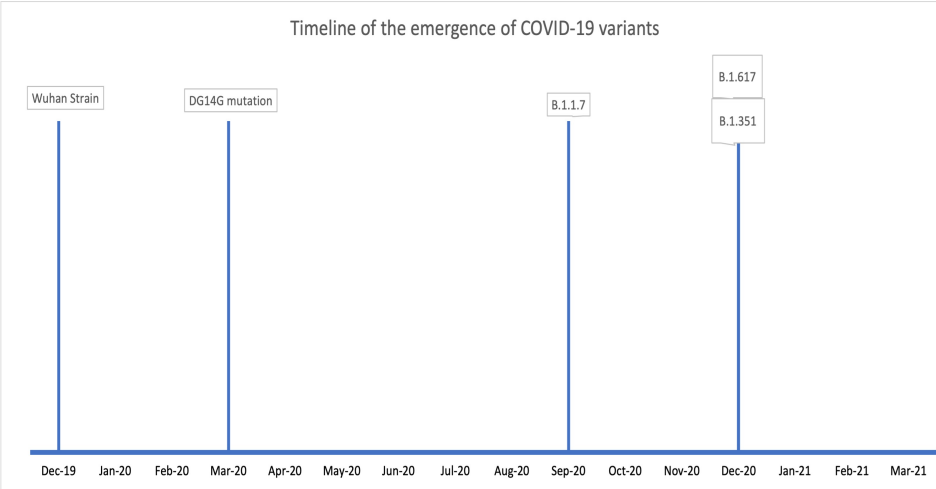


Feedback from operational stakeholders who manage or respond to outbreaks is that they are often too busy to review literature or obtain relevant background information to assist them with acute response. Unlike a traditional analytical outbreak investigation report, **Watching Briefs** are intended as a rapid resource for public health or other first responders in the field on topical, serious or current outbreaks, and provide a digest of relevant information including key features of an outbreak, comparison with past outbreaks and a literature review. They can be completed by responders to an outbreak, or by anyone interested in or following an outbreak using public or open source data, including news reports.

Watching brief	
Title	The evolution and impact of COVID-19 variants B.1.1.7, B.1.351, P.1 and B.1.617
Authors	Authors: Hermione Williams, Danielle Hutchinson, Haley Stone
Date of first report of the outbreak	<p>First Identified Dates Original Strain: Late December 2019 (1) D614G mutation: 24 March 2020 (2) UK variant (B.1.1.7): 20 September 2020 (3) South African variant (B.1.351): 18 December 2020 (3, 4) Brazilian variant (P.1): 2 January 2021 (4, 5) Double variant (B.1.617): 7 December 2020 (6, 7) This lineage comprises several sub-lineages (9). B.1.671.3 was first detected as early as October 2020 in India. Very few samples contain this sub-lineage (8, 9). The two other sub-lineages B.1.617.1 and B.1.617.2 were first detected in December 2020 (9) .</p> <p>Figure 1. Timeline showing when each variant of concern emerged</p>  <p>The figure is a vertical timeline titled "Timeline of the emergence of COVID-19 variants". The x-axis represents time from December 2019 to March 2021. Key events are marked with vertical lines and boxes: Wuhan Strain (Dec-19), DG14G mutation (Mar-20), B.1.1.7 (Sep-20), B.1.617 (Dec-20), and B.1.351 (Dec-20).</p>



	<p>Due to a lack of genome testing, it is hard to determine whether the first cases are accurate for B.1351, P.1 and B.1.617.</p>
Disease or outbreak	COVID-19 variants of concern (VOC): B.1.1.7, B.1.351. P.1 and B.1.617
Origin (country, city, region)	<p>Original Strain: Wuhan, Hubei Province, China (1). D614G: March 2020 Globally (10, 11). B.1.1.7: Detected in Kent, in the South East of England on 20 September 2020 (10, 12, 13). B.1.351: First found at Nelson Mandela Bay, South Africa on 18 December 2020 (3, 14, 15) (16). P.1: First identified in four Brazilian travellers by the National Institute of Infectious Diseases in Japan sampled during routine screening in airports on January 2 2021 (17, 18). It was circulating in Manaus, northern Brazil at the time (15, 19). B.1.617: Unknown origin, first reported in COVID-19 samples from Maharashtra, India around December 2020 to January 2021 (20, 21). There were very few known cases of B.1.617 lineage till February 2021 (9). The first cases of the variant detected outside of India were found in late February 2021 (9, 22, 23). United Kingdom recorded cases on 22 February, United States detected cases on 23 February and Singapore on 26 February (9, 22-24).</p>
Suspected Source (specify food source, zoonotic or human origin or other)	<p>The suspected source of the COVID-19 pandemic is zoonotic (25). The animal origin is yet to be determined (25, 26). However, the virus was found in environmental samples taken from a live animal market in Wuhan and human cases have been epidemiologically linked to that market (27). The most likely scenario of how the virus was transmitted from animals to humans was through an intermediary animal host (28).</p> <p>All viruses change over time. Mutations, which are a change in the genetic material (RNA) of a virus i.e., changes to the genomic sequence, are a by-product of viral replication. Genomes which differ in sequences are termed variants (8). Many mutations occur by chance or by random and do not have direct benefit to the virus in terms of increasing its infectiousness/transmissibility or virulence (10, 29). Changes to the virus' genome can also arise as a result of certain evolutionary challenges and/or selection pressures. Mutations, which have a competitive advantage will be replicated and those that do not will be culled. VOCs are variants that are favoured due to their evolutionary benefits (10, 29). Due to high human to human transmission, the SARS-COV-2 has undergone multiple mutations with high variability. Currently, there are ~3990 individual genomes found of SARS-COV-2, with the notable B.1.1.7, B.1.351 and P.1 all rising independently of one another (4).</p> <p>How and when the B.1.1.7 variant originated is unclear as it is not phylogenetically related to other COVID-19 viruses circulating at the time B.1.1.7 was found in the United Kingdom. Within a few weeks, it replaced all</p>

	<p>other circulating virus lineages in South East England and London. It is hypothesised that the unusual genetic diversity of B.1.1.7 is the result of viral evolution within a chronically-infected immunosuppressed patient (16).</p> <p>B.1.351 rapidly spread through three provinces in South Africa in late 2020. It is not phylogenetically related to B.1.1.7. It is believed to have evolved through rapid spreading from person to person; gaining more mutations over several months (3, 14). B.1.1.7 appears to have a fitness advantage and is becoming dominant in many countries.</p> <p>Environmental conditions have an impact on a pathogen's success (30). Population density, climate, and host factors such as immunosuppression can affect infection, transmission and selective pressure for mutations to emerge (30). Hence, high-density populations with limited access to healthcare such as Brazil and India where the P.1 and B.1.617 variants respectively were found, may be at risk for variants to originate and grow.</p>
<p>Date of outbreak beginning</p>	<p>A cluster of pneumonia cases with an unknown aetiology was identified in late December 2019 in Wuhan (25). In early January 2020, Chinese authorities identified the cause of the outbreak as being a novel betacoronavirus (31). The new strain was named 2019-nCoV (31). In early February 2020, the World Health Organisation (WHO) named the virus SARS-CoV-2 and called the disease COVID-19 (14).</p>
<p>Date outbreak declared over</p>	<p>Ongoing pandemic (2019 – onwards). Emergence suspected around October to November of 2019 and first reported cases in December 2019 (32)</p>
<p>Affected countries & regions</p>	<p>Detection of arising VOCs or interest is highly dependent on the testing and genome sequencing capacity of health systems throughout the globe. Therefore, information below is based on countries with these established systems of detection.</p> <p>Original Strain and D614G:</p> <ul style="list-style-type: none"> ○ The Wuhan strain was largely found in China. The D614G was responsible for worldwide spread from March 2020 onward and was the dominant global strain in 2020 (1). <p>B.1.1.7</p> <ul style="list-style-type: none"> ○ 118 countries have been verified (23). ○ Dominant strain in the UK, Ireland and Cambodia (33). ○ Dominant strain in the US (34, 35). ○ Second most common variant found in India in the last 60 days (as at April 16) (33). Prevalent in the North of India in Punjab (21). ○ Widespread in much of Europe, dominant strain in Germany, Bulgaria, Sweden, Greece, Italy (33, 36, 37). <p>B.1.351</p> <ul style="list-style-type: none"> ○ 81 countries have been verified (23). ○ Dominant strain in Comoros, Malawi and Botswana, Zimbabwe (38).

