# Efficacy of COVID-19 vaccines on SARS-CoV-2 variants

Like other viruses, SARS-CoV-2 evolves over time .Most mutations have little to no impact on the virus' properties. However, some changes may affect the virus's properties, such as how easily it spreads, the associated disease severity, or the performance of vaccines, therapeutic medicines, diagnostic tools, or other public health and social measures.

WHO, in collaboration with partners, expert networks, national authorities, institutions and researchers have been monitoring and assessing the evolution of SARS-CoV-2 since January 2020. During late 2020, the emergence of variants that posed an increased risk to global public health prompted the characterization of specific Variants of Interest (VOIs) and Variants of Concern (VOCs), in order to prioritize global monitoring and research, and ultimately to inform the ongoing response to the COVID-19 pandemic.

Each variant has several designations based on the nomenclature used by distinct phylogenetic classification systems; the (WHO) has also designated labels for notable variants based on the Greek alphabet .

## ☒ Variants of Concern

A SARS-CoV-2 variant that meets the definition of a VOC through a comparative assessment has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:

- Increase in transmissibility or detrimental change in COVID-19 epidemiology; or

-Increase in virulence or change in clinical disease presentation; or

- Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

**SARS-CoV-2 Variants of Concern**

| WHO label[1] | Name (Pango lineage*) | Name (Nextstrain*) | Spike protein substitutions (receptor-binding domain substitutions in bold) | First detected | Known attributes |
|---|---|---|---|---|---|
| **Alpha** | **B.1.1.7**¶ | 20I/501Y.V1 | Δ69/70<br>Δ144Y<br>**(E484K**◊**)**<br>**(S494P**◊**)**<br>**N501Y**<br>A570D<br>D614G<br>P681H | United Kingdom | ▪ ~50% increased transmission[2]<br>▪ Potential increased severity based on hospitalizations and case fatality rates[3]<br>▪ Minimal impact on neutralization by monoclonal antibody therapies§<br>• Bamlanivimab-etesevimab: No change in susceptibility[4]<br>• Casirivimab-imdevimab: No change in susceptibility[5]<br>• Sotrovimab: No change in susceptibility[6]<br>▪ Minimal impact on neutralization by convalescent and post-vaccination sera[7-13] |
| **Beta** | **B.1.351** | 20H/501.V2 | **K417N**<br>**E484K**<br>**N501Y**<br>D614G | South Africa | ▪ ~50% increased transmission[14]<br>▪ Significant impact on neutralization by some monoclonal antibody therapies§<br>• Bamlanivimab-etesevimab: Unlikely to be active (>45-fold decrease in susceptibility)[4]<br>• Casirivimab-imdevimab: No change in susceptibility[5]<br>• Sotrovimab: No change in susceptibility[6]<br>▪ Moderate reduction in neutralization by convalescent and post-vaccination sera |

| | | | | | |
|---|---|---|---|---|---|
| **Gamma** | **P.1** | 20J/501Y.V3 | **K417N/T**<br>**E484K**<br>**N501Y**<br>D614G | Japan/Brazil | ▪ Significant impact on neutralization by some monoclonal antibody therapies[§]<br>• Bamlanivimab-etesevimab: Unlikely to be active (>511-fold decrease in susceptibility)[4]<br>• Casirivimab-imdevimab: No change in susceptibility[5]<br>• Sotrovimab: No change in susceptibility[6]<br>▪ Reduced neutralization by convalescent and post-vaccination sera[15] |
| **Delta** | **B.1.617.2**[¥] | 20A | T19R<br>(G142D[◊])<br>Δ156<br>Δ157<br>R158G<br>**L452R**<br>**T478K**<br>D614G<br>P681R<br>D950N | India | ▪ Increased transmissibility compared with B.1.1.7 (Alpha)[16]<br>▪ Potential minimal reduction in neutralization by monoclonal antibody therapies[‡]<br>▪ Potential moderate reduction in neutralization by convalescent and post-vaccination sera[17] |
| **Epsilon** | **B.1.427** and **B.1.429**[†] | 20C/S:452R | **L452R**<br>D614G<br>S13I (B.1.429 only)<br>W152C (B.1.429 only) | US-California | ▪ ~20% increased transmissibility[18]<br>▪ Significant impact on neutralization by some monoclonal antibody therapies[§]<br>• Bamlanivimab-etesevimab: Unlikely to be active (7.4-fold decrease in susceptibility)[4]<br>• Casirivimab-imdevimab: No change in susceptibility[5]<br>• Sotrovimab: No change in susceptibility[6]<br>▪ Moderate reduction in neutralization by convalescent and post-vaccination sera[18] |

