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SARS-CoV-2 variants of concern are emerging in India

To the Editor—The current outbreak of COVID-19 in India, which started in early March 2021, has created a new world record even beyond the outbreaks in the UK, the United States and Brazil. Prior to March 2021, less than 0.7% of the Indian population was infected with COVID-19. This current second wave took only 2 months to infect an additional ~0.36% of the population, and India is now recording over 0.4 million new cases per day (as of 23 April 2021). The true number is probably even higher, with some estimates putting the number of daily new cases at over 1 million, more than five times the officially recorded number[1].

The sudden surge in COVID-19 cases in India coincides with high prevalence of more-transmissible variants, associated with diagnostic test failures and antibody escape[2]. These coronavirus SARS-CoV-2 variants of concern—B.1.1.7 (501Y.V1), B.1.351 (501Y.V2) and B.1.1.28.1 (501Y.V3; also known as P.1)—were observed during the sudden surge in COVID-19 cases in the UK, South Africa and Brazil, respectively, with subsequent local transmission across the world[2,3] (Fig. 1a).

In India, the frequency of 501Y.V1 is higher than that of 501Y.V2 and 501Y.V.3 (Fig. 1b). The recently designated variant of concern B.1.617 and variant of interest B.1.618 have also been gaining attention in India[3] (Fig. 1a–c). Variant B.1.617.1 shows co-occurrence of three key mutations in sequence encoding the viral spike protein: L452R, E484Q and P681R. L452R raised concerns in the United States as part of the California variants B.1.427 and B.1.429 and conferred resistance to the neutralizing monoclonal antibodies X593 and P2B-2F6[4]. E484Q shares antibody-escape features similar to those of mutation E484K, seen in variants 501Y.V2, 501Y.V3 and B.1.618[2]. P681R may enhance processing by host proteases by extending the polybasic 'RRAR' motif, which results in a greater viral load and the potential for increased transmission. Another similar variant of concern, B.1.617.2, with mutations L452R, T478K and P681R, is highly prevalent in the state of Gujrat in India[3]. There was enrichment for the mutation T478K or T478R when SARS-CoV-2 was subjected to weak neutralizing antibodies, which indicates this mutation may lead to antibody escape. Variant B.1.618, which has the E484K mutation, is prevalent in the state of West Bengal, India[3] (Fig. 1c).

New variants are thought to be responsible for re-infections, either after natural infection or after vaccination, as observed in Brazil and the United States, respectively[5,6]. There is evidence that re-infections are already happening in India; a recent survey identified a re-infection proportion of 4.5% from a pool of 1,300 participants infected between January 2020 and October 2020 (ref. [7]).

Another concern about the emergence of new variants is the potential failure of RT-PCR tests for diagnostics. Failure to target the gene encoding the spike protein was observed during detection of the 501Y.V1 variant in the UK[2]. According to the latest guidelines of the Indian Council of Medical Research, approved test kits employ multiplex RT-PCR assays, as tests assessing only the spike protein may fail and thereby underestimate the true number of cases.

During mid-January 2021, vaccination programs commenced in India with the BBV152 (Covaxin) and ChAdOx1 (Covishield) vaccines. Although India is administering more than 3 million single doses of vaccine per day, an amount similar to that in the United States and China, the share of the population fully vaccinated against COVID-19 remains much lower than the global average and remains lower than that in some other nations with a high COVID-19 burden, such as Brazil (Fig. 1e). Adding to these worries, the new variants of concern and variants of interest may be able to escape immunity, induced by natural infection or vaccines, although more data on this are needed[2]. The vaccines BBV152 (Covaxin), ChAdOx1 (Covishield) and Gam-COVID-Vac (Sputnik V), which is soon to be administered, have all shown effectiveness in neutralizing the 501Y.V1 (UK) variant. The current vaccines also seem to provide protection from serious disease and death, but not necessarily from infection[8].

