*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.*

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| 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** | **First Identified Dates**  **Original Strain:** Late December 2019 ([1](#_ENREF_1))  **D614G mutation:** 24 March 2020 ([2](#_ENREF_2))  **UK variant (B.1.1.7):** 20 September 2020 ([3](#_ENREF_3))  **South African variant (B.1.351):** 18 December 2020 ([3](#_ENREF_3), [4](#_ENREF_4))  **Brazilian variant (P.1):** 2 January 2021 ([4](#_ENREF_4), [5](#_ENREF_5))  **Double variant (B.1.617):** 7 December 2020 ([6](#_ENREF_6), [7](#_ENREF_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](#_ENREF_8), [9](#_ENREF_9)). The two other sub-lineages B.1.617.1 and B.1.617.2 were first detected in December 2020 ([9](#_ENREF_9)) .  **Figure 1. Timeline showing when each variant of concern emerged**  Chart  Description automatically generated  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.** |
| **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*)** | **Original Strain:** Wuhan, Hubei Province, China ([1](#_ENREF_1)).  **D614G:** March 2020 Globally ([10](#_ENREF_10), [11](#_ENREF_11)).  **B.1.1.7**: Detected in Kent, in the South East of England on 20 September 2020 ([10](#_ENREF_10), [12](#_ENREF_12), [13](#_ENREF_13)).  **B.1.351:** First found at Nelson Mandela Bay, South Africa on 18 December 2020 ([3](#_ENREF_3), [14](#_ENREF_14), [15](#_ENREF_15)) ([16](#_ENREF_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](#_ENREF_17), [18](#_ENREF_18)). It was circulating in Manaus, northern Brazil at the time ([15](#_ENREF_15), [19](#_ENREF_19)).  **B.1.617:** Unknown origin, first reported in COVID-19 samples from Maharashtra, India around December 2020 to January 2021 ([20](#_ENREF_20), [21](#_ENREF_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](#_ENREF_9), [22-24](#_ENREF_22)). |
| **Suspected Source (specify food source, zoonotic or human origin or other)** | The suspected source of the COVID-19 pandemic is zoonotic ([25](#_ENREF_25)). The animal origin is yet to be determined ([25](#_ENREF_25), [26](#_ENREF_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](#_ENREF_27)). The most likely scenario of how the virus was transmitted from animals to humans was through an intermediary animal host ([28](#_ENREF_28)).  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](#_ENREF_10), [29](#_ENREF_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](#_ENREF_10), [29](#_ENREF_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](#_ENREF_4)).  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 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](#_ENREF_16)).  **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](#_ENREF_3), [14](#_ENREF_14)). **B.1.1.7** appears to have a fitness advantage and is becoming dominant in many countries.  Environmental conditions have an impact on a pathogen’s success ([30](#_ENREF_30)). Population density, climate, and host factors such as immunosuppression can affect infection, transmission and selective pressure for mutations to emerge ([30](#_ENREF_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. |
| **Date of outbreak beginning** | A cluster of pneumonia cases with an unknown aetiology was identified in late December 2019 in Wuhan ([25](#_ENREF_25)). In early January 2020, Chinese authorities identified the cause of the outbreak as being a novel betacoronavirus ([31](#_ENREF_31)). The new strain was named 2019-nCoV ([31](#_ENREF_31)). In early February 2020, the World Health Organisation (WHO) named the virus SARS-CoV-2 and called the disease COVID-19 ([14](#_ENREF_14)). |
| **Date outbreak declared over** | Ongoing pandemic (2019 – onwards). Emergence suspected around October to November of 2019 and first reported cases in December 2019 ([32](#_ENREF_32)) |
| **Affected countries & regions** | **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.**  **Original Strain and D614G:**   * 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](#_ENREF_1)).   **B.1.1.7**   * 118 countries have been verified ([23](#_ENREF_23)). * Dominant strain in the UK, Ireland and Cambodia ([33](#_ENREF_33)). * Dominant strain in the US ([34](#_ENREF_34), [35](#_ENREF_35)). * Second most common variant found in India in the last 60 days (as at April 16) ([33](#_ENREF_33)). Prevalent in the North of India in Punjab ([21](#_ENREF_21)). * Widespread in much of Europe, dominant strain in Germany, Bulgaria, Sweden, Greece, Italy ([33](#_ENREF_33), [36](#_ENREF_36), [37](#_ENREF_37)).   **B.1.351**   * 81 countries have been verified ([23](#_ENREF_23)). * Dominant strain in Comoros, Malawi and Botswana, Zimbabwe ([38](#_ENREF_38)). * Fairly common in Bangladesh, causing 80% of known cases ([39](#_ENREF_39)).   **P.1:**   * 47% of cases confirmed in Brazil are P.1 ([5](#_ENREF_5), [40](#_ENREF_40)). * 40 countries have been verified ([23](#_ENREF_23)).   **B.1.617:**   * At least 18 countries have been verified ([22](#_ENREF_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](#_ENREF_22), [41](#_ENREF_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](#_ENREF_42)). * On April 1, **B.1.617** accounted for 80% of all analysed genome sequences sent from India to GISAID ([20](#_ENREF_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](#_ENREF_21)). However, prevalence patterns may be inaccurate due to low levels of genome sequencing ([21](#_ENREF_21)). Between 60-80% of cases in Maharashtra are suspected of having **B.1.617** ([21](#_ENREF_21)). |
