New variant, C.1.2, may be more infectious, evade vaccine protection: Study

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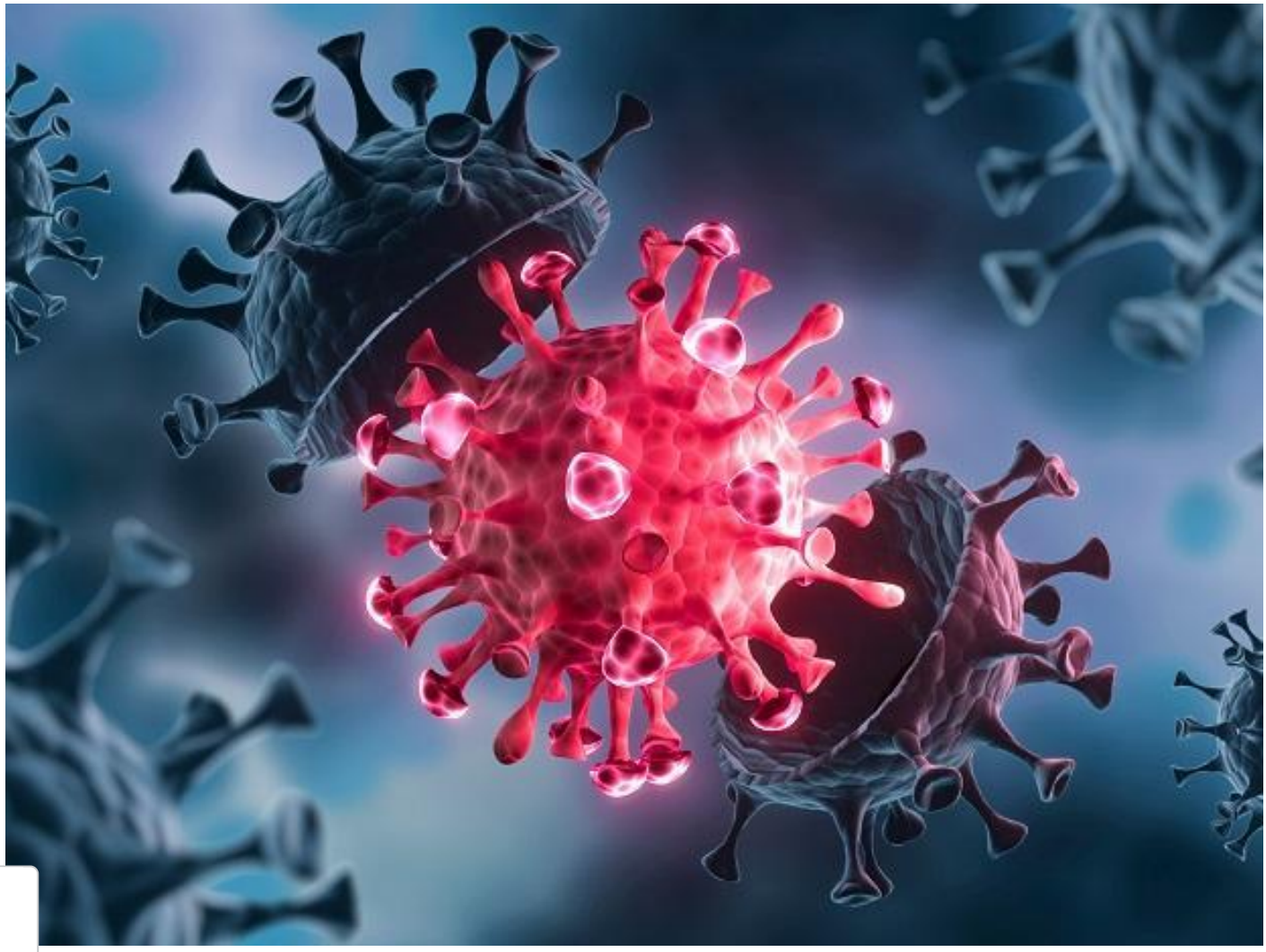

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A new variant of SARS-CoV-2, the virus which cause COVID-19, has been detected in South Africa and many other countries globally which could be more transmissible and evade protectio by vaccines, according to study.

Scientists from National Institute for Communicable Diseases (NICD) and the KwaZulu-Natal Research Innovation and Sequencing Platform (KRISP) in South Africa said the potential variant of interest, C.1.2, was first detected in the country in May this year.

C.1.2 has since been found in China, the Democratic Republic of the Congo, Mauritius, England, New Zealand, Portug l and Switzerland as of August 13, they said.

According to the yet-to-be peer-reviewed study posted on the preprint repository MedRxiv on August 24, C.1.2 has mutated

substantially compared to C.1, one of the lineages which dominated the SARS-CoV-2 infections in the first wave in South Africa.

The new variant has more mutations than other variants of concern (VOCs) or variants of interest (VOIs) detected worldwide so far, the researchers said.

They noted that the number of available sequences of C.1.2 may be an underrepresentation of the spread and frequency of the variant in South Africa and around the world.

The study found consistent increases in the number of C.1.2 genomes in South Africa each month, rising from 0.2 per cent of genomes sequenced in May to 1.6 per cent in June and then to 2 per cent in July.

"This is similar to the increases seen with the Beta and Delta variants in the country during early detection," the authors of the study said.

According to the study, C.1.2 lineage has a mutation rate of about 41.8 mutations per year, which is about twice as fast as the current global mutation rate of the other variants.

Over half of the C.1.2 sequences have 14 mutations, but additional variations have been noticed in some of the sequences.

"Though these mutations occur in the majority of C.1.2 viruses, there is additional variation within the spike region of this lineage, suggesting ongoing intra-lineage evolution," the authors of the study noted.

About 52 per cent of the mutations in the spike region of the C.1.2 sequences have previously been seen in other VOCs and VOIs.

The spike protein is used by the SARS-CoV-2 virus to infect and enter human cells, and most vaccines target this region.

The mutations N440K and Y449H, which have been associated with immune escape from certain antibodies, have also been noticed in C.1.2 sequences.

"While these mutations are not characteristic of current VOCs/VOIs, they have been associated with escape from certain class 3 neutralising antibodies," the authors wrote.

They noted that these mutations together with changes in other parts of the virus likely help the virus evade antibodies, and immune response, including in patients who have already developed antibodies for the Alpha or Beta variants.

"While the phenotypic characteristics and epidemiology of C.1.2 are being defined, it is important to highlight this lineage given its concerning constellations of mutations," the authors added.

REVEALED: ALL 31 COVID VARIANTS ON THE UK'S WATCHLIST.

VARIANTS OF CONCERN

Alpha
The Alpha variant has a mutation called N501Y which could help it spread more easily.

Beta
The Beta variant also contains the troublesome N501Y mutation that speeds up transmission. Additionally, it features the E484K mutation that can help it escape antibodies against other variants.

Gamma
The variant which first originated in Brazil has both the N501Y and E484K mutation.

Delta
The Delta variant has two mutations that may speed up transmission and escape antibodies: E484Q and L452R.

VARIANTS UNDER INVESTIGATION

Zeta (E484K)

Eta (E484K)

B.1.1.318 (E484K)

Theta (E484K and N501Y)

Kappa (B.1.617.1)

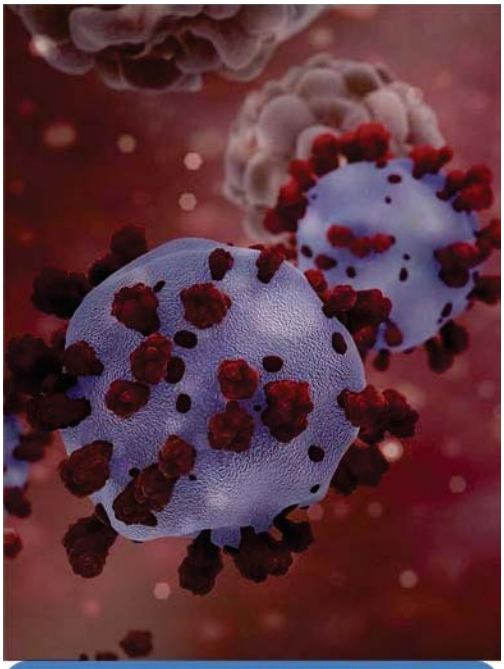
B.1.617.3 (E484Q and L452R)

AV.1

C.36.3

Lambda (L452Q and F490S)

B.1.621 (N501Y and E484K)



The coronavirus, called SARS-CoV-2, is mutating all the time as a result of genetic errors when it multiplies. Most mutations are harmless (stock)

... AND THE OTHERS THAT ARE BEING MONITORED

B.1.1.7 with E484K

Epsilon (B.1.427/B.1.429)

B.1.1.7 with S494P

A.27

Iota (B.1.526)

B.1.1.7 with Q677H

B.1.620

B.1.214.2

R.1

B.1 with 214insQAS

Delta like variant with E484A

Lineage A with R346K, T478R and E484K

AT.1

P.1 + N501T and E484Q

B.1.629

B.1.619

C.1.2

Can we predict the limits of SARS-CoV-2 variants and their phenotypic consequences?

As eradication of SARS-CoV-2 will be unlikely, we have high confidence in stating that there will always be variants. The number of variants will depend on control measures.

We describe hypothetical scenarios by which SARS-CoV-2 could further evolve and acquire, through mutation, phenotypes of concern, which we assess according to possibility. For this purpose, we consider mutations in the ‘body’ of the virus (the viral genes that are expressed in infected cells and control replication and cell response), that might affect virus fitness and disease severity, separately from mutations in the spike glycoprotein that might affect virus transmission and antibody escape.

