Received: 23 June 2021 | Revised: 15 August 2021 | Accepted: 16 August 2021

DOI: 10.1002/ajhb.23671

COMMENTARY

American Journal of Human Biology WILEY

Understanding the devastating second wave of COVID-19 pandemic in India

Sreedhar Chinnaswamy

Infectious Disease Genetics, National Institute of Biomedical Genomics, Kalyani, West Bengal, India

Correspondence
Sreedhar Chinnaswamy, Associate Professor, DBT-Wellcome India Alliance Intermediate Fellow, National Institute of Biomedical Genomics (NIBMG), Kalyani-741251, Nadia, West Bengal, India.
Email: sc2@nibmg.ac.in

Funding information
India Alliance; Wellcome Trust

1 | BACKGROUND

India was one of those few countries where the initial/first wave of the corona virus disease 2019 (COVID-19) pandemic had a mild course of infection, that left experts around the world bewildered by this rather unanticipated outcome (Frayer, 2021; Cohen, 2021; Biswas, 2021a; Ravikumar & Jamkhandikar, 2021; Patel, 2021). While the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected the hosts in developed countries leading to huge mortality, surprisingly, it caused a mild disease in India and resulted in one of the lowest case fatality rates (CFR) in the world (Chinnaswamy, 2020; Patel, 2021), at least until early 2021. I had explained this by arguing that Indians had a trained innate immune system that protected them from a severe form of the infection (Chinnaswamy, 2020). Innate immunity that includes (among other cells and mechanisms) NK (natural killer) cells and the non-canonical B1-B cells, can raise a strong barrier against mucosal viral infections. Macrophages and dendritic cells can contribute directly by eliminating virus-infected cells, but their main job is to act as messengers that shape the adaptive immunity. However, there are two limitations in the protection these cells can offer: (1) they must be constantly 'trained' for optimal functioning, by exposing them to intracellular pathogens since they lack a permanent memory; (2) the protection offered even though is significant, lacks specificity and hence not robust enough when confronted with a large inoculum of a highly infectious virus.

1.1 | A devastating second wave hits India in March 2021

Experts analyzing the pandemic felt that India had already reached the 'shore' with the prospects for a second wave being low (Ravikumar & Jamkhandikar, 2021). While India was basking in this unexpected success, it also began its vaccination drive from mid-January 2021 albeit at a very slow pace even though it was only targeting people above 45 year of age (India used two vaccines at this stage: an inactivated whole virus and an adenovector-based spike protein-generating vaccine). But little did it realize that a tsunami was heading towards it in the form of a ferocious second wave in early-mid 2021. Such was the devastation of the second wave that all the fears that had gripped the country in 2020 (Chinnaswamy, 2020), seemed to have come real in 2021. The poverty in India's public health infrastructure came to the fore like never and was there for everyone to see (Biswas, 2021b). In one way, the stark reality of the second wave reinforced my argument that the first wave was so mild in the country that it could have resembled a 'bump' in the background of other debilitating infectious diseases that are common in India (Chinnaswamy, 2020). So, what changed in India from 2020 to 2021, that such contrasting waves of infection (Figure 1A) were seen? While the mild first wave in India surprised many experts (Frayer, 2021; Ravikumar & Jamkhandikar, 2021; Biswas, 2021a), the devastating second wave has deepened the mystery even further (Chadha, 2021). In this article, I try to understand the second wave, not in

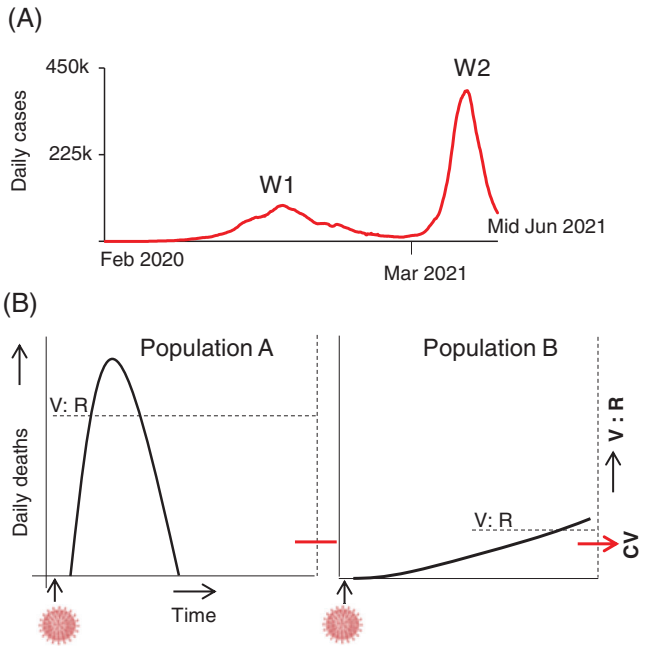

FIGURE 1 India sees contrasting waves of infection within a year. (A) Daily COVID-19 cases recorded in India from the beginning of the pandemic to mid-June 2021. W = wave. The data was obtained from ourworldindata.org. (B) A model for two populations that explain the COVID-19 daily mortality curve. The populations will have a mix of vulnerable (V) and resistant (R) hosts. V:R ratio of a certain critical value (CV, red line on y-axis) decides the shape of the mortality curve: A higher V:R ratio gives a steep curve, and a lower ratio will give a shallow curve. The horizontal dotted line shows the actual V:R ratio for the two populations

isolation but in the context of, and in comparison, to the first wave and then try to draw my opinion about what may have resulted in the second wave.

1.2 | Host population structure and waves of infection in COVID-19

From what we saw in the initial waves of the COVID-19-pandemic, there seems to be at least two classes of hosts in a population: the resistant and the vulnerable. A vulnerable host is one that supports the infection by a given strain of the virus leading to a symptomatic disease that may lead to the death of the host in a subset of cases (as determined by CFR that will be specific for a given population); a resistant host is the one that will not allow a given strain of the virus to readily infect and propagate in it. Any given population will have a mix of vulnerable and resistant hosts that encounter the virus in the initial wave of a pandemic. A primary/first wave of deaths due to infection could have a sharp rising curve with a peak, or it could be a flat curve with a plateau (Figure 1B), with several intermediaries within these two extreme shapes in different populations. Deaths largely correlate with cases (i.e., those with a symptomatic disease) in all populations, even though the CFR may vary. The proportion of vulnerable to resistant hosts (V:R) in the given population will decide the shape of the curve (Figure 1B). A large V:R ratio in a population that encounters the virus during the primary wave, leads to a sharp curve of cases/deaths, since the ratio is far higher than a certain critical value (CV, or the inclination point). Whereas if resistant hosts in the population outnumber the vulnerable ones, then the virus takes a longer time to reach enough vulnerable hosts to show its peak in the first wave, by which time the curve would have taken a flatter shape. The latter was seen in the COVID-19 morbidity/mortality curve of India during the first wave that began sometime during Mar 2020 and tapered off towards the end of the year (Chinnaswamy, 2020). India being a hotbed of endemic intracellular pathogens was supposedly protected by trained innate immunity during this first wave (Chinnaswamy, 2020).