"Variants of Concern" have evidence of an increase in transmissibility, greater risk of severe disease, a significant reduction in neutralization by antibodies generated during previous infection or vaccination, or reduced effectiveness of treatments or vaccines. These variants share one specific mutation called D614G. This mutation was one of the first documented in the United States in the initial stages of the pandemic, after having initially circulated in Europe. There is evidence that variants with this mutation spread more quickly than viruses without this mutation. In the United States, the proportion of circulating variants in each state can be found on the CDC website.

EUA: emergency use authorization; BEI resources: Biodefense and Emerging Infections Research resources; NIAID: National Institute of Allergy and Infectious Diseases; CDC: United States Centers for Disease Control and Prevention.

* Pango lineage (or Pangolin) and Nextstrain are resources that compile reported SARS-CoV-2 genome sequences and assign them to a most likely phylogenetic lineage. Each tool uses its own nomenclature.

¶ As of April 2021, the B.1.1.7 variant is the most common lineage circulating in the United States.

◊ Detected in some sequences but not all.

§ These estimates were established by manufacturers' assessments of neutralizing activity against pseudoviruses bearing the key spike protein mutations found in each variant. Key mutations in B.1.526/20C, a Variant of Interest (distinct from a Variant of Concern) that was first identified in New York and contains the E484K mutation, was also assessed for susceptibility to monoclonal antibody therapy and showed a 17-fold reduction in susceptibility to bamlanivimab-etesevimab and no change in susceptibility to casirivimab-imdevimab and sotrovimab.[4-6]

¥ This lineage has been designated a Variant of Concern by the World Health Organization and a Variant of Interest by the CDC in the United States.

‡ B.1.617.2 does not contain mutations associated with reduced susceptibility to bamlanivimab-etesevimab, casirivimab-imdevimab, or sotrovimab.[5,6,17]

† These lineages have been designated Variants of Concern by the CDC in the United States and Variants of Interest by the World Health Organization.

## ☒ Variants of Interest

A SARS-CoV-2 isolate is a Variant of Interest (VOI) if, compared to a reference isolate, its genome has mutations with established or suspected phenotypic implications, and either:

- Has been identified to cause community transmission/multiple COVID-19 cases/clusters, or has been detected in multiple countries; OR

-Is otherwise assessed to be a VOI by WHO in consultation with the WHO SARS-CoV-2 Virus Evolution Working Group.

| WHO label | Pango lineage | GISAID clade/lineage | Nextstrain clade | Earliest documented samples | Date of designation |
|---|---|---|---|---|---|
| Epsilon | B.1.427/B.1.429 | GH/452R.V1 | 21C | United States of America, Mar-2020 | 5-Mar-2021 |
| Zeta | P.2 | GR/484K.V2 | 20B/S.484K | Brazil, Apr-2020 | 17-Mar-2021 |
| Eta | B.1.525 | G/484K.V3 | 21D | Multiple countries, Dec-2020 | 17-Mar-2021 |
| Theta | P.3 | GR/1092K.V1 | 21E | Philippines, Jan-2021 | 24-Mar-2021 |
| Iota | B.1.526 | GH/253G.V1 | 21F | United States of America, Nov-2020 | 24-Mar-2021 |
| Kappa | B.1.617.1 | G/452R.V3 | 21B | India, Oct-2020 | 4-Apr-2021 |
| Lambda | C.37 | GR/452Q.V1 | 20D | Peru, Dec-2020 | 14-Jun-2021 |