We assess which scenarios are the most likely and what impact they might have and consider how these scenarios might be mitigated. We provide supporting information based on the evolution of SARS-CoV-2, human and animal coronaviruses as well as drawing parallels with other viruses.

Scenario One: A variant that causes severe disease in a greater proportion of the population than has occurred to date. For example, with similar morbidity/mortality to other zoonotic coronaviruses such as SARS-CoV (~10% case fatality) or MERS-CoV (~35% case fatality). This could be caused by:

1. Point mutations or recombination with other host or viral genes. This might occur through a change in SARS-CoV-2 internal genes such as the polymerase proteins or accessory proteins. These genes determine the outcome of infection by affecting the way the virus is sensed by the cell, the speed at which the virus replicates and the anti-viral response of the cell to infection. There is precedent for Coronaviruses (CoVs) to acquire additional genes or sequences from the host, from themselves or from other viruses.

2. By recombination between two VOC or VUIs. One with high drift (change in the spike glycoprotein) from the current spike glycoprotein gene used in the vaccine and the other with a more efficient replication and transmission determined by internal genes, for example, a recombination between beta and alpha or delta variants respectively. Alternatively, recombination may occur between two different variants with two different strategies for overcoming innate immunity, combining to give an additive or synergistic change of phenotype resulting in higher replication of the virus – and potentially increased morbidity and mortality.

   Likelihood of genotypic change in internal genes: Likely whilst the circulation of SARS-CoV-2 is high.

   Likelihood of increased severity phenotype: Realistic possibility.

   Impact: High. Unless there is significant drift in the spike glycoprotein gene sequence, then the current spike glycoprotein-based vaccines are highly likely to continue to provide protection against serious disease. However, an increase in morbidity and mortality would be expected even in the face of vaccination since vaccines do not provide absolute sterilising immunity i.e. they do not fully prevent infection in most individuals.

   What can we do?

   - Consider vaccine booster doses to maintain protection against severe disease.
   - Reduce transmission of SARS-CoV-2 within the UK (to reduce risk of point mutations, recombination).
   - Minimise introduction of new variants from other territories (to reduce risk of recombination between variants).
   - Targeted surveillance for reverse zoonoses, and if necessary, consider animal vaccination, slaughter, or isolation policies.
   - Continue to monitor disease severity associated with variants (to identify changes in phenotype).
   - Continue to develop improved prophylactic and therapeutic drugs for SARS-CoV-2 and disease symptoms.
   - Consider stockpiling prophylactic and therapeutic drugs for SARS-CoV-2.

Scenario Two: A variant that evades current vaccines. This could be caused by:

3. Antigenic 'shift': Natural recombination events that insert a different spike gene sequence (or partial sequence) from human CoVs MERS-CoV (highly unlikely due to the low frequency of MERS-CoV infections), or from currently circulating endemic human CoVs (more likely due to the prevalence of these viruses). This would recombine into the 'body' of SARS-CoV-2 that is capable of high replication in human cells. The consequence could be a virus that causes disease at a level similar to COVID-19 when it first emerged but against which our current battery of spike glycoprotein-based vaccines would not work.

   Likelihood: Realistic possibility.

   Impact: High for a completely new spike, medium/low if a spike from a seasonal CoV is introduced since we expect a proportion of the population to have antibodies to these endemic viruses.

   What could we do? In the case of introduction of a completely different spike glycoprotein, a similar vaccine platform could be rapidly employed as has been used successfully on the original Wuhan SARS-CoV-2 and subsequent variants. However, there would be a time lag for roll out whilst these vaccines were generated in sufficient quantities to control and mitigate the effects of infection.

4. A longer-term version of shift whereby SARS-CoV-2 undergoes a reverse zoonotic event into an animal reservoir(s). This virus is then on a separate evolutionary trajectory because the virus animals is subject to different selection processes than in humans. The SARS-CoV-2 decedents then re-emerge into humans at a later time when vaccines that have been updated to keep pace with drift in humans sufficiently mismatched so as not able to provide immunologic cross protection.

   Likelihood: Realistic possibility. Impact: Medium.

   What could we do? Maintain a capacity to make vaccines with updated/different spike protein variants and begin to develop broader CoV immunity in the human population to diverse coronaviruses. For example, begin to develop a universal coronavirus vaccine with strong cross protection to other CoVs potentially using other viral proteins rather than just the spike glycoprotein.

5. Antigenic drift: A gradual or punctuated accumulation of antigenic variation that eventually leads to current vaccine failure. Worst case is that this drift combines with significant antigenic sin (vaccination resulting in an immune response that is dominated by antibodies to previously experienced viruses/vaccines) meaning that it becomes difficult to revaccinate to induce antibodies to the new strains. Genetic and antigenic drift are almost inevitable. Antigenic sin has not yet been reported for SARS-CoV-2 so we consider this possibility less likely.

Likelihood: Almost certain. Impact: Medium.

What could we do? Need to continue vaccinating vulnerable age groups at regular periods with updated vaccines to the dominant antigenic drift variants to increase an individual's immunological protection against SARS-CoV-2 variants.

- Monitor antigenic variants and update candidate vaccines to cover antigenic escape variants.
- Conduct clinical trials of re-vaccination with antigenically distant vaccines
- Consider clinical trials of multi-valent vaccines.
- Re-vaccinate vulnerable age groups at regular periods with updated vaccines to the dominant antigenic drift variants to increase an individual's immunological landscape to SARS-CoV-2 variants.
- Reduce transmission of SARS-CoV-2 within the UK (to reduce risk of point mutations, recombination).
- Minimise introduction of new variants from other territories (to reduce risk of recombination between variants).
- Monitor for reverse zoonoses and if necessary, consider animal vaccination, slaughter, or isolation policies.
- Continue to develop improved prophylactic and therapeutic drugs for SARS-CoV-2.
- Stockpile prophylactic and therapeutic drugs for SARS-CoV-2.

Scenario Three: Emergence of a drug resistant variant after anti-viral strategies. This could be caused by:

6. Emergence of new variants following the administration of directly acting antiviral therapies. As we begin to use directly acting antiviral drugs it is highly likely a variant will be selected that had resistance to individual agents. For example, drugs that target the viral 3C protease, drugs that target the polymerase, monoclonal antibodies that target the spike glycoprotein. If the drugs are used as a mono therapy, then resistant variants have a high probability of emerging. This may render all drugs in that category unusable.

   Likelihood: Likely - unless the drugs are used correctly. Impact: medium unless a scenario arises where drugs are needed more widely.

   What can we do? Use the deep knowledge of deploying antivirals against RNA viruses such as HIV and influenza virus.

   - Only use antiviral combination therapy, using ≥2 drugs with different targets or mechanism of action.
   - Preserve antiviral use for an emergency in which a SARS-CoV-2 variant is more severe, and a matched vaccine is unavailable and takes time to develop.
   - Use antivirals cautiously in immunocompromised people in whom long term evolution can happen – monitor for treatment failure and resistance, minimise risk of onwards transmission of resistant variants using appropriate PPE.

Scenario Four: SARS-CoV-2 follows an evolutionary trajectory with decreased virulence. This could be caused by:

7. Variants arising with increased transmissibility but decreased pathogenesis/virulence as the virus becomes fully adapted to the human host becoming an endemic infection. Coupled with the likelihood of eventual high populations immunity the infection produces less disease. In other words, this virus will become like other human CoV that causes common colds, but with much less severe disease predominantly in the old or clinically vulnerable.

   Likelihood: Unlikely in the short term, realistic possibility in the long term.

General considerations for further reducing the impacts of variants:

8. Whilst we feel that current vaccines are excellent for reducing the risk of hospital admission and disease, we propose that research be focused on vaccines that also induce high and durable levels of mucosal immunity in order to reduce infection of and transmission from vaccinated individuals. This could also reduce the possibility of variant selection in vaccinated individuals.

9. The UK should continue to proactively support a strategy of worldwide effective vaccination in order to drive down global viral load reducing the likelihood of dangerous variants emerging in other parts of the world.

10. Implement a long-term strategy for national and global genomic surveillance of SARS-CoV-2 to monitor for variants and the rapid assessment of their affects.

11. Genomic surveillance alone is not enough as phenotypes cannot be unambiguously predicted. Therefore, we recommend ensuring sustainability for the rapid laboratory phenotypic evaluation of variants at scale to run alongside clinical observations to assess risk compared to contemporary variants.

12. Invest in laboratory-based studies that can be used to predict forward evolution of variants and further interpret genomic surveillance.

13. Given the current state of predictive capabilities of artificial intelligence (AI) in biological systems we are unlikely to be able to identify new variants of risk using these approaches alone at the moment. We recommend a long-term strategy where systems are in place in peace time for quick genomic surveillance and phenotyping but where the data can be integrated with AI methods to build their utility.

14. We recommend that the UK lead on processes and legislation for the rapid obtaining and sharing of viral sequence, clinical and biological materials, especially virus isolates, on the global stage. This will allow for the rapid study and evaluation of the threat posed by novel variants.

15. We recommend process and onshoring of capacity is undertaken to reduce the time to identify and manufacture vaccines and medical countermeasures to mitigate the impact of new variants that have a more significant clinical impact.

16. We recommend careful use of antivirals, as in the face of a threat posed by new variants, these therapeutic options are precious resources and should not be squandered.

Supporting information:

17. In addition to the oldest human endemic CoV (NL63), in the last 150 years there have been 5 known coronavirus incursions from animals into humans, of these three ended up as human endemic pathogens (229E, OC43 & HKU1) and two have caused limited but severe disease (SARS-CoV & MERS-CoV). Therefore, CoV zoonosis appears a common consequence of human proximity to animals.

18. Since the beginning of the SARS-CoV-2 outbreak in Wuhan in October/November 2019, an estimated 175 million people have been infected. The outbreak has seen multiple waves of infection, latterly with genetic variants of the virus, each with differing potential public health concerns.