In stark contrast, the second wave that struck India showed that there were more vulnerable hosts than resistant ones (Figure 1A, B). How can this be possible in the same population? I offer two complementary possibilities below, to explain this. First, it seems that the original strain of the virus was 'less fit', hence could not penetrate the strong natural immunity barrier supposedly present in most Indian hosts. This barrier could have been in the form of cross-protection due to exposure to other coronaviruses (Ansari et al., 2021) and/or trained innate immunity from other pathogens (Panda et al., 2020). A highly heterogenous set of hosts in India in terms of various parameters like economic, social, religious, and geographical/climatic variation may also have played a role in keeping the spread of the virus in check during the first wave. However, the original strain underwent substantial changes to emerge as a new 'delta variant' that was significantly more infectious than the parent strain (Mendez, 2021; outbreak.info 2021). The mutations may have helped the virus: (1) by altering the physicochemical properties such that the new strain could easily spread in air as particles rather than droplets (ex. aggregation property of the virus changes); (2) by facilitating better interactions of the spike protein with the ACE2 receptor; and (3) by increasing the replication efficiency of the virus. A combination of these properties made the new strain capable of penetrating the natural innate immunity barrier more efficiently. One factor that was critical could be the significant increase in virus inoculum that the hosts were exposed to with the new strain of the virus. Second, it is

also possible that the hosts in each population are stratified, and the virus does not infect all the strata at a given point of time (Banerjee, 2021). This way, the virus picks a stratum at a time, the ensuing infection within the stratum is reflected as one wave, and essentially the waves could reflect the different strata of the population being infected. The herd immunity, therefore, works only in definite strata and not uniformly across a population of hosts. This model is comprehensible if it is possible to explain that the virus cannot attain fitness if the hosts are heterogeneous and therefore it looks out for a stratum within the population, wherein the hosts are most homogenous, where it can attain maximum fitness (fitness is defined as the ability of a virus to infect and produce progeny in a set of hosts).

A given human population will have certain level of variation due to the inherent differences in the immunobiology among its different hosts who can allow a successful SARS-CoV-2 infection. This would be determined by several known factors such as gender, age, genetic background, and environmental factors including biocultural factors. It is reasonable to presume that any such population can be stratified based on a combination of factors that are collectively responsible for varying susceptibility to and pathogenesis from SARS-CoV-2 infection. Ex. older individuals, people with extreme comorbid conditions are more likely to fall under one stratum (Figure 2, top), whereas younger adults and children may fall in to two different strata. A virus can achieve maximal fitness if it can find, in proximity, all the hosts in a single stratum or closely related strata. Infections under such circumstances will lead to the characteristic sharp infection curve. A sharp rise in the infection curve will usually accompany a sharp fall too, after it attains the peak, suggesting that the virus gained peak fitness and lost it due to unavailability of more hosts in the same stratum/strata after reaching the peak of infection (Figure 1). At this point, the fittest virus population declines, giving way for the 'flattest' virus populations (i.e., those viruses populating the mutation landscape of a given viral species present as swarms of genetically distinct subspecies, but in lower frequencies) to compete for the next wave of infection, that will obviously be targeting the next, immunobiologically stronger, stratum of hosts (Figure 2, bottom). One obvious requirement for the new set of viral variants is to attain features that make them infect more hosts at a faster rate. Reports showing that the newly identified delta variant infects more youth than the parent strain (Qureshi, 2021) and that it is more transmissible than the parental strain (Li et al., 2021), give evidence for the 'stratum-wave theory'. Also, the low rate of reinfections in different parts of the world is additional proof to say that the virus selected its hosts differently in different waves of infection (Perez et al., 2021; Pilz et al., 2021).

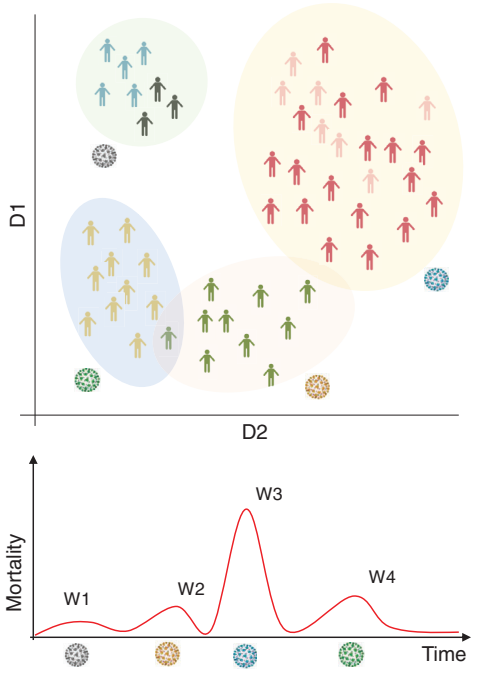

FIGURE 2 A hypothetical model showing the different hosts in a population with varying immunobiology stratified based on several parameters after dimensionality reduction (top; D-dimension). A different viral variant may achieve maximal fitness in each of the different strata in a population giving rise to characteristic waves that represent the underlying host population structure (bottom)

1.3 | Quasispecies, immune escape, and mass-vaccination during pandemics

RNA viruses exist as 'quasispecies' in nature (Domingo & Perales, 2019) and emergence of new variants is quite natural in a pandemic setting. Increasing immune pressure, be it due to resistance developing in hosts after a natural infection or following vaccination, is a potent driver of emergence of mutant viruses. However, in the absence of any vaccinal intervention, the time lag needed for emergence of dominant viral strains with altered characteristics is generally longer due to inherent evolutionary competition between different circulating and emerging strains. This is especially true in a host population where there is a high level of natural innate immunity that acts as a barrier against the virus and keeps it from achieving a high infection rate, which in turn lessens the chances of acquiring mutations under immune pressure from the host. On the other hand, a vaccine, that is usually a pharmacological preparation

from derivatives of an older strain, if it cannot prevent infection completely (i.e., if it cannot provide sterilizing immunity), has the potential to significantly decrease the time lag required for the emergence of new strains since they disrupt the 'competitive balance' between the circulating strains in the population and allows for selection of new variants (McLean, 1995) (Figure 3). The danger is larger if the circulating strains have significant immune escape properties. Despite this limitation, we have successfully dealt with several human viral diseases by following mass-vaccination programs (Ex. measles); some of the probable reasons on why such vaccine-induced mutant pathogens have not been a problem in the past has been discussed elsewhere (McLean, 1998).

With our previous experience, we see that vaccines against viruses have worked best under the following circumstances: (1) the target population are children (children have an untrained and developing adaptive immune system, hence makes perfect sense to use vaccines to strengthen their adaptive immunity arm); (2) the vaccines are used prophylactically, that is, introduced in the susceptible hosts before they are exposed to the virus; and (3) the susceptible hosts are mass-vaccinated such that herd immunity thresholds are achieved, again, before the arrival of the infection. However, in the current pandemic, none of the above seem to hold any relevance: we are mostly mass-vaccinating adults, who have a well-developed, memorized, cross-protection-generating adaptive immunity against natural viral infections; we are vaccinating during an ongoing pandemic and importantly many poorer countries are staring at huge vaccine deficits leaving large masses of their populace without even getting a single dose. In a country like India where there are not only logistical issues involved that circumvent a complete or near-complete vaccination coverage of its population, media reports showed that there was a huge vaccine