## Delta variants

**B.1.617.2** lineage (Delta) — This lineage, also known as 20A/S:478K, was first identified in India in December 2020 and has become one of the prevalent variants there and in several other countries . Data from the United Kingdom suggest that B.1.617.2 is more transmissible than B.1.1.7 lineage (Alpha) ; the proportion of SARS-CoV-2 infections caused by B.1.617.2 rose as that caused by B.1.1.7 declined, and the secondary household infection rate associated with B.1.617.2 infection was 13.6 percent compared with 9.0 percent for B.1.1.7 . The same report also suggests that B.1.617.2 is associated with a higher risk of hospitalization than B.1.1.7. Unpublished studies suggest that vaccine effectiveness of two doses of BNTb162b (Pfizer COVID-19 vaccine) or ChAdOx-1/ADZ1222 (AstraZeneca vaccine) was high for B.1.617.2 but slightly less than for B.1.1.7; effectiveness against B.1.617.2 after a single dose of each vaccine was low.

**The Delta Plus variant** – also known as B.1.617.2.1 or AY.1 – contains a new mutation in the spike protein the virus uses to enter human cells, called K417N. As it's still closely linked to Delta, it's been called Delta Plus rather than another letter in the Greek alphabet, according to WHO's naming system for COVID-19 variants. So far, Delta Plus has been found in relatively low numbers.

## Efficacy of vaccines

Currently, there are four main types of COVID-19 vaccine: nucleic acid (mRNA and DNA), viral vector, protein subunit, and inactivated virus. Two COVID-19 mRNA vaccines (BNT162b2 developed by Pfizer-BioNTech and mRNA-1273 by Moderna) have been authorized by the (FDA) and European Medicines Agency (EMA). In addition, Ad26.COV2.S (Johnson & Johnson/Janssen) was approved by the FDA and EMA and ChAdOx1 nCoV-19 (AstraZeneca) was authorized by the EMA, both of which are viral vector vaccines. People are considered fully vaccinated 2 weeks after their second dose

in a 2-dose series (such as the Pfizer or Moderna vaccines), or 2 weeks after a single-dose vaccine (such as Johnson & Johnson's Janssen vaccine)

The results from recent studies suggest that the emergence of resistant SARS-CoV-2 variants may nullify the effects of current COVID-19 vaccines. However, COVID-19 vaccines can elicit not only neutralizing antibodies, but also SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T-cell responses. Vaccination with various vaccine platforms, including mRNA and viral vectors, has been shown to elicit SARS-CoV-2-specific $CD4^+$ and $CD8^+$ T-cell responses. In principle, it is more difficult to evade T-cell responses than a neutralizing antibody response because multiple T-cell epitopes are scattered across viral proteins, whereas neutralizing antibody targets a narrow region in the viral protein. Although SARS-CoV-2 mutations that abrogate binding to major histocompatibility complex have been reported, Tarke et al. recently reported an insignificant impact of SARS-CoV-2 variants on both $CD4^+$ and $CD8^+$ T-cell responses in COVID-19 convalescents and recipients of COVID-19 mRNA vaccines. T-cell responses to the variants B.1.1.7, B.1.351, P.1, and CAL.20C (emerged in Southern California) were not differ from those to the ancestral strain of SARS-CoV-2. Most SARS-CoV-2 T-cell epitopes were conserved despite the mutations in the variants.

Data on whether vaccine-induced immunity can protect against these variants are limited. Based on preliminary, largely unpublished reports from efficacy trials and immunogenicity studies, COVID-19 vaccines likely retain efficacy against some of the variants (eg, B.1.1.7 [Alpha]).

