Second Wave in India: Rapid Rise of Dangerous Variant of COVID-19

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India is witnessing a second wave of the coronavirus pandemic covid-19. This pandemic has proved to the most unpredictable due to the quick spread new variant of coronavirus. The infection and its trajectory is still evolving across the globe. India is currently experiencing a massive covid-19 surge (Fig. 1). Neither the Indian Government or public was prepared for this pandemic. Till date, active cases of covid-19 in India crossed the four lac mark for the first time. Handlining such a volume can be debilitating for any country like India that has a shortage of resources including life-saving resources such as medicine, hospital beds, oxygen, ventilators, even ambulances, and their management. There has been shocking, collective policy failure. Some states have created so-called war room for managing resources at hospital and others have made portals showing live-availability of beds and oxygen but execution of such measures is not carried out properly. However, there are report mismanagement of proper information about the availability of beds, medicine and oxygen. Deaths in many states are still could on the basis of reporting from hospitals. The deaths of patients while waiting outside a hospital for a bed or while under home quarantine, with or without a covid-19 test report, are never included in official statistics. The real deaths toll is for higher than official figures. Numerous crematoriums in Delhi have been forces to expand into footpaths, nearby parks, car parks and open ground.

The WHO chief Tedros Tedros says that the situation in India is beyond heartbreaking. India's deadly covid-19 second wave was cased by a 'perfect storm' of mass gatherings, low vaccination and more contagious variants. The WHO also said unnecessary pressure was being put on India's healthcare system by people who were going to hospital in a panic when they could recover from covid-19 at home. The massive struggle for hospital beds, medicine and oxygen are affecting the mental well-being of people. The WHO spokesperson Tarik Jasarevic also warned against blaming mutation of a virus at the sole cause of the Tsunami of cases that have engulfed India in second wave, collapsing the country's healthcare system.

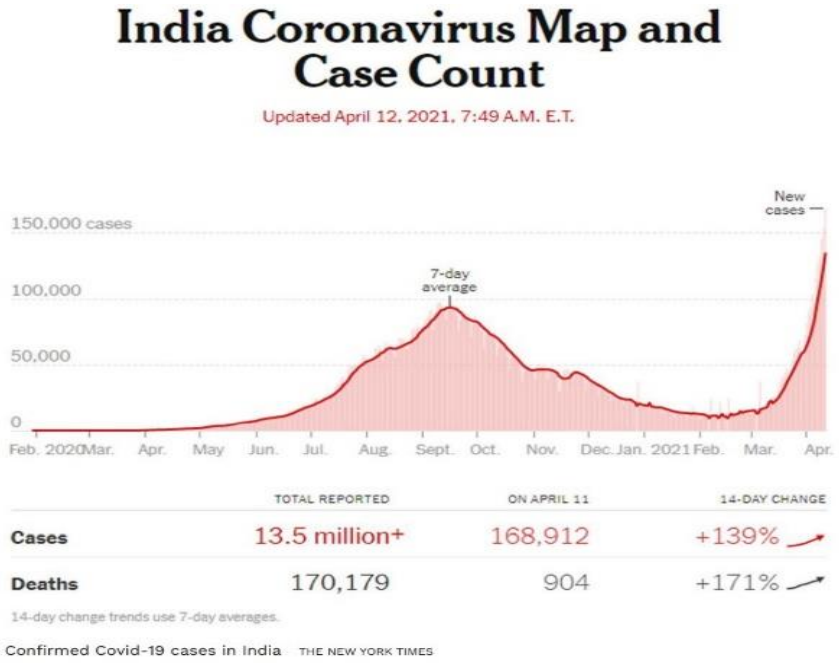


Fig.1 X Confirmed cases of Covid-19 in India (Source: The New York Times)

Emergence of New Variant

Since clinical diagnosis of infection caused by this variant has not been defined yet due to cases of negative in the RT-PCR but positive after a CT scan or chest X-ray. Some experts have said that the current wave is propelled by emerging mutant variant. A mutation is a change in a genetic sequence, occurring in nucleotide, the basic substance that make up the big RNA and DNA molecules. The sequence of these nucleotides in the RNA or DNA determines the amino-acid sequence. Amino acids are the building blocks of proteins which are species-specific. A mutation in a viral genome can change the encoded amino acid sequences which further can change the structure of the proteins. There are two types mutations; deletions and substitutions. Substitutions can be autocorrected by a proofreading mechanism, but deletion will not be autocorrected.

