CORONAVIRUS

Elevated risk of infection with SARS-CoV-2 Beta, Gamma, and Delta variants compared with Alpha variant in vaccinated individuals

Stijn P. Andeweg†, Harry Vennema†, Irene Veldhuijzen, Naomi Smorenburg, Dennis Schmitz, Florian Zwagemaker, Arianne B. van Gageldonk-Lafeber, Susan J. M. Hahné, Chantal Reusken, Mirjam J. Knol*†, Dirk Egginк†, on behalf of the SeqNeth Molecular surveillance group‡ and RIVM COVID-19 Molecular epidemiology group‡

The extent to which severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (VOCs) break through infection- or vaccine-induced immunity is not well understood. We analyzed 28,578 sequenced SARS-CoV-2 samples from individuals with known immune status obtained through national community testing in the Netherlands from March to August 2021. We found evidence of an increased risk of infection by the Beta (B.1.351), Gamma (P.1), or Delta (B.1.617.2) variants compared with the Alpha (B.1.1.7) variant after vaccination. No clear differences were found between vaccines. However, the effect was larger in the first 14 to 59 days after complete vaccination compared with ≥60 days. In contrast to vaccine-induced immunity, there was no increased risk for reinfection with Beta, Gamma, or Delta variants relative to the Alpha variant in individuals with infection-induced immunity.

INTRODUCTION

The worldwide spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with the evolution and emergence of mutated viral variants. Although many nucleotide mutations are synonymous and do not directly affect viral fitness, multiple amino acid substitutions in functional domains of the Spike protein have been observed, some of which have been shown to affect transmissibility, disease severity, and preexisting immunity (*1*).

SARS-CoV-2 variants with multiple mutations that are suspected to affect viral virulence, transmission, or efficacy of diagnostics, vaccines, and antivirals have been designated variants of concern (VOCs) (*2*). As of December 2021, five VOCs had been defined by the European Centre for Disease Prevention and Control (ECDC) and World Health Organization (WHO): Alpha (B.1.1.7, first detected in September 2020 in the United Kingdom), Beta (B.1.351, first detected in May 2020 in South Africa), Gamma (P.1, first detected in November 2020 in Brazil), Delta (B.1.617.2, first detected in October 2020 in India), and Omicron (B.1.1.529, first detected in November 2021 in multiple countries) (*2*). All these VOCs contain amino acid substitutions in the receptor binding domain and N-terminal domain of the Spike protein, which are known to be the main targets of neutralizing antibodies. Several studies have shown decreased neutralization of VOCs by convalescent and postvaccination sera in vitro, with little or no reduction in sensitivity for the Alpha variant and the highest reduction in sensitivity of Beta and Omicron and, to a lesser extent, of Gamma and Delta (*3*–*6*).

These observations, and the rapid global spread of VOCs like Alpha and then Delta, caused concerns in early 2021 that SARS-CoV-2 VOCs may escape preexisting immunity and may still be able to infect and be transmitted by vaccinated and previously infected individuals. There are indications that the vaccine effectiveness (VE), especially against SARS-CoV-2 infection or mild coronavirus disease 2019 (COVID-19), is lower for the Beta, Gamma, and Delta variants (*7*). After vaccination, an increase in the proportion of individuals infected with the Alpha and Beta variants compared with the parental strain was observed (*8*). Less is known about the association between the Beta and Gamma variants and reinfection. In a (case-)matched test-negative design, no differences were found for infection-induced protection between the Alpha and Delta variants (*9*). Although an ecological study from the United Kingdom did not find an increase in the reinfection rate for the Alpha variant relative to preexisting variants in the last quarter of 2020 (*10*), increased risk of reinfection by the Beta, Gamma, or Delta variants compared with the Alpha variant still needs to be established. For the Omicron BA.1 variant, we showed that infection- and vaccine-induced protection was largely reduced compared with Delta (*11*).

In January 2021, the COVID-19 vaccination program was rolled out in the Netherlands, which first prioritized health care workers, nursing home residents, and the elderly. Current approved vaccines are based on either an mRNA vector [Comirnaty (BNT162b2, BioNTech/Pfizer), Spikevax (mRNA-1273/Moderna)], or an adenovirus-based vector system [Vaxzevria (ChAdOx1/AstraZeneca) or Ad26.COV2.S (Janssen)] and are aimed at eliciting a Spike protein–specific humoral immune response that induces antibodies that prevent virus entry and replication (*12*, *13*). All persons 12 years and older have been offered COVID-19 vaccination in the Netherlands as of July 2021. As of May 2022, 86% of all adults were fully vaccinated, and 89% received at least one dose (*14*). In the vaccination program in the Netherlands, Comirnaty has been the most commonly used vaccine and has been offered to all age groups (76.0% of all administered doses). Spikevax has been used primarily for residents of long-term care facilities, health care workers, high–medical risk groups, and later for the general population <60 years old

Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Antonie van Leeuwenhoeklaan 9, 3720 BA Bilthoven, Netherlands.
*Corresponding author. Email: mirjam.knol@rivm.nl (M.J.K.); dirk.egginк@rivm.nl (D.E.)
†These authors contributed equally to this work.
‡Members of the SeqNeth Molecular surveillance group and RIVM COVID-19 Molecular epidemiology group are listed at the end of this paper.

