pISSN 2394-6032 | eISSN 2394-6040

### **Review Article**

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20213047

# COVID-19: sudden and dramatic upsurge in the number of cases in India

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Received: 10 June 2021 Accepted: 13 July 2021

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### **ABSTRACT**

The second wave of coronavirus disease 2019 (COVID-19) in India, which commenced in March'21, continues to create a major crisis of medications, hospital beds, oxygen, and Intensive Care Units at very rapid rate which has placed the country on the verge of a humanitarian crisis. While no definite treatment for SARS-CoV-2 has been found, different types of vaccines have been manufactured which have shown some effectiveness in preventing disease progression and severity. The objective of this manuscript is to review the available data from the pandemic and highlight the factors that have contributed to the development of second wave in India which has led to crisis. In this review, using available scientific literature on various indexes such as PubMed, Google Scholar, Medline and news articles- where appropriate, we dive into understanding newer virus variants, vaccines and their effectiveness against new strains, overwhelming burden on the Indian healthcare system and socio-politico-environmental factors responsible for upsurge. The sudden upsurge in the number of cases is multifactorial, which includes virus variants, complacency in following COVID-19 appropriate behaviour, burden over the health care system, various socio-politico-environmental factors. As the definitive treatment is yet to be discovered, vaccination remains at the top.

Keywords: COVID-19, Second wave, India, Upsurge, Vaccine, Healthcare burden

#### **INTRODUCTION**

As the Coronavirus Disease 2019 (COVID-19) continues to dominate the world into 2021, healthcare infrastructures are overwhelmed worldwide. World's largest democracy, ie. India has been hit by a massive second wave of COVID-19 cases and is experiencing a major healthcare burden. As India continues to combat the second wave, the medical supplies, medications, hospital beds, ventilators, and Intensive Care Units (ICU) are being exhausted at a very rapid rate which puts India on the brink of a humanitarian catastrophe. In late 2019, Wuhan, Hubei, China reported an outbreak of a pneumonia-like illness, COVID-19, caused by the Ribonucleic acid (RNA) virus Severe Acute

Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), a beta coronavirus with a nearly 30 kb positive-sense, single-strand RNA genome that encodes 29 proteins.<sup>3</sup> The first case of COVID-19 was reported on January 30, 2020 in India.3 In the early pandemic, it was the elderly, those with comorbidities (including hypertension, diabetes, asthma and chronic lung disorders), and the immunocompromised individuals who were more susceptible to the adverse effects of COVID-19 infection. However, it is known that the demographics of the most affected populations may change due to the mutations/adaptations in the viral genes that cause new variants of the original strain of SARS-CoV-2 to emerge, perhaps resulting in the new lineages of the virus. It was noted that the SARS-CoV-2 strain in India

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has acquired new mutations at the rate of ~2 changes per month.<sup>3</sup> On the other hand, nations around the globe are on a mission to vaccinate their population; however, the rising cases of variants have stirred up questions about the effectiveness of the current vaccines against the new variants.3 While some scientists remain confident that it will be effective, studies are underway to determine the effectiveness of vaccines against new strains.<sup>3,4</sup> Amidst the raging pandemic, India has reported a record-breaking one day high of the COVID-19 positive cases for multiple days in April 2021 which has put the nation's healthcare system in disarray and the population is left searching for appropriate care. There are multiple factors responsible for the sudden upsurge in the cases. An unexpected rise in reported COVID-19 cases in December 2020 was attributed to the emergence of the new SARS-CoV-2 variants 501Y.V1 (B.1.1.7) in the United Kingdom (UK) and 501Y.V2 (B.1.351) in South Africa.5 It is deduced that the variants may show high transmissibility and may develop multiple new escape variants in future and lead to severe epidemic rebound.<sup>4,5</sup> This is quite evident in India as the "double mutant" variant is being considered as one of the factors contributing to their massive second wave.<sup>6</sup> Based on this, it can be debated that the emergence of the new variants might've been the culprit for India's devastating second wave alongside other factors.3