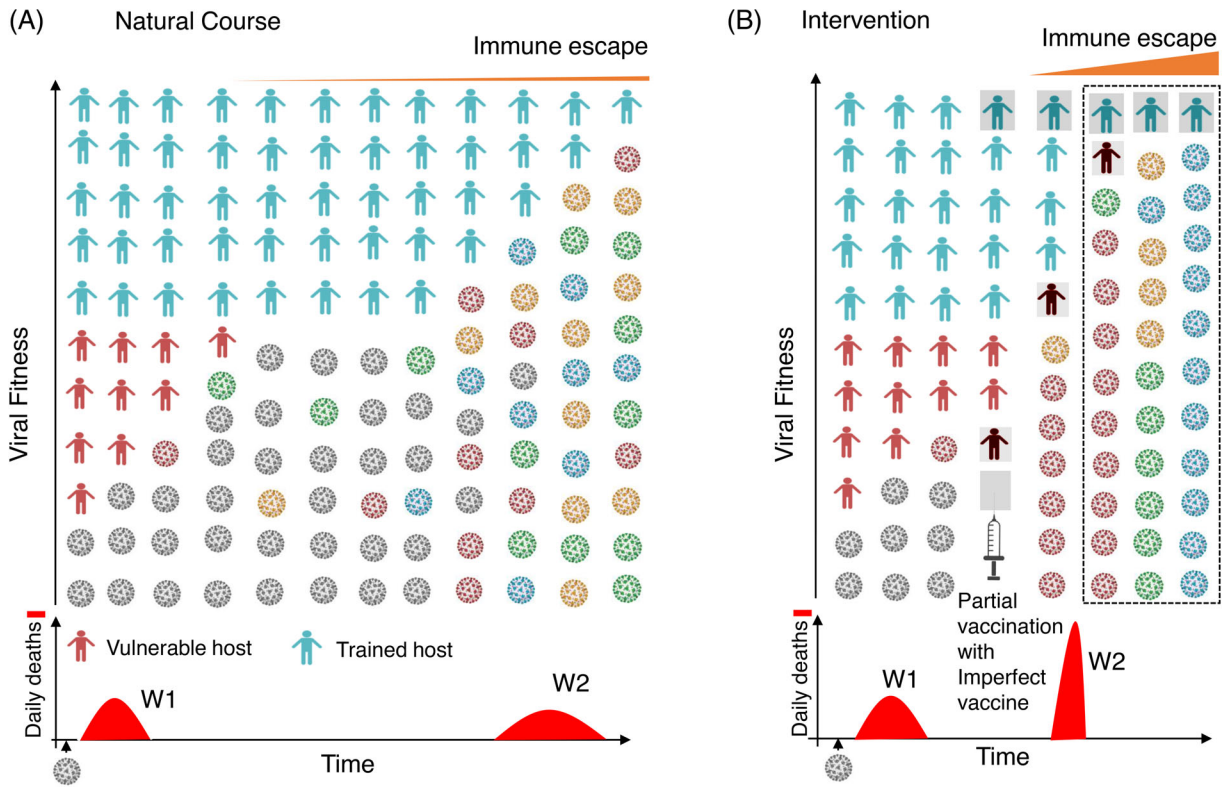

FIGURE 3 Viral immune escape in natural course versus vaccinal intervention. (A) During a natural course of infection in each population, the initial/parental strain of the virus (depicted in gray) competes with emerging variants (depicted in other colors) but eventually loses out to them due to immune pressure in a prolonged time frame. In this case, the mortality will be less, and the death curve will be flatter, relatively. Two hosts are shown that represent two immunity states. The vulnerable host has the least resistance to the parental strain of the virus, while a trained host is resistant to the parental strain, but can succumb to an emerging, more fit, strain/variant of the virus. W = wave. (B) If a vaccine that is imperfect (cannot prevent infection and transmission, but only prevents disease) is used as an intervention in only a limited number of hosts, the competitive balance between the parental and emerging strains is disrupted, leading to quick emergence of more infectious variant strains in the vaccinated population that invade naïve unvaccinated host stratum and cause disease and deaths much quicker than expected from a natural course of viral evolution; also the heterogeneity in the viral population decreases due to highly selective immune pressure in vaccinated hosts

hesitancy in the rural areas where most of the Indian population resides (Mallick, 2021; Nadimpally, 2021). Such a situation left a large number of unprotected hosts amidst a very small number of 'semi-protected' vaccinated ones exposed to a highly infectious delta variant. Modeling studies have predicted that this vaccine inequity among and within populations could be a dangerous platform for emergence and propagation of immune escape variants (Gerrish et al., 2021).

Even if the vaccines are providing a partial protection to the vaccinees without allowing a severe disease in them, it should be beneficial in terms of combating the pandemic, provided they are not interfering with the viral dynamics either at individual or population level. However, even though vaccination drives across the world began somewhere at the end of 2020 or beginning of 2021, we are seeing a continuous emergence and propagation of new, highly infectious strains of the virus in recent months (ECDC, 2021; Outbreak, 2021). Besides, it has been observed that the mutational diversity of B-cell epitopes of the spike protein of SARS-CoV-2 has been reducing all over the world, since vaccines were introduced (Niesen et, 2021); the sequence diversity of the spike protein is lesser in viruses sequenced from infections originating in vaccinated versus unvaccinated individuals suggesting that vaccines are indeed interfering with viral evolution (Niesen et, 2021). Curiously, India's devastating second wave of infection which was driven by the highly infectious delta strain/variant (Mascarenhas, 2021; Sadam, 2021) has closely followed India's vaccination drive, with a slight lag in time (Figure 4), before tapering off. This is indeed very interesting. The takeover of infection by the delta variant (B.1.617.2) strikingly follows the vaccination curve and the second wave of the pandemic in India (Figure 4). It is quite possible that the vaccinal antibodies selectively suppressed the dominant strains circulating in India when infections happened in the vaccinated individuals. The question then is, did the small but increasing number of vaccinees in India become breeding grounds for the delta variant to emerge and initiate the second wave? In a country like India that had a huge number of unvaccinated and most likely unexposed (to the adaptive immune system) hosts, the delta variant found a fertile ground to stabilize itself in the population. Yes, the curves shown in Figure 4 seem to be mere correlations and not evidence to believe that vaccines drove the second wave of infection in India; but, absence of evidence for