19. SARS-CoV-2 uses RNA as a genetic material. RNA viruses are known to make errors as they replicate, leading to mutations (genetic changes in the genome) and therefore accumulation of genetic diversity over time.

20. The genome of SARS-CoV-2 in infected humans and animals can and has been sequenced to great effect. Sequencing the genetic material of a virus provides information on the spread and evolution of the virus and potentially allows prediction of how changes in its genome may influence future infection waves.

21. Genetic variation of a viral pathogen is a natural and expected process. The overall rate of accumulation of genetic changes, and therefore the risk of a new variant emerging with altered biological properties, is dependent on the virus mutation rate, the incidence and prevalence of infection, and the advantage a new variant has over other co-circulating variants.

22. When a human (or animal) is infected with SARS-CoV-2, multiple viruses with slightly different genetic sequences are generated as replication ensues which leads to a population of viral variation with an individual person.

23. Over time, the relative proportions of variants of SARS-CoV-2 will change within the infected individual, and specific variants may come to dominate if they confer the virus with a fitness advantage. This process happens both within single infected individuals, and across the population as variants are transmitted.

24. Over the course of the SARS-CoV-2 outbreak, several variants with transmission advantages have come to dominate in infection waves. These include the alpha variant and the delta variant that have dominated the second and third waves in the UK. These variants have come to prominence through founder effect and selection favouring increase transmission, allowing alpha and then delta to out-compete previous variants. In addition, the beta and gamma variants that have circulated in South Africa and Brazil respectively may have a fitness advantage because they are antigenically distant from first wave viruses and can reinfect people more efficiently.

25. Several different processes can lead to change or growth in mutation/variant frequency and not all observed changes in variant frequency will be due to the action of natural section. It is not possible to predict with any certainty what or when new variants will emerge, or their phenotypic significance. Assessing diverse streams of data, including genetic characterisation, epidemiological trends, and laboratory studies of measurable virus properties, are necessary to evaluate the significance of new variants. What can be said is that the more virus in circulation the greater number of variants.

26. The observation that a mutation or variant has increased in frequency (or even become fixed) is not, by itself, sufficient evidence to conclude that it confers a selective benefit to the virus. New variants can rise in frequency due to events that are unrelated to the functional effect of the mutations it carries, especially when numbers of infections are low (e.g. introduction into a new location, so called ‘founder’ effect). Further, an inconsequential mutation may increase in frequency because it happens to be present on the same genome as another mutation that is beneficial to the virus (‘genetic hitchhiking’). Therefore, it is essential to use all data available to determine if changes in absolute and relative frequency are a result of a variant being “luckier” or “more fit”.

27. Mutations that enable variants to infect new hosts more rapidly and effectively will be favoured by natural selection and may increase in frequency. Mutations that enhance onward transmission can be associated with many different aspects of virus biology, including changes to disease severity, the kinetics of infection, enhancement to virus shedding or cell binding, evasion of immune responses, etc.

How does genetic change occur in SARS-COV-2?

28. Genetic change in SARS-CoV-2 can occur in several ways: point mutations due to polymerase copying errors leading to single nucleotide polymorphisms and recombination allowing acquisition of new genetic material including viral and host.

    a) RNA is made up of building blocks known as nucleotides. These can be any one of four different types: A, G, C, or U. The RNA genome of SARS-CoV-2 is about 30,000 nucleotides in length. Every time the viral replication factory copies the genome, random genetic change can occur. For example, an A nucleotide at a particular position on the genome could change to a U nucleotide. This is known as a single nucleotide polymorphism, or SNP. The intrinsic error rate of coronavirus genome replication is in the order of 1×10^{-6} to 1×10^{-7} mutations per nucleotide per genome replication (1 mutation in 1-10 million nucleotides replicated). As the virus genome is about 30,000 nucleotides long, then 1 mutation is introduced about every 33-330 replications. In an infected person the peak number of virus genomes exceeds 100 million genomes; therefore, the virus has the potential to mutate every nucleotide of its genome hundreds of times per infected person, therefore variant generation is common. Many SNPs do not result in an amino acid change, many cause deleterious changes and some are compatible with a viable virus, and it is these that can result in changes to amino acids in viral proteins giving them new properties. An example of this is the D614G SNP, a defining feature of an amino acid change in the spike glycoprotein leading to a change from the B to B1 lineage early in the outbreak. Phenotypic assessment showed this change is associated with increased transmission because it enhances the ability of the Spike protein to bind to the ACE2 receptor.

b) Recombination is the process by which viruses swap genetic material between genomes, producing new combinations of genetic sequences. This can have several effects: parts of the genome can be deleted, or new sequences can be incorporated into the genome as small insertions or as whole extra genes producing a chimeric virus. New sequence can be acquired from the same type of coronavirus or a different source of RNA altogether. For example, SARS-CoV-2 is thought to have arisen by a recombination event(s) between other animal coronaviruses and/or host RNA. The presence of a furin protease cleavage site at the S1/S2 junction in the spike glycoprotein gene of SARS-CoV-2 is a consequence of such recombination. This furin site is associated with increased disease and transmission in animal models. Importantly, certain regions of the coronavirus genome have higher frequency of recombination, so called 'hotspots', one of which occurs at the Spike gene, promoting recombination that could lead to new virus receptor usage and alter species or cell type tropism.

29. The accumulation of genetic change has consequences for the emergence of new variants. These changes can be neutral (no effect), deleterious (decreases viral fitness) or advantageous (increases viral fitness) depending on the selection pressure.

30. SARS-CoV-2 variants are constantly being generated during infection and these provide the raw material for the virus to respond to different selection pressures. Keeping national and global levels of SARS-CoV-2 low through vaccination and/or isolation/containment will reduce the number of possible future variants.

What are the effects of genetic change on viral genome biology and protein function?

31. A change in the genotype (genetic information) of a virus is not always associated with a change in its phenotype (its observable characteristics). However, on occasion, a change in the genetic sequence of a virus may be associated with a change in its transmissibility, severity, or other characteristic such as susceptibility to immune control, vaccines or drugs.

32. Examples of changes in the genetic sequence of SARS-CoV-2 that have been associated with changes in its phenotype have been seen in the spike glycoprotein region of all variants of concern (VOCs). For example, mutation at position P681H of spike of alpha variant has been shown to increase the efficiency of furin cleavage, enhancing entry of the virus into the cell. In addition, the alpha variant contains other important mutations amongst the constellation of mutations that define the alpha lineage. A deletion in the spike protein ΔH69/ΔV70 (Δ = a deletion) is associated with higher infectivity, compared to wild type, and a further mutation N501Y in spike enhances the interaction with the ACE2 receptor.

33. Several viral RNA structures and proteins are critical for virus biology and infection and therefore mutations in these regions can be lethal to the virus (and therefore not passed on). However, other regions are non-essential to critical function. For example, there are several variants with deletions of viral proteins involved in subverting the innate immune response. One of these was identified in the ORF8 region of SARS-CoV-2 in patients in Singapore. This deletion was associated with a milder disease profile. In contrast the B.1.1.7 variant has a mutation that led to changes in several genes including a deletion in nsp6, mutations in ORF8 protein and mutations that affect potentially lead to production of new versions of viral proteins, along with the mutations in the spike glycoprotein described in point 32 above. The alpha variant is associated with greater transmissibility than previous strains but a relationship with increased morbidity and mortality were harder to establish and this particular variant has since been outpaced by others. Therefore, crucially the whole virus genome and the complete set of virus proteins contribute to a complex phenotype for the virus.

What can we learn from animal coronaviruses and how does this apply to SARS-CoV-2?

34. Coronaviruses have been studied for many decades and what has happened in other coronaviruses infections of humans and animals may paint a picture of the evolutionary journey of SARS-CoV-2.

35. Variants can lead to escape from current vaccines. Infectious bronchitis virus (IBV) is a coronavirus that infects chickens causing mainly respiratory disease. Gene translocations, deletions and recombination between IBVs from different genetic lineages have contributed to a complex population of IBV. As seen for SARS-CoV-2, the S1 region of spike is sufficient to induce good protective immunity. However, only a few amino acid differences in the spike glycoprotein gene of IBV have a detrimental impact on immunologic protection, consequently a large number of antigenic escape mutants have evolved. The further away in sequence space from the vaccine strain the spike glycoprotein gene of a particular variant, the less cross protective immunity is conferred by a vaccine. Whilst vaccines can control disease as for SARS-CoV-2, there can be sustained asymptomatic transmission leading to further evolution. Current vaccine strategies for IBV employ a combination of initial immunisation with a live attenuated vaccines followed by boosting with inactivated vaccines in order to provide cross protection, but this option is not available for SARS-CoV-2.

36. Radical changes in pathogenesis can occur in an infected individual through genetic change in animal coronaviruses. In 10% of cats infected with feline enteric coronavirus (FeCV), mutations occur in the viral genome, many targeted to the furin cleavage site in the spike glycoprotein. This allows white blood cells to become infected and causes a new disease, feline infectious peritonitis virus (FIPV) with increased morbidity and mortality. Similar changes have been observed in IBV, where variants cause more severe disease by infecting the kidney, oviduct and testes. For SARS-CoV-2 mutation in the furin cleavage site has been associated with increases in virulence and transmission. However, variants with a greatly divergent phenotype have not yet been observed for SARS-CoV-2 nor for seasonal human coronaviruses.