### **SARS-COV-2 AND VARIANTS**

The novel coronavirus SARS-CoV-2, belongs to the group of enveloped viruses having the largest genome with a positive-sense single-stranded RNA. The genetic makeup of SARS-CoV-2 consists of 13-15 ORFs (open reading frames). The first ORF (ORF1a/b) translates two polyproteins, pp1a and pp1ab which encodes 16 nonstructural proteins including replicase and protease. The remaining ORFs encode the four structural proteins which include spike (S), envelope (E), membrane (M) and nucleocapsid proteins (N). The main mechanism of viral entry into the host cell genome is through the S1 subunit of the spike protein binding to the host cell ACE-2 (Angiotensin Convertase Enzyme-2) receptor through its receptor-binding domain (RBD), which is followed by S2 subunit binding to the host cell membrane. Following this, all the other structural and non-structural proteins help in viral replication, transcription, assembly and packaging. The RBD of the spike protein is the most variable part of the virus which is concluded from the difference in the MSA (Multiple Sequence Alignment) profiles of the other CoVs. Mutation in the spike protein leads to conformational changes which can result in altered antigenicity.7

Some variants circulating in India are - B.1.1.7 or 20I/501Y.V1 which was detected in the United Kingdom in October 2020 which has been partially correlated with N501Y mutation in Receptor Binding Domain (RBD) of Spike protein; B.1.351 detected in the South African population, which could infect more younger people and had three primary mutations in the RBD of Spike protein,

namely, N501Y, K417N and E484K; P.1 detected in January 2021 in the Brazilian population had three mutations of concern in Spike RBD, namely, N501Y, K417T and E484K.<sup>8,9</sup> All these variants which have been named as Variants of Concern (VoC) have been found in India.10 According to the database of the Indian SARS-CoV-2 Genomics Consortium (INSACOG) on 5th May 2021; among the 3900 samples collected across India and detected with having a variant; a total of 1922, 127 and 1 sample (or samples) have been found with B.1.1.7, B.1.351 and P.1 variants respectively. Although the lineage B1.1.7 has now reached community level transmission in India, INSACOG states that it has been relatively declining in proportion across the country in the last 1½ months.<sup>10</sup>

However, a new B.1.617 lineage, first identified in India on 12th March 2021 and recognized as Variant of Interest (VoI), has been found in a total of 1850 samples in the INSACOG database. A phylogenetic analysis done during the sudden upsurge of the disease in Maharashtra since January 2021 found that there was a distinct newly identified lineage B.1.617 with some common mutations -G142D, L452R, E484Q, D614G, P681R in the spike protein and the RBD. Structural analysis showed that these mutations result in increased binding to the ACE-2 receptor and rate of S1-S2 cleavage, therefore, implying increased transmissibility. It is the combination of these mutations, and not the mutations itself that is unique in the B.1.617 lineage.

Since we have noted the mutations associated with the B.1.617 lineage, let us further discuss each mutation in this lineage and how they increase infectivity of the virus. Korber et al and Volz et al implied that the D614G mutation in the Wuhan reference strain is found to be associated with higher viral load, increased infectivity and younger age group even though it does not affect the severity of the disease which was measured using hospitalization outcome. 12,13 Furthermore, structural analysis shows that this mutation alters the receptor binding in a way that it increases ACE binding and fusion. 14 It also creates an additional serine protease (elastase) cleavage site near the S1-S2 spike junction that may enhance virus membrane fusion by several times and might have a competitive advantage at the furin binding domain which was probably responsible for the upsurge.<sup>15</sup> In a California based study, it was concluded that L452R mutation in the spike protein promotes structural changes in the region that promotes the interaction between RBD and the receptor thus increasing infectivity which was implied by prior studies as well. 16 Other studies by Jangra et al and Tortorici et al showed that mutations at the E484 (E484K/Q) affect binding of the serum neutralizing antibodies to the recombinant virus which results in higher infectivity. 17,18 Kumar et al observed that E484Q mutation results in increase in intra-chain interaction in the spike protein which can affect the interaction of human antibodies with the spike protein leading to higher infectivity rate.19