(8.5% of all administered doses). Vaxzevria has been used mostly in health care workers and the 60- to 65-year-old age group (12.1% of all administered doses). The Janssen COVID-19 vaccine has been used mostly in the 50- to 59-year-old age group and young adults (3.4% of all administered doses) (*15*). Vaccination has proven to be highly effective against COVID-19, especially against hospitalization and death, and has reduced the secondary attack rate within households (*16*–*20*).

Infection with SARS-CoV-2 can also elicit a protective immune response, but reinfections are possible. Studies comparing infection rates during the first and second surges of the SARS-CoV-2 pandemic between people who tested reverse transcription polymerase chain reaction (RT-PCR)– or antigen-negative and -positive in Denmark, Austria, and Italy reported protection against repeat infection of 81, 91, and 94%, respectively (*21*–*23*). A prospective cohort study among health care workers in the United Kingdom found an 84% lower risk of infection after a previous infection (*24*).

In the Netherlands, randomly selected SARS-CoV-2 RT-PCR–positive specimens are sequenced to continuously monitor changes in the virus (*25*). The Alpha variant started to increase rapidly from January 2021 and quickly became the dominant strain in the Netherlands. From June 2021, the Delta variant increased rapidly and caused nearly all infections from August 2021 onward. In this study, we aimed to investigate whether vaccine- or infection-induced immunity protected less well against infection by specific variants using national epidemiological and molecular surveillance data from March to August 2021. We used a case-only approach in which we compared the immune status among cases infected with the Beta, Gamma, or Delta variants versus the Alpha variant. We assessed the relative effectiveness of vaccination against Beta, Gamma, or Delta compared with the Alpha variant (*26*). Similarly, we analyzed the protective effect of previous SARS-CoV-2 infection against a new infection with Beta, Gamma, or Delta versus Alpha variants. Previous studies used a similar design and found relative protection differences between Alpha-Beta and Delta–Omicron BA.1 (*8*, *11*).

RESULTS

From 1 March to 31 August 2021, a total of 661,658 SARS-CoV-2–positive cases were collected in the national surveillance database (Table 1). Of these, 38,261 (5.8%) cases were partially vaccinated individuals, 25,933 (3.9%) were fully vaccinated individuals, and 10,565 (1.6%) had a known previous infection (fig. S1). Among vaccinated individuals, most received Comirnaty (65.0%), followed by Vaxzevria (19.3%), Janssen COVID-19 vaccine (9.8%), and Spikevax (5.9%). We included data of 29,305 samples that were sequenced through the national SARS-CoV-2 surveillance program (Table 1). In addition, 1516 additional randomly selected samples were sequenced to gain insight into variants present during infections after vaccination and reinfections.

Up until June 2021, 94.4% (14,068 of 14,903) of infections were caused by the Alpha variant, with a small proportion caused by the Beta (1.3%) and Gamma (1.3%) variants. The proportion of Delta increased from 0.9% (42 of 4874) in May to 98.7% (4561 of 4620) in August 2021. This pattern was observed over different immune statuses (Fig. 1 and fig. S2). In total, 17,890 (58.0%) Alpha, 209 (0.7%) Beta, 250 (0.8%) Gamma, 11,937 (38.7%) Delta, and 535 (1.7%) other variant sequences were observed.

Logistic regression analysis showed that full vaccination was significantly associated with infection by the Beta, Gamma, or Delta variants compared with the Alpha variant {adjusted odds ratio (OR):

Table 1. Characteristics of notified SARS-CoV-2–positive cases overall and for which variant information was available, 1 March to 31 August 2021, the Netherlands. NA, not available.