| **Number of cases (specify at what date if ongoing)** | **Total number of cases worldwide:** There were 141,057,106 confirmed cases and 3,015,043 deaths ([1](#_ENREF_1)). The case numbers of variants are affected by rates of genomic sequencing, which vary by country and within countries.  **B.1.1.7:** 439, 970 cases, 33% of cases worldwide ([23](#_ENREF_23), [33](#_ENREF_33))  **B.1.351:** 11, 781 cases ([23](#_ENREF_23))  **P.1:** 6190 cases, 42% prevalence in Brazil ([23](#_ENREF_23), [40](#_ENREF_40))  **B.1.617:** 1413 cases ([23](#_ENREF_23))  **B.1.617 in India and total number of recorded cases in India**  B.1.617 sequenced as of April 27: 1413 ([22](#_ENREF_22)). Sequencing capacity low.  Total number of cases: 17, 313, 163. There have been 352,991 cases reported in the last 24 hours ([1](#_ENREF_1))  **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**](#_ENREF_43)**)**  Map  Description automatically generated  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.**  Chart, bar chart  Description automatically generated |
| **Clinical features** | **High asymptomatic infection rate (**[**27**](#_ENREF_27)**)**  **Main clinical features** ([27](#_ENREF_27), [44](#_ENREF_44))   * Cough * Fever (temperature ≥ 38°c) * Shortness of breath/difficulty breathing * Fatigue or weakness * Loss of appetite * Loss of smell and/or taste   **Other less common symptoms** ([27](#_ENREF_27), [44](#_ENREF_44))   * Sore throat * Body aches * Dizziness * Headache * Nausea * Vomiting * Diarrhoea   **Severe cases** ([27](#_ENREF_27), [44](#_ENREF_44))   * Pneumonia * Cardiovascular complications including thrombosis * Gastrointestinal symptoms * Multi-organ failure   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](#_ENREF_45)). More severe symptoms, a longer sickness period and higher mortality are correlated with a higher viral load ([46](#_ENREF_46)).  **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](#_ENREF_47)). Frequently reported symptoms included cough, sore throat, myalgia and fatigue ([47](#_ENREF_47)). There was no evidence of a difference in gastrointestinal symptoms, shortness of breath or headaches ([48](#_ENREF_48)). Patients with **B.1.1.7** infections have been shown to have an increased severity of illness and risk of hospitalisation ([49](#_ENREF_49)).  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](#_ENREF_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](#_ENREF_50)). There has also been an increase in symptoms of joint pain and a loss of appetite ([50](#_ENREF_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](#_ENREF_50)). However, these, are preliminary findings so the clinical manifestations of **B.1.617** cannot be confirmed. |
| **Mode of transmission (dominant mode and other documented modes)** | **In general terms:**  The **dominant mode** of transmission is through the respiratory route and aerosols, especially in an indoor space with poor ventilation ([44](#_ENREF_44)). Specifically, exposure to the airborne respiratory aerosols of an infected individual and inhalation risk are thought to cause infection ([51-53](#_ENREF_51)).  **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](#_ENREF_54), [55](#_ENREF_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](#_ENREF_56)). * Zoonotic transmission: this is speculated as the origin of SARS-COV-2 but has not been documented ([28](#_ENREF_28)). * Ocular transmission is possible ([57](#_ENREF_57)). * Transmission from deceased patients through autopsy or funerals ([58](#_ENREF_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](#_ENREF_59)). **B.1.1.7** also possesses the **P681H** mutation,a mutation with importance for infection and transmission ([60](#_ENREF_60)).  A higher viral load has been noted in preliminary studies on **B.1.351**, which may confer increased transmissibility ([3](#_ENREF_3), [46](#_ENREF_46)). One modelling study estimates that it is 50% more transmissible than other circulating variants (64, [65](#_ENREF_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](#_ENREF_66)). Increased transmissibility is due to the **N501Y** mutation in the receptor binding domain (RBD) of the spike protein ([66](#_ENREF_66)).  The **P.1** has shown evidence of increased transmissibility with 1.4-2.2 times more transmissible than previous variants ([67](#_ENREF_67), [68](#_ENREF_68)). This is partly due to the presence of the **N501Y** mutation ([69](#_ENREF_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](#_ENREF_70), [71](#_ENREF_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](#_ENREF_72)). They have also been associated with an elevated household secondary attack rate suggesting higher transmissibility ([72](#_ENREF_72)). The **B.1.617**, due to its shared mutations with other circulating variants, may confer increased transmissibility ([7](#_ENREF_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](#_ENREF_50)). Unconfirmed reports from Delhi also report high secondary household attack rates. This is in contrast to 30-40% in the first wave ([50](#_ENREF_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 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](#_ENREF_73)).  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](#_ENREF_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](#_ENREF_74)). |