It is important to note that the current prevalence estimates for variants 501Y.V1, 501Y.V2, B.1.617 and B.1.618 are limited to just a few Indian states, as little or no sequencing data have been available from many Indian states, including those in the north and east of the country (Fig. 1c). Despite India's having ten national centers of excellence for genetic sequencing, with capacity for over 30,000 sequences per month, the surveillance of SARS-CoV-2 variants has been slow and has involved only ~2,700 sequenced samples collected from eight states between January 2021 and April 2021 (ref. [3]). The potential for new variants to increase transmission and reduce the effectiveness of vaccines[2,6] means that it is crucial to scale up Indian sequencing efforts and characterize the distribution of variants across all states.

This is especially important because in some Indian states, the current reproduction number (R_t; January 2021 to April 2021) has increased to more than 2, compared with an R_t of 1.5 for all of India (Fig. 1f). Prioritizing mass immunization, along with variant-guided vaccination drives, which prioritize vaccination in the states reporting new variants and/or a high R_t, will do the most to reduce the impact of COVID-19, in terms of morbidity, mortality and the economy. Early talk of a K-shaped recovery, with growth in the gross domestic product of 4–5% in 2021, now seems far-fetched.

Confirmed daily new cases in India have spiked from 53 per million population (up to March 2021) to >200 per million population (after mid-March 2021) (Fig. 1d). A glimmer of hope lies in an apparently low case-fatality ratio of <1.5%, compared with >3% between July 2020 and August 2020 (Fig. 1d), although many researchers question the official fatality rates. In contrast, the ratio of daily recoveries to daily new cases from the beginning of March 2021 have dropped steeply, reflective of the severe burden of the outbreak on the healthcare infrastructure in India (Fig. 1d). Leading hospitals in Delhi, Mumbai, Bangalore, Hyderabad and Chennai have shortages of essential supplies, and over 130 Indian cities have reported increased numbers of deaths of patients with COVID-19 who are in intensive care, due to a shortage of medical-grade oxygen and life-saving medicines. India can learn from the responses to COVID-19 of other nations such as France, Germany, Spain, Canada and Italy, where the number of hospitalized critically ill patients during the second wave was almost double that in the first wave[9].

If this second wave of COVID-19 in India continues unabated, daily deaths in India could escalate above 15,000 before the second wave subsides and could account for 1.49 million deaths by September 2021 (according to data