	Notifications	Variant information from genomic surveillance	Variant information from additional sampling
Total	661,658	29,305	1,516
Immune status			
Naïve	487,063 (73.6%)	20,804 (71.0%)	NA
Recently vaccinated	47,565 (7.2%)	2,140 (7.3%)	18 (1.2%)
Partially vaccinated	38,261 (5.8%)	2,016 (6.9%)	707 (46.6%)
Fully vaccinated	25,933 (3.9%)	1,791 (6.1%)	516 (34.0%)
Previous infection	10,565 (1.6%)	284 (1.0%)	191 (12.6%)
Vaccinated and previous infection	2,065 (0.3%)	62 (0.2%)	49 (3.2%)
Unknown	50,206 (7.6%)	2,208 (7.5%)	35 (2.3%)
Age group			
0–9	42,666 (6.4%)	1,818 (6.2%)	4 (0.3%)
10–19	125,782 (19.0%)	5,869 (20.0%)	111 (7.3%)
20–29	157,896 (23.9%)	7,018 (23.9%)	283 (18.7%)
30–39	92,400 (14.0%)	4,162 (14.2%)	187 (12.3%)
40–49	85,492 (12.9%)	3,851 (13.1%)	222 (14.6%)
50–59	87,112 (13.2%)	3,652 (12.5%)	265 (17.5%)
60–69	44,226 (6.7%)	1,828 (6.2%)	251 (16.6%)
70–79	21,074 (3.2%)	848 (2.9%)	86 (5.7%)
80+	5,010 (0.8%)	259 (0.9%)	107 (7.1%)
Sex			
Male	330,247 (49.9%)	14,437 (49.3%)	629 (41.5%)
Female	331,411 (50.1%)	14,868 (50.7%)	692 (58.5%)
Symptoms			
Yes	556,214 (84.1%)	25,478 (86.9%)	1,355 (89.4%)
No	66,593 (10.1%)	2,248 (7.7%)	121 (8.0%)
Unknown	38,851 (5.9%)	1,579 (5.4%)	40 (2.6%)
Month (sampling date)			
March	149,103 (22.5%)	5,408 (18.5%)	177 (11.7%)
April	171,534 (25.9%)	4,621 (15.8%)	335 (22.1%)
May	114,536 (17.3%)	4,874 (16.6%)	137 (9.1%)
June	24,904 (3.8%)	3,162 (10.8%)	97 (6.4%)
July	146,978 (22.2%)	6,620 (22.6%	438 (28.9%)
August	54,603 (8.3%)	4,620 (15.8%)	331(21.8%)

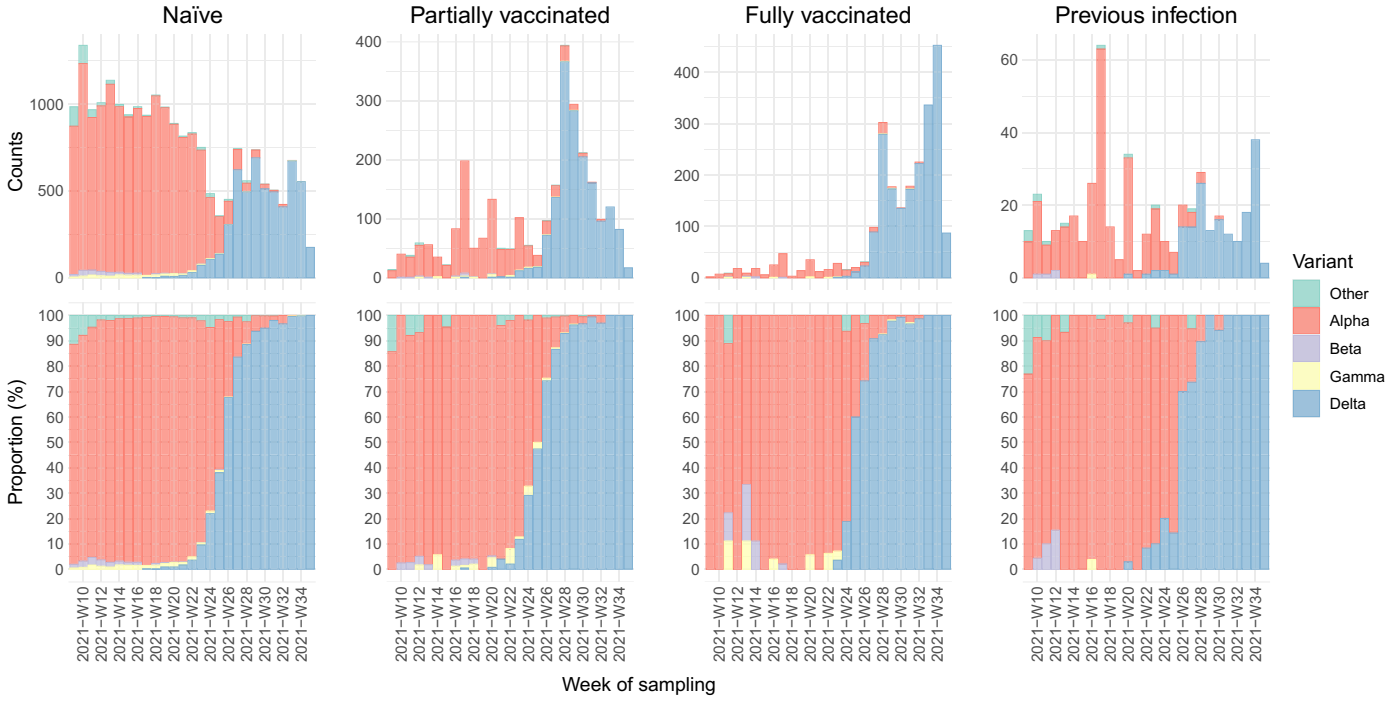

Fig. 1. Variants found in SARS-CoV-2–positive samples of individuals with naïve (unvaccinated and no known previous infection), vaccine-induced, or infection-induced immune status. Number of naïve, partially vaccinated, fully vaccinated, and reinfected documented SARS-CoV-2–positive individuals by variant from 1 March to 31 August 2021 (**top**) and proportion of the respective groups (**bottom**) per week of sampling (in ISO 8601 format).