	<ul style="list-style-type: none"> ○ Fairly common in Bangladesh, causing 80% of known cases (39). <p>P.1:</p> <ul style="list-style-type: none"> ○ 47% of cases confirmed in Brazil are P.1 (5, 40). ○ 40 countries have been verified (23). <p>B.1.617:</p> <ul style="list-style-type: none"> ○ At least 18 countries have been verified (22). ○ These include: India, Guadeloupe, Singapore, Sint Maarten, Australia, Belgium, Germany, Turkey, Ireland, Namibia, New Zealand, Singapore, Italy, Greece, Spain, Switzerland, Netherlands and the United Kingdom (England and Scotland) and the United States, specifically in the San Francisco Bay Area of California (22, 41). ○ In the days leading up to April 14, 77 cases of the Indian variant have been found across the UK, 73 in England and 4 in Scotland (42). ○ On April 1, B.1.617 accounted for 80% of all analysed genome sequences sent from India to GISAID (20). A high prevalence of B.1.617 is in Maharashtra, which was the hotspot region of India's second wave of COVID-19 (21). However, prevalence patterns may be inaccurate due to low levels of genome sequencing (21). Between 60-80% of cases in Maharashtra are suspected of having B.1.617 (21).
<p>Number of cases (specify at what date if ongoing)</p>	<p>Total number of cases worldwide: There were 141,057,106 confirmed cases and 3,015,043 deaths (1). The case numbers of variants are affected by rates of genomic sequencing, which vary by country and within countries.</p> <p>B.1.1.7: 439, 970 cases, 33% of cases worldwide (23, 33)</p> <p>B.1.351: 11, 781 cases (23)</p> <p>P.1: 6190 cases, 42% prevalence in Brazil (23, 40)</p> <p>B.1.617: 1413 cases (23)</p> <p>B.1.617 in India and total number of recorded cases in India B.1.617 sequenced as of April 27: 1413 (22). Sequencing capacity low. Total number of cases: 17, 313, 163. There have been 352,991 cases reported in the last 24 hours (1)</p> <p>Figure 2. Geographical distribution of B.1.617 cases in India as of April 19. Data obtained from GISAID who utilised samples retrieved by The Microbial Containment Complex of the National Institute of Virology, a BSL4 lab based in Pune, India. (43)</p>

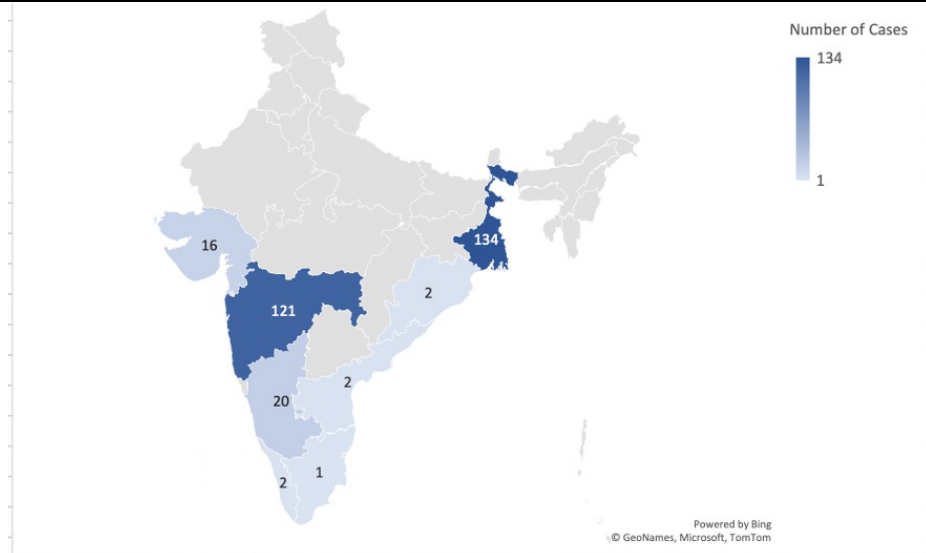
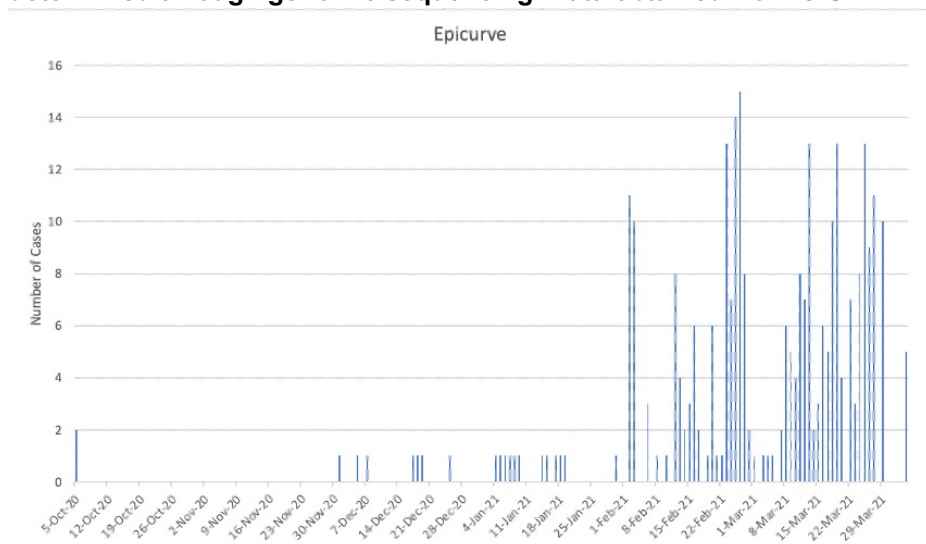


Figure 2. shows the frequency of COVID-19 cases with **B.1.617** in India. The majority of infections are in the south of India. Currently, the most affected states are Maharashtra with 121 cases and West Bengal with 134 cases.

Figure 3. Cases of B.1.617 from October 2020 to March 2021 as determined through genomic sequencing. Data obtained from GISAID.



Clinical features

High asymptomatic infection rate (27)

Main clinical features (27, 44)

- Cough
- Fever (temperature $\geq 38^{\circ}\text{C}$)
- Shortness of breath/difficulty breathing
- Fatigue or weakness
- Loss of appetite
- Loss of smell and/or taste



	<p>Other less common symptoms (27, 44)</p> <ul style="list-style-type: none">○ Sore throat○ Body aches○ Dizziness○ Headache○ Nausea○ Vomiting○ Diarrhoea <p>Severe cases (27, 44)</p> <ul style="list-style-type: none">○ Pneumonia○ Cardiovascular complications including thrombosis○ Gastrointestinal symptoms○ Multi-organ failure <p>There is a high risk of severe symptoms and the need for hospitalisation for those who are older, immunosuppressed, obese, smokers, elderly and/or those who suffer from pre-existing conditions (e.g. diabetes, hypertension and cancer) (45). More severe symptoms, a longer sickness period and higher mortality are correlated with a higher viral load (46).</p> <p>Impact of COVID-19 variants on presentation of symptoms: There is some evidence which shows different clinical features arising in patients infected with certain COVID-19 variants. Less common symptoms seen in those infected with B.1.1.7 were a loss of smell and taste (47). Frequently reported symptoms included cough, sore throat, myalgia and fatigue (47). There was no evidence of a difference in gastrointestinal symptoms, shortness of breath or headaches (48). Patients with B.1.1.7 infections have been shown to have an increased severity of illness and risk of hospitalisation (49).</p> <p>Currently, there is little to no evidence to suggest that the B.1.351 and the P.1 variants produce different symptoms to the initial strain. Limited data is available on the B.1.617 variant. However, data gathered from hospitals in India on people testing positive for COVID-19 have shown unusual viral symptoms (50). Patients are presenting with abdominal pain, nausea, vomiting, diarrhea and hearing impairments. Symptoms seen in patients with the B.1.1.7 variant such as myalgia and weakness are being seen in B.1.617 patients (50). There has also been an increase in symptoms of joint pain and a loss of appetite (50). Some infected individuals are experiencing no fever or a delayed onset of fever. Due to these unusual clinical features, medical professionals are encouraging anyone who feels unwell to get tested (50). However, these, are preliminary findings so the clinical manifestations of B.1.617 cannot be confirmed.</p>
<p>Mode of transmission (dominant mode and other documented modes)</p>	<p>In general terms:</p> <p>The dominant mode of transmission is through the respiratory route and aerosols, especially in an indoor space with poor ventilation (44). Specifically, exposure to the airborne respiratory aerosols of an infected individual and inhalation risk are thought to cause infection (51-53).</p>



Other documented modes of transmission include:

- Faecal transmission: It is dependent on viral concentration and viability, as well as aerosolisation of faecal material through flushing (54, 55).
- Contact with a contaminated surface: It is rare and is dependent on the viability of the virus on that specific surface and the type of surface (56).
- Zoonotic transmission: this is speculated as the origin of SARS-COV-2 but has not been documented (28).
- Ocular transmission is possible (57).
- Transmission from deceased patients through autopsy or funerals (58).

Specifics:

The **B.1.1.7** has shown to be 40-90% more transmissible than the original strain. The variant possesses the **N501Y** mutation. This has been linked to enhanced transmissibility due to increased affinity with host cell receptors, such as ACE2 on epithelial cells, thereby allowing the virus to better establish and propagate infection (59-63). **B.1.1.7** also possesses the **P681H** mutation, a mutation with importance for infection and transmission (60).

A higher viral load has been noted in preliminary studies on **B.1.351**, which may confer increased transmissibility (3, 46). One modelling study estimates that it is 50% more transmissible than other circulating variants (64, 65). The increase in transmissibility can be seen in the spread of the virus through Western Cape in South Africa. The variant reached 100,000 cases 50% more quickly than in the first COVID-19 wave (66). Increased transmissibility is due to the **N501Y** mutation in the receptor binding domain (RBD) of the spike protein (66).