However, for variants with mutations found in the B.1.351 (Beta) variant, vaccine efficacy may be less when compared with the original wild-type virus. Overall efficacies of Ad26.COV2.S (Janssen vaccine), NVX-CoV2373 (Novavax vaccine), and ChAdOx1 nCoV-19/AZD1222 (University of Oxford/AstraZeneca vaccine) were lower in South Africa, where the B.1.351 variant was circulating, compared with other locations where B.1.351 was not prevalent. For Ad26.COV2.S, efficacy against severe/critical disease remained high in all locations; impact on severe disease in South Africa was not assessed for the other two vaccines. Whether the difference in overall efficacy in South Africa compared with other sites could be related

to local factors other than B.1.351 is uncertain. Observational evidence suggests that BNT162b2 effectiveness against any infection with B.1.351 is slightly lower than with B.1.1.7, but remains high against severe infection. Similarly, preliminary evidence suggests that vaccine effectiveness against the B.1.617.2 (Delta) variant is preserved but may be slightly lower than with B.1.1.7.
There have also been reports of breakthrough infections in fully vaccinated individuals caused by other SARS-CoV-2 variants that share some mutations with variants of concern (such as E484K, which is associated with reduced neutralization by convalescent plasma from individuals with wild-type infection) ; however, in at least one report, the risk of infection with a variant that contained E484K was still lower among vaccinated compared with unvaccinated individuals .

## BNT162b2

Plasma from trial participants vaccinated with BNT162b2(developed by Pfizer-BioNTech) appears to maintain neutralizing activity against B.1.1.7 (Alpha), a variant of concern first identified in the United Kingdom that has become the most commonly circulating variant in many other countries, including the United States . It also neutralizes virus containing spike protein mutations found in B.1.351 (Beta), a variant of concern that has emerged as the dominant variant in South Africa, and B.1.617.2 (Delta), a variant first identified in India, although neutralizing titers are lower than those for other circulating strains . Another unpublished study similarly suggested that neutralizing titers in serum from vaccine recipients were lower (about three- to fourfold lower) for B.1.351 compared with wild-type virus but were still higher than titers in convalescent plasma against wild-type virus.

The vaccine also appears effective against SARS-CoV-2 variants that have become prevalent since the initial trial. In a study of over 23,000 health care workers in the United Kingdom, covering a time frame when the B.1.1.7 variant (Alpha) was prevalent, vaccine effectiveness against SARS-CoV-2 infection (both asymptomatic and symptomatic) was estimated at

85 percent 7 days or more after the second dose . Additionally, in a study of the national COVID-19 database in Qatar, where over 265,000 individuals had received two doses of BNT162b2 and both the B.1.1.7 and B.1.351 (Beta) variants were predominant, vaccine effectiveness was estimated at 90 percent (95% CI 86-92) for any B.1.1.7 infection, 75 percent (95% CI 71-79) for any B.1.351 infection, and 100 percent for severe, critical, or fatal infection with either variant . Similarly, in an unpublished study from the United Kingdom, estimated effectiveness against B.1.617.2 (Delta) was 90 percent compared with 93 percent for B.1.1.7 .

Although some of these data suggest some efficacy of a single vaccine dose, the actual magnitude and duration of protection from a single dose are unknown because most participants in the trial and the observational studies received the second dose three weeks after the first. Additionally, studies suggest that a single dose of BNT162b2 is not associated with high effectiveness against the B.1.1.7, B.1.351, and B.1.617.2 variants .

- **ChAdOx1 nCoV-19/AZD1222 (University of Oxford, AstraZeneca, and the Serum Institute of India)**

Efficacy of ChAdOx1 nCoV-19/AZD1222 against variants of concern may be attenuated. In an analysis of one of the randomized trials, vaccine efficacy against symptomatic COVID-19 caused by B.1.1.7 (Alpha) was not statistically different compared with other variants (70 versus 82 percent), despite induction of lower neutralizing activity against the B.1.1.7 variant . However, according to preliminary results of a phase I/II trial in South Africa, ChAdOx1 nCoV-19/AZD1222 did not reduce the rate of mild to moderate COVID-19 (at least one symptom but no tachypnea, hypoxia, or organ failure) over a time frame when B.1.351 (Beta) was the dominant variant circulating . Because the trial was small and the number of cases was low, the estimate of vaccine efficacy had very wide confidence intervals (21.9 percent, 95% CI -49.9 to 59.8). Impact on severe disease, which was rare in the young, healthy trial population, could not be assessed. In an unpublished study from the United Kingdom, estimated effectiveness against B.1.617.2 (Delta) was 60 percent compared with 66 percent for B.1.1.7 .

