not necessarily reflect the official policy or position of any agency.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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