Table1 SARS-CoV2 variants of interest (VOI) and variants of concerns (VOC) as on 27 April, 2021 (Source: WHO)

	Nextstrain clade	Pango lineage	GISAID clade	Alternate name	First detected in	Earliest samples	Characteristic spike mutations
VOC	20I/501Y.V1	B.1.1.7	GR/501Y.V1	VOC 202012/01†	United Kingdom	Sep 2020	69/70del, 144del, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H
	20H/501Y.V2†	B.1.351	GH/501Y.V2†	VOC 202012/02	South Africa	Aug 2020	D80A, D215G, 241/243del, K417N, E484K, N501Y, D614G, A701V
	20J/501Y.V3	B.1.1.28.1, alias P.1†	GR/501Y.V3	VOC 202101/02	Brazil and Japan	Dec 2020	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G H655Y, T1027I, V1176F
VOI	20A/S.484K	B.1.525	G/484K.V3	-	United Kingdom and Nigeria	Dec 2020	Q52R, A67V, 69/70del, 144del, E484K, D614G, Q677H, F888L
	20C/S.452R	B.1.427/ B.1.429	GH/452R.V1	CAL.20C/L452R	United States of America	Jun 2020	S13I, W152C, L452R, D614G
	20B/S.484K	B.1.1.28.2, alias P.2	GR	-	Brazil	Apr 2020	E484K, D614G, V1176F
	-	B.1.1.28.3, alias P.3	-	PHL-B.1.1.28	Philippines and Japan	Feb 2021	141/143del, E484K, N501Y, D614G P681H, E1092K, H1101Y, V1176F
	20C	B.1.526 with E484K or S477N	GH	-	United States of America	Nov 2020	L5F, T95I, D253G, D614G, A701V, E484K or S477N
	20C	B.1.616	GH	-	France	Jan 2021	H66D, G142V, 144del, D215G, V483A, D614G, H655Y, G669S, Q949R, N1187D
	-	B.1.617†	G/452R.V3	-	India	Oct 2020	L452R, D614G, P681R, ±E484Q

†*While work is ongoing to establish standardized nomenclature for key variants, these are the names by which WHO will refer to them in this publication.*

Most of the variants of concerns (VOC) (Table1) contain an extensive set of mutations in the structural proteins, the replication enzymes ad the accessory proteins. B.1.617 is no exception. This carries one mutation in each of the replication enzymes, NSP3, NSP6, NSP13, NSP15 and NSP16 as well as mutation in the accessory protein, orf3a, orf6 and orf7a. But what is the unique about this variant is that it has all the hallmarks of a very dangerous virus. It is this variant that is driving the unprecedented exponential increase in infection in India. SARS-CoV-2 is the first variant that have two mutation, enabling it to evade antibodies and increase infectivity. This ‘double mutant’ virus, casing the spread of pandemic India has a formal scientific classification: B.1.617 (Fig. 2).