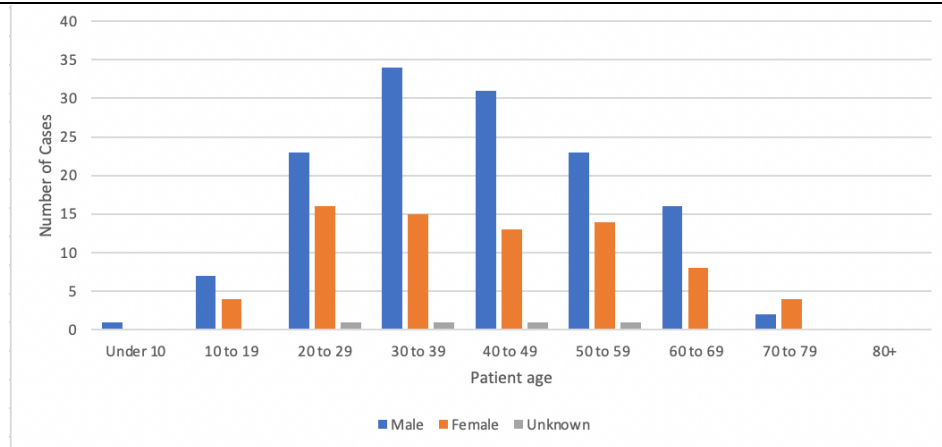
The **P.1** has shown evidence of increased transmissibility with 1.4-2.2 times more transmissible than previous variants (67, 68). This is partly due to the presence of the **N501Y** mutation (69)

B.1.617 possesses the **L452R** mutation which results in a large increase in free energy at the RBD and ACE2 binding complex, leading to stronger virus-cell attachment and therefore an increase in infectivity (70, 71). The **L452R** mutation is also found in the **B.1.429** and **B.1.427** variants which originated in California. The California variants arose independently to **B.1.617**. The California variants, which carry the **L452R** mutation showed a 53% increase in positive test samples in January 2021 compared to November 2020 (72). They have also been associated with an elevated household secondary attack rate suggesting higher transmissibility (72). The **B.1.617**, due to its shared mutations with other circulating variants, may confer increased transmissibility (7).

While there is little evidence at the current time, the second wave of COVID-19 in India, where **B.1.617** was first found, is showing a higher rate of secondary infection. Around 60-90% of people who come into contact with an infected individual are testing positive (50). Unconfirmed reports from Delhi also report high secondary household attack rates. This is in contrast to 30-40% in the first wave (50). However, this is anecdotal evidence in its preliminary stages. This could be due to the presence of **P681R** mutation, also found in **B.1.1.7**, which sits adjacent to the furin cleavage site. Combined



	<p>with the other known mutations such as L452R, the P681H increases binding and subsequent cleavage of the spike protein thereby enhancing systemic infection and membrane fusion and possibly resulting in enhanced transmission (73).</p> <p>Dr Randeep Guleria, the director of the All India Institute of Medical Sciences, has stated that the increased rates of infection seen in the second wave are multifactorial and cannot be confirmed as linked to B.1.617 (74). Due to vaccinations which commenced in January-February and the corresponding drop in infections, the community became lax with preventative measures and many mass gatherings were held (74).</p>
<p>Demographics of cases</p>	<p>B.1.1.7 In a study conducted in the South East of France, the B.1.1.7 variant affected mainly younger and healthier patients (75). In the United States where the B.1.1.7 has become the dominant strain, younger people are more likely to be hospitalised, with an increase seen in the number of 18-64 year old's visiting emergency departments in the U.S (76). Michigan state reported an all-time high for those aged 19 and younger reporting to hospital (77).</p> <p>P.1 P.1 is thought to be responsible for the increase in mortality of young Brazilians in the last few months, therefore signifying increased severity (68). There is increasing evidence that young people are more likely to be infected with the P.1 variant and end up dying from it (68). Cases of individuals in the 30-50 age bracket have dramatically increased. Cases of individuals in their 30s, 40s and 50s have increased by 565%, 626% and 525% respectively since the start of 2021 (68). In March 2021, the risk of individuals in the 18-45 age bracket ending up in intensive care due to COVID-19 was three times as great as what it was in November 2020 (78, 79). In the first wave of COVID-19, data showed that around 70% of the population of Manaus had been infected with the virus 7 months after its arrival in the city. However, there were reports of previously infected individuals getting reinfected in the second wave, suggesting that seasonal coronavirus may not result in long-lasting immunity (80).</p> <p>B.1.351 There is no evidence for demographics other than age groups being more affected by the variant.</p> <p>B.1.617 Figure 4. Demographics of B.1.617 in India as determined through genome sequencing. Data obtained from GISAID.</p>



The demographic of **B.1.617** in India suggests a normal COVID-19 demographic (81, 82) (Figure 4), with the majority of cases reported in those aged 20- 59 (81, 83). Men made up a higher proportion of cases in all age groups excluding the 70-79 group.

The data sourced for Figure 4 is from the GISAID database. The actual number of cases in India with the **B.1.617** strain is unknown and sequencing capacity is low. The data available on GISAID only represents a small sample size of the cases in India, and it is therefore uncertain whether Figure 4 is an accurate representation of the demographics.

While there is limited evidence at the moment, there has been a suggestion that the variant may be responsible for the current increase in the infection of children. Dr. Krishan Chugh, Director and Head of the department of paediatrics at Fortis Memorial Research Institute, Gurgaon, stated that there was a much higher frequency of children being infected with COVID-19 than seen in the first wave (50, 84). Over 79,000 children have tested positive for COVID-19 in five states (Maharashtra, Chhattisgarh, Karnataka, Uttar Pradesh and Delhi) between March 1 to April 4 (84). However, in all cities with severe epidemics, paediatric cases have risen (85, 86). Further, in countries that have vaccinated older people first, a rise in proportional paediatric cases has been seen (87). India commenced vaccinations in January 2021, and it is estimated that 5% of the population is vaccinated.

Case fatality rate

The case fatality rate (CFR) is heavily influenced by age and underlying comorbidities. There is some evidence that other factors such as ethnicity are independent risk factors (88). The CFR also increases with the severity of illness and has been seen to reach 49% in patients who are critically ill (89). The CFR is different in each country but may be affected by the age structure of the population. There is some difficulty in determining the CFR in some countries due to lack of reporting cases and deaths, consequently affecting the accuracy of reported incidence and mortality rates. The age adjusted infection fatality rate is a better measure than crude CFR (90).

B.1.1.7

The estimated risk of mortality significantly increased, from 2.5 to 4.1 deaths



	<p>per 1,000 cases (91, 92). Average infections last 13.3 days compared with 8.2 days for other variants (91, 93).</p> <p>P.1 A significant increase in the CFR among adults of all age groups was seen in Parana, Brazil after confirmation that P.1 strain had been identified in the area (94). There is limited data available on the P.1 strain, however through comparison of data on other variants like B.1.1.7, the shared mutations between the two variants could confer increased mortality (66, 94).</p> <p>B.1.351 South Africa saw in-hospital mortality rise 20% in the second COVID-19 wave compared to the first wave. This is thought to be as a result of greater transmissibility leading to an overburdened healthcare system which impacted hospital care and not as a result of increased severity (66).</p> <p>B.1.617 Limited information is available at this time.</p>
<p>Complications</p>	<p>Complications can arise in multiple areas of the body. These include respiratory system conditions (e.g., pneumonia), circulatory system conditions (e.g., cardiac arrest, thrombosis), hematologic disorders (e.g., disseminated intravascular coagulation), renal disorders (e.g., acute kidney failure) and disturbances of smell and taste (95).</p>
<p>Available prevention</p>	<p>Non-pharmaceutical measures (96-98)</p> <ul style="list-style-type: none"> ○ Contact tracing ○ Case isolation ○ Quarantine ○ Social distancing (school closures, closing workplaces, restrictions on transport, mass gatherings and public events, and restrictions on freedom of movement (city lockdowns)) ○ PPE (mask wearing) ○ Travel restrictions <p>The effectiveness of these measures on COVID-19 is evident. It has been shown to reduce reproduction numbers, bringing R_0 closer to below 1 (98). However, extreme measures i.e., long lockdown periods would be needed to efficiently lower deaths and reduce the burden on the healthcare system (99).</p> <p>The WHO has focused specifically on recommendations such as hand washing and hygiene procedures which reduce the chance of infection through droplet transmission (100). With strong evidence of airborne transmission, many clinical experts are lobbying for the WHO to focus more on recommendations which will reduce the chances of airborne transmission (100, 101). Evidence of widespread transmission (beyond 2 metres from an infected person) can be seen in the case of a Chinese restaurant where the virus spread from one table to multiple other tables without any evidence of contact (indirect or direct) between the customers. A CCTV surveillance video captured the evening in which the virus spread within the restaurant with no visible evidence of contact between the customers (102). Medical officials have suggested that even ventilation of closed spaces can assist in reducing airborne transmission, particularly in lower-income countries where other interventional</p>

measures such as re-directing ventilation systems are not plausible due to high costs (100).

The **B.1.1.7** variant, due to its high infectivity and evidence of aerosol transmission has led the Public Health England to alter the NHS Infection Prevention Control. The alterations now ensure that FFP3 masks are given to staff performing aerosol generating procedures, as surgical masks are ineffective (103). No other information has been found on changing non-pharmaceutical measures for other countries with the **B.1.1.7** variant. No information has been found on changing preventative measures for **B.1.351** and **P.1** either.

With oxygen shortages in India, the Australian Government has offered to send “500 non-invasive ventilators, 1 million surgical masks, 500,000 PPE N95 masks, 100,000 surgical gowns, 100,000 goggles, 100,000 pairs of gloves, 20,000 face shields” to assist India’s healthcare system (104).