- **(Johnson & Johnson/Janssen)**

In July 1, 2021 , Johnson & Johnson Company announced data that demonstrated its single-shot COVID-19 vaccine generated strong, persistent activity against the rapidly spreading Delta variant and other highly prevalent SARS-CoV-2 viral variants. In addition, the data showed that the durability of the immune response lasted through at least eight months, the length of time evaluated to date.

A preprint submitted by the Company today to *bioRxiv* contains a new analysis from blood samples obtained from a subset of participants (n=8) in the Phase 3 ENSEMBLE study. These data showed that the Johnson & Johnson single-shot COVID-19 vaccine elicited neutralizing antibody activity against the Delta variant at an even higher level than what was recently observed for the Beta (B.1.351) variant in South Africa where high efficacy against severe/critical disease was demonstrated.

In the ENSEMBLE trial, Johnson & Johnson's single-dose COVID-19 vaccine was 85 percent effective against severe/critical disease and demonstrated protection against hospitalization and death. The vaccine was consistently effective across all regions studied globally, including in South Africa and Brazil, where there was a high prevalence of rapidly emerging Beta and Zeta (P.2) variants during the study period.

A single dose of the Johnson & Johnson COVID-19 vaccine generated neutralizing antibodies against a range of SARS-CoV-2 variants of concern, which increased over time (the average neutralizing titer at eight months exceeded that average at 29 days), including against the increasingly prevalent and more transmissible Delta (B.1.617.2) variant, the partially neutralization-resistant Beta (B.1.351), the Gamma (P.1) variants and others, including the Alpha (B.1.1.7), Epsilon (B.1.429), Kappa (B.1.617.1) and D614G variants, as well as the original SARS-CoV-2 strain (WA1/2020).

- **mRNA 1273 (Moderna vaccine)**

In Jun. 29, 2021, Moderna company announced new results from in vitro neutralization studies of sera from individuals vaccinated with the Moderna COVID-19 Vaccine showing activity against variants of SARS-CoV-2. Vaccination with the Moderna COVID-19 Vaccine produced neutralizing titers against all variants tested, including additional versions of the Beta variant (B.1.351, first identified in South Africa), three lineage variants of B.1.617 (first identified in India), including the Kappa (B.1.617.1) and the Delta variants (B.1.617.2); the Eta variant (B.1.525, first identified in Nigeria); and the A.23.1 and A.VOI.V2 variants first identified in Uganda and Angola, respectively.

This additional analysis showed minimal impact on neutralizing titers against the Alpha and A.23.1 variants relative to those against the ancestral strain (D614G). This analysis also showed a modest reduction in neutralizing titers against the Delta (2.1-fold), Gamma (P.1, 3.2-fold), Kappa (3.3-3.4-fold), and Eta (4.2-fold) variants relative to those against the ancestral strain. Consistent with previous results, a 7.3 or 8.4-fold reduction in neutralizing titers was observed with the additional versions of the Beta variant relative to the ancestral strain. Additionally, an 8.0-fold reduction in neutralizing titers relative to the ancestral strain was observed with A.VOI.V2, the variant first identified in Angola, but currently not designated as a Variant of Concern or Interest.

- **Role of booster vaccinations** — Because of the possibility of waning immunity and decreased efficacy against variants that escape the immune response directed against spike proteins targeted by the original vaccines (such as B.1.351), the role of booster vaccinations to prolong and broaden immunity is being investigated.

According to a press release report of a small study of individuals who had received mRNA-1273 (Moderna COVID-19 vaccine) six to eight months prior, a boosting dose of mRNA-1273 or mRNA-1273.351, a modified vaccine that targets the spike protein of the B.1.351 (Beta) variant, resulted in neutralizing antibody levels against wild-type virus and the B.1.351

and P.1 (Gamma) variants that were as high as or higher than those elicited against wild-type virus following the initial vaccine series . The rate and severity of adverse reactions following the booster dose were similar to those following the second dose in prior trials.

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