37. New variants can arise through interactions between wild type and vaccine strains. Transmissible gastroenteritis virus (TGEV), a coronavirus infecting pigs, has close similarity to porcine epidemic diarrhoea virus (PEDV). Mice and cats can also act as reservoirs for the transmission of PEDV. Different genotypes (variants) of PEDV can be highly virulent leading to 80-100% morbidity and up to 100% mortality in pigs. Such viruses have arisen through recombination between low pathogenic attenuated vaccine strains of TGEV and pathogenic circulating PEDV strains. This is a common feature in coronavirus vaccines in the animal world and in the closely related virus species the arteriviruses. This strongly suggests that any move to live attenuated vaccines for SARS-CoV-2 should be resisted.

38. New human coronaviruses can originate from domesticated animals. HCoV-OC43 is thought to have originated from cattle in the 19th century, possibly after a recombination event that allowed it to acquire a new gene from an influenza virus. This strongly indicates the plasticity of the genome and the potential for domesticated animals to serve as reservoirs for new variants of SARS-CoV-2 that can remerge into humans.

What type of changes have we seen so far in SARS-CoV-2 and what might we expect?

39. Although genetic change accumulates at random, environmental factors known as selection pressures will influence whether that genetic change increases or decreases viral fitness and therefore rises or declines in the population. In the case of SARS-CoV-2, there are particular selection pressures that are more concerning because they may encourage the emergence of variants that may be more harmful or more difficult to control.

40. There is a remarkable degree of convergent evolution evident amongst the variants of SARS-CoV-2 that have thus far emerged. In different combinations and using slightly different coding changes, all variants have mutations in the spike protein that appear to enhance the direct binding to ACE2 receptor, the presentation of the receptor binding domain and often the efficiency of entry via enhanced furin cleavage that primes for fusion. Variants also all harbour mutations in other part of the genome likely enhance polymerase activity (P323L in nsp12) or affect the virus' ability to antagonize the host innate response (changes to ORF8, nsp6 deletions and changes in spectrum of viral gene expression). There are multiple insertions and deletions as well as SNPs, but so far, the virus has not acquired any whole new genes. Taken together, the constellations of mutations enhance the interaction of the virus with its new human host. As more information is uncovered about the way SARS-CoV-2 interacts with human cells, we might foresee some concerning possibilities for further evolution.

41. For example, the interferon system is a major determinant of disease outcome, individuals deficient in interferon fare badly. The interferon system works by sensing the presence of an invading virus and responding by production of hundreds of host proteins that have antiviral activity. Emerging data suggests the alpha variant has evolved to be less readily sensed by the infected cell. Transfer by recombination of the genetic determinants of this phenotype to other variants or independent acquisition by forward evolution is expected to increase transmission and disease severity by tipping a balance in favour of virus over host.

42. A second example is the possibility for the virus to acquire additional interferon antagonists by recombination. Emerging data finds that one particularly potent interferon stimulated gene that controls SARS-CoV-2 replication in infected cells is oligoadenylate synthetase 1 (OAS1). OAS1 expression reduces the amount of virus replication and controls infection. Other coronaviruses are also sensitive to OAS1 but have overcome this by acquiring an enzyme called PDE from the host. It is to be expected that if SARS-CoV-2 acquired PDE by recombination with another human coronavirus such as OC43 or from a host cell, the capacity to replicate in the face of an interferon response would be increased and this would lead to higher transmission and disease.

43. As vaccines against SARS-CoV-2 are deployed across populations, it is possible to create a selection pressure for variants that can escape the vaccine-acquired immune response. Over the past few months, several variants have emerged which show a reduced susceptibility to vaccine-acquired immunity, though none appears to escape entirely. These variants largely emerged before vaccination was widespread, thus selection pressure from vaccines is unlikely to have made a significant contribution to their emergence. However, as vaccines become more widespread, the transmission advantage gained by a virus that can evade vaccine-acquired immunity will increase.

44. The extent of vaccine escape is difficult to predict. The SARS-CoV-2 spike protein appears to be quite plastic accommodating a plethora of new mutations, similar to what occurs in animal coronaviruses. Deep mutational scanning has been used to try to predict which (single) mutations in spike will evade antibodies. So far, the approaches use artificial methods to generate and express the spike variants such as yeast, phage or expression on another virus, VSV. None of these enable the full spectrum of mutational possibilities generated by the coronavirus polymerase. Nonetheless, important mutations were predicted by these methodologies such as the E484K mutation the spike receptor binding domain that is the most potent of all single point escape mutations thus far seen.

45. The use of anti-viral therapies also presents a selection pressure for the evolution of drug resistance, as virus that can evade the treatment will replicate, and possibly transmit to others as readily happens with anti-influenza drugs. Indeed, all antiviral drugs used to date (against HIV, Herpesviruses, influenza virus) have generated drug resistant mutants that limited the effectiveness of the drugs. Where the anti-viral therapy consists of more than one antiviral drug (combination therapy), the emergence of escape variants is less likely. These combinations act to keep viral load very low and thus statistically there are less variants. If combination therapy was used for SARS-CoV-2, the virus would need to develop resistance to multiple drugs simultaneously to replicate, this is unlikely. Extreme care in deployment of anti-SARS-CoV-2 drugs is therefore critical, particularly if monotherapy is considered.

46. In immunocompromised hosts, viral replication and shedding may be prolonged. This increases the potential for emergence of escape variants, particularly under the pressure of monoclonal antibodies therapy targeting the spike protein or convalescent plasma treatment, again mainly targeting the spike glycoprotein. Case studies have documented the emergence of unusually high numbers of genetic changes in immunosuppressed individuals treated with convalescent plasma.

47. Evolution in immunocompromised hosts may be a way by which viruses traverses a fitness landscape through accumulating constellations of mutations that confer phenotypes and epistatic mutations that compensate for fitness costs. It is notable that all the current SARS-CoV-2 VOCs harbour constellations of mutations across the genome implying they either evolved during long term persistent infection, occurred in under circumstances of intense transmission with wide selection bottlenecks or occurred in environments were sustained but undocumented transmission occurred. On the other hand, it is noteworthy that single point mutants on top of VOCs such as alpha and delta have not (yet) emerged to predominate over the existing VOCs.

48. Variants can potentially change the transmission of the virus leading to different modes of infection within community or demographies associated with potential novel properties, for example a faecal oral transmission rather than respiratory. Examining other coronavirus in animals and humans show faecal oral transmission can occur as an efficient additional means of transmission as was the cases with SARS-CoV and transmission in the Amoy Garden Complex. There is not yet evidence for alternate routes of transmission for SARS-CoV-2 but delta variant has been associated with increased frequency of GI symptoms.

49. SARS-CoV-2 can infect a wide range of animals both in nature/farms (such as minks) laboratory animals (several species of non-human primates, mice, rats, ferrets and hamsters) and companion animals (cats and dogs). SARS-CoV-2 is thought to have originated from bats. Thus SARS-CoV-2 has a broad host range and is capable of continuous interchange between humans and an animal reservoir (e.g. mink farms) which could lead to the generation and selection of new variants.

50. Infections in mink farms have been observed throughout the world. The widespread presence of the virus in an animal population will render eradication even more unlikely. There is likely to be a different level of risk of exposure and potential for new variants between farmed animals (high density) and companion animals. In either case, reverse zoonosis may occur (already seen in Denmark from mink). Zoonotic reservoirs could lead to a large, expanded population of the virus with the potential for future dramatic variant change in the virus through recombination with another coronavirus already prevalent in that animal species, akin to antigenic shift in influenza virus in terms of conferring new virus properties.

51. Re-infection following SARS-CoV-2 infection is well described in case reports. The frequency of re-infection and the predisposing risk factors are less well understood. Evidence is emerging from PHE/UK based longitudinal cohorts and international publications that prior infection is generally protective against re-infection over at least a 9-12 month period in most people. Estimates from SIREN, a large national HCW cohort and from the PHE Care homes study indicate that re-infection occurs in <5% individuals and that the serological profile in cases of re-infection suggests that low levels of neutralising antibody confer susceptibility. However, most of these data relate to the alpha VOCs and these data may change when the delta VOC is considered. Reinfections are likely to drive further evolution.

52. The immune response to SARS-CoV-2 involves multiple mechanisms, including innate defences, antibodies, T cells, and B cells. While virus-neutralising antibodies are usually against specific sites exposed on the surface of virus proteins, T cells recognise peptide fragments from a wider range of viral proteins that may be conserved between viral variants, reducing the likelihood that immune escape will emerge. SARS-CoV-2 infection induces strong T cell responses, which may provide additional selection pressure for SARS-CoV-2 evolution. For example, there is some suggestion that, in addition to increased transmissibility and a level of antibody escape, the delta variant escapes T cell responses in one HLA type common in Asia. How many T cell epitope escape mutations are needed to decrease T cell immunity and if there is a hierarchy of crucial T cell epitopes is not known.

53. Non-pharmaceutical interventions such as mask-wearing and social distancing shape the environment in which a virus transmits and may act as selection pressures for increased viral transmission. For example, where social distancing exists, virus that is able to better transmit through air may have a fitness advantage, and therefore be better able to survive and replicate.

54. Should a genetic change that benefits the virus arise under any of these selection pressures, there is no guarantee that it will rise to dominance. If the change occurs in conjunction with others which are deleterious, then the variant in which it is present may die out, because there is no overall benefit to the combination. Even if the variant is fitter than others, in order to become dominant, it must also be able to spread between people and communities. If population mixing and transmission is low, new variants are less likely to spread.

Antivirals could provide a major selection pressure in the emergence of drug-resistant variants.

55. The replication of the SARS-CoV-2 leads to many of the clinical manifestations of COVID-19. Specific antiviral drugs, which work by inhibiting or suppressing viral replication and thereby minimising the impact of tissue damage caused by SARS-CoV-2, are therefore being investigated for the treatment of COVID-19.