The Telangana Government in India has imposed a night curfew in response to the recent spike in COVID-19 cases, likely linked to the emergence of **B.1.617** (105). Rajasthan, Uttar Pradesh, Delhi and Maharashtra have orchestrated similar night curfews and either full or partial lockdowns of the states to curb the spread of infection (106).

The **B.1.617** is considered by the WHO as a “variant of interest” and not a “variant of concern”, which means that according to the WHO, it has not yet represented a cause or need for stronger public health actions (7). The Public Health England on April 23 added India to the red list for travel restrictions, with 119 confirmed cases of **B.1.617** in England in the last week (April 22) (42, 107). As of April 27, Australia has also suspended all flights both direct and indirect from India until mid-May due to the troubling situation in the country. Similarly, Canada has placed a temporary ban on direct passenger flights from India after the detection of **B.1.617** in the country (108). In fact, around 15 countries have imposed travel bans or suspensions as a result of the second covid-19 wave and the emergence of the new COVID-19 variant **B.1.617** (109).

Current vaccines:

- **Pfizer-BioNTech:** Pfizer and BioNTech have announced the analysis of a potential third dose of the vaccine and are evaluating whether it would increase immunity to the COVID-19 variants while maintaining safety standards (February 25) (110)
- **Oxford-AstraZeneca:** EMA finds a potential linkage to vaccine induced thrombotic thrombocytopenia (VITT), which dictated a change in many countries’ vaccine regime (111)
- **Moderna:** Much like above, they are currently working on developing booster doses (112)
- **Novavax:** They are currently developing a booster to protect against variants, with the aim to commence trials later in 2021 (January 28) (113)
- **Johnson & Johnson:** Halted in the U.S due to VITT in women, but resumed in April 2021 (114)

The current approved COVID-19 vaccines; Pfizer BioNTech, Moderna, and Oxford AstraZeneca are based on the defining spike protein within SARS-CoV-2. These vaccines were based on the predominant strain in early 2020, which is the D146G strain. Additionally, all of the VOCs contain mutations within the spike protein, which



impacts the potential effectiveness of the vaccines (115).

Researchers are fairly confident the vaccines will continue to work against them as due to the large size of the spike protein, many mutations would be needed to completely evade the vaccine (115, 116). However, there is speculation that protection could be reduced. The preliminary trials of the first vaccines approved for use by the FDA, Moderna and Pfizer-BioNTech vaccines, were performed predominantly in the United States prior to any VOCs being detected and reported in the US (115). Moreover, the majority of information currently available on the efficacy of the messenger RNA (mRNA) vaccines (e.g. Pfizer-BioNTech and Moderna) against the VOCs have come from studies conducted in laboratories where scientists have used serum samples taken from immunised individuals and exposed them to genetically engineered versions of the variants then measured against the neutralising antibody titres. These studies have revealed that the vaccines mentioned above produce neutralising antibodies at a lower level against the VOCs as compared to the **D614G** strain (116, 118, 119).

As of April 26, 933,824,012 vaccine doses have been administered worldwide (1). Most of these vaccines, however, have been developed and are largely based on the original wild type strain. Changes to the genetic sequence of this original strain led to the advent of the new variants and their defining mutations (120). The effectiveness of these vaccines in protecting society against these new variants comes into question.

B.1.1.7

The effectiveness of the vaccines against the **B.1.1.7** due to the susceptibility of neutralising antibodies seems minimal (121, 122). Additionally, no evidence shows that reinfection is higher than other strains (3, 123). The deletion of $\Delta\text{H69}/\Delta\text{V70}^*$ in the spike protein has arisen independently in multiple lineages, which is due for concern because of the enhancement of viral infectivity in-vitro and potential linkage to immune-escape in immunocompromised patients (59, 124)

*This deletion is also responsible for certain commercial testing kits failing to detect the spike glycoprotein gene (59, 124)

B.1.351

The **B.1.351** variant has been found to be resistant to neutralising antibodies formed by **D614G** and other previously dominant strains, and consequently poses a significant risk of re-infection (65, 125, 126). This is largely due to the presence of the **E484K** mutation (62, 118, 119, 127). The Oxford-AstraZeneca vaccine has 0-10% efficacy against this variant (128). Additional vaccine trials conducted within South Africa of the AstraZeneca, Novavax and Johnson & Johnson found lower vaccine efficacy as compared to other trials where B.1.351 was not the dominant strain (117).

P.1

Of the positive cases reported between 15 to 23 December 2020, 42% were attributed to the **P.1** lineage (65, 129). Additionally, a rapid increase in infections within locations that were sources of large outbreaks earlier in the pandemic could indicate the potential for re-infection rates or a variant with higher transmissibility than the past dominant strain (5, 130). Information is still limited. However, the **E484K** has been linked to reduced vaccine efficacy (118).

B.1.617

The Indian variant contains the **E484Q** mutation. The mutation at residue position 484 has been found in other circulating VOCs (**B.1.351** and **P.1**) (73). This mutation has been linked to reducing convalescent serum neutralisation, neutralisation of antibodies and the ability to reinfect individuals who have not previously been infected with a variant that carries this mutation (118, 127). There is little evidence on the level of



vaccine resistance that **B.1.617** possesses. However, a recent study has suggested that the Bharat Biotech's Covaxin, being manufactured in India, effectively neutralised **B.1.617** in both previously vaccinated individuals and previously infected individuals (131). The Indian Council of Medical Research are currently conducting trials at the moment to test the variant's capability to immune escape (20).

Table 1. Vaccine effectiveness of COVID-19 variants

	Original COVID-19 strain	B.1.1.7	B.1.351	P.1	B.1.617
Pfizer-BioNTech	94.6% (95% CI: 89.9-97.3%) % for symptomatic infection, 90% (95% CI) for severe COVID-19 (63, 106) 90% (95% CI:68-97%) effective for any infection (132)	Largely unaffected (119) Decreased by 2x (63)	Decreased by <6.5x (63)	Decreased by 6.7x. (63)	n/a
Oxford AstraZeneca	62.01% (95% CI:41.0-75.7%) for symptomatic COVID-19 (133, 134)	70.4% (95% CI, 43.6-84.5%) (133, 134)	No efficacy 10.4% (95% CI: 59-73.4%) (128). Complete immune escape, decreased by <86x (63)	n/a	n/a
Moderna	94.1% (95% CI: 89.3-96.8%) for symptomatic COVID-19 (108) 90% (95% CI: 68-97% for any infection	Largely unaffected (115) Decreased by 1.8x (63)	Decreased by <8.6x (63)	Decreased by 4.5x (63)	n/a
Janssen/Johnson & Johnson	66.90% (95%CI: 59.0-73.4%) prevention for symptomatic	57% (130)	52.0% (130)	n/a	n/a



	<table border="1"> <tr> <td data-bbox="472 555 683 745">Novavax Based off their press release (113, 135)</td> <td data-bbox="683 416 842 745">c COVID-19. 85% for severe COVID-19. (63, 130) 96.4% (95% CI: 73.8- for symptomatic (135)</td> <td data-bbox="842 416 951 745">86% (109,131). Decreased by 1.8x (66)</td> <td data-bbox="951 416 1110 745">48.6% (95% CI, 28.4 to 63.1 (109,131)</td> <td data-bbox="1110 416 1238 745">n/a</td> <td data-bbox="1238 416 1377 745">n/a</td> </tr> </table>	Novavax Based off their press release (113, 135)	c COVID-19. 85% for severe COVID-19. (63, 130) 96.4% (95% CI: 73.8- for symptomatic (135)	86% (109,131). Decreased by 1.8x (66)	48.6% (95% CI, 28.4 to 63.1 (109,131)	n/a	n/a
Novavax Based off their press release (113, 135)	c COVID-19. 85% for severe COVID-19. (63, 130) 96.4% (95% CI: 73.8- for symptomatic (135)	86% (109,131). Decreased by 1.8x (66)	48.6% (95% CI, 28.4 to 63.1 (109,131)	n/a	n/a		
<p>Available treatment</p>	<p>Treatment options have not altered for those infected with COVID-19 variants. Treatments which have been used during the COVID-19 pandemic are as follows:</p> <ul style="list-style-type: none"> • Remdesivir <ul style="list-style-type: none"> ○ Remdesivir is an RNA polymerase inhibitor. It is intended for treatment of the Ebola virus and appears to show in vitro activity against COVID-19 (136). ○ Remdesivir, approved for use in October 2020 by the FDA. It has been used to treat symptoms of COVID-19 in children over 12 years and adults who have been hospitalised with symptoms (137). ○ Clinical trials have shown remdesivir to speed up recovery time, however it has been shown by the WHO to have little to no effect on mortality (137). ○ Experiments have shown efficacy against B.1.1.7 (138). However, efficacy of the antiviral is increased when used in combination with other antiviral agents (138). ○ Limited evidence available on the effectiveness of remdesivir on B.1.351, P.1 and B.1.617. ○ India, where a lot of international pharmacology factories are based, has now imposed a ban on all exports of the drug due to the growing strain on demand for the treatment in the country with ever-rising cases (139). • Lopinavir–ritonavir <ul style="list-style-type: none"> ○ These are HIV protease inhibitors (140). ○ A benefit has not been shown in clinical trials. It has no significant improvement on clinical symptoms or reducing mortality (141) (140, 142). ○ It was discontinued from solidarity trial conducted by the WHO (143). • Corticosteroids <ul style="list-style-type: none"> ○ Dexamethasone remains effective in reducing mortality rates for patients infected with B.1.1.7 (144). ○ Reduction in effectiveness for patients infected with a variant that possesses the E484K mutation as found in B.1.351 and P.1 (62). 						