According to data from GISAID (Global Initiative for Sharing Avian Influenza Data), the Indian variant is 60% more transmissible than the UK variant and 2.6% more transmissible than the original strain.<sup>20</sup> From the total samples collected and sequenced over past weeks, 59% (1239 of 2121 samples) attributed to B.1.617 lineage.<sup>21</sup>

### **VACCINES FOR COVID-19**

The antiviral vaccines fall into various categories like the Live attenuated, virus-like particle (VLP), viral vectors, protein-based, DNA-based, and mRNA-based vaccines. Various vaccines are under development across the globe that amount to close to 300 vaccine projects.<sup>22</sup> Some of them currently in use are Pfizer-BioNTech, Moderna, Oxford-Astrazeneca, Janssen, Covaxin and Sputnik V.<sup>23</sup>

As of now, 8 Covid-19 vaccines are under trial in India of which, 3 are approved by the Drugs Controller General of India (DCGI) for emergency use; which are Covaxin, Covishield and Sputnik V.<sup>24</sup> The Oxford–AstraZeneca vaccine is a viral vector vaccine which contains chimpanzee adenovirus as a vector which is genetically engineered so that it cannot grow in humans and made in India under trade name of 'Covishield' by Serum Institute of India which was studied in the 4 RCTs conducted by Knoll et al.<sup>24-26</sup> In these RCTs, the investigators pooled results from the UK, Brazil and South Africa for the ChAdOx1 nCoV-19 (AZD1222) Oxford-AstraZeneca vaccine in adults aged 18 years and older in December 2020, found out that Vaccine efficacy after more than 14 days from the 2nd dose was 70.4% in 5807 participants in the ChAdOx1 nCoV-19 group versus 101 [1·7%] of 5829 participants in the control group).26 In another trial conducted in the United States, Peru and Chile, no participant who had been vaccinated had to be admitted for serious COVID-19 related complications.<sup>27</sup>

Inactivated whole-virion SARS-CoV-2 vaccine BBV152 (COVAXIN) developed by Bharat Biotech, India, uses a complete infective SARS-CoV-2 viral particle made of RNA surrounded by a protein shell, modified to not replicate. An article by Thiagarajan et al, stated 81% vaccine efficacy post the second dose of vaccine. These interim results of phase III trials included 25,800 participants. 9

Last but not least, the latest approved COVID-19 vaccine in India is 'Sputnik V' developed by Gamaleya Research Institute Epidemiology and Microbiology, Health Ministry of the Russian Federation. It is a non-replicating adenovirus (rAd26-S + rAd5-S) type vaccine. Sputnik V is made of 2 components which makes up the first and second doses of the vaccine regime. One component is with the recombinant adenovirus vector based on the human adenovirus type 26 and another with the adenovirus vector based on the human adenovirus type 5, both containing the SARS-CoV-2 S protein gene. Sputnik V had successfully cleared preclinical trials on various animals and it had also cleared Phase 1 and 2 clinical trials for its safety and

efficacy in humans.<sup>28</sup> The vaccine has completed its phase 3 trials with 19866 participants in India and has shown strong antibody and cellular immune response. There were no serious adverse effects associated with vaccination.<sup>29</sup>

# NEUTRALIZING ABILITY OF THE AVAILABLE VACCINES

As discussed earlier in the article, many vaccines have been developed and approved for use against SARS-CoV-2. At the same time, virus has undergone rapid mutations. Few studies have been done to know whether the existing vaccines are effective against existing and the newly mutated viruses.