56. For antiviral drugs, it is important to find viral targets which can be selectively inhibited, so as to minimise the impact on host cell replication. Typically, key points in viral replication cycle can be targeted, including:

    a) Viral entry (via the angiotensin-converting enzyme 2 [ACE2] receptor and transmembrane serine protease 2 [TMPRSS2]).

    b) Viral membrane fusion and endocytosis.

    c) Viral replication involving the RNA-dependent RNA polymerase complex.

    d) Viral protein or RNA synthesis involving the activity of viral enzymes, such as the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro).

57. Neutralising mAbs have been given emergency use authorisation and recently shown to be effective in treatment of symptomatic disease. This class of molecule is an attractive and flexible approach to therapy for emerging viral infections. Monotherapy with single target mAbs is likely to generate pressure for the emergence of viral variants. Cocktails of mAbs will provide a higher barrier to the emergence of escape variants. Activity of mAbs can also be reduced by variants that escape convalescent or vaccine induced antibody immunity.

58. There is no historic precedent for the mass administration of antiviral medication in the community as prophylaxis, apart from the use of anti influenza Neuraminidase Inhibitors, which were used to a limited extent in this way in the early phases of Influenza Pandemic of 2009 in the UK. The safety and efficacy profile must be extremely well established for a mass administration strategy to work and poor compliance will likely rapidly lead to the selection of drug resistant variants, rendering such a strategy short lived.

59. Combination therapy is recognised as a way of minimising viral evasion, typically involving two or more drugs or drugs and/or mAbs combined targeting different viral functions, creating a higher barrier to the evolution of resistance. However, mass administration of combination therapy is an even harder strategy to achieve.

The Washington Post
Democracy Dies in Darkness

‘The war has changed’: Internal CDC document urges new messaging, warns delta infections likely more severe

The internal presentation shows that the agency thinks it is struggling to communicate on vaccine efficacy amid increased breakthrough infections

By Yasmeen Abutaleb, Carolyn Y. Johnson and Joel Achenbach

Yesterday at 8:58 p.m. EDT

   7.6k

The delta variant of the coronavirus appears to cause more severe illness than earlier variants and spreads as easily as chickenpox, according to an internal federal health document that argues officials must “acknowledge the war has changed.”

The document is an internal Centers for Disease Control and Prevention slide presentation, shared within the CDC and obtained by The Washington Post. It captures the struggle of the nation’s top public health agency to persuade the public to embrace vaccination and prevention measures, including mask-wearing, as cases surge across the United States and new research suggests vaccinated people can spread the virus.

The document strikes an urgent note, revealing the agency knows it must revamp its public messaging to emphasize vaccination as the best defense against a variant so contagious that it acts almost like a different novel virus, leaping from target to target more swiftly than Ebola or the common cold.

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It cites a combination of recently obtained, still-unpublished data from outbreak investigations and outside studies showing that vaccinated individuals infected with delta may be able to transmit the virus as easily as those who are unvaccinated. Vaccinated people infected with delta have measurable viral loads similar to those who are unvaccinated and infected with the variant.

“I finished reading it significantly more concerned than when I began,” Robert Wachter, chairman of the Department of Medicine at the University of California at San Francisco, wrote in an email.

CDC scientists were so alarmed by the new research that the agency earlier this week significantly changed guidance for vaccinated people even before making new data public.

The data and studies cited in the document played a key role in revamped recommendations that call for everyone — vaccinated or not — to wear masks indoors in public settings in certain circumstances, a federal health official said. That official told The Post that the data will be published in full on Friday. CDC Director Rochelle Walensky privately briefed members of Congress on Thursday, drawing on much of the material in the document.

One of the slides states that there is a higher risk among older age groups for hospitalization and death relative to younger people, regardless of vaccination status. Another estimates that there are 35,000 symptomatic infections per week among 162 million vaccinated Americans.

The document outlines "communication challenges" fueled by cases in vaccinated people, including concerns from local health departments about whether coronavirus vaccines remain effective and a "public convinced vaccines no longer work/booster doses needed."

The presentation highlights the daunting task the CDC faces. It must continue to emphasize the proven efficacy of the vaccines at preventing severe illness and death while acknowledging milder breakthrough infections may not be so rare after all, and that vaccinated individuals are transmitting the virus. The agency must move the goal posts of success in full public view.

The CDC declined to comment.

"Although it's rare, we believe that at an individual level, vaccinated people may spread the virus, which is why we updated our recommendation," according to the federal health official, who spoke on the condition of anonymity because they were not authorized to speak publicly. "Waiting even days to publish the data could result in needless suffering and as public health professionals we cannot accept that."

The presentation came two days after Walensky announced the reversal in guidance on masking among people who are vaccinated. On May 13, people were told they no longer needed to wear masks indoors or outdoors if they had been vaccinated. The new guidance reflects a strategic retreat in the face of the delta variant. Even people who are vaccinated should wear masks indoors in communities with substantial viral spread or when in the presence of people who are particularly vulnerable to infection and illness, the CDC said.

The document presents new science but also suggests a new strategy is needed on communication, noting that public trust in vaccines may be undermined when people experience or hear about breakthrough cases, especially after public health officials have described them as rare.

Matthew Seeger, a risk communication expert at Wayne State University in Detroit, said a lack of communication about breakthrough infections has proved problematic. Because public health officials had emphasized the great efficacy of the vaccines, the realization that they aren't perfect may feel like a betrayal.

"We've done a great job of telling the public these are miracle vaccines," Seeger said. "We have probably fallen a little into the trap of over-reassurance, which is one of the challenges of any crisis communication circumstance."

The CDC's revised mask guidance stops short of what the internal document calls for. "Given higher transmissibility and current vaccine coverage, universal masking is essential to reduce transmission of the Delta variant," it states.

The document makes clear that vaccination provides substantial protection against the virus. But it also states that the

CDC must “improve communications around individual risk among [the] vaccinated” because that risk depends on a host of factors, including age and whether someone has a compromised immune system.

The document includes CDC data from studies showing that the vaccines are not as effective in immunocompromised patients and nursing home residents, raising the possibility that some at-risk individuals will need an additional vaccine dose.

The presentation includes a note that the findings and conclusions are those of the authors and do not necessarily represent the CDC’s official position.

The internal document contains some of the scientific information that influenced the CDC to change its mask guidance. The agency faced criticism from outside experts this week when it changed the mask guidance without releasing the data, a move that violated scientific norms, said Kathleen Hall Jamieson, director of the Annenberg Public Policy Center at the University of Pennsylvania.

“You don’t, when you’re a public health official, want to be saying, ‘Trust us, we know, we can’t tell you how,’” Jamieson said. “The scientific norm suggests that when you make a statement based on science, you show the science. … And the second mistake is they do not appear to be candid about the extent to which breakthroughs are yielding hospitalizations.”

The breakthrough cases are to be expected, the CDC briefing states, and will probably rise as a proportion of all cases because there are so many more people vaccinated now. This echoes data seen from studies in other countries, including highly vaccinated Singapore, where 75 percent of new infections reportedly occur in people who are partially and fully vaccinated.

The CDC document cites public skepticism about vaccines as one of the challenges: “Public convinced vaccines no longer work,” one of the first slides in the presentation states.

Walter A. Orenstein, associate director of the Emory Vaccine Center, said he was struck by data showing that vaccinated people who became infected with delta shed just as much virus as those who were not vaccinated. The slide references an outbreak in Barnstable County, Mass., where vaccinated and unvaccinated people shed nearly identical amounts of virus.

“I think this is very important in changing things,” Orenstein said.

A person working in partnership with the CDC on investigations of the delta variant, who spoke on the condition of anonymity because they were not authorized to speak, said the data came from a July 4 outbreak in Provincetown, Mass. Genetic analysis of the outbreak showed that people who were vaccinated were transmitting the virus to other vaccinated people. The person said the data was “deeply disconcerting” and a “canary in the coal mine” for scientists who had seen the data.

If the war has changed, as the CDC states, so has the calculus of success and failure. The extreme contagiousness of delta makes herd immunity a more challenging target, infectious-disease experts said.

“I think the central issue is that vaccinated people are probably involved to a substantial extent in the transmission of delta,” Jeffrey Shaman, a Columbia University epidemiologist, wrote in an email after reviewing the CDC slides. “In some sense, vaccination is now about personal protection — protecting oneself against severe disease. Herd immunity

some sense, vaccination is now about personal protection — protecting oneself against severe disease. Herd immunity is not relevant as we are seeing plenty of evidence of repeat and breakthrough infections."

The document underscores what scientists and experts have been saying for months: It is time to shift how people think about the pandemic.

Kathleen Neuzil, a vaccine expert at the University of Maryland School of Medicine, said getting more people vaccinated remains the priority, but the public may also have to change its relationship to a virus almost certain to be with humanity for the foreseeable future.

"We really need to shift toward a goal of preventing serious disease and disability and medical consequences, and not worry about every virus detected in somebody's nose," Neuzil said. "It's hard to do, but I think we have to become comfortable with coronavirus not going away."

ORIGINAL ARTICLE

Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant

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ABSTRACT

BACKGROUND

The B.1.617.2 (delta) variant of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19), has contributed to a surge in cases in India and has now been detected across the globe, including a notable increase in cases in the United Kingdom. The effectiveness of the BNT162b2 and ChAdOx1 nCoV-19 vaccines against this variant has been unclear.

METHODS

We used a test-negative case–control design to estimate the effectiveness of vaccination against symptomatic disease caused by the delta variant or the predominant strain (B.1.1.7, or alpha variant) over the period that the delta variant began circulating. Variants were identified with the use of sequencing and on the basis of the spike (S) gene status. Data on all symptomatic sequenced cases of Covid-19 in England were used to estimate the proportion of cases with either variant according to the patients' vaccination status.