	<ul style="list-style-type: none">• Hydroxychloroquine<ul style="list-style-type: none">○ Hydroxychloroquine is a DMARD (disease modifying anti rheumatic drug) usually used to treat rheumatoid arthritis and systemic lupus erythematosus (137)○ Its ability to act as a immunomodulator is why it was considered as a potential treatment for COVID-19 (137)○ Shown to have no effect on ventilation requirements, reducing mortality, or hospital duration (145)○ In May 2020, the Director-General of the WHO removed it from the solidarity trial due to evidence suggesting harmful and ineffective impacts on COVID-19 sufferers (143)○ On 30 July 2020, the ASCOT committee announced they would be removing hydroxychloroquine from the trial due to low efficacy (146) • Monoclonal Antibodies<ul style="list-style-type: none">○ Monoclonal antibodies work by recognising the virus' spike protein (137, 147).○ For B.1.1.7, the neutralising activity of most antibodies tested against the variant were still potent (119).○ B.1.351 variant managed to abolish the neutralising activity of four antibody treatments. Casirivimab was 58 % less effective against this variant (119).○ P.1 has a moderate impact on neutralisation by monoclonal antibody treatments (120).○ Evidence has shown bamlanivimab to be effective in the treatment for variants containing E484Q or L452R mutations. Health regulators in the US halted distribution of that antibody treatment, saying it wasn't that effective as a stand-alone treatment against the new variants and are now looking into the drug being used instead in combined drug therapy with another antibody treatment, etesevimab, (148). <p>The CDC has asked the WHO to report updates on treatment options to ensure therapeutic treatments remain current and effective.</p>
<p>Critical analysis</p>	<p>The B.1.617 variant possess the L452R mutation known to increase transmissibility (70). Due to this suspected increased transmissibility, cases in India have been rising exponentially. Moreover, due to the densely populated cities in India and a large population as a whole, many individuals are not being tested for COVID-19. India has also acknowledged an insufficiency in their genome sequencing and the effect it has had on disease management and surveillance (149). Medical experts have asked the Indian Government to increase genome sequencing as a response to the discovery of B.1.617 (6). Genomic sequencing in India has been very low for a few reasons. It is partially due to the high incidence rate and also due to a lack of resources. These factors have resulted in inaccuracies in the recording of cases and variants. The large numbers of cases in India have overwhelmed the healthcare system and its resources. The B.1.617 variant has yet to be linked to increased severity. However, due to the overburdened health care system, many preventable deaths are occurring and increasing the mortality rate with roughly 2000 people dying each day (1).</p>



What is the impact on effectiveness of current Public Health measures and supportive care options?

The sharp increase in the number of cases being recorded in India during its second wave, coupled with the emergence of **B.1.617**, has challenged the current public health measures and supportive care options intended to curb the spread of infection. The daily cases in India have been continuously on the increase in the last 10 days (April 27) (1). India on April 26, broke the global record of cases reported in the last 24 hours for the fourth consecutive day, recording 352, 991 new cases (1).

Being the first pandemic in over 100 years since the Spanish Flu, COVID-19 and its variants have highlighted the vulnerabilities in most countries' healthcare systems and the lack of importance previously placed on Emergency Medicine. With reference to India, its second wave has overwhelmed the healthcare system. The majority of hospitals have run out of basic medical supplies and the mortality rate for COVID-19 has risen, predominantly due to an inability to house and treat individuals e.g. shortage of ICU beds and a shortage of oxygen (150). On April 23, 25 COVID-19 patients died as a result of the oxygen shortages in a government hospital in Delhi (146). The lack of supportive care resources is as a result of an earlier Government decision, supported at the time by the Indian health minister Harsh Vardhan, to increase the exportation of medical resources to other countries. This was done under the assumption that as a result of decreasing COVID-19 cases (believed to be due to the vaccination programs), India was in the "endgame" of the pandemic (151). Exports of oxygen supplies were increased by 734% in January 2021 and over 193 vaccine doses were exported (151).

Public health measures were also underprepared for the COVID-19 second wave. Upon commencement of its vaccination program in January, India relaxed many non-pharmacological measures such as social distancing and mask wearing and allowed mass gatherings such as cultural festivals to proceed. Moreover, the Indian Prime Minister Narendra Modi failed to take action in providing public information and guidance in the crisis and ignored warnings of a second wave when cases began to rise again in February (151).

The **B.1.1.7** variant is thought to be primarily responsible for the second wave in India, with the **B.1.617** now believed to be contributing to surges in certain Indian states such as Maharashtra and other countries including Bangladesh and Pakistan (151).

Would the introduction of booster doses that target the B.1.351 and P.1 variants be effective against the B.1.617?

The **B.1.617** possesses both the **L452R** and **E484Q** mutation, a similar mutation to **E484K**, which have both been linked to increased immune escape in both individuals previously vaccinated and those with acquired immunity. Due to the high potential for reinfection, this leaves many individuals vulnerable. Booster doses can help improve immune escape, increasing



immunity to the original COVID-19 strain whilst also combatting the vaccine resistance of emerging variants. Booster doses are currently being designed to increase vaccine effectiveness against **B.1.351** and **P.1** variants and have shown effectiveness in doing so (152). The booster doses that are being designed, however, are focused on tackling the effects of the **E484K** mutation. It is unclear if they will have the same desired effect on the **B.1.617** and its similar **E484Q** mutation.

What do the results mean for a vaccination program? Should vaccines be updated to target new variants?

The Public Health England is advocating for a new vaccine strategy known as a heterologous prime-boost (98, 153). This immunisation strategy has been used previously against Ebola and HIV spread. It involves the mixing of vaccines, whereby an individual may receive two doses of two different vaccines. Oxford plans to trial combinations of the AstraZeneca vaccine mixed with Russia's Sputnik vaccine (153). Sputnik, which has shown to have over 90% effectiveness, is itself a heterologous prime boost made up of different viral components in its two doses (154). The benefits of this new approach would aid in both speeding up vaccinations and reducing the impact of supply chain disruptions (153). A great advantage of this new approach would be that it may further strengthen the immune response and aid in combatting emerging COVID-19 variants that are showing resistance to current vaccines. There has been evidence of the effectiveness in producing a strong immune response and preventing COVID-19 in mice using a combined vector vaccine (155). This could be a great option for countries such as India, who are suffering the effects of vaccine resistant variants coupled with a limited supply of vaccine doses.

Why is surveillance so important?

COVID-19 variants are altering and challenging the current scientific understanding of the novel COVID-19 virus and the knowledge of its transmissibility, severity and vaccine resistance. Through tracking systems such as EpiWatch and GISAID, these variants can be effectively monitored, enabling scientists, epidemiologists and medical professionals to gain insight into how they operate so that their future impacts and effects can be anticipated.



Key questions	<p>The impact of these variants leads us to question certain protocols in place currently:</p> <ul style="list-style-type: none">• How can we manage the risks?• How much of the second wave in India can be explained by B.1.617?• What explains the emergence of multiple variants independently around the world, all with common mutations?• Will countries enforce mandatory travel vaccination?• How will this affect border control policies in both countries affected by the COVID-19 variants and countries who are currently unaffected?• Will there be a change to current public health policies in countries with the COVID-19 variants? Will changes also occur in other countries currently not affected by the COVID-19 variants?• How would the arrival of the new double variant impact Australia?• Is a Universal SARS-COV-2 vaccine that targets all variants possible?• Could mixing vaccines provide a better immune response?
References	<ol style="list-style-type: none">1. WHO. WHO Coronavirus (COVID-19) Dashboard In: Organisation WH, editor.: World Health Organisation; 2021.2. Plante JA, Liu Y, Liu J, Xia H, Johnson BA, Lokugamage KG, et al. Spike mutation D614G alters SARS-CoV-2 fitness. <i>Nature</i>. 2021;592(7852):116-21.3. WHO. SARS-CoV-2 variants. In: Organisation WH, editor. 2020.4. NextStrain: CoVariants [Internet]. 2021. Available from: https://covariants.org/.5. Sabino EC, Buss LF, Carvalho MPS, Prete CA, Jr., Crispim MAE, Fraiji NA, et al. Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. <i>The Lancet</i>. 2021;397(10273):452-5.6. BBCNews. Coronavirus: 'Double mutant' Covid variant found in India2021. Available from: https://www.bbc.com/news/world-asia-india-56507988.7. Xinhua. Variant emerging from India might be more contagious: WHO official Xinhua Net 2021.8. WHO. Weekly epidemiological update on COVID-19 - 27 April 20212021. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---27-april-2021.9. Lineage B.1.617 [Internet]. PANGO Lineages. 2021. Available from: https://cov-lineages.org/lineages/lineage_B.1.617.html.10. Luring AS, Hodcroft EB. Genetic Variants of SARS-CoV-2—What Do They Mean? <i>JAMA</i>. 2021;325(6):529-31.11. Mercatelli D, Giorgi FM. Geographic and Genomic Distribution of SARS-CoV-2 Mutations. <i>Front Microbiol</i>. 2020;11:1800.12. Wise J. Covid-19: New coronavirus variant is identified in UK. <i>BMJ</i>. 2020;371:m4857.13. Variants: distribution of cases data In: England PH, editor.: UK Government 2021.14. WHO. Coronavirus disease (COVID-19): Virus Evolution. In: Organisation WH, editor. 2020.15. CDC. Science Brief: Emerging SARS-CoV-2 Variants. In: CDC,