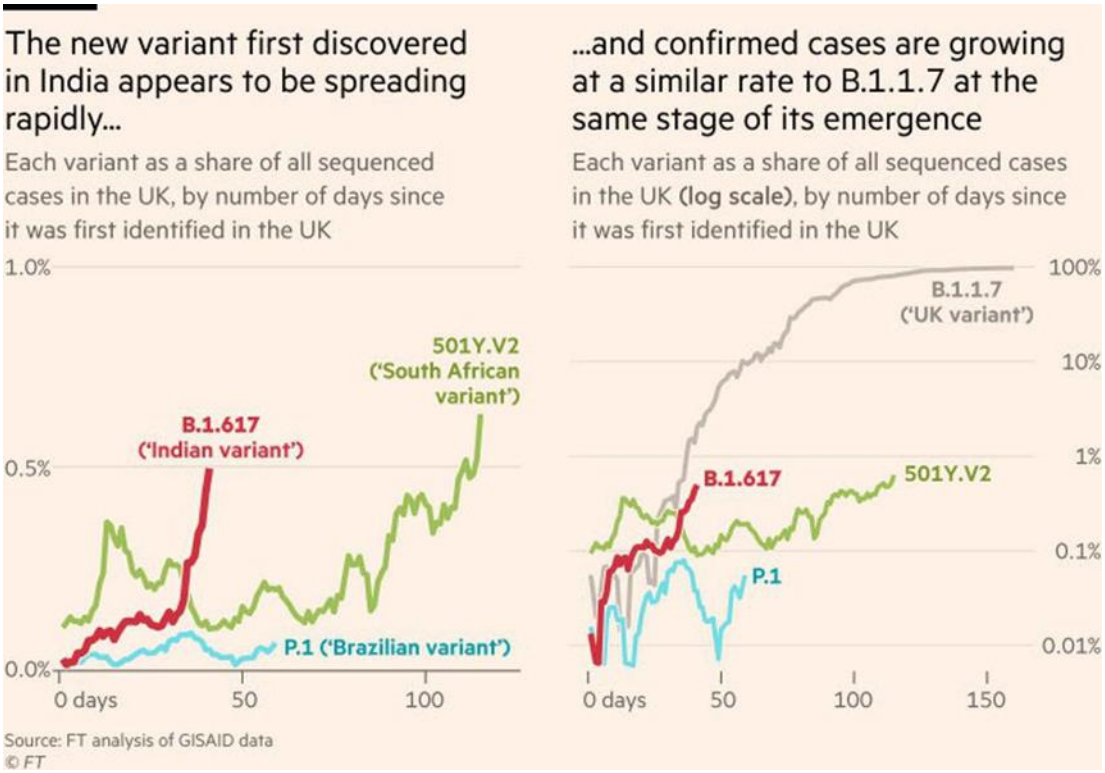
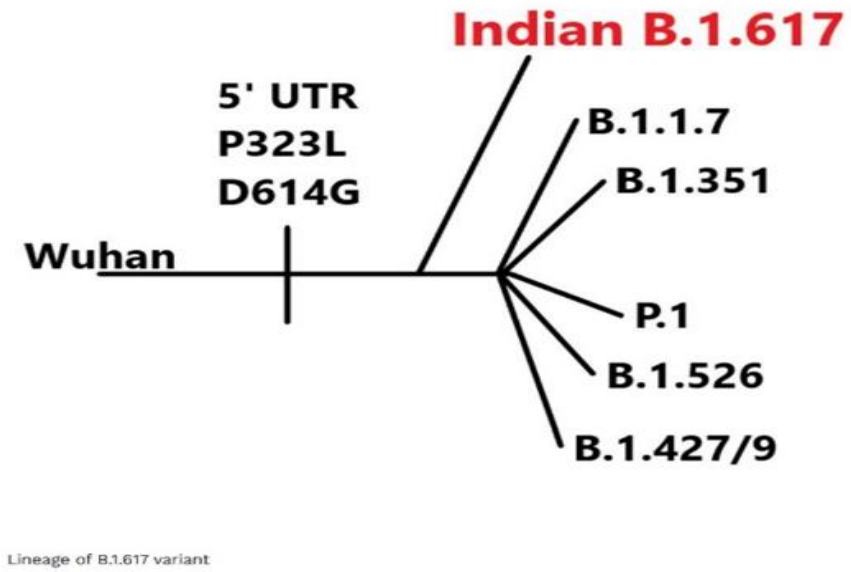


Figure 2: Spreading of various variants based on dated of FT analysis (Source: Financial Times and GISAID)

The strain has been detected in at least five Indian states and the Indian variant designed as B.1.617 and other variants such as B.1.1.7 (United Kingdom), B.1.351 (South Africa), P.1 (Brazil), are also circulating India (Fig. 3). Detailed analysis of the genome and proteins of B.1.617 revealed its independently in India. The INSACOG, the consortium of laboratories that's sequencing a sample of genomes from coronavirus patients in India, B.1.617 was first detected in India December 7, 2020.