RESULTS

Effectiveness after one dose of vaccine (BNT162b2 or ChAdOx1 nCoV-19) was notably lower among persons with the delta variant (30.7%; 95% confidence interval [CI], 25.2 to 35.7) than among those with the alpha variant (48.7%; 95% CI, 45.5 to 51.7); the results were similar for both vaccines. With the BNT162b2 vaccine, the effectiveness of two doses was 93.7% (95% CI, 91.6 to 95.3) among persons with the alpha variant and 88.0% (95% CI, 85.3 to 90.1) among those with the delta variant. With the ChAdOx1 nCoV-19 vaccine, the effectiveness of two doses was 74.5% (95% CI, 68.4 to 79.4) among persons with the alpha variant and 67.0% (95% CI, 61.3 to 71.8) among those with the delta variant.

CONCLUSIONS

Only modest differences in vaccine effectiveness were noted with the delta variant as compared with the alpha variant after the receipt of two vaccine doses. Absolute differences in vaccine effectiveness were more marked after the receipt of the first dose. This finding would support efforts to maximize vaccine uptake with two doses among vulnerable populations. (Funded by Public Health England.)

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India has experienced a surge in cases of coronavirus disease 2019 (Covid-19) since late March 2021, reaching more than 400,000 cases and 4000 deaths reported each day in early May 2021.[1] This increase has resulted in hospital services becoming overwhelmed and in a scarcity of oxygen supplies.[2] Although only a small proportion of samples have been sequenced, B.1.617 lineages of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have dominated. The B.1.617.2 (delta) variant was first detected in India in December 2020 and became the most commonly reported variant in the country starting in mid-April 2021.[1] As of May 19, 2021, the variant had been detected in 43 countries across six continents in GISAID (originally an acronym for global initiative on sharing avian influenza data but more recently a site for compiling sequence data on viruses, particularly influenza and coronaviruses, that threaten to cause a pandemic).[3] In the United Kingdom, a rapid increase in cases with this variant has been seen associated with travel from India and with community transmission.[4]

In the United Kingdom, vaccination was initially prioritized for older adults, caregivers, and health and social care workers, with subsequent rollout to persons in clinical risk groups and younger-age cohorts.[5] At an early stage of the rollout, a policy decision, based on advice from the Joint Committee on Vaccination and Immunisation, was made to use an extended administration interval of up to 12 weeks in order to maximize the number of vulnerable persons receiving the first dose during the second wave of the pandemic in the context of constraints on vaccine supply and delivery.[6]

Vaccines have been found to be highly efficacious at preventing symptomatic disease, as shown by clinical trials[7-9] and real-world evidence.[10-14] The B.1.1.7 (alpha) variant, first identified in the United Kingdom, was the predominant lineage seen between January and May 2021. Levels of protection against the alpha variant that are conferred by vaccination are similar to those observed in clinical trials, with additional protection against severe disease.[10,11,15-17] Laboratory data indicate that the B.1.351 (beta) variant has reduced neutralization, according to analysis of serum samples obtained from vaccinated persons.[18,19] Observational data from Qatar indicated modestly reduced effectiveness against symptomatic disease caused by this variant but high levels of effectiveness against severe, critical, or fatal disease in persons vaccinated with the BNT162b2 vaccine (Pfizer–BioNTech).[17] Furthermore, a trial of the NVX-CoV2373 vaccine (Novavax) showed 51.0% efficacy against the beta variant.[20] Finally, high levels of neutralization have been seen with the P.1 (gamma) variant in serum samples obtained from persons vaccinated with the BNT162b2 vaccine, and one study showed only minimally reduced vaccine effectiveness against test-positive cases with one dose of messenger RNA vaccine.[19,21,22]

The delta variant is characterized by the spike protein mutations T19R, Δ157-158, L452R, T478K, D614G, P681R, and D950N.[1] Several of these mutations may affect immune responses directed toward the key antigenic regions of receptor-binding protein (452 and 478) and deletion of part of the N-terminal domain.[23] P681R is at the S1–S2 cleavage site, and it appears that strains with mutations at that site may have increased replication, which leads to higher viral loads and increased transmission.[24] Data on the effectiveness of Covid-19 vaccines against clinical outcomes with this variant have been limited. In this study, we aimed to estimate the effectiveness of two Covid-19 vaccines, BNT162b2 and ChAdOx1 nCoV-19 (AstraZeneca), against symptomatic disease caused by the delta variant.

Methods

Study Design

We used two approaches to estimate the effect of vaccination on the delta variant. First, we used a test-negative case–control design to estimate vaccine effectiveness against symptomatic disease caused by the delta variant, as compared with the alpha variant, over the period that the delta variant has been circulating. This approach has been described in detail elsewhere.[10] In brief, we compared vaccination status in persons with symptomatic Covid-19 with vaccination status in persons who reported symptoms but had a negative test. This approach helps to control for biases related to health-seeking behavior, access to testing, and case ascertainment.

For the secondary analysis, the proportion of persons with cases caused by the delta variant

relative to the main circulating virus (the alpha variant) was estimated according to vaccination status. The underlying assumption was that if the vaccine had some efficacy and was equally effective against each variant, a similar proportion of cases with either variant would be expected in unvaccinated persons and in vaccinated persons. Conversely, if the vaccine was less effective against the delta variant than against the alpha variant, then the delta variant would be expected to make up a higher proportion of cases occurring more than 3 weeks after vaccination than among unvaccinated persons. Details of this analysis are described in Section S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

DATA SOURCES

Vaccination Status

Data on all persons in England who have been vaccinated with Covid-19 vaccines are available in a national vaccination register (the National Immunisation Management System). Data regarding vaccinations that had occurred up to May 16, 2021, including the date of receipt of each dose of vaccine and the vaccine type, were extracted on May 17, 2021. Vaccination status was categorized as receipt of one dose of vaccine among persons who had symptom onset occurring 21 days or more after receipt of the first dose up to the day before the second dose was received, as receipt of the second dose among persons who had symptom onset occurring 14 days or more after receipt of the second dose, and as receipt of the first or second dose among persons with symptom onset occurring 21 days or more after the receipt of the first dose (including any period after the receipt of the second dose).

SARS-CoV-2 Testing

Polymerase-chain-reaction (PCR) testing for SARS-CoV-2 in the United Kingdom is undertaken by hospital and public health laboratories, as well as by community testing with the use of drive-through or at-home testing, which is available to anyone with symptoms consistent with Covid-19 (high temperature, new continuous cough, or loss or change in sense of smell or taste). Data on all positive PCR tests between October 26, 2020, and May 16, 2021, were extracted. Data on all recorded negative community tests among persons who reported symptoms were also extracted for the test-negative case–control analysis. Children younger than 16 years of age as of March 21, 2021, were excluded. Data were restricted to persons who had reported symptoms, and only persons who had undergone testing within 10 days after symptom onset were included, in order to account for reduced sensitivity of PCR testing beyond this period.[25]

Identification of Variant

Whole-genome sequencing was used to identify the delta and alpha variants. The proportion of all positive samples that were sequenced increased from approximately 10% in February 2021 to approximately 60% in May 2021.[4] Sequencing is undertaken at a network of laboratories, including the Wellcome Sanger Institute, where a high proportion of samples has been tested, and whole-genome sequences are assigned to Public Health England definitions of variants on the basis of mutations.[26]

Spike gene target status on PCR was used as a second approach for identifying each variant. Laboratories used the TaqPath assay (Thermo Fisher Scientific) to test for three gene targets: spike (*S*), nucleocapsid (*N*), and open reading frame 1ab (*ORF1ab*). In December 2020, the alpha variant was noted to be associated with negative testing on the *S* target, so *S* target–negative status was subsequently used as a proxy for identification of the variant. The alpha variant accounts for between 98% and 100% of *S* target–negative results in England. Among sequenced samples that tested positive for the *S* target, the delta variant was in 72.2% of the samples in April 2021 and in 93.0% in May (as of May 12, 2021).[4] For the test-negative case–control analysis, only samples that had been tested at laboratories with the use of the TaqPath assay were included.

Data Linkage

The three data sources described above were linked with the use of the National Health Service number (a unique identifier for each person receiving medical care in the United Kingdom). These data sources were also linked with data on the patient's date of birth, surname, first

name, postal code, and specimen identifiers and sample dates.

Covariates

Multiple covariates that may be associated with the likelihood of being offered or accepting a vaccine and the risk of exposure to Covid-19 or specifically to either of the variants analyzed were also extracted from the National Immunisation Management System and the testing data. These data included age (in 10-year age groups), sex, index of multiple deprivation (a national indication of level of deprivation that is based on small geographic areas of residence,[27] assessed in quintiles), race or ethnic group, care home residence status, history of foreign travel (i.e., outside the United Kingdom or Ireland), geographic region, period (calendar week), health and social care worker status, and status of being in a clinically extremely vulnerable group.[28] In addition, for the test-negative case–control analysis, history of SARS-CoV-2 infection before the start of the vaccination program was included. Persons were considered to have traveled if, at the point of requesting a test, they reported having traveled outside the United Kingdom and Ireland within the preceding 14 days or if they had been tested in a quarantine hotel or while quarantining at home. Postal codes were used to determine the index of multiple deprivation, and unique property-reference numbers were used to identify care homes.[29]

STATISTICAL ANALYSIS

For the test-negative case–control analysis, logistic regression was used to estimate the odds of having a symptomatic, PCR-confirmed case of Covid-19 among vaccinated persons as compared with unvaccinated persons (control). Cases were identified as having the delta variant by means of sequencing or if they were *S* target–positive on the TaqPath PCR assay. Cases were identified as having the alpha variant by means of sequencing or if they were *S* target–negative on the TaqPath PCR assay.