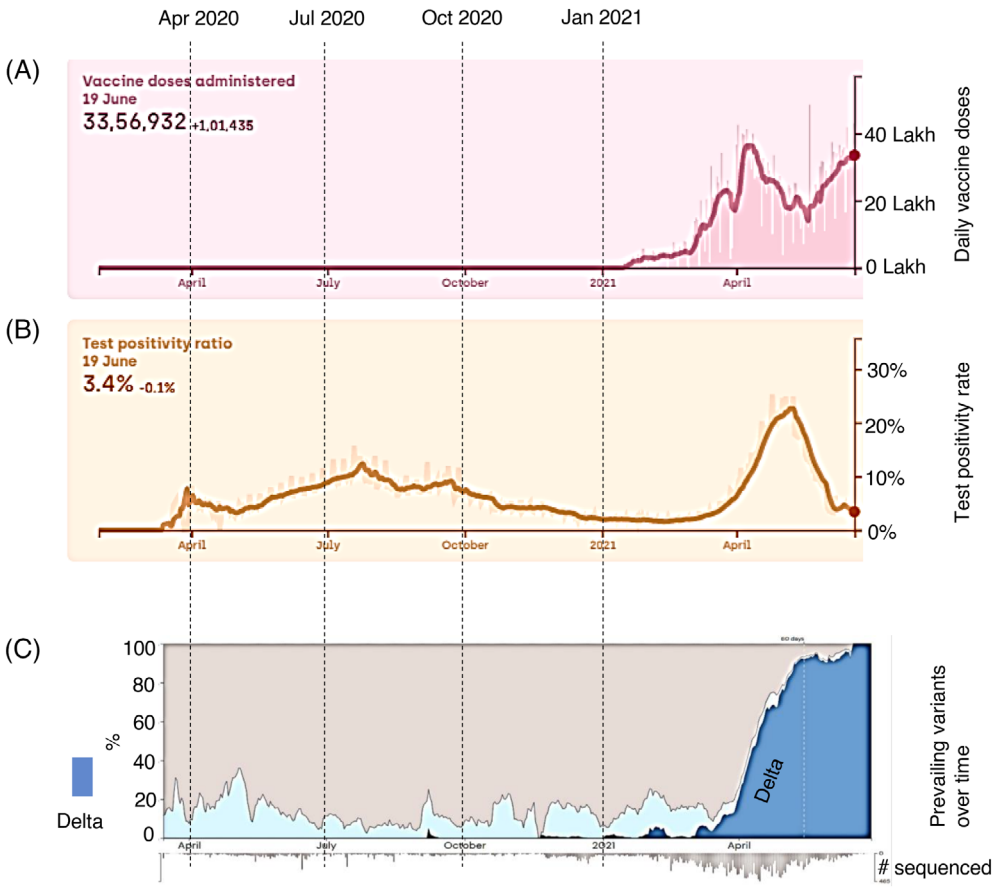

FIGURE 4 The spread of infection in India's second COVID-19 wave, marked by the emergence of the delta variant, closely follows the vaccination 'wave' in the country. Vaccinations began in India from mid-January 2021 and the initial rise in the wave happens ~1.5 months later. Daily test positivity rate (B) is shown below the daily vaccine doses (A) administered till June 19, 2021 (7-day moving averages). Source of data and image in A and B: Covid19india.org (2021). The evolution of different variant strains is shown at the bottom (C) (Source of data and image in C: outbreak.info)

causation is not evidence for absence of causation either! When two events happen simultaneously during a raging pandemic, there is no way to show that one event is causing the other, in which case we should invoke other forms of evidence. There is proof from experiments in livestock that shows, 'leaky or imperfect vaccines' "*can facilitate the evolution of pathogen strains that put unvaccinated hosts at greater risk of severe disease*" (Read et al., 2015).

If one must prove the hypothesis that vaccines facilitate the emergence of viral mutants, then clinical trial stage is the appropriate time when such a study can be done. In fact, researchers in the USA had prewarned about this issue when vaccine trials were taking place (Kennedy & Read, 2020). In this context, it is interesting to note that, Kate Bingham of the UK vaccine task force had written even before the vaccines came, "*The first generation of vaccines is likely to be imperfect, and we should be prepared that they might not prevent infection but rather reduce symptoms, and, even then, might not work for everyone or for long*" (Bingham, 2020). Even though it is difficult to test the 'vaccines selecting-for-mutants' hypothesis during a pandemic (Cobey et al., 2021), two observational studies, one from India (Dhar et al., 2021) and another from Israel (Kustin et al., 2021a and 2021b), have provided evidence that corroborates this concept by showing that vaccinated individuals were 'disproportionately infected' with viral variants compared to unvaccinated individuals who were infected during the same time. Another recent report from the Indian Council of Medical Research shows that >86% samples from vaccine breakthrough infections had the delta strain of the virus (Gupta et al., 2021). A plausible explanation for this is that the individuals who were vaccinated with the imperfect vaccines, got infected with the circulating strains (the delta variant was circulating, albeit at very low levels in India as early as December 2020, outbreak.info; Figure 4C) and gave a conduit to the emerging delta variant to escape, both from the host immune pressure and from competition from the dominant strains which were selectively suppressed by the vaccinal antibodies (Figures 3 and 4) (Gerrish et al., 2021). A counter argument to this would be: since an immune response, whether it is from a previous exposure or due to vaccination, would be selective against a previous circulating strain, reinfections in recovered individuals could also have led to the evolution of the delta variant in India under selective immune pressure, so why blame vaccinees for that? (Mlcochova et al., 2021). Two lines of evidence discredit this theory: (1) even though the delta variant was in circulation in India, it did not emerge as a dominant strain until vaccines were introduced (Figure 4) in the population; (this may be because the mutational diversity of the spike protein is selectively downregulated by vaccines [Niesen et al., 2021]); and (2) a recent observation from Israel, has documented that, vaccine breakthrough infections are 6.72 times more likely to occur than reinfections (Horowitz, 2021; Rosenberg, 2021). It is noteworthy, that the delta variant did not cause a severe disease in the vaccinees (Gupta et al., 2021), but it did cause high mortality in the unvaccinated and most likely unexposed hosts, especially in rural India. The Israel observation (Horowitz, 2021; Rosenberg, 2021) also raises another important scientific question for India: could the vaccines have precipitated infections, even though not severe, among the vaccinees during the beginning of the second wave? The answer to this question is important to prove the hypothesis that the vaccines used in India gave rise to the second wave.

Vaccines against SARS-CoV-2 were given emergency approval by the authorities in many countries, including India. Vaccines would be the best tools to fight the pandemic if they can provide sterilizing immunity, that is, limit infection (therefore transmission) and not just disease, from all the prevalent/emerging strains of virus (McKenna, 2021). This would happen only if the vaccine could provide a broad cross-protective sterilizing immunity against all emergent/circulating strains. While initial studies showed promising results (Hall, et al., 2021) about vaccines preventing infection, later studies have shown declining effectiveness of the current vaccines against emerging strains (Sheikh et al., 2021; Madhi et al., 2021; Hacisuleyman et al., 2021; Dhar et al., 2021; Gupta et al., 2021; Kustin et al., 2021a and 2021b; Mallapaty, 2021; Steenhuysen et al., 2021). Besides, anecdotal evidence and reports in the media, including those covering a study conducted by a premier medical institute, have documented vaccine breakthrough infections happening during the second wave of pandemic in India (Basu, 2021; Ghosh, 2021; Kumar, 2021; Rubin et al., 2021) and have continued therafter. If vaccines prevent only disease and not infection (and therefore transmission), then the purpose of developing vaccines against any virus, which is to eradicate it, is defeated; also, achieving herd immunity through vaccines becomes a meaningless concept.

In terms of eradicating the viral pandemic, why is the immunity generated against a natural infection better than vaccine-induced immunity? Vaccines are different from a natural infection by a virus in the following ways: (1) a vaccine cannot always be delivered in the same route as the natural route of viral entry in to the host (ex. this limits the vaccine responses to mostly in the blood and not at the mucosal surfaces where the virus enters); (2) a vaccine invariably lacks the ability to trigger an immune response akin to a robust viral infection,

hence a multidimensional response is achieved in the latter compared to a less varied response from the former (Ex. a vaccine-mediated immunity is mostly antibody-dependent); and (3) most importantly, a natural viral infection exposes the immune system to the viral quasispecies, which a vaccine fails to do. Almost in agreement, real-world data from one of the most vaccinated countries in the world, Israel, shows that by mid-July 2021, 57% of vaccinated, compared to only 1% of recovered individuals were infected by the highly infectious delta variant (Kovler, 2021). Mathematical Biologist Angela McLean opines, '*Vaccines induce a generally weaker and less cross-reactive immunity than naturally acquired immunity, that the opportunity for new strains to evolve is greater in a vaccinated population*' (McLean, 1995).