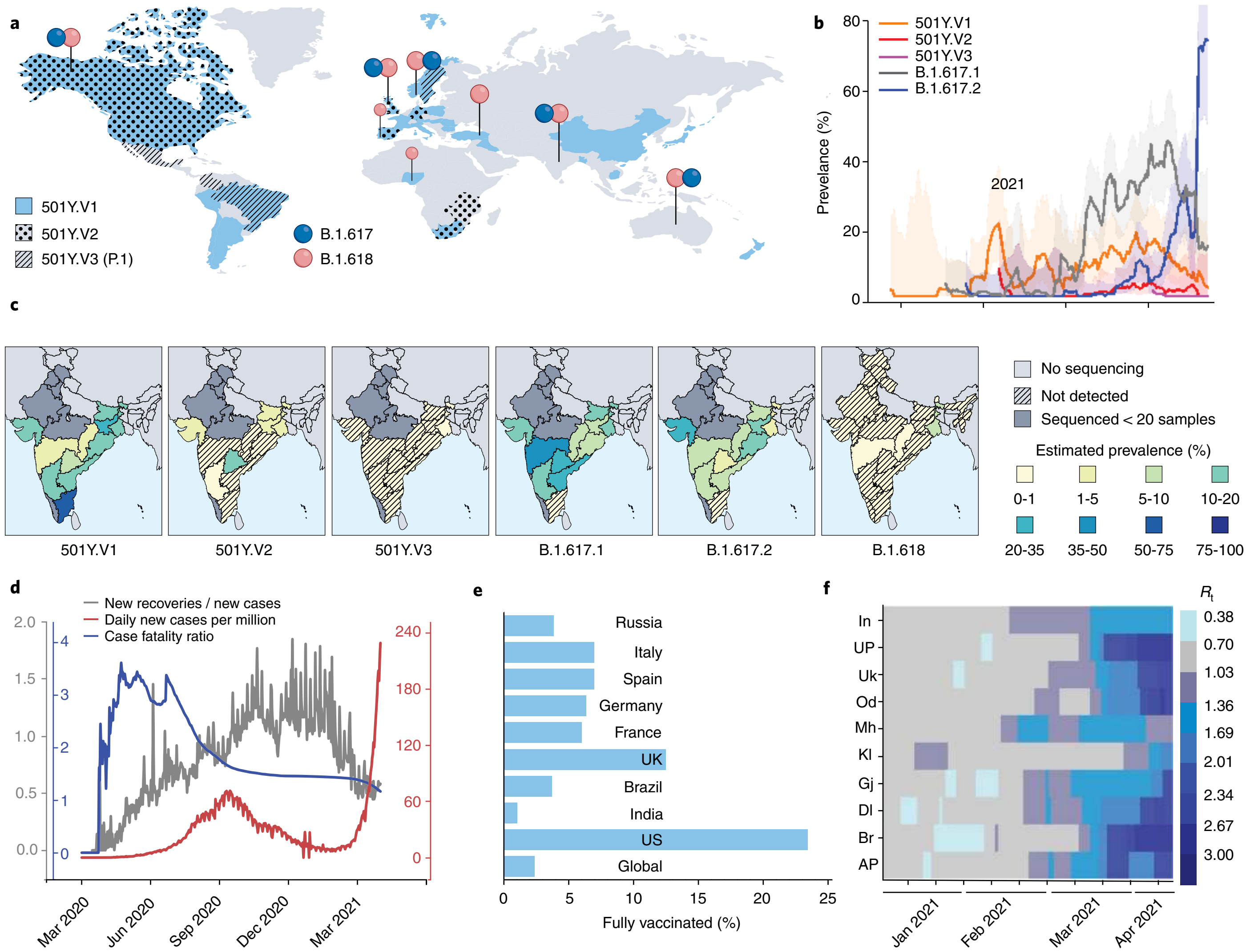

Fig. 1 | Distribution of emerging variants of concern and interest and COVID-19 burden in India. a, Global map indicating where local transmission of variants of concern (501Y.V1, 501Y.V2 and 501Y.V3; left key) has been reported (adapted from the Global Report Investigating Novel Coronavirus Haplotypes website (https://cov-lineages.org/global_report.html)). The 'pinned' locations show nations that have reported the presence of variant of concern B.1.617 and variant of interest B.1.618 (right key), identified through sequence analysis. **b**, Apparent cumulative prevalence of various variants of concern (key) in India, presented as a 7-day rolling average of the percentage of total sequences; shading shows 95% confidence intervals. **c**, Estimated prevalence (bottom key) of variants of concern and the variant of interest B.1.618 (below plots) in various states of India. Data were plotted with a minimum size of 20 sequences within 130 days before 11 May 2021, with GISAID data[10]. Plots and maps in **b**,**c** adapted from the Outbreak.info database[3]. **d**, Plot of the ratio of daily new recoveries to daily new cases, daily confirmed COVID-19 cases per million population and case-fatality rate for India (key; matches axis colors). Data source: Ministry of Health and Family Welfare, India, and COVID19 INDIA (https://www.covid19india.org/). **e**, Share of the global population that has received all vaccination doses, as prescribed by national vaccination protocols. Data adapted from COVID-19 data of the Johns Hopkins University Center for Systems Science and Engineering[8]. **f**, Contour plot of the change in the current reproduction number (R_t) of SARS-CoV-2 (key) for all of India (In) and various Indian states (left margin), from January 2021 to April 2021: Uttar Pradesh (UP), Uttrakhand (Uk), Odisha (Od), Maharashtra (Mh), Kerala (Kl), Gujrat (Gj), Delhi (Dl), Bihar (Br) and Andhra Pradesh (AP). Data obtained from the Ministry of Health and Family Welfare for States and Union territories, adapted from the COVID-19 India-Timeline website (http://www.isibang.ac.in/~athreya/incovid19/indiar.php). Publ. note: Springer Nature is neutral about jurisdictional claims in maps.

from the Institute of Health Metrics and Evaluation: http://www.healthdata.org/covid). Rising infections, hospitalizations and deaths can be mitigated through mass vaccination, better management of health resources and appropriate non-pharmaceutical interventions. The experience of other countries suggests that, apart from new variants, human behavior will also be major issue to worry about in the pandemic.