3.1 [95% confidence interval (CI): 1.3 to 7.3], 2.1 (95% CI: 1.1 to 4.2), and 1.8 (95% CI: 1.4 to 2.4), respectively; Fig. 2}. The association for partial vaccination was less strong and not significant for Beta and Gamma but was significant for Delta when compared with Alpha [adjusted OR: 1.6 (95% CI: 1.3 to 2.0); Fig. 2]. We did not find a significant association between previous infection and the Beta, Gamma, or Delta variant over Alpha [adjusted OR: 1.4 (95% CI: 0.5 to 3.8), 0.3 (95% CI: 0.0 to 1.8), and 0.9 (95% CI: 0.6 to 1.5), respectively; Fig. 2]. Younger age was significantly associated with prevalence of the Delta variant in age groups 10 to 19 [adjusted OR: 1.4 (95% CI: 1.1 to 1.8)] and 20 to 29 [adjusted OR: 1.3 (95% CI: 1.0 to 1.7)] years old, which highlights the importance of adjustment for age group (fig. S3 shows multivariable analysis). Analysis of data using only genomic surveillance, and excluding data from additional sampling of vaccinated and reinfected cases, revealed similar ORs for the Delta variant [OR: 1.7 (95% CI: 1.2 to 2.3) for fully vaccinated], although no significance was measured for Beta and Gamma, likely due to insufficient observations for these variants.

When stratified by vaccine type, the point estimates differ somewhat between the different vaccines, although the CIs are wide and overlapping (Table 2). The association between partial vaccination and the Delta variant was significant for Comirnaty [OR: 1.7 (95% CI: 1.3 to 2.1)] and Vaxzevria [OR: 2.0 (95% CI: 1.2 to 3.4)] but not Spikevax [OR: 1.0 (95% CI: 0.5 to 1.7)]. In addition, we stratified the fully vaccinated by time since vaccination. The association for individuals with less time (14 to 59 days) between onset and last dose was higher [OR: 2.3 (95% CI: 1.6 to 3.4)] compared with individuals with ≥60 days between onset and last dose [OR: 1.4 (95% CI: 0.9 to 2.0)] for the Delta variant. A similar trend was observed for the Beta and Gamma variants, although these analyses resulted in wider CIs (Table 2).

DISCUSSION

Using national epidemiological and whole-genome sequencing surveillance data from March to August 2021 in the Netherlands, our analysis provides evidence for an increased risk of infection by the Beta, Gamma, or Delta variants compared with the Alpha variant after full vaccination, regardless of the vaccine used. This indicates lower VE against infection with the Beta, Gamma, and Delta variants compared with the Alpha variant. No clear differences between vaccine types were observed because CIs largely overlapped. We did not find a significant difference between susceptibility to any of the investigated VOCs among individuals with immunity due to a previous infection compared to naïve individuals. Of note, these analyses do not aim to determine the probability of getting infected after vaccination or previous infection but rather to calculate the likelihood of getting infected with specific VOCs.

The association with vaccination status was higher for Beta and Gamma (OR of 3.1 and 2.1, respectively) than for Delta (OR of 1.8), although CIs for Beta and Gamma were wide because of low numbers. This is in line with literature showing lower VE estimates against infection for Beta and Gamma compared with Delta (*7*). An OR for Delta of 1.8 implicates a reduction of VE from ~90 to 80%, which has been shown in the United Kingdom (*27*, *28*). Current literature still shows a high VE of 90 to 95% against severe COVID-19 for the Delta variant (*7*, *19*), which is reassuring. However, note that with very high VE, a difference of a factor 1.5 to 2.0 between two variants could go unnoticed, because it would only mean a decrease in effectiveness of, for example, 95 to 92%.

Spike binding and neutralization have been shown to be substantially reduced against Beta, Gamma, and Delta, with the largest reduction in neutralization against Beta (*3*–*5*), which is consistent