Lineage of B.1.617 variant

Figure 3: Lineage of B.1.617 variant (Indian Variant) (Source:?)

Genome analysis of New Variants

COVID-19 is a positive-sense single stranded RNA virus belonging to a large family of viruses known as Coronaviridae. The spike protein of the novel coronavirus has a total lengths of 1273 amino acids, numbered from 1 to 1273. The most significant part of the spike protein is the receptor binding protein (RBD), which is responsible for attaching the SARS-CoV-2 virus to the human ACE2 receptor on some cells, to infiltrate those cells. RBD is denoted by residues number from 319 to 541 (Fig. 4). The main functional motif in RBD is the receptor-binding motif, which form the interface between the spike proteins and human ACE2 receptor and represent residue from 438 to 506. Any mutation that occurs at amino acid residues from 219 to 540, especially between 318-506, may significantly impact the virus's infectiousness, transmissibility, severity and /or its immunity-evading potential.

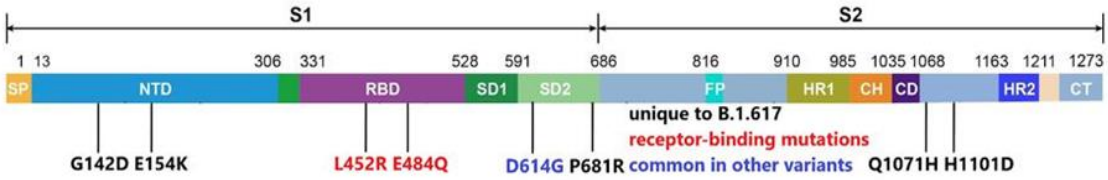


Figure 4: Genome of Indian Variant – B.1.617 (Source:?)

Certain variants of the coronavirus such as B.1.1.7 (UK) and B.1.351 (South Africa) have mutations associated with large spikes reduces the efficacy of vaccines and are termed 'variants of concerns' (VOC). The B.1.1.7 variant has got an N501Y mutation (substitutions) at the 501 residue, N asparagine has been replaced with Y tyrosine. Both the B.1.351 and the P.1 variants have other substitutions apart from N501Y. The B.1.351 variant has E484K (glutamic acid E replaced with lysine) and K417N (lysine K replaced with asparagine N). The P.1 variant has the E484K and the K417T mutations.

Though these mutations have individually been found in several other coronavirus variants, but their presence of both these mutations together (double mutants) have been first found in some coronavirus genomes from India. The variant has a couple of defining mutation, E484Q and L425R, that enable them to become more infectious as well as evade antibodies. The double mutant strain with E484Q and L452R have point substitutions which fall in the key RGM (438-506) region of the RBD. So, they may induce major changes in the virus's properties. This is based on the recent study on the California lineage (B.1.427/B.1.429) involving the L452R mutation (leucine L replaced with argine R at 452), which is could have strong immunity-evading potential (Fig. 5).