The important question then is, were the vaccines against SARS-CoV-2 beneficial or not? To analyze this, I pick the same nine countries whose morbidity and mortality data that I had juxtaposed with that of India, to infer that India bucked the trend in the first wave (Chinnaswamy, 2020). In Figure 5A, I show the test positivity rate (which is the best indicator of the spread of the disease) recorded till June 21, 2021 for all the 10 countries. This data clearly shows: (1) there was certainly a post-vaccination bump/wave in all countries except the UK (boxed region in Figure 5A); and (2) except for India, the positivity rate in all the countries that show the post-vaccination bump/wave, has not exceeded the positivity rates that occurred in the previous waves. This would suggest that even though there was a negative effect at the population level on the spread of the infection post-vaccination, the effect was lesser in all the other countries, except for India. Most strikingly, when we look at the percent share of people in each of these countries who received at least one dose of the vaccine, it reveals that UK with the highest vaccination rate (63% on June 20, 2021), has no post-vaccination increase in test positivity rate, at least until the end of June 2021, whereas India, with the lowest vaccination rate (16% on June 20, 2021) has the highest post-vaccination test positivity rate (Figure 5B).

However, from the end of June and beginning of July 2021, the delta variant has taken over infections throughout the world. UK, like many European countries and the USA, is seeing a huge increase in cases from July 2021 due to the rapid spread of the delta variant. But what is different is that, for the first time in the pandemic, the morbidity and mortality curves seem to have got largely delinked, thanks to the effect of vaccines in all those countries that have relatively higher vaccination rates (ourworldindata,org. 2021). While the delta variant has devasted many south Asian countries with low vaccination coverage, it is now slowly but surely, threatening the high vaccination coverage countries too and only time will reveal the damage that it would cause in these countries. More disturbingly, some unpublished and published data from Israel and UK have shown more hospitalization and deaths occurring among vaccinated than the unvaccinated individuals infected with the delta variant (J-Hoffman, 2021; Louise, 2021, PHE, 2021). The message seems to be clear: it may be a mistake to use an imperfect vaccine during a pandemic, but it is a blunder to not cover sufficient proportion (ideally 80%–90%) of the target population in quick time, once we begin vaccinating. There is clear evidence in the form of circulating highly infectious variants in the post-vaccination period to show that the COVID-19 vaccines are not 'evolution-proof' and hence are imperfect (outbreak.info; Read & Kennedy, 2020). The CDC of the USA has released data that shows that the viral load in vaccinated individuals is the same as in unvaccinated individuals who get infected with the delta variant (Abutaleb et al., 2021), implying that even the mRNA vaccines used in the USA, which showed the best efficacy in clinical trials are not able to prevent infection from (and transmission of) the delta variant. With such imperfect vaccines, the best strategy is, we either vaccinate all, or none (Kennedy, 2015; Moore, 2021), lest we allow the immune escape variants to run amok among the unprotected hosts, like it probably happened in India's second wave. The developed countries may succeed with these vaccines, since they have the resources to vaccinate all (and revaccinate against newer strains, if need be). But the underdeveloped and developing countries will suffer from vaccine breakthrough infections, if they initiate vaccination but cannot achieve herd immunity threshold status in quick time, leading to the emergence of more infectious variants, that can cause severe damage to their unprotected hosts.

To conclude, vaccines against SARS-CoV-2 seem to be beneficial in some but not other populations. It is beneficial in those populations where the attack rates were high in the initial phases of the pandemic; in these populations the infection pressure was high to begin with, and variants had already emerged and caused much damage even before vaccines came into the scene (Ex. B.1 in Europe; alpha variant in the UK). These populations had probably gone past the worst phases of the pandemic by the time the vaccines came, and it is likely that a large proportion of their susceptible hosts had been eliminated by then. Hence, even if the imperfect vaccines could prevent disease, and not necessarily infection, and save their remaining proportion of susceptible hosts from death, it is indeed a major gain for these populations. But, in those populations where attack rates were lower in the early phases of the pandemic (ex. south

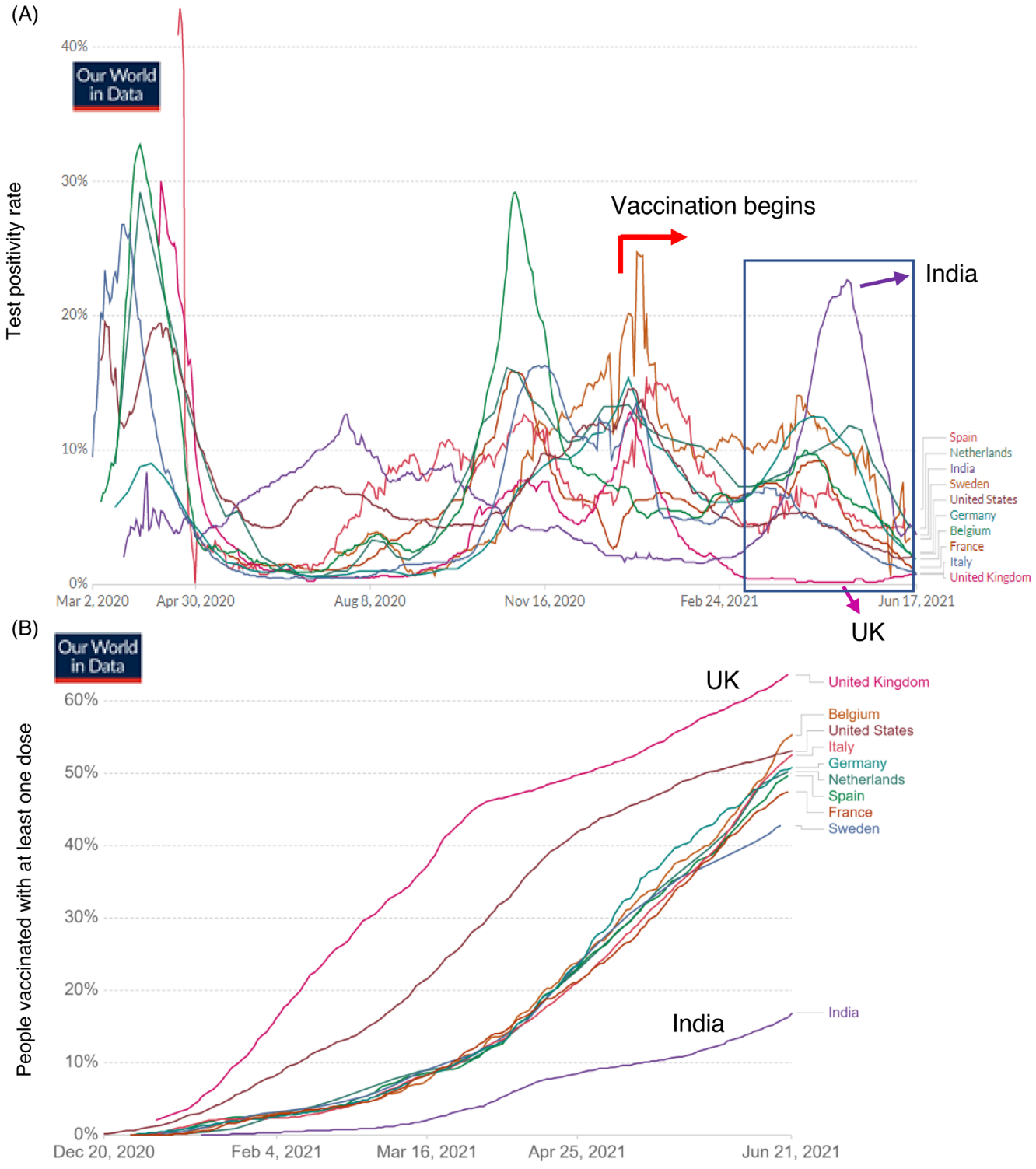

FIGURE 5 India and UK have the highest and lowest post-vaccination test positivity rates, respectively. (A) Test positivity rates from the beginning of the pandemic to June 21, 2021, are shown for eight European countries, USA, and India. Vaccination began in all the depicted countries between December 2020 and January 2021. A post-vaccination increase in test positivity is seen for all countries except UK (boxed region). India has the highest positivity rate during this period, higher than any time before, which is not the case for other countries. (B) Share of people vaccinated with at least a single dose in the 10 countries depicted in (A), from December 2020 to mid-June 2021. The data and images for both (A) and (B) are taken from ourworldindata.org

Asia, Africa), stronger waves of infection and deaths, driven mainly by the delta variant, have invariably and dubiously coevolved with vaccination curves (ourworldindata), thereby questioning the utility of the vaccines in these populations.