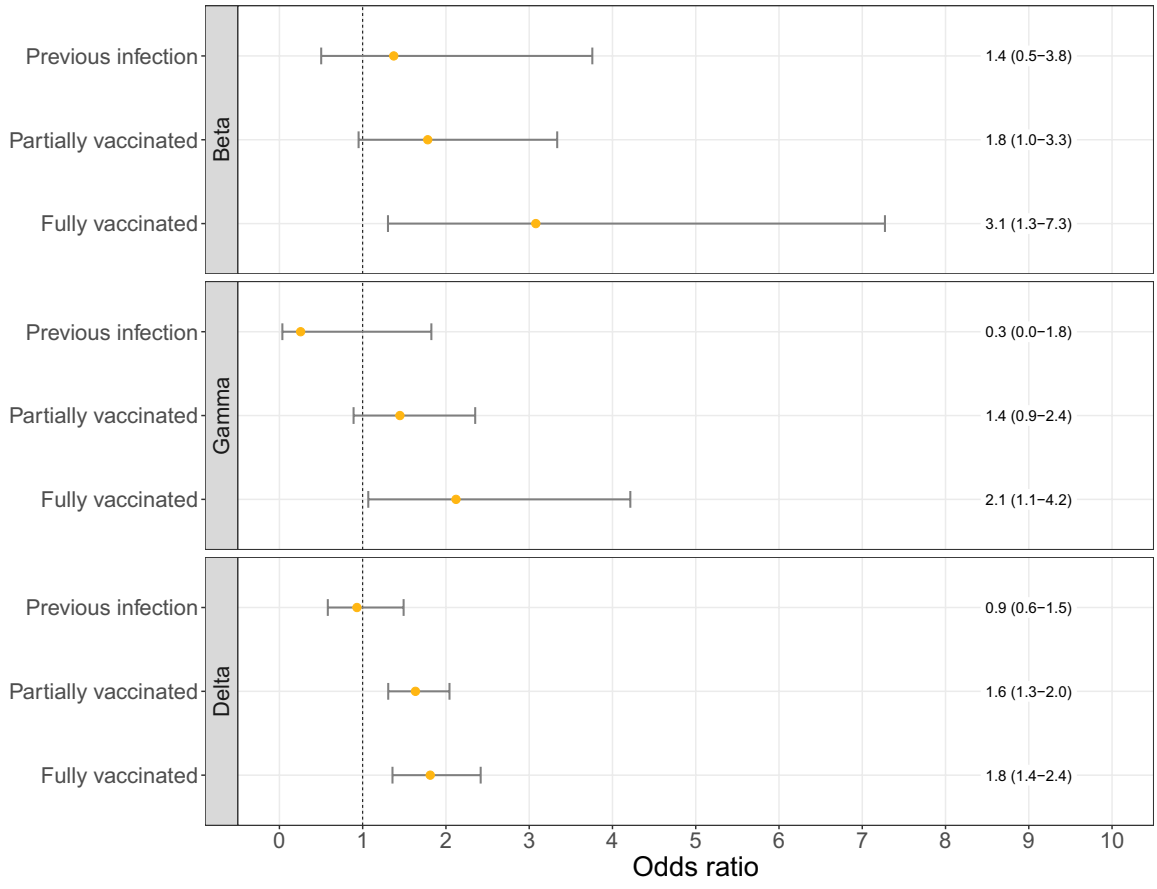

Fig. 2. ORs of the logistic regression models for the association between immune status and VOC (Beta, Gamma, or Delta over the Alpha variant). Logistic regression models are adjusted for week of sampling, sex, and 10-year age group. Error bars correspond to the 95% CIs.

with our results. This observation did not differ for infection- or vaccine-induced immunity, although convalescent sera from mild infections showed lower levels of neutralization potency to VOCs compared with hospitalized cases and vaccinated individuals (*3*). However, in Alpha and Beta, a reduction was not observed for T cell–mediated immunity (*29*).

We observed a larger effect of vaccination in the first 14 to 59 days after vaccination [i.e., OR: 2.3 (95% CI: 1.6 to 3.4) for Delta] compared with 60 days and longer [i.e., OR: 1.4 (95% CI: 0.9 to 2.0) for Delta], suggesting that the difference in VE between Delta and Alpha variants reduces over time since vaccination, possibly because of waning immunity. The decline of VE with time since vaccination is described in a systematic review (*30*). A large cohort study describes an effect of waning and a small effect of the circulating variant (i.e., Delta versus non-Delta) on the VE against SARS-CoV-2 infection (*31*). The authors observed a non-Delta VE of 97% and a Delta VE of 93% 1 month after vaccination, which meant a ratio of 2.3 between non-Delta VE and Delta VE. Four to 5 months after vaccination, VE estimates of 67 and 53% for non-Delta and Delta were observed, respectively, at a ratio of 1.4, and this corresponds with our results. Given the broad and sometimes overlapping CIs of these data, however, the differences need to be interpreted with caution.

We found no association between previous infection and a new infection with Beta, Gamma, or Delta versus Alpha, suggesting that there is no difference in protection from a previous infection between Beta, Gamma, and Delta variants compared to the Alpha variant. This is in line with the similar relative risk reductions for reinfection found for the Alpha and Delta variants (*9*). Early studies showed that previous infection conferred better protection than vaccination without previous infection during the Delta period (*32*, *33*). The best protection was induced by the combination of vaccination and previous infection. However, primary infection comes with a risk of hospitalization or death, especially in older persons or individuals with underlying conditions. Even if infection-induced immunity protects better against reinfection with novel variants, vaccination is preferred over infection to protect individuals against severe disease because the cumulative risk from two infections should be considered.