If a person had tested positive on multiple occasions within a 90-day period (which may represent a single illness episode), only the first positive test was included. A maximum of three randomly chosen negative test results were included for each person. Negative tests in which the sample had been obtained within 3 weeks before a positive result or after a positive result could have been false negatives; therefore, these were excluded. Tests that had been administered within 7 days after a previous negative result were also excluded. Persons who had previously tested positive before the analysis period were also excluded in order to estimate vaccine effectiveness in fully susceptible persons. All the covariates were included in the model as had been done with previous test-negative case–control analyses, with calendar week included as a factor and without an interaction with region.

With regard to *S* target–positive or –negative status, only persons who had tested positive on the other two PCR gene targets were included. Assignment to the delta variant on the basis of *S* target status was restricted to the week commencing April 12, 2021, and onward in order to aim for high specificity of *S* target–positive testing for the delta variant.[4]

Vaccine effectiveness for the first dose was estimated among persons with a symptom-onset date that was 21 days or more after receipt of the first dose of vaccine, and vaccine effects for the second dose were estimated among persons with a symptom-onset date that was 14 days or more after receipt of the second dose. Comparison was made with unvaccinated persons and with persons who had symptom onset in the period of 4 to 13 days after vaccination in order to help account for differences in underlying risk of infection. The period from the day of vaccine administration (day 0) to day 3 was excluded because reactogenicity to the vaccine can cause an increase in testing that biases results, as previously described.[10]

RESULTS

DATA LINKAGE

Among all the sequenced samples that were linked to the SARS-CoV-2 testing data set, 92.9% were linked to data on vaccination status. Over the course of the study period, there were 38,592 linked sequenced tests. In an analysis that was restricted to including only persons at least 16 years of age who had symptomatic Covid-19 caused by the alpha or delta variant and who had been vaccinated with either ChAdOx1 nCoV-19 or BNT162b2 according to an appropriate schedule, 19,109 sequenced cases were included (Fig. S1 in the Supplementary Appendix). The alpha

variant was detected in 14,837 samples, and the delta variant in 4272 samples.

DESCRIPTIVE CHARACTERISTICS

The characteristics of persons with Covid-19 in the study population according to variant are shown in Table 1. Key differences with the delta variant included a higher proportion of persons with a history of foreign travel; a higher proportion of persons with cases in the most recent weeks (calendar weeks 18 to 20); a higher proportion of persons with cases in the northwest region, London, and the east of England; and a higher proportion of persons in the "Indian or British Indian," "Pakistani or British Pakistani," or "any other Asian background" ethnic groups. Little difference in the distribution of age or index of multiple deprivation was seen. Few cases of either variant were seen in persons older than 70 years of age, and only nine cases (all of which were with the alpha variant) occurred among care home residents.

Among sequenced samples that were originally tested with the use of the TaqPath assay, a high correlation was seen between *S* target status and the two variants under investigation, with 95.3% of the *S* target–positive cases identified as having the delta variant and 99.6% of the *S* target–negative cases identified as having the alpha variant (Tables S1 and S2). The distribution of intervals between the receipt of vaccine doses is shown in Figure S2.

VACCINE EFFECTIVENESS ESTIMATES

Results of the test-negative case–control analysis are shown in Table 2 and Figure 1. In the "any vaccine" analysis, in which data from the persons who received either vaccine were pooled, effectiveness was notably lower after the first vaccine dose among persons with the delta variant (30.7%; 95% confidence interval [CI], 25.2 to 35.7) than among those with the alpha variant (48.7%; 95% CI, 45.5 to 51.7). Results for the first dose were similar for both vaccines, with an absolute difference in vaccine effectiveness against the delta variant as compared with the alpha variant of 11.9 percentage points with the BNT162b2 vaccine and 18.7 percentage points with the ChAdOx1 nCoV-19 vaccine.

The difference in vaccine effectiveness was much smaller among persons who had received the second dose of vaccine. In the "any vaccine" analysis, the vaccine effectiveness was 87.5% (95% CI, 85.1 to 89.5) with the alpha variant and 79.6% (95% CI, 76.7 to 82.1) with the delta variant. With the BNT162b2 vaccine, a small difference in effectiveness between variants was seen after the second dose: 93.7% (95% CI, 91.6 to 95.3) with the alpha variant and 88.0% (95% CI, 85.3 to 90.1) with the delta variant. The effectiveness with two doses of the ChAdOx1 nCoV-19 vaccine was lower than with the BNT162b2 vaccine; however, with the ChAdOx1 nCoV-19 vaccine, the difference in effectiveness between the alpha and delta variants was small (74.5% [95% CI, 68.4 to 79.4] and 67.0% [95% CI, 61.3 to 71.8], respectively).

Table S3, in which the period after the first dose is stratified according to the period of 21 to 55 days and the period of 56 or more days, shows a possible indication of waning efficacy against the alpha variant with the BNT162b2 vaccine and against the delta variant with the ChAdOx1 nCoV-19 vaccine. Section S1 and Tables S4 through S6 show the results of the secondary analysis.

DISCUSSION

We found that the absolute difference in vaccine effectiveness against symptomatic disease with one dose of vaccine with the delta variant as compared with the alpha variant was approximately 12 to 19 percentage points. However, the differences in vaccine effectiveness after two doses were small. This was the case for both the BNT162b2 and ChAdOx1 nCoV-19 vaccines. In the test-negative case–control analysis, the estimated vaccine effectiveness against symptomatic disease with the delta variant was approximately 36% with a single dose of the BNT162b2 vaccine and approximately 30% with a single dose of the ChAdOx1 nCoV-19 vaccine; the effectiveness was approximately 88% with two doses of the BNT162b2 vaccine and approximately 67% with two doses of the ChAdOx1 nCoV-19 vaccine.

A clear effect was noted with both vaccines, with high levels of effectiveness after two doses. Vaccine effectiveness against either variant was smaller after the receipt of two doses of the ChAdOx1 nCoV-19 vaccine than after the receipt of two doses of the BNT162b2 vaccine, a finding that is consistent with reported clinical trial findings.[7,8] Differences between the two vaccines

Table 1. Characteristics of Persons with Covid-19 in the United Kingdom, According to Variant.*

Characteristic	Alpha Variant (N = 14,837)	Delta Variant (N = 4272)	Total (N = 19,109)
Percent of total cases	77.6	22.4	100
Age — no. (%)			
16–29 yr	5,325 (35.9)	1571 (36.8)	6,896 (36.1)
30–39 yr	4,199 (28.3)	1164 (27.2)	5,363 (28.1)
40–49 yr	2,923 (19.7)	834 (19.5)	3,757 (19.7)
50–59 yr	1,532 (10.3)	465 (10.9)	1,997 (10.5)
60–69 yr	657 (4.4)	178 (4.2)	835 (4.4)
70–79 yr	163 (1.1)	47 (1.1)	210 (1.1)
≥80 yr	38 (0.3)	13 (0.3)	51 (0.3)
History of travel — no. (%)†			
No	14,689 (99.0)	4219 (98.8)	18,908 (98.9)
Yes	100 (0.7)	52 (1.2)	152 (0.8)
Unknown	48 (0.3)	1 (<0.1)	49 (0.3)
Week that sample was obtained — no. (%)‡			
14	3,316 (22.3)	19 (0.4)	3,335 (17.5)
15	2,780 (18.7)	53 (1.2)	2,833 (14.8)
16	2,517 (17.0)	184 (4.3)	2,701 (14.1)
17	2,156 (14.5)	372 (8.7)	2,528 (13.2)
18	1,775 (12.0)	737 (17.3)	2,512 (13.1)
19	1,263 (8.5)	1111 (26.0)	2,374 (12.4)
20	1,030 (6.9)	1796 (42.0)	2,826 (14.8)
Week of symptom onset — no. (%)‡			
12	28 (0.2)	0	28 (0.1)
13	1,431 (9.6)	8 (0.2)	1,439 (7.5)
14	3,089 (20.8)	26 (0.6)	3,115 (16.3)
15	2,547 (17.2)	89 (2.1)	2,636 (13.8)
16	2,381 (16.0)	230 (5.4)	2,611 (13.7)
17	1,965 (13.2)	501 (11.7)	2,466 (12.9)
18	1,622 (10.9)	917 (21.5)	2,539 (13.3)
19	1,178 (7.9)	1311 (30.7)	2,489 (13.0)
20	596 (4.0)	1190 (27.9)	1,786 (9.3)
Sex — no. (%)			
Female	7,681 (51.8)	2047 (47.9)	9,728 (50.9)
Male	7,151 (48.2)	2222 (52.0)	9,373 (49.1)
Missing data	5 (<0.1)	3 (0.1)	8 (<0.1)
Index of multiple deprivation — no. (%)§			
1	4,780 (32.2)	1446 (33.8)	6,226 (32.6)
2	3,302 (22.3)	950 (22.2)	4,252 (22.3)
3	2,592 (17.5)	654 (15.3)	3,246 (17.0)
4	2,302 (15.5)	687 (16.1)	2,989 (15.6)

Table 1. (Continued.)