It is of utmost importance to understand the neutralizing ability of vaccines against the B.1.617 variant which is considered to be responsible for sudden upsurge in the cases in India. Yadav et al collected neutralizing-antibody (NAb) titres against B.1.167.1 and prototype B.1 variant from sera of COVID-19 naive subjects and COVID-19 recovered subjects; both groups had received two doses of Covishield. The study showed that COVID-19 recovered subjects had higher NAb titres as compared to COVID-19 naive subjects. And there was a significant difference in NAb titres of B.1 and B.1.167.1. The researchers also concluded that Covishield induced NAb titres were likely to limit severity and mortality of disease in vaccinated individuals.<sup>30</sup> In one other study, the researchers collected sera samples from individuals infected from B.1.351, B.1.1.7, B.1.1.28.2 and B1 variants and from recipients of BBV152 (Covaxin). They used the sera to perform plaque reduction neutralization test (PRNT50) against the B.1.617 variant. The researchers compared the results and demonstrated that neutralizing capacity against the variant is similar from sera of vaccinated individuals and that from recovered cases.31 Edara et al demonstrated neutralizing antibody response to the B.1.617.1 variant in serum from infected and vaccinated (with mRNA Vaccines) individuals. The results showed that the new variant was 6.8-fold less susceptible to neutralization by sera from infected and vaccinated individuals. Despite this, sera from all the vaccinated individuals and sera from majority convalescent individuals, was able to neutralize the variant. The researchers concluded that individuals vaccinated with mRNA vaccines are likely to retain protection against B.1617.32 However, the study is limited with a small sample size.

Singh et al quantitatively assessed the antibody titre in sera of healthcare workers at four time points between 21 days or more, after the first dose to 6 months after the second dose. The study was done as a part of Pan India, Cross-sectional, Coronavirus Vaccine-induced Antibody Titre (COVAT) study. The study showed that both the vaccines available in India i.e Covishield (ChAdOx1-nCoV) and Covaxin (BBV-152), elicited an immune response and the seropositivity rates were significantly higher with covishield after first dose.<sup>33</sup>

Madhi et al conducted a randomized control trial to study the efficacy of ChAdOx nCoV-19 (Covishield/ AZD1222) vaccine against the B.1.351 variant which was first identified in South Africa. The neutralization assays post vaccination showed greater resistance to the B.1.351 variant in serum samples obtained from vaccine recipients as compared to placebo recipients and concluded that the two dose regimen of ChAdOx1 nCoV-19 was not protective against mild to moderate COVID-19 due to the new variant.<sup>34,35</sup>

Emary et al reported an analysis of the efficacy of Covishield against the B.1.17 variant which was the dominant cause of COVID-19 in the United Kingdom. The study revealed that the vaccine was efficacious against the B.1.1.7 variant of SARS-CoV-2.<sup>36</sup>

Khoury et al made a predictive model showing neutralization and efficacy against viral variants. They analyzed the relationship between in vitro neutralization levels and observed protection from SARS-CoV-2 infection using data from seven current vaccines and from convalescent cohorts. They used neutralization titers available from seven published vaccine studies and normalized the titers using similar assay in all studies. On comparing the normalized neutralization levels against corresponding protective efficacy from seven phase 3 clinical trials. The analysis suggested that the mean in vitro neutralization level of a vaccine measured early after vaccination was predictive of the subsequent protective efficacy measured in phase 3 trials, and estimated that the 50% neutralization level for SARS-CoV-2 approximately 20% of the mean convalescent titer.<sup>37</sup>