There are some limitations to our study, including the issue of asymptomatic or mild cases with low viral load being less likely to be identified, and only detectable infections could be sequenced and included in analyses. In addition, sequencing is more successful in samples with low to medium Ct values (high to medium viral load). If infection with Beta, Gamma, or Delta leads to lower Ct values than Alpha, and Ct values are higher for infections after vaccination (*34*–*36*), this could have led to an overestimation of the studied association. Another limitation is that prior infections could go undetected, especially if they occurred during the first wave when there was no mass scale testing capacity. This could lead to an underestimation

Table 2. ORs and 95% CIs for the association between immune status and VOC (Beta, Gamma, or Delta over the Alpha variant) by vaccine type and days between onset and last dose, both adjusted for week of sampling, sex, and 10-year age group. n/a, not available.

	Beta	Gamma	Delta
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Naïve	Reference	Reference	Reference
Partially vaccinated			
Comirnaty	1.2 (0.3–4.4)	2.0 (1.0–3.9)	1.7 (1.3–2.1)
Spikevax	n/a	2.7 (0.6–11.3)	1.0 (0.5–1.7)
Vaxzevria	2.0 (1.0–4.0)	1.0 (0.5–2.1)	2.0 (1.2–3.4)
Fully vaccinated			
Comirnaty	3.2 (1.4–7.6)	2.1 (1.0–4.7)	2.1 (1.4–3.2)
Spikevax	n/a	n/a	1.3 (0.4–4.1)
Vaxzevria	n/a	2.7 (0.6–12.0)	1.4 (0.9–2.3)
Janssen	n/a	3.7 (0.5–31.0)	2.2 (1.1–4.0)
Naïve	Reference	Reference	Reference
Fully vaccinated			
14–60 days	3.4 (1.3–8.8)	2.9 (1.2–6.8)	2.3 (1.6–3.4)
>60 days	2.1 (0.3–15.4)	1.5 (0.5–4.2)	1.4 (0.9–2.0)

of cases with a previous infection, because we do not directly measure preexisting infection-induced immunity.

In conclusion, our results confirm a lower VE against infection for the Delta variant, and similarly the Beta and Gamma variants, compared with Alpha. This effect was largest early after complete vaccination. These findings are informative for considerations of vaccine updates, future vaccination, and pandemic control strategies and similar analyses for novel variants, such as Omicron variants or other future variants.

MATERIALS AND METHODS

Study design

The aim of this study was to assess whether there is an increased risk of infection for the Beta, Gamma, or Delta variant compared with Alpha for individuals with infection- or vaccine-induced immunity. Start and end points for used SARS-CoV-2 isolates were based on the variant circulation measured in the Dutch national SARS-CoV-2 molecular surveillance program (*37*). The starting point was defined by the dominance of the Alpha variant because this is our dependent variable in the regression analysis, and endpoint was based on the disappearance of this variant from the surveillance data because almost all isolates contained the Delta variant from August up to November 2021.

Data

Persons testing positive for SARS-CoV-2 either by community testing or in a hospital are notified by Public Health Services (PHS) to the national surveillance database. Community testing is available through the PHS. Testing is encouraged for individuals experiencing COVID-19–like symptoms, who had contact with a positive case, returning from another country, or upon a positive self-test. Data relevant for source and contact tracing and for surveillance were collected in the national surveillance database through a telephone interview, including data on vaccination status (i.e., number of doses, type of vaccine, and date of vaccination).

The Dutch national SARS-CoV-2 molecular surveillance program sequences whole-virus genomes of randomly selected SARS-CoV-2–positive specimens from both community testing (via PHS) and hospitals, using nationwide geographical distribution. In the current analysis, only samples with information on vaccination status or previous infection could be used. This information is collected in the national surveillance database and linked to sequence data using a sample identifier supplied during community testing. Sequences from hospital samples [5893 of the total 42,662 (13.8%) sequences of the SARS-CoV-2 genomic surveillance samples] and 7464 of the 36,769 sequenced community samples were excluded because these could not be linked to the national surveillance database for required metadata. Because our study period was during the rollout of the vaccination program, the number of sequenced samples among vaccinated persons was small. Therefore, additional sequencing was done on a random sample of positive tests of vaccinated persons to increase the statistical power of the study for analysis of the association between vaccination and variant, and this was also done for positive tests from persons with a previous infection. This additional random sampling was done on a triweekly basis and resulted in an additional inclusion of 1516 cases. In the current analyses, cases with a sampling date between 1 March and 31 August 2021 were included.

Ethics

The Centre for Clinical Expertise at the National Institute for Public Health and the Environment (RIVM) assessed the research proposal following the specific conditions as stated in the law for medical research involving human subjects. The work described was exempted for further approval by the ethical research committee. Pathogen surveillance is a legal task of the RIVM and is carried out under the responsibility of the Dutch Minister of Health, Welfare and Sports. The Public Health Act provides that RIVM may receive pseudonymized data for this task without individual consent.