Characteristic	Alpha Variant (N = 14,837)	Delta Variant (N = 4272)	Total (N = 19,109)
5	1,828 (12.3)	524 (12.3)	2,352 (12.3)
Missing data	33 (0.2)	11 (0.3)	44 (0.2)
Clinically extremely vulnerable group — no. (%)¶			
No	14,582 (98.3)	4211 (98.6)	18,793 (98.3)
Yes	255 (1.7)	61 (1.4)	316 (1.7)
Care home resident — no. (%)			
No	14,828 (99.9)	4272 (100)	19,100 (100)
Yes	9 (0.1)	0	9 (<0.1)
Health or social care worker — no. (%)			
No	14,621 (98.5)	4181 (97.9)	18,802 (98.4)
Yes	216 (1.5)	91 (2.1)	307 (1.6)
Race or ethnic group — no. (%)‖			
Bangladeshi or British Bangladeshi	230 (1.6)	98 (2.3)	328 (1.7)
Chinese	54 (0.4)	18 (0.4)	72 (0.4)
Indian or British Indian	458 (3.1)	705 (16.5)	1,163 (6.1)
Pakistani or British Pakistani	1,024 (6.9)	510 (11.9)	1,534 (8.0)
Any other Asian background	278 (1.9)	188 (4.4)	466 (2.4)
Black African or Caribbean	277 (1.9)	113 (2.6)	390 (2.0)
White	9,662 (65.1)	1801 (42.2)	11,463 (60.0)
Mixed	234 (1.6)	71 (1.7)	305 (1.6)
Any other ethnic group	442 (3.0)	139 (3.3)	581 (3.0)
Missing data	2,178 (14.7)	629 (14.7)	2,807 (14.7)
Region — no. (%)			
East Midlands	1,822 (12.3)	380 (8.9)	2,202 (11.5)
East of England	1,178 (7.9)	510 (11.9)	1,688 (8.8)
London	1,062 (7.2)	536 (12.5)	1,598 (8.4)
Northeast	977 (6.6)	69 (1.6)	1046 (5.5)
Northwest	2,664 (18.0)	2138 (50.0)	4,802 (25.1)
Southeast	847 (5.7)	198 (4.6)	1045 (5.5)
Southwest	198 (1.3)	63 (1.5)	261 (1.4)
West Midlands	1,538 (10.4)	241 (5.6)	1,779 (9.3)
Yorkshire and Humber	4,550 (30.7)	135 (3.2)	4,685 (24.5)
Missing data	1 (<0.1)	2 (<0.1)	3 (<0.1)

* B.1.1.7 is the alpha variant, and B.1.617.2 the delta variant, of the severe acute respiratory syndrome coronavirus 2, the virus that causes coronavirus disease 2019 (Covid-19). Percentages may not total 100 because of rounding.
† Persons were considered to have traveled if, at the point of requesting a test, they reported having traveled outside the United Kingdom and Ireland within the preceding 14 days or if they had been tested in a quarantine hotel or while quarantining at home.
‡ The week number is the calendar week in 2021.
§ The index of multiple deprivation is a national indicator of level of deprivation on the basis of small geographic areas of residence; the index ranges from 1 (least deprived) to 5 (most deprived).[27]
¶ The status of being in a clinically extremely vulnerable group was defined according to NHS Digital.[28]
‖ Race or ethnic group was determined from data in the National Immunisation Management System register.

Table 2. Vaccine Effectiveness against the Alpha Variant or *S* Target–Negative Status and the Delta Variant or *S* Target–Positive Status, According to Dose and Vaccine Type.*

Vaccination Status	Test-Negative Status	Alpha Variant or *S* Target–Negative Status			Delta Variant or *S* Target–Positive Status		
	Controls	Cases	Case:Control Ratio	Adjusted Vaccine Effectiveness (95% CI)	Cases	Case:Control Ratio	Adjusted Vaccine Effectiveness (95% CI)
	no.	*no.*		%	*no.*		%
Unvaccinated	96,371	7313	0.076	Reference	4043	0.042	Reference
Any vaccine							
Dose 1	51,470	2226	0.043	48.7 (45.5–51.7)	1493	0.029	30.7 (25.2–35.7)
Dose 2	23,993	143	0.006	87.5 (85.1–89.5)	340	0.014	79.6 (76.7–82.1)
BNT162b2 vaccine							
Dose 1	8,641	450	0.052	47.5 (41.6–52.8)	137	0.016	35.6 (22.7–46.4)
Dose 2	15,749	49	0.003	93.7 (91.6–95.3)	122	0.008	88.0 (85.3–90.1)
ChAdOx1 nCoV-19 vaccine							
Dose 1	42,829	1776	0.041	48.7 (45.2–51.9)	1356	0.032	30.0 (24.3–35.3)
Dose 2	8,244	94	0.011	74.5 (68.4–79.4)	218	0.026	67.0 (61.3–71.8)

* The adjusted analysis of vaccine effectiveness was adjusted for period (calendar week), travel history, race or ethnic group, sex, age, index of multiple deprivation, clinically extremely vulnerable group, region, history of positive test, health or social care worker, and care home residence. CI denotes confidence interval.

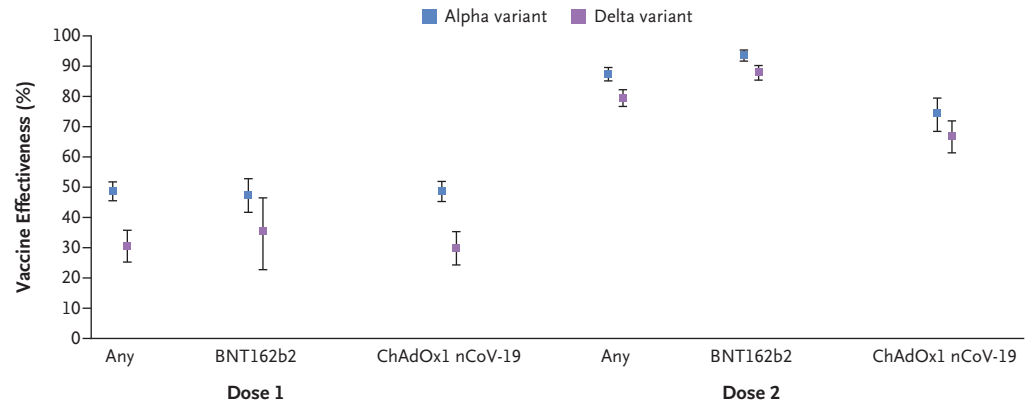

Figure 1. Vaccine Effectiveness against the Alpha and Delta Variants, According to Dose and Vaccine Type.
Shown is the effectiveness of one dose and two doses of the BNT162b2 and ChAdOx1 nCoV-19 vaccines, or either vaccine ("any"), against symptomatic disease with the B.1.1.7 (alpha) or B.1.617.2 (delta) variant of the severe acute respiratory syndrome coronavirus 2. I bars indicate 95% confidence intervals.

are further discussed in Section S2. The numbers of cases and follow-up periods are currently insufficient for the estimation of vaccine effectiveness against severe disease, including hospitalization and death.

One study from India that reported neutralization data in the broader B.1.617 variant category suggested that convalescent serum samples from persons with Covid-19 and from recipients of the BBV152 vaccine (Covaxin) were able to

neutralize variants in the B.1.617 lineage.[30] As compared with recent findings from Qatar on the effectiveness of the BNT162b2 vaccine against the alpha and beta variants,[17] our findings suggest that effectiveness against the delta variant after a full vaccination course lies somewhere between these two. A comparison with previously reported estimates of vaccine effectiveness against the alpha variant is discussed in Section S2.

The large scale of testing and whole-genome sequencing in the United Kingdom, as well as the recording of vaccination status in a national vaccination register, allowed us to analyze vaccine effectiveness within a few weeks of the delta variant first emerging in the United Kingdom. We used two distinct analytic approaches that gave broadly similar results, and findings with our control analysis (using the alpha variant) are consistent with those that have been reported previously.[7,8,10,17] Findings were also similar to those in cases that occurred during the first 2 weeks after receipt of the first vaccine dose (Table S4), which helps to rule out unmeasured confounders associated with both the likelihood of being vaccinated and the likelihood of being exposed to a variant. The use of a test-negative case–control design helped us to control for differences in health-seeking behavior between vaccinated persons and unvaccinated persons.

Our study has several limitations. The findings are observational and should be interpreted with caution. Low sensitivity or specificity of PCR testing could result in cases and controls being misclassified, which would attenuate the estimates of vaccine effectiveness. Low sensitivity or specificity of PCR testing could also affect one variant more than another, although this might be expected to affect the alpha variant more than the delta variant, given that, with an emerging variant, more cases may be detected earlier in infection, which may result in higher viral loads and increased sensitivity and specificity. Although we controlled for race or ethnic group, region, and an index of multiple deprivation, differences in vaccine coverage among population groups that may have more or less exposure to the delta variant may have affected the secondary analysis but should not have affected the test-negative case–control design. There may also be differences among the populations that received each vaccine — for example, in younger age groups, health care workers are more likely to have received the BNT162b2 vaccine, whereas persons in clinical risk groups are more likely to have received the ChAdOx1 nCoV-19 vaccine.[11] Furthermore, the analysis also relied on the assumptions that any residual confounding in the test-negative case–control design would affect the two estimates of vaccine effectiveness equally or at least would not bias the adjusted odds ratio for the comparison of vaccine effectiveness for a given vaccine against the two variants; that is, the accuracy of the sequencing would not depend on the variant and the propensity among symptomatic persons to get tested would not differ according to variant.

Overall, we found high levels of vaccine effectiveness against symptomatic disease with the delta variant after the receipt of two doses. These estimates were only modestly lower than the estimate of vaccine effectiveness against the alpha variant. Our finding of reduced effectiveness after the first dose would support efforts to maximize vaccine uptake with two doses among vulnerable groups in the context of circulation of the delta variant.

Surveillance of coronavirus disease 2019 (Covid-19) testing and vaccination is undertaken under Regulation 3 of the Health Service (Control of Patient Information) Regulations 2002 to collect confidential patient information (www.legislation.gov.uk/uksi/2002/1438/regulation/3/made) under Sections 3(i) (a) to (c), 3(i)(d) (i) and (ii), and 3. The study protocol was subject to an internal review by the Public Health England Research Ethics and Governance Group and was found to be fully compliant with all regulatory requirements. Given that no regulatory issues were identified and that ethics review is not a requirement for this type of work, it was decided that a full ethics review would not be necessary.

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