India has a population of 1.4 billion people, so the large number of cases is helping to drive global cases to unprecedented heights. This outbreak can be tackled only by the leadership in India, which should suspend mass gatherings, increase the vaccination of its population, and prioritize viral genome sequencing for surveillance and community tracking. ❐

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Competing interests

The authors declare no competing interests.

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Brazil needs a coordinated and cooperative approach to tackle COVID-19

To the Editor—After more than 14 months under siege, Brazilians continue to suffer as they see thousands of people dying every day, killed by the fast-moving respiratory pathogen SARS-CoV-2. Families are struggling to secure their livelihoods, quell hunger and, in some cases, adjust to the long-term toll of having survived infection with SARS-CoV-2. With the surge in cases, overcrowding of hospitals and high lethality, those on the front lines understand that Brazil is at war with COVID-19. The assault has been brutal[1]. A quarter of all deaths from COVID-19 in Brazil were officially recorded in April 2021. Meanwhile, a SARS-CoV-2 variant of concern, lineage P.1 (B.1.1.28.1), continues to be detected in an ever-increasing share of infections, on the basis of the small number of genomes sequenced across the country[2].

Many factors explain why the toll of the pandemic on Brazil has been so extraordinary, including its close transport connectivity with world markets, the marked socioeconomic vulnerabilities of its many populations[3], and persistent inequities. A crucial factor in the COVID-19 crisis in Brazil is the lack of central command, strategic planning and clear evidence-based recommendations from the outset[4]. As the fourth minister of health to be appointed since the pandemic began attempts to guide the response, Brazil remains the epicenter of the COVID-19 pandemic in Latin America. The battle against SARS-CoV-2 will be lost without a central command and leaves behind a bitterly divided country.

To win, Brazil needs a unified front coordinated with a common goal: eliminating COVID-19's assault. Multiple fronts must be coordinated, and weapons need to be mobilized commensurate with the threat at hand. The plan must begin through recognition of what is working. There are numerous lessons from other countries and from within Brazil. In the few exceptional cases in which stricter lockdowns were imposed, such as in Araraquara, São Paulo, and surveillance strategies focused on the primary care response, such as in São Caetano do Sul, São Paulo, these measures proved to be extremely effective. The strategy must be clear, coherent and coordinated. Leaders who can build consensus are badly needed to help identify a common agenda of fundamental principles and the policies that can be adopted as part of a national pact.

First, clear and concise evidence-based communication to society is crucial. Handling the COVID-19 pandemic demands that national leaders act to build trust and cooperation. Science has become visible and more valued in society, and it is time for the nation's leaders to show that they are ready to use science as the most important weapon in tackling COVID-19. There is no longer room for government officials to prioritize political opportunism and the spreading of fake news[5].

Second, mathematical models confirm that Brazil needs to adopt stricter measures of physical distancing and, in some states, a lockdown[6]. In contrast, non-pharmaceutical interventions need to be coordinated across states, and social assistance programs need to be targeted to meet the needs of vulnerable populations, such as the economically disadvantaged, racial and ethnic minorities, low-income children, the elderly, the homeless, and those who are infected with human immunodeficiency virus or have other chronic health conditions. Polls suggest that the majority of Brazilians support stricter physical-distancing policies despite the short-term economic hardship[7]. However, in the absence of stricter policies, the level of adherence to social distancing is falling, in part because the majority of people in Brazil cannot work from home.

Third, a strict lockdown will be effective only if the country's ability to predict and respond to SARS-CoV-2 transmission is improved. Testing programs need to be ramped up and focused on identifying people who are transmitting the virus to others, combined with tracing and testing of their contacts. In regions with limited laboratory infrastructure, the widespread use of antigen tests, with their faster turnaround times, will contribute to earlier quarantining. The rapid scaling-up of testing needs to be aligned with a vastly expanded effort to undertake genetic sequencing to detect existing and new variants of concern.

Fourth, the speed of efforts to vaccinate the Brazilian population needs to be increased to warp speed. Local vaccine-finishing production is currently