# BURDEN OVER EXISTING HEALTH CARE SYSTEM

As evident from history, a pandemic can overwhelm the healthcare system of a country, especially in a developing country like India.38 The COVID-19 pandemic has put an immense burden over the health care system globally. India being home to 1.3 billion people has not enough health care infrastructure to cater to this massive population. 39,40 India has 5 beds per 10,000 population as recorded in 2017 and 9 physicians per 10,000 population as recorded in 2019.40,41 This available resource is still below the recommended levels suggested by the World Health Organization (WHO). Meanwhile, the health minister has also admitted that India has entered into a state of community transmission.<sup>42</sup> Currently, India is facing a second wave of Covid-19. 60% of India's total population resides in rural India.<sup>38</sup> Also, there is a shortfall at all tiers of rural health care system i.e Sub-Centres, Primary Health Centre (PHC) and Community Health Centres (CHC), and the workforce availability here is below recommended levels suggested by the WHO.43 The rural and urban healthcare set up differs with regards to resources and patient load. Due to lack of availability of enough resources, medicines and health care professionals at rural setup, there is a ripple effect causing the patients from rural areas to attend tertiary health care services in urban areas.<sup>38,44</sup> This further leads to overwhelming of tertiary care setup. In urban setup, resources such as mechanical ventilators are not in adequate numbers to meet the suddenly increased demand, and thus burden over the existing health care system has amplified.<sup>39</sup> The pandemic has also caused health disparities, as the existing public health system has been allocated into COVID response to meet the increased burden, and thus disrupting the routine health services.<sup>45</sup> India will need to address the decades of underinvestment in public health systems and social health, which may leave it struggling at this time of crisis.<sup>39</sup>

The COVID-19 pandemic has exposed our frontliners Health Care Workers (HCWs) to a unique set of stressors and challenges. The HCWs are facing mental health issues such as severe anxiety and depression, burnouts, harassment, resource related issues, physical and mental fatigue, presenteeism phenomenon, uncertainties in workplace and future, public stigma, discrimination and self stigma. He In a global survey by Schneider et al, they reported that there was no difference in anxiety levels between countries with a high incidence rate as compared to countries with few COVID-19 cases. Adequate rest, mental support, family support, personal protection, rewards and appreciation can contribute to the well-being of HCWs and higher quality of patient care.

# SOCIO-POLITICO-ENVIRONMENTAL FACTORS FOR UPSURGE

Epidemiology of infectious diseases is commonly explained through the host, vector and environment triad. Multiple socio-political events started after the lifting of a 9 month long complete/partial lockdown with eminent personalities declaring that the nation has won the war against COVID-19 which might have resulted in complacency in following the COVID-19 protocols. 2 weeks before the lowest dip in recorded daily new cases, India began its First phase of vaccination drive on 16th January'21 which included Frontline workers.<sup>48</sup>

The month of February marks the beginning of wedding season in India. Many weddings that occurred in February'21 reported some of their attendants turning COVID-19 positive after attending the gathering. 49,50 India marked the beginning of the second wave in mid February.<sup>51</sup> Various political rallies for state assembly election, and elections in local municipality and nagar palika were seen in the month February and March. As reported by media, the rallies did not observe COVID Appropriate Behaviour which might have added to the surge.<sup>52</sup> Kumbh Mela- a religious gathering which occurs once in every 12 years, observed the first Shahi Snan alongside the elections. The religious event mandated a negative RT-PCR report to participate in the event.<sup>53</sup>

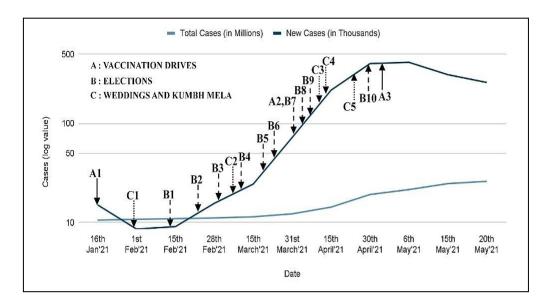


Figure 1: Infographic showing the series of events with respect to timeline and corresponding changes in the graph depicting the second wave. Note that weddings are pan India and elections in many states.