1.4 | Concluding thoughts

The emerging data from countries such as UK and Israel with high vaccination rates are showing that the vaccinated individuals are certainly protected from severe disease; but this benefit from vaccines appears to have come at a cost. The cost is seen as: increased infection rates overall (even though the delta variant may be the primary reason), and disproportionately higher hospitalization rates and deaths among the previously unexposed and/or unvaccinated individuals (Ex. Hamrick, 2021). Hence, if the original strain of SARS-CoV-2 exposed one form of inequity in the society (Gravlee, 2020), the variants in the postvaccination era will likely expose another form, which is based on vaccine privilege, vaccine hesitancy and in many instances, lack of access to critical information on what vaccines can and cannot do.

In hindsight, if the delta variant indeed emerged as a 'vaccine escape variant' from India, then it should find it easy to spread in other vaccinated populations; not surprisingly therefore, the delta variant has spread very fast in UK (Hartmann, 2021), Spain, Israel (Pflughoeft, 2021) which have high vaccination coverage (ourworldindata). In the USA, where a large proportion of people are still unvaccinated, experts believe that the vaccinated individuals may be helping the spread of the delta variant (Brueck, 2021). Even though the currently available COVID-19 vaccines are not going to provide herd immunity in the manner they were intended to, they might provide it nonetheless, by allowing the propagation of a highly infectious delta variant in the population. The vaccines seem to have diverted the virus, through genetic evolution, from being concentrated on a small number of highly vulnerable hosts to having it spread across a larger number of less vulnerable ones; this way the infectivity can remain high, but mortality will be in check (a situation witnessed by many countries dealing with the delta variant, currently). Unfortunately, India, due to its sheer size of the population seems to have had a large stratum of the less vulnerable, including those in the borderline between the less vulnerable and vulnerable, who were unvaccinated or unexposed to the virus in the first wave, that succumbed in large numbers in the second wave; the highly vulnerable who were shielded by a lesser infective strain of the virus in the first wave may also have succumbed and contributed to huge mortality (officially recorded or otherwise).

ACKNOWLEDGMENTS

The author thanks National Institute of Biomedical Genomics, Kalyani for the facilities. The author is the recipient of the DBT/Wellcome Trust India Alliance Fellowship (grant number IA/I/17/1/503122).

CONFLICT OF INTEREST

None to declare.

DATA AVAILABILITY STATEMENT

The data used in the manuscript are from publicly maintained open sources.

ORCID

Sreedhar Chinnaswamy https://orcid.org/0000-0003-0095-3453

REFERENCES

Abutaleb, Y., Johnson, C. Y., & Achenbach, J. (2021). *'The war has changed': Internal CDC document urges new messaging, warns delta infections likely more severe*. The Washington Post https://www.washingtonpost.com/health/2021/07/29/cdc-mask-guidance/

Ansari, A., Arya, R., Sachan, S., Jha, S. N., Kalia, A., Lall, A., Sette, A., Grifoni, A., Weiskopf, D., Coshic, P., Sharma, A., & Gupta, N. (2021). Immune memory in mild COVID-19 patients and unexposed donors reveals persistent T cell responses after SARS-CoV-2 infection. *Frontiers in Immunology*, *12*, 636768. https://doi.org/10.3389/fimmu.2021.636768

Banerjee, S. (2021). Understanding the dynamics of pathogenic infection in a population. *Preprints*. https://doi.org/10.20944/preprints202105.0664.v1

Basu, M. (2021). Virus variant in India can infect those vaccinated, but unlikely to cause severe Covid: Study. https://theprint.in/science/virus-variant-in-india-can-infect-those-vaccinated-but-unlikely-to-cause-severe-covid-study/656633/

Bingham, K. (2020). The UK government's vaccine taskforce: Strategy for protecting the UK and the world. *The Lancet*, *397*, 68–70. https://doi.org/10.1016/S0140-6736(20)32175-9

Biswas, S. (2021a). Coronavirus: Is the epidemic finally coming to an end in India? https://www.bbc.com/news/world-asia-india-56037565

Biswas, S. (2021b). Covid-19: How India failed to prevent a deadly second wave. https://www.bbc.com/news/world-asia-india-56771766

Brueck, H. (2021). A leading US disease expert says there's 'no doubt in my mind' that vaccinated people are helping spread Delta. *Business Insider* https://www.businessinsider.in/science/news/a-leading-us-disease-expert-says-theres-no-doubt-in-my-mind-vaccinated-people-are-helping-spread-delta/articleshow/84211849.cms

Chadha, S. (2021). Is India's second wave Corona crisis engineered? https://timesofindia.indiatimes.com/blogs/blunt-frank/is-indias-second-wave-corona-crisis-engineered/

Chinnaswamy, S. (2020). SARS-CoV-2 infection in India bucks the trend: Trained innate immunity? *American. J. Human Biology*. https://doi.org/10.1002/ajhb.23504

Cobey, S., Larremore, D. B., Grad, Y. H., & Lipsitch, M. (2021). Concerns about SARS-CoV-2 evolution should not hold back

efforts to expand vaccination. *Nature Reviews. Immunology*, *21*, 330–335. https://doi.org/10.1038/s41577-021-00544-9

Cohen, J. (2021). Will India's devastating COVID-19 surge provide data that clear up its death 'paradox'? *Science* https://www.sciencemag.org/news/2021/04/will-india-s-devastating-covid-19-surge-provide-data-clear-its-death-paradox

Covid19india.org. (2021) https://www.covid19india.org/

Dhar, M. S., Marwal, R., Radhakrishnan, V. S., Ponnusamy, K., Jolly, B., Bhoyar, R. C., Fatihi, S., Datta, M., Singh, P., Sharma, U., Ujjainia, R., Naushin, S., Bhateja, N., Divakar, M. K., Sardana, V., Singh, M. K., Imran, M., Senthivel, V., Maurya, R., ... Rakshit, P. (2021). Genomic characterization and epidemiology of an emerging SARS-CoV-2 variant in Delhi, India. *medRxiv*. https://doi.org/10.1101/2021.06.02.21258076

Domingo, E., & Perales, C. (2019). Viral quasispecies. *PLoS Genetics*, *15*(10), e1008271. https://doi.org/10.1371/journal.pgen.1008271

ECDC (European Centre for Disease Prevention and Control); 2021). SARS-CoV-2 variants of concern as of 18 June 2021. https://www.ecdc.europa.eu/en/covid-19/variants-concern

Frayer, L. (2021). The Mystery Of India's Plummeting COVID-19 Cases. https://www.npr.org/sections/goatsandsoda/2021/02/01/962821038/the-mystery-of-indias-plummeting-covid-19-cases