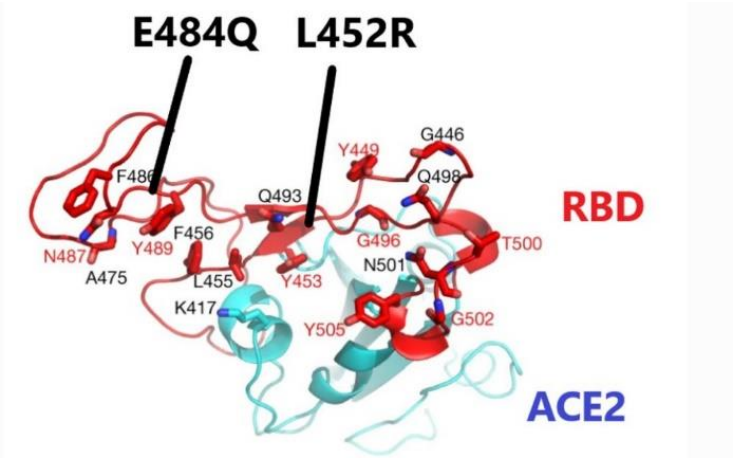


Figure 5: 3D structure of a protein part of variant B.1.417 indicating interaction of RBD with ACE2

First mutant involves the change of leucine to arginine substitutions at amino acid 452 (L452R). This change is the same change found in the California variant. This changes both increases the affinity of the spike for the receptor and decrease antibody recognition. Second mutation of interest occurs at amino acid 484. E484 is a known vaccine immunity evader mutation. The Indian variant B.1.617 is also mutated at position 484, but mutation is different. The glutamic acid is substituted by the polar uncharged amino acid glutamine (E484Q). This change confers increased ACE2 binding and immune evasion properties.

Efficacy of Vaccines against Double Mutant

The mutation L452R are reported to make coronavirus resistant to T cells - a class of cells necessary to target and destroy virus-infected cells. T-cells are different from antibodies that are useful in blocking coronavirus particles and preventing it from proliferating. Some international studies demonstrated the reduced efficacy of vaccines against to certain variants from Moderna, Novavax and Pfizer. India has conducted limited lab trials for efficacy. Many have raised questions about the COVID-19 vaccines, against the new variants circulating in many states. These vaccines are Covishield and Covaxin, and have been given out since January 16 this year.

Should we continue using Covishield where the B.1.1.7 variant and other new variants are emerging? Will Covaxin be more efficacious? The B.1.1.7 variant is not usually considered to belong to an immune-escape lineage. The new vaccines that have been tested against this variant (Novavax in efficacy trial, Pfizer-BioNTech and Moderna vaccines in laboratory studies) have found only modest reductions in efficacy or neutralisation titres. A study recently published in The Lancet reports that Covishield retains a meaningful degree of efficacy against the B.1.1.7 variant. Covishield also failed to offer any reasonable protection against the B.1.351 variant. Two other vaccines, Novavax and Janssen (Johnson & Johnson), afforded a reasonable degree of protection.

Remember that the B.1.351 variant contains the E484K point mutation (a substitution) that has also been found in many samples from around India. This mutation is also involved in the 'double mutant'. Since the 484 residue is strongly associated with immune evasion, the chances of Covishield providing any significant efficacy against symptomatic illness is quite remote. However, it can retain reasonable protection against severe disease and death owing to good T-cell immunity. There has been no study of Covishield's efficacy against different variants in India. There is an urgent need to perform such studies, including to understand and/or quantify reinfection rates among people who have received either Covaxin or Covishield. There is also no efficacy data available for Covaxin against different variants.

We should now urgently ramp up our genetic-sequencing programme. A sincere attempt should be made to assess the efficacy of existing, approved vaccines against the new variants. Other, more efficacious COVID-19 vaccines like Novavax's protein-subunit and Janssen's Ad26 vector vaccines, which have demonstrated higher efficacy against variants with the E484K mutation, must be approved on an emergency use basis. Russia's Sputnik V vaccine is another candidate that India has approved to use on an emergency use basis and 1.5 lac doses of vaccines has been received from Russia on May1, 2021 to be used on urgent basis. Now, the government needs to do a better job of taking care of the ill by setting ups field hospitals using stadium, schools, community centers, and many more infra-structures like these; increasing oxygen supply and medicines on emergency as well as on war-scale. The government should declare a medical emergency before it gets worse and set-up a central controlling authority for the best possible top-priority management to control this second wave of pandemic coronavirus.

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