RT-PCR amplification and Nanopore sequencing

Most isolates were sequenced according to the following representative sequence method. Total nucleic acid from combined nasopharyngeal and oropharyngeal swabs was extracted using MagNApure 96 (MP96) with the total nucleic acid kit small volume (Roche). Total nucleic acid was eluted in 50 µl of Tris-EDTA buffer. SARS-CoV-2–specific RT-PCR amplification and sequencing were performed using the Nanopore protocol based on the ARTIC v3 amplicon sequencing protocol (*38*). Several modifications to the protocol were made for optimization: (i) The total volume of the complementary DNA reaction is 12 µl, with a volume of 0.4 µl of SuperScript IV instead of 0.6 µl. (ii) Primer concentrations and primer sequence were adjusted for several amplicons to optimize amplicon yield and to match novel variants. Updated primer sequences are available upon request. (iii) No distinction was made on the basis of Cq (quantification cycles) value, and PCR was performed using 47 cycles. After the combination of PCR reactions A and B, the samples were quantified with Qubit, and samples with a concentration of >35 ng/µl were diluted to 6 ng/µl in water. Diluted PCR mix (5 µl) was used in the end-prep reaction. This end-prep was incubated

for 15 min at 20°C and 15 min at 65°C. Barcoding was performed using the NEBNext Ultra II Ligation Module (E7595). In short, 1.3 µl of end-prepped DNA were added to 2.5 µl of water, 6 µl of NEBNext Ultra II Ligation Master Mix, 0.2 µl of NEBNext Ligation Enhancer, and 2 µl of native barcode SQK-LSK109 (EXP-NBD196). The barcoding was incubated for 30 min at 20°C and 20 min at 65°C. Barcoded fragments were washed twice with 870 µl of short fragment buffer (SFB) and once with 150 µl of ethanol and eluted in 74 µl after 4 min of incubation with the beads. Adapter ligation was performed using NEBNext Quick Ligation Module (NEB) in a total volume of 50 µl using 25 µl of AMPure XP beads. After washing with 125 µl of SFB, the pellet was resuspended in 15.5 µl of elution buffer. Last, 45 ng of library preparation were loaded on a flow cell (Nanopore), and sequencing was performed on an R9.4.1 flow cell multiplexing 48 up to 96 samples per sequence run for a run time of 30 hours on GridION (Nanopore).

GridION data were analyzed to get consensus genomes with the SARS2seq pipeline and additional manual curation (*39*). These genomes were analyzed with Pangolin (version 3.1.11) and NextClade (version 1.3.0) to get a final variant call (*40*, *41*).

Vaccination and previous infection status

Vaccination status was determined relative to the date used for statistics (DUFS). For symptomatic cases, this was the date of symptom onset or, if missing, the date of a positive test result minus 2 days. For asymptomatic cases, the DUFS was the date of positive test result. Fully vaccinated was defined as having received two doses of Comirnaty, Spikevax, or Vaxzevria at least 14 days before DUFS or one dose of Janssen COVID-19 vaccine at least 28 days before DUFS. Partially vaccinated was defined as having received one dose of Comirnaty, Spikevax, or Vaxzevria at least 14 days before DUFS or two doses of Comirnaty, Spikevax, or Vaxzevria less than 14 days before DUFS. A case was defined as recently vaccinated after one dose of Comirnaty, Spikevax, or Vaxzevria 0 to 13 days or Janssen COVID-19 vaccine 0 to 27 days before DUFS. Individuals with a subsequent positive RT-PCR or antigen test result with an interval of at least 8 weeks after a previous positive test, including a period without symptoms, were defined as reinfections. This was either reported in the notification by the PHS or identified using record linkage by date of birth, sex, and six-digit postal code. Previous infection history was mostly based on a previous positive test in the national surveillance database, although in a small number of cases it was based on a self-reported positive test (13 cases, 2.7% of all previous infections).

Statistical analyses

We compared the proportions of the four VOCs (Alpha, Beta, Gamma, and Delta variants) between four immune status groups: (i) unvaccinated cases without a known previous infection (naïve), (ii) partially vaccinated cases without a known previous infection, (iii) fully vaccinated cases without a known previous infection, and (iv) unvaccinated cases with a previous infection. In a secondary analysis, fully vaccinated cases were further stratified by time between infection and last vaccination (<60 days versus ≥60 days). Cases who were recently vaccinated, irrespective of their previous infection status, were excluded from the analyses because of a possible incomplete immune response. Because the number of vaccinated cases with a previous infection was small (n = 111), this group was excluded.