Gerrish, P. J., Saldana, F., Galeota-Sprung, B., Colato, A., Rodriguez, E. E., & Hernadez, J. V. (2021). How unequal vaccine distribution promotes the 1 evolution of vaccine escape. *The Lancet*. https://doi.org/10.2139/ssrn.3827009

Ghosh, P. (2021). Delta Covid-19 variant can infect vaccinated people, claims AIIMS study. https://www.hindustantimes.com/india-news/delta-covid-19-variant-can-infect-vaccinated-people-claims-aiims-study-101623307391151.html

Gravlee, C. C. (2020). Systemic racism, chronic health inequities, and COVID-19: A syndemic in the making? *American Journal of Human Biology*, *32*, e23482. https://doi.org/10.1002/ajhb.23482

Gupta, N., Kaur, H., Yadav, P., Mukhopadhyay, L., Sahay, R. R., Kumar, A., Nyayanit, D. A., Shete, A. M., Patil, S., Majumdar, T., Rana, S., Gupta, S., Narayan, J., Vijay, N., Barde, P., Natrajan, G., Kumari, A. M., Kumari, M. P., Biswas, D., ... Abraham, P. (2021). Clinical characterization and genomic analysis of COVID-19 breakthrough infections during second wave in different states of India. *medRxiv*. https://doi.org/10.1101/2021.07.13.21260273

Hacisuleyman, E., Hale, C., Saito, Y., Blachere, N. E., Bergh, M., Conlon, E. G., Schaefer-Babajew, D. J., DaSilva, J., Muecksch, F., Gaebler, C., Lifton, R, Nussenzweig, M. C., Hatziioannou, T., Bieniasz, P. D., & Darbell, R. B. (2021). Vaccine breakthrough infections with SARS-CoV-2 variants. *The New England Journal of Medicine*, *384*, 2212–2218. https://doi.org/10.1056/NEJMoa2105000

Hall, V. J., Faulkes, S., Saei, A., Andrews, N., Oguti, B., Charlett, A., Wellington, E., Stowe, J., Gillson, N., Atti, A., Islam, J., Karagiannis, I., Munro, K., Khawam, J., Chand, M. A., Brown, C. S., Ramsay, M., Lopez-Bernal, J., Hopkins, S., & SIREN study group (2021). COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): A prospective, multicentre, cohort study. *Lancet*. https://doi.org/10.1016/S0140-6736(21)00790-X

Hamrick, B. (2021). COVID-19 patients total 170 at local hospitals, not a single one vaccinated. *WLWT5* https://www.wlwt.com/article/covid-19-patients-total-170-at-local-hospitals-not-a-single-one-vaccinated/36356774#

Hartmann, J. (2021). COVID: The reason cases are rising among the double vaccinated-it's not because vaccines aren't working. *Mint* https://www.livemint.com/science/health/covid-the-reason-cases-are-rising-among-the-double-vaccinated-it-s-not-because-vaccines-aren-t-working-11627015105720.html

Horowitz, D. (2021). Israeli government data shows natural immunity from infection much stronger than vaccine-induced immunity. *Blaze Media* https://www.theblaze.com/op-ed/horowitz-israeli-government-data-shows-natural-immunity-from-infection-much-stronger-than-vaccine-induced-immunity

Jaffe-Hoffman, M. (2021). Coronavirus in Israel: What do we know about the 143 hospitalized people? *The Jerusalem Post* https://www.jpost.com/health-science/coronavirus-in-israel-what-do-we-know-about-the-143-hospitalized-people-674508

Kennedy, B. K. (2015). Some Vaccines Support Evolution of More-Virulent Viruses. https://science.psu.edu/news/some-vaccines-support-evolution-more-virulent-viruses

Kennedy, D. A., & Read, A. F. (2020). Monitor for COVID-19 vaccine resistance evolution during clinical trials. *PLoS Biology*, *18*(11), e3001000. https://doi.org/10.1371/journal.pbio.3001000

Kovler, A. (2021). Inside Israel's Delta outbreak part I: the data. https://arieh.substack.com/p/inside-israels-delta-outbreak-part

Kumar, A. (2021). Delta variant behind most breakthrough infections, infecting even after vaccine jabs: AIIMS study. https://www.timesnownews.com/india/article/delta-variant-behind-most-breakthrough-infections-infecting-even-after-covishield-covaxin-jabs-aiims-study/768229

Kustin, T., Harel, N., Finkel, U., Perchik, S., Harari, S., Tahor, M., Caspi, I., Levy, R., Leshchinsky, M., Dror, S. K., Bergerzon, G., Gadban, H., Gadban, F., Eliassian, E., Shimron, O., Saleh, L., Ben-Zvi, H., Taraday, E. K., Amichay, D., ... Stern, A. (2021a). Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2-mRNA-vaccinated individuals. *Nature Medicine*, *27*, 1379–1384. https://doi.org/10.1038/s41591-021-01413-7

Kustin, T., Harel, N., Finkel, U., Perchik, S., Harari, S., Tahor, M., Capsi, I., Levy, R., Leshchinsky, M., Dror, S. K., Bergerzon, G., Gabdan, H., Gabdan, F., Eliassian, E., Shimron, O., Saleh, L., Ben-Zvi, H., Taraday, E. K., Amichay, D., ... Stern, A. (2021b). Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2 mRNA vaccinated individuals. *medRxiv*. https://doi.org/10.1101/2021.04.06.21254882

Li, B., Deng, A., Li, K., Hu, Y., Li, Z., Xiong, Q., Liu, Z., Guo, Q., Zou, L., Zhang, H., Zhang, M., Quyang, F., Su, J., Su, W., Xu, J., Lin, H., Sun, J., Peng, J., Jiang, H., ... Lu, J. (2021). Viral infection and transmission in a large, well-traced outbreak caused by the SARS-CoV-2 Delta variant. *medRxiv*. https://doi.org/10.1101/2021.07.07.21260122

Louise, N. (2021). Data from Public Health England shows that more vaccinated people died of the Delta variant in the UKthan the unvaccinated (death rate is 8.45 times higher for the vaccinated). *Tech Startups* https://techstartups.com/2021/06/30/data-public-health-england-shows-vaccinated-people-died-delta-variant-uk-unvaccinated-death-rate-8-45-times-higher-vaccinated/

Madhi, S. A., Baillie, V., Cutland, C. L., Voysey, M., Koen, A. L., Fairlie, L., Paeds, F. C., Padayachee, S. D., Dheda, K.,

Barnabas, S. L., Bhorat, Q. E., Briner, C., Kwatra, G., Ahmed, K., Aley, P., Bhikha, S., Bhiman, J. N., ... VIDA COVID Group (2021). Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B.1.351 variant. *The New England Journal of Medicine*. https://doi.org/10.1056/NEJMoa2102214

Mallapaty, S. (2021). COVID vaccines slash viral spread – but delta is an unknown. *Nature*, *596*, 17–18. https://doi.org/10.1038/d41586-021-02054-z

Mallick, A. (2021). 42% People in Parts of UP, Bihar, MP Say Won't Take COVID Vaccine. https://www.thequint.com/news/webqoof/misinformation-impacts-covid-19-vaccine-process-rural-india-uttar-pradesh-bihar-madhya-pradesh

Mascarenhas, A. (2021). Delta variant behind April wave in Delhi, shows NCDC study. https://indianexpress.com/article/cities/pune/delta-variant-delhi-covid-wave-ncdc-study-7344804/

McKenna, S. (2021). Vaccines need not completely stop COVID transmission to curb the pandemic. *Scientific American* https://www.scientificamerican.com/article/vaccines-need-not-completely-stop-covid-transmission-to-curb-the-pandemic1/

McLean, A. R. (1995). Vaccination, evolution and changes in the efficacy of vaccines: A theoretical framework. *Proceedings of the Royal Society*, *261*, 389–393.