- editor.: U.S. Department of Health & Human Services; 2021.
16. Choi B, Choudhary MC, Regan J, Sparks JA, Padera RF, Qiu X, et al. Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host. *New England Journal of Medicine*. 2020;383(23):2291-3.
 17. Alam I, Radovanovic A, Incitti R, Kamau AA, Alarawi M, Azhar EI, et al. CovMT: an interactive SARS-CoV-2 mutation tracker, with a focus on critical variants. *The Lancet Infectious Diseases*. 2021.
 18. Fujino T, Nomoto H, Kutsuna S, Ujiie M, Suzuki T, Sato R, et al. Novel SARS-CoV-2 variant in travelers from Brazil to Japan. *Emerging infectious diseases*. 2021;27(4):1243.
 19. Barbosa GR, Leão Moreira LV, Oliveira Justo AF, Perosa AH, Cunha Chaves AP, Bueno MS, et al. Rapid spread and high impact of the Variant of Concern P.1 in the largest city of Brazil. *medRxiv*. 2021:2021.04.10.21255111.
 20. Koshy J. Coronavirus | Indian 'double mutant' strain named B.1.617. *The Hindu*. 2021.
 21. Binayak Dasgupta AD. 'Double mutant' most common variant now: India's genome data. *Hindustan Times* 2021.
 22. B.1.617 Lineage Report [Internet]. *outbreak.info*. 2021. Available from: <https://outbreak.info/situation-reports?pango=B.1.617&loc=IND&loc=GBR&loc=USA&selected=IND>.
 23. hCoV-19 Tracking of Variants [Internet]. *GISAID*. 2021. Available from: <https://www.gisaid.org/>.
 24. Expert reaction to cases of variant B.1.617 (the 'Indian variant') being investigated in the UK Science Media Centre; 2021.
 25. Baghchechi M, Jaipaul N, Jacob SE. The rise and evolution of COVID-19. *International Journal of Women's Dermatology*. 2020;6(4):248-54.
 26. Burki T. The origin of SARS-CoV-2. *The Lancet Infectious Diseases*. 2020;20(9):1018-9.
 27. Gandhi RT, Lynch JB, del Rio C. Mild or Moderate Covid-19. *New England Journal of Medicine*. 2020;383(18):1757-66.
 28. Opriessnig T, Huang Y-W. Third update on possible animal sources for human COVID-19. *Xenotransplantation*. 2021;28(1):e12671.
 29. Grubaugh ND, Petrone ME, Holmes EC. We shouldn't worry when a virus mutates during disease outbreaks. *Nature Microbiology*. 2020;5(4):529-30.
 30. Jewell M. A Primer on Coronavirus, Variants, Mutation and Evolution 2021. Available from: <https://cals.ncsu.edu/applied-ecology/news/a-primer-on-coronavirus-variants-mutation-and-evolution/>.
 31. Mackenzie JS, Smith DW. COVID-19: a novel zoonotic disease caused by a coronavirus from China: what we know and what we don't. *Microbiol Aust*. 2020:Ma20013.
 32. Li X, Zai J, Zhao Q, Nie Q, Li Y, Foley BT, et al. Evolutionary history, potential intermediate animal host, and cross-species analyses of SARS-CoV-2. *Journal of Medical Virology*. 2020;92(6):602-11.
 33. B.1.1.7 Lineage Report [Internet]. *outbreak.info*. 2021. Available from: https://outbreak.info/situation-reports?pango=B.1.1.7&loc=GBR&loc=USA&loc=USA_US-CA&selected=GBR.
 34. Chow D. U.K. coronavirus variant is now the dominant strain in the



	<p>U.S., CDC says 2021. Available from: https://www.nbcnews.com/science/science-news/uk-coronavirus-variant-now-dominant-strain-us-rcna606.</p> <ol style="list-style-type: none">35. Walensky RP, Walke HT, Fauci AS. SARS-CoV-2 Variants of Concern in the United States—Challenges and Opportunities. <i>JAMA</i>. 2021;325(11):1037-8.36. Vock I. How widespread is the British variant of Covid-19 in Europe? In: <i>NewStatesman</i>, editor. 2021.37. Grint DJ, Wing K, Williamson E, McDonald HI, Bhaskaran K, Evans D, et al. Case fatality risk of the SARS-CoV-2 variant of concern B.1.1.7 in England. <i>medRxiv</i>. 2021:2021.03.04.21252528.38. B.1.351 Lineage Report [Internet]. <i>outbreak.info</i>. 2021. Available from: https://outbreak.info/situation-reports?pango=B.1.351&selected=ZAF&loc=ZAF&loc=USA&loc=USA_US-CA.39. South African variant became most prevalent in Bangladesh in mid-March. <i>BDNews24</i> [Internet]. Available from: https://bdnews24.com/coronavirus-pandemic/2021/04/08/south-african-variant-became-most-prevalent-in-bangladesh-in-mid-march-study40. P.1 Lineage Report [Internet]. <i>outbreak.info</i>. 2021. Available from: https://outbreak.info/situation-reports?pango=P.1&selected=BRA&loc=BRA&loc=USA&loc=USA_US-CA.41. Hwang K. 'Double mutant' COVID variant cases detected in Bay Area. Here's what we know. <i>San Francisco Chronicle</i> 2021.42. McTaggart I, Carpani J, Team GHS. 'Real questions' about why India is not on red list, says professor of public health <i>The Telegraph</i>. 2021.43. WHO. WHO Consultative Meeting on High/Maximum Containment (Biosafety Level 4) Laboratories Networking 2017. Available from: https://apps.who.int/iris/bitstream/handle/10665/311625/WHO-WHE-CPI-2018.40-eng.pdf.44. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. <i>New England Journal of Medicine</i>. 2020;382(18):1708-20.45. CDC. Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19. U.S. Department of Health & Human Services; 2020.46. Fajnzylber J, Regan J, Coxen K, Corry H, Wong C, Rosenthal A, et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. <i>Nature Communications</i>. 2020;11(1):5493.47. Jewell BL. Monitoring differences between the SARS-CoV-2 B.1.1.7 variant and other lineages. <i>The Lancet Public Health</i>. 2021.48. Mahase E. Covid-19: Sore throat, fatigue, and myalgia are more common with new UK variant. <i>BMJ</i>. 2021;372:n288.49. Bager P, Wohlfahrt J, Fonager J, Albertsen M, Yssing Michaelsen T, Holten Møller C, et al. Increased risk of hospitalisation associated with infection with SARS-CoV-2 lineage B. 1.1. 7 in Denmark. 2021.50. Shob K. New Symptoms, High Viral Load, Here's How India's Second Wave Of Covid-19 Looks Different From The First 2021. Available from: https://www.dailyrounds.org/blog/new-symptoms-high-viral-load-heres-how-indias-second-wave-of-covid-19-looks-different-from-the-first/.
--	---



51. Tang S, Mao Y, Jones RM, Tan Q, Ji JS, Li N, et al. Aerosol transmission of SARS-CoV-2? Evidence, prevention and control. *Environ Int.* 2020;144:106039.
52. Jayaweera M, Perera H, Gunawardana B, Manatunge J. Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. *Environmental research.* 2020:109819.
53. Greenhalgh T, Jimenez JL, Prather KA, Tufekci Z, Fisman D, Schooley R. Ten scientific reasons in support of airborne transmission of SARS-CoV-2. *Lancet.* 2021.
54. Hindson J. COVID-19: faecal–oral transmission? *Nature Reviews Gastroenterology & Hepatology.* 2020;17(5):259-.
55. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. *New England Journal of Medicine.* 2020;382(10):929-36.
56. Lewis D. COVID-19 rarely spreads through surfaces. So why are we still deep cleaning?2021. Available from: <https://www.nature.com/articles/d41586-021-00251-4>.
57. Coroneo MT, Collignon PJ. SARS-CoV-2: eye protection might be the missing key. *The Lancet Microbe.*
58. Sriwijitalai W, Wiwanitkit V. COVID-19 in forensic medicine unit personnel: Observation from Thailand. *Journal of Forensic and Legal Medicine.* 2020;72:101964.
59. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science.* 2021;372(6538):eabg3055.
60. Peacock TP, Goldhill DH, Zhou J, Baillon L, Frise R, Swann OC, et al. The furin cleavage site of SARS-CoV-2 spike protein is a key determinant for transmission due to enhanced replication in airway cells. *bioRxiv.* 2020:2020.09.30.318311.
61. van Oosterhout C, Hall N, Ly H, Tyler KM. COVID-19 evolution during the pandemic – Implications of new SARS-CoV-2 variants on disease control and public health policies. *Virulence.* 2021;12(1):507-8.
62. Wise J. Covid-19: The E484K mutation and the risks it poses. *BMJ.* 2021;372:n359.
63. McCarthy KR, Rennick LJ, Nambulli S, Robinson-McCarthy LR, Bain WG, Haidar G, et al. Natural deletions in the SARS-CoV-2 spike glycoprotein drive antibody escape. *bioRxiv.* 2020:2020.11.19.389916.
64. Carl AB Pearson TWR, Nicholas G Davies, Adam J Kucharski, CMMID/COVID-19 working group, W John Edmunds, Rosalind M Eggo. Estimates of severity and transmissibility of novel South Africa SARS-CoV-2 variant501Y.V2. *Centre for Mathematical Modelling of Infectious Diseases* 2021.
65. CCIU. Evidence Check: SARS-CoV-2 Variants. In: Unit C-CI, editor.: NSW Government 2021.
66. Abdool Karim SS, de Oliveira T. New SARS-CoV-2 Variants—Clinical, Public Health, and Vaccine Implications. *New England Journal of Medicine.* 2021.
67. Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DdS, Mishra S, et al. Genomics and epidemiology of a novel SARS-CoV-2 lineage in Manaus, Brazil. *medRxiv.* 2021:2021.02.26.21252554.
68. Taylor L. Covid-19: Brazil's spiralling crisis is increasingly affecting