| **Demographics of cases** | **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](#_ENREF_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](#_ENREF_76)). Michigan state reported an all-time high for those aged 19 and younger reporting to hospital ([77](#_ENREF_77)).  **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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_78), [79](#_ENREF_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](#_ENREF_80)).  **B.1.351**  There is no evidence for demographics other than age groups being more affected by the variant.  **B.1.617**  **Figure 4. Demographics of B.1.617 in India as determined through genome sequencing. Data obtained from GISAID.**  **Chart, bar chart  Description automatically generated**  Thedemographic of **B.1.617** in India suggests a normal COVID-19 demographic ([81](#_ENREF_81), [82](#_ENREF_82)) (Figure 4), with the majority of cases reported in those aged 20- 59 (81, [83](#_ENREF_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](#_ENREF_50), [84](#_ENREF_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](#_ENREF_84)). However, in all cities with severe epidemics, paediatric cases have risen ([85](#_ENREF_85), [86](#_ENREF_86)). Further, in countries that have vaccinated older people first, a rise in proportional paediatric cases has been seen ([87](#_ENREF_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](#_ENREF_88)). The CFR also increases with the severity of illness and has been seen to reach 49% in patients who are critically ill ([89](#_ENREF_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](#_ENREF_90)).  **B.1.1.7**  The estimated risk of mortality significantly increased, from 2.5 to 4.1 deaths per 1,000 cases ([91](#_ENREF_91), [92](#_ENREF_92)). Average infections last 13.3 days compared with 8.2 days for other variants ([91](#_ENREF_91), [93](#_ENREF_93)).  **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](#_ENREF_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](#_ENREF_66), [94](#_ENREF_94)).  **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](#_ENREF_66)).  **B.1.617**  Limited information is available at this time. |
| **Complications** | 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](#_ENREF_95)). |
| **Available prevention** | **Non-pharmaceutical measures** ([96-98](#_ENREF_96))   * 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   The effectiveness of these measures on COVID-19 is evident. It has been shown to reduce reproduction numbers, bringing Ro closer to below 1 ([98](#_ENREF_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](#_ENREF_99)).  The WHO has focused specifically on recommendations such as hand washing and hygiene procedures which reduce the chance of infection through droplet transmission ([100](#_ENREF_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](#_ENREF_100), [101](#_ENREF_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](#_ENREF_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 measures such as re-directing ventilation systems are not plausible due to high costs ([100](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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**](#_ENREF_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](#_ENREF_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](#_ENREF_42), [107](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_110)) * **Oxford-AstraZeneca**: EMA finds a potential linkage to vaccine induced thrombotic throbocytopenia (VITT), which dictated a change in many countries’ vaccine regime ([111](#_ENREF_111)) * **Moderna:** Much like above, they are currently working on developing booster doses ([112](#_ENREF_112)) * **Novavax:** They are currently developing a booster to protect against variants, with the aim to commence trials later in 2021 (January 28) ([113](#_ENREF_113)) * **Johnson & Johnson**: Halted in the U.S due to VITT in women, but resumed in April 2021 ([114](#_ENREF_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](#_ENREF_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](#_ENREF_115), [116](#_ENREF_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](#_ENREF_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](#_ENREF_116), [118](#_ENREF_118), [119](#_ENREF_119)).  As of April 26, 933,824,012 vaccine doses have been administered worldwide ([1](#_ENREF_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](#_ENREF_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](#_ENREF_121), [122](#_ENREF_122)). Additionally, no evidence shows that reinfection is higher than other strains ([3](#_ENREF_3), [123](#_ENREF_123)). The deletion of **∆H69/∆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](#_ENREF_59), [124](#_ENREF_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](#_ENREF_65), [125](#_ENREF_125), [126](#_ENREF_126)). This is largely due to the presence of the **E484K** mutation ([62](#_ENREF_62), [118](#_ENREF_118), [119](#_ENREF_119), [127](#_ENREF_127))**.