A1: 16th January'21- Beginning of First phase of vaccination drive. 1st February'21 - Lowest number of new cases since last peak in Sept'20. A2: 1st April'21 - Beginning of Second phase of vaccination drive. A3: 1st May'21 - Beginning of Third phase of vaccination drive. B1: 14th February'21 - Punjab municipal corporation elections. B2: 21st February'21 - Gujarat municipal corporation elections. B3: March'21 - Election rallies across 4 states. B4: 10th March'21 - Andhra Pradesh municipal corporation elections. B5: 20th March'21- Goa municipal council elections. B6: 27th March'21- 1st Phase of election in West Bengal and Assam. B7: 1st April'21 - Elections in West Bengal and Assam. B8: 6th April'21 - Elections in West Bengal, Assam, Kerala, Tamil Nadu. B9: 7th April'21 - Himachal Pradesh municipal corporation election. B10: 30th April'21 - Telangana municipal corporation election. C1: February'21 - Wedding season in India. C2: 11th March'21 - 1st Shahi Snan of Kumbh Mela. C3: 12th April'21 - 2nd Shahi Snan of Kumbh. C4: 14th April'21 - 3rd Shahi Snan of Kumbh. C5: 27th April'21 - 4th Shahi Snan of Kumbh.6th May'21 - Highest number of new cases recorded.

The second phase of vaccination which included elderly citizens aged 45 and plus, started on 1st April, 2021 right after the election campaigns that occurred in 4 major states. Crowded vaccine centres may have also passed on the virus to unsuspecting recipients either during their first dose or second dose. <sup>54</sup> Meanwhile, the Kumbh witnessed second, third and fourth Shahi Snan in the month of April. <sup>53</sup> There was intense media and administrative focus on the Kumbh event and the surge in India coincided with this event.

The third phase of vaccination which included the youth (age: 18-44) of India started by 1st of May, 2021 almost near to the recorded highest peak of daily cases that the country saw on 6th May, 2021.<sup>55</sup> This phase also saw the shortfall of vaccines and due to the fear of the pandemic and with various lockdowns since the last week of April, it may not have contributed much to virus transmissions as there was fear in the air.

The government data shows that 88% of the population that died due to COVID-19 disease up to December 2020 were above the age of 45 years. People under the age of 45 years account for 65% of the COVID cases but constituted only 12% of the total deaths. <sup>56</sup> The data of population age group across India for second wave has not been released yet, but the data from Maharashtra (the most affected state in both the waves of pandemic) shows that the total percentage of children and adults (up to 50 years) infected was around 65%, while the percentage of senior citizens

(above 60) testing positive was 18%, as released by the state health department.<sup>57</sup> These data suggest that the younger population is more affected in the second wave as compared to the first wave. It is likely that the elderly population may have escaped hospitalization and severe disease due to vaccines, since vaccination for elderly began before the second wave.

### **CONCLUSION**

The sudden upsurge in the cases of Covid-19 across the country is multifactorial and can be attributed to liberalisation of laws, complacency of people, vaccine hesitancy, unpreparedness of the healthcare system and lack of resources in healthcare settings. Also, the virus itself has undergone mutations, which has increased its infectivity and transmissibility. Due to the exponential increase in the number of cases and inadequacy of the healthcare infrastructure and resources, the nation has entered into a state of crisis. The demand and supply remains unbalanced. Moreover, definitive treatment of the disease is yet to be discovered. Only ramping up vaccination can prove India in its battle against COVID-19. Vaccination-Sanitizing-Masking-Social distancing (V-SMS) remains the gold standard in this fight, while vaccination being a cherry on top.

Funding: No funding sources Conflict of interest: None declared Ethical approval: Not required

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Cite this article as: Barot KS, Naik SH, Patel MH, Mankad SP, Akash A. Patel AA, Pandya et al. COVID-19: sudden and dramatic upsurge in the number of cases in India. Int J Community Med Public Health 2021;8:4089-93.