- young people. BMJ. 2021;373:n879.
69. ECDC. Risk assessment: Risk related to spread of new SARS-CoV-2 variants of concern in the EU/EEA. In: Control ECfDPa, editor. 2021.
 70. Chen J, Wang R, Wang M, Wei GW. Mutations Strengthened SARS-CoV-2 Infectivity. J Mol Biol. 2020;432(19):5212-26.
 71. Tchesnokova V, Kulakesara H, Larson L, Bowers V, Rechkina E, Kisiela D, et al. Acquisition of the L452R mutation in the ACE2-binding interface of Spike protein triggers recent massive expansion of SARS-Cov-2 variants. bioRxiv. 2021:2021.02.22.432189.
 72. Kurtzman L. COVID-19 Study Finds Increase of Coronavirus Variants in San Francisco's Mission District2021. Available from: <https://www.ucsf.edu/news/2021/02/419896/covid-19-study-finds-increase-coronavirus-variants-san-franciscos-mission>.
 73. Cherian S, Potdar V, Jadhav S, Yadav P, Gupta N, Das M, et al. Convergent evolution of SARS-CoV-2 spike mutations, L452R, E484Q and P681R, in the second wave of COVID-19 in Maharashtra, India. bioRxiv. 2021:2021.04.22.440932.
 74. Banerjea A. AIIMS director lists out two main causes of rapid COVID-19 spread in India. Mint 2021.
 75. Courjon J, Contenti J, Demonchy E, Levraut J, Barbry P, Rios G, et al. Spread of the SARS-CoV-2 UK-variant in the South East of France: impact on COVID-19 patients' age, comorbidity profiles and clinical presentation. medRxiv. 2021:2021.04.12.21253817.
 76. Berkeley LJ. More young people are getting hospitalized as Covid variants spread. Here's what we know2021. Available from: <https://www.cnbc.com/2021/04/16/covid-more-young-people-hospitalized-as-more-contagious-variants-spread.html>.
 77. MDHHS. April 16, 2021 - Gatherings and Face Mask Order. In: (MDHHS) MDoHaHS, editor.: Michigan Government 2021.
 78. Peet C. 'A miracle I survived': Younger Brazilians hit by COVID surge2021. Available from: <https://www.aljazeera.com/news/2021/3/28/miracle-i-survived-younger-brazilians-hit-covid-surge>.
 79. Rivers M. Why are more young people getting sick with Covid-19 in Brazil? CNN. 2021.
 80. Buss LF, Prete CA, Jr., Abraham CMM, Mendrone A, Jr., Salomon T, de Almeida-Neto C, et al. Three-quarters attack rate of SARS-CoV-2 in the Brazilian Amazon during a largely unmitigated epidemic. Science. 2021;371(6526):288-92.
 81. NNDSS. COVID-19 cases by age group and sex. In: Health Do, editor. 2021.
 82. NCHS. Provisional death counts for coronavirus disease 2019 (COVID-19). Weekly Updates by Select Demographic and Geographic Characteristics. 2020.
 83. Venkatesan P. The changing demographics of COVID-19. The Lancet Respiratory Medicine. 2020;8(12):e95.
 84. Lalwani V. BAD TO WORSE: Is India's second Covid-19 wave impacting more youth and kids than the first?2021. Available from: <https://qz.com/india/1997559/indias-second-covid-19-may-be-impacting-more-youth-and-kids/>.
 85. Kim L, Whitaker M, O'Halloran A, Kambhampati A, Chai SJ, Reingold A, et al. Hospitalization Rates and Characteristics of Children Aged <18 Years Hospitalized with Laboratory-Confirmed COVID-19 -

	<p>COVID-NET, 14 States, March 1-July 25, 2020. <i>MMWR Morb Mortal Wkly Rep.</i> 2020;69(32):1081-8.</p> <p>86. Bialek S, Gierke R, Hughes M, McNamara LA. Coronavirus disease 2019 in children—United States, february 12–april 2, 2020. <i>Morbidity and Mortality Weekly Report.</i> 2020;69(14):422.</p> <p>87. Kershner I, Belluck P. When Covid Subsided, Israel Reopened Its Schools. It Didn't Go Well. <i>The New York Times</i> 2021.</p> <p>88. Raharja A, Tamara A, Kok LT. Association Between Ethnicity and Severe COVID-19 Disease: a Systematic Review and Meta-analysis. <i>J Racial Ethn Health Disparities.</i> 2020:1-10.</p> <p>89. Ludwig S, Zarbock A. Coronaviruses and SARS-CoV-2: A Brief Overview. <i>Anesth Analg.</i> 2020;131(1):93-6.</p> <p>90. Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. <i>European Journal of Epidemiology.</i> 2020;35(12):1123-38.</p> <p>91. Davies NG, Jarvis CI, van Zandvoort K, Clifford S, Sun FY, Funk S, et al. Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7. <i>Nature.</i> 2021.</p> <p>92. Challen R, Brooks-Pollock E, Read JM, Dyson L, Tsaneva-Atanasova K, Danon L. Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: matched cohort study. <i>BMJ.</i> 2021;372:n579.</p> <p>93. Horby P, Huntley, C., Davies, N., Edmunds, J., Ferguson, N., Medley, G., & Semple, C. . NERVTAG: note on B. 1.1. 7 severity. In: (NERVTAG) NaERV TAG, editor.: UK Government; 2021.</p> <p>94. Santos de Oliveira MH, Lippi G, Henry BM. Sudden rise in COVID-19 case fatality among young and middle-aged adults in the south of Brazil after identification of the novel B.1.1.28.1 (P.1) SARS-CoV-2 strain: analysis of data from the state of Parana. <i>medRxiv.</i> 2021:2021.03.24.21254046.</p> <p>95. Murk W, Gierada M, Fralick M, Weckstein A, Klesh R, Rassen JA. Diagnosis-wide analysis of COVID-19 complications: an exposure-crossover study. <i>Cmaj.</i> 2021;193(1):E10-e8.</p> <p>96. Institute of Medicine (US) Forum on Microbial Threats: Ethical and Legal Considerations in Mitigating Pandemic Disease: Workshop Summary. Washington, D.C: National Academies Press (US); 2007. Available from: https://www.ncbi.nlm.nih.gov/books/NBK54163/.</p> <p>97. Public Health Orders and restrictions In: Department NH, editor.: NSW Government 2021.</p> <p>98. Islam N, Sharp SJ, Chowell G, Shabnam S, Kawachi I, Lacey B, et al. Physical distancing interventions and incidence of coronavirus disease 2019: natural experiment in 149 countries. <i>BMJ.</i> 2020;370:m2743.</p> <p>99. Davies NG, Kucharski AJ, Eggo RM, Gimma A, Edmunds WJ, Jombart T, et al. Effects of non-pharmaceutical interventions on COVID-19 cases, deaths, and demand for hospital services in the UK: a modelling study. <i>The Lancet Public Health.</i> 2020;5(7):e375-e85.</p> <p>100. Dyer O. Covid-19: Airborne transmission is being underestimated, warn experts. <i>BMJ.</i> 2020;370:m2720.</p> <p>101. Morawska L, Milton D. It Is Time to Address Airborne Transmission of Coronavirus Disease 2019 (COVID-19) <i>Clin. Infect</i></p>
--	---