** The Oxford-AstraZeneca vaccine has 0-10% efficacy against this variant ([128](#_ENREF_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](#_ENREF_65), [129](#_ENREF_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](#_ENREF_5), [130](#_ENREF_130)). Information is still limited. However, the **E484K** has been linked to reduced vaccine efficacy ([118](#_ENREF_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](#_ENREF_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](#_ENREF_118), [127](#_ENREF_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](#_ENREF_131)). The Indian Council of Medical Research are currently conducting trials at the moment to test the variant’s capability to immune escape ([20](#_ENREF_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](#_ENREF_132)) | Largely unaffected ([119](#_ENREF_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](#_ENREF_133), [134](#_ENREF_134)) | 70.4% (95% CI, 43.6-84.5%)  ([133](#_ENREF_133), [134](#_ENREF_134)) | No efficacy 10.4% (95% CI: 59-73.4%)  ([128](#_ENREF_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](#_ENREF_1)) | 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 COVID-19. 85% for severe COVID-19. ([63,](#_ENREF_1) 130) | 57% (130) | 52.0% (130) | n/a | n/a | | Novavax  Based off their press release  ([113](#_ENREF_113), [135](#_ENREF_135)) | 96.4% (95% CI: 73.8- for symptomatic ([135](#_ENREF_135)) | 86% (109,131). Decreased by 1.8x ([66](#_ENREF_66)) | 48.6% (95% CI, 28.4 to 63.1 (109,131) | n/a | n/a | |
| **Available treatment** | 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:   * **Remdesivir** * 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](#_ENREF_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](#_ENREF_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](#_ENREF_137)). * Experiments have shown efficacy against **B.1.1.7** ([138](#_ENREF_138)). However, efficacy of the antiviral is increased when used in combination with other antiviral agents ([138](#_ENREF_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](#_ENREF_139)). * **Lopinavir–ritonavir** * These are HIV protease inhibitors ([140](#_ENREF_140)). * A benefit has not been shown in clinical trials. It has no significant improvement on clinical symptoms or reducing mortality ([141](#_ENREF_141)) ([140](#_ENREF_140), [142](#_ENREF_142)). * It was discontinued from solidarity trial conducted by the WHO ([143](#_ENREF_143)). * **Corticosteroids** * Dexamethasone remains effective in reducing mortality rates for patients infected with **B.1.1.7** ([144](#_ENREF_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](#_ENREF_62)). * **Hydroxychloroquine** * Hydroxychloroquine is a DMARD (disease modifying anti rheumatic drug) usually used to treat rheumatoid arthritis and systemic lupus erythematous ([137](#_ENREF_137)) * Its ability to act as a immunomodulator is why it was considered as a potential treatment for COVID-19 ([137](#_ENREF_137)) * Shown to have no effect on ventilation requirements, reducing mortality, or hospital duration ([145](#_ENREF_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](#_ENREF_143)) * On 30 July 2020, the ASCOT committee announced they would be removing hydroxychloroquine from the trial due to low efficacy ([146](#_ENREF_146)) * **Monoclonal Antibodies**   + Monoclonal antibodies work by recognising the virus’ spike protein ([137](#_ENREF_137), [147](#_ENREF_147)).   + For **B.1.1.7**, the neutralising activity of most antibodies tested against the variant were still potent ([119](#_ENREF_119)).   + **B.1.351** variant managed to abolish the neutralising activity of four antibody treatments. Casirivimab was 58 % less effective against this variant ([119](#_ENREF_119)).   + **P.1** has a moderate impact on neutralisation by monoclonal antibody treatments ([120](#_ENREF_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](#_ENREF_148)).   The CDC has asked the WHO to report updates on treatment options to ensure therapeutic treatments remain current and effective. |
| **Critical analysis** | The **B.1.617** variant possess the **L452R** mutation known to increase transmissibility ([70](#_ENREF_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](#_ENREF_149)). Medical experts have asked the Indian Government to increase genome sequencing as a response to the discovery of **B.1.617** ([6](#_ENREF_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](#_ENREF_1)).  **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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_151)). Exports of oxygen supplies were increased by 734% in January 2021 and over 193 vaccine doses were exported ([151](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_98), [153](#_ENREF_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](#_ENREF_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](#_ENREF_154)). The benefits of this new approach would aid in both speeding up vaccinations and reducing the impact of supply chain disruptions ([153](#_ENREF_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](#_ENREF_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** | The impact of these variants leads us to question certain protocols in place currently:   * 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? |
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