McLean, A. R. (1998). Vaccines and their impact on control of disease. *British Medical Bulletin*, *54*(3), 545–556.

Mendez, R. (2021). Delta Covid variant first found in India spreads to 62 countries, hot spots form in Asia and Africa. *WHO says* https://www.cnbc.com/2021/06/02/delta-variant-first-found-in-india-spreads-to-62-countries-hot-spots-form-in-asia-and-africa-who-says-.html

Mlcochova, P., Kemp, S., Dhar, M. S., Papa, G., Meng, B., Mishra, S., Whittaker, C., Mellan, T., Ferreira, I., Datir, R., Collier, D. A., Singh, S., Pandey, R., Marwal, R., Datta, M., Sengupta, S., Ponnusamy, K., Radhakrishnan, V. S., Abdullahi, A., ... Gupta, R. (2021). SARS-CoV-2 B.1.617.2 Delta variant emergence and vaccine breakthrough. *Research Square*. https://doi.org/10.21203/rs.3.rs-637724/v1

Moore, J. P. (2021). Approaches for optimal use of different COVID-19 vaccines issues of viral variants and vaccine efficacy. *JAMA*, *4*, 2021–1252. https://doi.org/10.1001/jama.2021.3465

Mullen, J. L., Tsueng, G., Latif, A. A., Alkuzweny, M., Cano, M., Haag, E., Zhou, J., Zeller, M., Hufbauer, E., Matteson, N., Andersen, K. G., Wu, C., Su, A. I., Gangavarapu, K., Laura D., Hughes & Outbreak.info (2021). The Center for Viral Systems Biology outbreak.info. https://outbreak.info/

Nadimpally, S. (2021). Why vaccine hesitancy should not be tackled through a carrot and stick policy. https://scroll.in/article/997603/why-vaccine-hesitancy-should-not-be-tackled-through-a-carrot-and-stick-policy

Niesen, M. J. M., Anand, P., Silvert, E., Suratekar, R., Pawlowski, C., Ghosh, P., Lenehan, P., Hughes, T., Zemmour, D., O'Horo, J. C., Yao, J. D., Pritt, B. S., Norgan, A., Hurt, R. T., Badley, A. D., Venkatakrishnan, A. J., & Soundararajan, V. (2021). COVID-19 vaccines dampen genomic diversity of SARS-CoV-2: Unvaccinated patients exhibit more antigenic mutational variance. *medRxiv*. https://doi.org/10.1101/2021.07.01.21259833

Panda, A. K., Tripathy, R., & Das, B. K. (2020). Plasmodium falciparum infection may protect a population from SARS-CoV-2 infection. *Journal of Infectious Diseases*, *222*, 1570–1571. https://doi.org/10.1093/infdis/jiaa455

Patel, V. (2021). Covid vaccine is here, virus is already in retreat. Let's just wait our turn. https://indianexpress.com/article/opinion/columns/vaccine-is-here-virus-is-already-in-retreat-lets-just-wait-our-turn-7162802/

Perez, G., Banon, T., Gazit, S., Moshe, S. B., Wortsman, J., Grupel, D., Peretz, A., Tov, A. B., Chodick, G., Mizrahi-Reuveni, M., & Patalon, T. (2021). A 1 to 1000 SARS-CoV-2 reinfection proportion in members of a large healthcare provider in Israel: A preliminary report. *medRxiv preprint*. https://doi.org/10.1101/2021.03.06.21253051

Pflughoeft, A. (2021). A look inside Israel's recent coronavirus outbreak. *Deseret News* https://www.deseret.com/coronavirus/2021/7/20/22584134/whats-going-on-in-israels-outbreak-among-vaccinated-people

PHE (Public Heath England). (2021). SARS-CoV-2 variants of concern and variants under investigation in England. *Technical Briefing*, *17,* 1–69. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1001354/Variants_of_Concern_VOC_Technical_Briefing_17.pdf

Pilz, S., Chakeri, A., Ioannidids, J.-P. A., Richter, L., Theiler-Shwetz, V., Trummer, C., Krause, R., & Allerberger, F. (2021). SARS-CoV-2 reinfection risk in Austria. *European Journal of Clinical Investigation*, *51*, e13520.

Qureshi, S. (2021 Jun 6). Doctors explain why young people are more affected in second wave of Covid-19. https://www.indiatoday.in/coronavirus-outbreak/story/doctors-explain-young-people-more-affected-second-wave-1811619-2021-06-06

Ravikumar, S., & Jamkahndikar, S. (2021). India's COVID-19 'human barricade' to keep cases under control, say experts. https://www.reuters.com/article/health-coronavirus-india-idUSKBN2AH1K7

Read, A. F., Baigent, S. J., Powers, C., Kgosana, L. B., Blackwell, L., Smith, L. P., Kennedy, D. A., Walkden-Brown, s. W., & Nair, V. K. (2015). Imperfect vaccination can enhance the transmission of highly virulent pathogens. *PLoS Biology*, *13*(7), e1002198. https://doi.org/10.1371/journal.pbio.1002198

Read, A. F. & Kennedy, D. (2020). Virus evolution could undermine a COVID-19 vaccine – but this can be stopped. https://theconversation.com/virus-evolution-could-undermine-a-covid-19-vaccine-but-this-can-be-stopped-149234

Ritchie, H., Ortiz-Ospina, E., Beltekian, D., Mathieu, E., Hasell, J., Macdonald, B., Giattino, C., Appel, C., Rodés-Guirao, L., Roser, M., & Ourworldindata.org (2021). "Coronavirus Pandemic (COVID-19)". OurWorldInData.org

Rosenberg, D. (2021). Natural infection vs vaccination: Which gives more protection? IsraelNationalNews.com. https://www.israelnationalnews.com/News/News.aspx/309762

Rubin, E. J., Baden, L. R., Udwadia, Z. F., & Morrissey, S. (2021). Audio interview: India's Covid-19 crisis. *The New England Journal of Medicine*, *384*(18), e84. https://doi.org/10.1056/NEJMe2107728

Sadam, R. (2021). Delta variant behind India's 2nd wave, 7 strains circulating in & around Varanasi, study finds. *The Print* https://theprint.in/health/delta-variant-behind-indias-2nd-wave-7-strains-circulating-in-around-varanasi-study-finds/672288/

Sheikh, A., McMenamin, J., Taylor, B., & Robertson, C. (2021). SARS-CoV-2 Delta VOC in Scotland: Demographics, risk of hospital admission, and vaccine effectiveness. *Lancet*, *397*, 2461–2462. https://doi.org/10.1016/S0140-6736

Steenhuysen, J., Smout, A., & Rabinovitch, A. (2021). How the Delta variant upends assumptions about the coronavirus. *Reuters* https://www.reuters.com/world/china/how-delta-variant-upends-assumptions-about-coronavirus-2021-07-26/

How to cite this article: Chinnaswamy, S. (2021). Understanding the devastating second wave of COVID-19 pandemic in India. *American Journal of Human Biology*, *33*(6), e23671. https://doi.org/10.1002/ajhb.23671