	<p>Dis. 2020;6.</p> <p>102. Li Y, Qian H, Hang J, Chen X, Hong L, Liang P, et al. Evidence for probable aerosol transmission of SARS-CoV-2 in a poorly ventilated restaurant. medRxiv. 2020:2020.04.16.20067728.</p> <p>103. Wise J. Covid-19: Doctors and nurses demand better PPE for wider range of procedures. BMJ. 2021;372:n30.</p> <p>104. Motherwell S. How long is the India flight ban and when will Australians start coming home again?2021. Available from: https://www.abc.net.au/news/2021-04-28/australia-india-flights-travel-ban-covid-outbreak/100099906.</p> <p>105. Pandey A. Telangana imposes night curfew till April 30 day after HC warning on slow response to Covid crisis2021. Available from: https://www.indiatoday.in/india/story/telangana-imposes-night-curfew-till-april-30-1792950-2021-04-20.</p> <p>106. OutlookIndia. Covid-19 Surge: Here's A List Of States That Have Imposed Night Curfew, Partial Lockdown2021. Available from: https://www.outlookindia.com/website/story/india-news-covid-19-surge-heres-a-list-of-states-that-have-imposed-night-curfew-partial-lockdown/380304.</p> <p>107. SARS-CoV-2 variants of concern and variants under investigation in England. In: England PH, editor.: Public Health England; 2021.</p> <p>108. Zuber MC. COVID-19 variant of interest vs. variant of concern: What does it mean?2021. Available from: https://www.ctvnews.ca/health/coronavirus/covid-19-variant-of-interest-vs-variant-of-concern-what-does-it-mean-1.5398083.</p> <p>109. India Covid crisis: 15 countries that have imposed travel bans, suspensions. Khaleej Times 2021.</p> <p>110. Pfizer and BioNTech Initiate a Study as Part of Broad Development Plan to Evaluate COVID-19 Booster and New Vaccine Variants [press release]. Pfizer 2021.</p> <p>111. PRAC. AstraZeneca's COVID-19 vaccine: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets2021. Available from: https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood.</p> <p>112. Moderna Announces it has Shipped Variant-Specific Vaccine Candidate, mRNA-1273.351, to NIH for Clinical Study [press release]. 2021.</p> <p>113. Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial [press release]. 2021.</p> <p>114. Noah Weiland SLaCZ. Johnson & Johnson Vaccinations Paused After Rare Clotting Cases Emerge. The New York Times. 2021.</p> <p>115. Rubin R. COVID-19 Vaccines vs Variants-Determining How Much Immunity Is Enough. Jama. 2021;325(13):1241-3.</p> <p>116. Moore JP, Offit PA. SARS-CoV-2 Vaccines and the Growing Threat of Viral Variants. JAMA. 2021;325(9):821-2.</p> <p>117. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. New England Journal of Medicine. 2021;384(15):1412-23.</p>
--	---



118. Greaney AJ, Starr TN, Gilchuk P, Zost SJ, Binshtein E, Loes AN, et al. Complete mapping of mutations to the SARS-CoV-2 spike receptor-binding domain that escape antibody recognition. *bioRxiv*. 2020:2020.09.10.292078.
119. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature*. 2021.
120. Powers C, Feldman K, Rewari P, Choi M, Chen R. How COVID-19 variants impact treatments and vaccines. *ZS2021*.
121. Shen X, Tang H, McDanal C, Wagh K, Fischer W, Theiler J, et al. SARS-CoV-2 variant B.1.1.7 is susceptible to neutralizing antibodies elicited by ancestral Spike vaccines. *bioRxiv*. 2021:2021.01.27.428516.
122. Edara VV, Floyd K, Lai L, Gardner M, Hudson W, Piantadosi A, et al. Infection and mRNA-1273 vaccine antibodies neutralize SARS-CoV-2 UK variant. *medRxiv*. 2021:2021.02.02.21250799.
123. Graham MS, Sudre CH, May A, Antonelli M, Murray B, Varsavsky T, et al. Changes in symptomatology, re-infection and transmissibility associated with SARS-CoV-2 variant B.1.1.7: an ecological study. *medRxiv*. 2021:2021.01.28.21250680.
124. Kemp SA, Meng B, Ferreira IA, Datir R, Harvey WT, Papa G, et al. Recurrent emergence and transmission of a SARS-CoV-2 spike deletion H69/V70. *bioRxiv*. 2021:2020.12.14.422555.
125. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. *Nature Medicine*. 2021;27(4):622-5.
126. Zucman N, Uhel F, Descamps D, Roux D, Ricard J-D. Severe Reinfection With South African Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variant 501Y.V2. *Clinical Infectious Diseases*. 2021.
127. Liu Z, VanBlargan LA, Bloyet L-M, Rothlauf PW, Chen RE, Stumpf S, et al. Landscape analysis of escape variants identifies SARS-CoV-2 spike mutations that attenuate monoclonal and serum antibody neutralization. *bioRxiv*. 2021:2020.11.06.372037.
128. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. *New England Journal of Medicine*. 2021.
129. Faria NR, Claro IM, Candido D, Franco LAM, Andrade PS, Coletti TM. Genomic characterisation of an emergent SARS-CoV-2 lineage in Manaus: preliminary findings. *SARS-CoV-2 coronavirus: nCoV-2019 Genomic Epidemiology*. 20/03/21 ed. *Virological* 2021.
130. Paola Cristina Resende JFB, Romero Henrique Teixeira de Vasconcelos, Ighor Arantes, Luciana Appolinario, Ana Carolina Mendonça, Anna Carolina Paixao, Ana Carolina Duarte Rodrigues, Thauane Silva, Alice Sampaio Rocha¹, Alex Pauvalid-Corrêa, Fernando Couto Motta, Dalane Loudal Florentino Teixeira, Thiago Franco de Oliveira Carneiro, Francisco Paulo Freire Neto, Isabel Diniz Herbster, Anderson Brandao Leite, Irina Nastassja Riediger, Maria do Carmo Debur, Felipe Gomes Naveca, Walquiria Almeida, Mirian Livorati, Gonzalo Bello^{3A}, Marilda M Siqueira. Spike E484K mutation in the first SARS-CoV-2 reinfection case confirmed in Brazil. *SARS-CoV-2 coronavirus: nCoV-2019 Genomic Epidemiology*. 21/03/21 ed.

	<p>Virological2021.</p> <p>131. Yadav PD, Sapkal GN, Abraham P, Ella R, Deshpande G, Patil DY, et al. Neutralization of variant under investigation B.1.617 with sera of BBV152 vaccinees. bioRxiv. 2021:2021.04.23.441101.</p> <p>132. Thompson MG, Burgess JL, Naleway AL, Tyner HL, Yoon SK, Meece J, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19 vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers—eight US locations, December 2020–March 2021. Morbidity and Mortality Weekly Report. 2021;70(13):495.</p> <p>133. Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus B, Bibi S, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. The Lancet. 2021;397(10282):1351-62.</p> <p>134. Voysey M, Costa Clemens SA, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. The Lancet. 2021;397(10277):881-91.</p> <p>135. Novavax Confirms High Levels of Efficacy Against Original and Variant COVID-19 Strains in United Kingdom and South Africa Trials [press release]. Novavax2021.</p> <p>136. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-ncov) in vitro. Cell Respiratory 2020;30(1):269–71.</p> <p>137. HarvardMedicalSchool. Treatments for COVID-192021. Available from: https://www.health.harvard.edu/diseases-and-conditions/treatments-for-covid-19.</p> <p>138. Reuschl A-K, Thorne LG, Zuliani-Alvarez L, Bouhaddou M, Obernier K, Hiatt J, et al. Host-directed therapies against early-lineage SARS-CoV-2 retain efficacy against B.1.1.7 variant. bioRxiv. 2021:2021.01.24.427991.</p> <p>139. MedicalXpress. India bans export of Covid-19 treatment drug remdesivir2021. Available from: https://medicalxpress.com/news/2021-04-india-export-covid-treatment-drug.html.</p> <p>140. Horby PW, Mafham M, Bell JL, Linsell L, Staplin N, Emberson J, et al. Lopinavir&#x2013;ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet. 2020;396(10259):1345-52.</p> <p>141. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. New England Journal of Medicine. 2020;382(19):1787-99.</p> <p>142. Hung IF-N, Lung K-C, Tso EY-K, Liu R, Chung TW-H, Chu M-Y, et al. Triple combination of interferon beta-1b, lopinavir&#x2013;ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. The Lancet. 2020;395(10238):1695-704.</p> <p>143. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. New England Journal of Medicine.</p>
--	---



2020;384(6):497-511.

144. Reuters. Steroid should still work on new COVID variant - English medical official 2021. Available from: <https://www.reuters.com/business/healthcare-pharmaceuticals/steroid-should-still-work-new-covid-variant-english-medical-official-2021-01-25/>.
145. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *New England Journal of Medicine*. 2020;383(6):517-25.
146. NPS. Hydroxychloroquine and COVID-19 2021. Available from: <https://www.nps.org.au/hcq-and-covid-19>.
147. Chen J, Lu H. New challenges to fighting COVID-19: Virus variants, potential vaccines, and development of antivirals. *Biosci Trends*. 2021.
148. Higgins-Dunn N. With variants spreading, Eli Lilly cuts solo COVID-19 antibody out of its U.S. supply deal 2021. Available from: <https://www.fiercepharma.com/pharma/eli-lilly-modifies-covid-19-antibody-agreement-u-s-to-focus-therapy-duo>.
149. Srivastava S, Banu S, Singh P, Sowpati DT, Mishra RK. SARS-CoV-2 genomics: An Indian perspective on sequencing viral variants. *Journal of Biosciences*. 2021;46(1):22.
150. Yeung J. India is spiraling deeper into Covid-19 crisis. Here's what you need to know. *CNN* 2021.
151. Bhowmick N. How India's second wave became the worst COVID-19 surge in the world 2021. Available from: <https://www.nationalgeographic.com/science/article/how-indias-second-wave-became-the-worst-covid-19-surge-in-the-world>.
152. Nawrat A. Beating the Covid-19 crisis: the role of vaccine boosters 2021. Available from: <https://www.pharmaceutical-technology.com/features/covid19-vaccine-boosters-pandemic/>.
153. Ledford H. Could mixing COVID vaccines boost immune response? *Nature*. 2021.
154. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *The Lancet*. 2021;397(10275):671-81.
155. Spencer AJ, McKay PF, Belij-Rammerstorfer S, Ulaszewska M, Bissett CD, Hu K, et al. Heterologous vaccination regimens with self-amplifying RNA and Adenoviral COVID vaccines induce robust immune responses in mice. *bioRxiv*. 2021:2021.01.28.428665.