The association between immune status and the Beta, Gamma, and Delta variant was assessed using multinomial logistic regression. Immune status (group 2: partially vaccinated, group 3: fully vaccinated, and group 4: previous infection versus group 1: naïve) was included in the model as the independent variable and Beta, Gamma, or Delta versus Alpha as the dependent variable. We estimated ORs with 95% CI for any vaccine type and separately for Comirnaty, Spikevax, Vaxzevria, and Janssen COVID-19 vaccine. An OR of 1 would mean that the protection from vaccination or previous infection is the same against Beta, Gamma, or Delta infection and Alpha infection. An OR of >1 would mean that vaccination or previous infection gives lower protection against Beta, Gamma, or Delta infection than against Alpha infection. An additional analysis was performed on the time since vaccination, stratifying the fully vaccinated by 14 to 59 and more than 60 days between complete vaccination and DUFS. Because calendar time is related to both vaccination uptake and prevalence of a certain variant, i.e., a confounder, we corrected for calendar week of sample date in all regression models. We used a natural cubic spline (five knots) to adjust for calendar week to not restrict the association between calendar time and variant prevalence to follow a certain form, e.g., linear or exponential. In addition, all analyses were also adjusted for 10-year age group (40 to 49 years as reference) and sex.

SUPPLEMENTARY MATERIALS

www.science.org/doi/10.1126/scitranslmed.abn4338
Figs. S1 to S3
Table S1
Data file S1
MDAR Reproducibility Checklist

View/request a protocol for this paper from *Bio-protocol*.

REFERENCES AND NOTES

1. B. B. O. Munnink, N. Worp, D. F. Nieuwenhuijse, R. S. Sikkema, B. Haagmans, R. A. M. Fouchier, M. Koopmans, The next phase of SARS-CoV-2 surveillance: Real-time molecular epidemiology. *Nat. Med.* **27**, 1518–1524 (2021).
2. WHO, Tracking SARS-CoV-2 variants (WHO, 2021); https://who.int/en/activities/tracking-SARS-CoV-2-variants/.
3. T. G. Caniels, I. Bontjer, K. van der Straten, M. Poniman, J. A. Burger, B. Appelman, H. A. A. Lavell, M. Oomen, G. J. Godeke, C. Valle, R. Mögling, H. D. G. van Willigen, E. Wynberg, M. Schinkel, L. A. van Vught, D. Guerra, J. L. Snitselaar, D. N. Chaturbhuj, I. C. Martin, J. P. Moore, M. D. de Jong, C. Reusken, J. J. Sikkens, M. K. Bomers, G. J. de Bree, M. J. van Gils, D. Eggink, R. W. Sanders, Emerging SARS-CoV-2 variants of concern evade humoral immune responses from infection and vaccination. *Sci. Adv.* **7**, eabj5365 (2021).
4. T. A. Bates, H. C. Leier, Z. L. Lyski, S. K. McBride, F. J. Coulter, J. B. Weinstein, J. R. Goodman, Z. Lu, S. A. R. Siegel, P. Sullivan, M. Strnad, A. E. Brunton, D. X. Lee, A. C. Adey, B. N. Bimber, B. J. O'Roak, M. E. Curlin, W. B. Messer, F. G. Tafesse, Neutralization of SARS-CoV-2 variants by convalescent and BNT162b2 vaccinated serum. *Nat. Commun.* **12**, 5135 (2021).
5. J. Liu, Y. Liu, H. Xia, J. Zou, S. C. Weaver, K. A. Swanson, H. Cai, M. Cutler, D. Cooper, A. Muik, K. U. Jansen, U. Sahin, X. Xie, P. R. Dormitzer, P.-Y. Shi, BNT162b2-elicited neutralization of B.1.617 and other SARS-CoV-2 variants. *Nature* **596**, 273–275 (2021).
6. A. Netzl, S. Tureli, E. Legresley, B. Mühlemann, S. H. Wilks, D. J. Smith, Analysis of SARS-CoV-2 omicron neutralization data up to 2021-12-22. bioRxiv 2021.12.31.474032 [Preprint]. 7 January 2022. https://doi.org/10.1101/2021.12.31.474032.
7. P. R. Krause, T. R. Fleming, R. Peto, I. M. Longini, J. P. Figueroa, J. A. C. Sterne, A. Cravioto, H. Rees, J. P. T. Higgins, I. Boutron, H. Pan, M. F. Gruber, N. Arora, F. Kazi, R. Gaspar, S. Swaminathan, M. J. Ryan, A. M. Henao-Restrepo, Considerations in boosting COVID-19 vaccine immune responses. *Lancet* **398**, 1377–1380 (2021).
8. T. Kustin, N. Harel, U. Finkel, S. Perchik, S. Harari, M. Tahor, I. Caspi, R. Levy, M. Leshchinsky, S. Ken Dror, G. Bergerzon, H. Gadban, F. Gadban, E. Eliassian, O. Shimron, L. Saleh, H. Ben-Zvi, E. Keren Taraday, D. Amichay, A. Ben-Dor, D. Sagas, M. Strauss, Y. Shemer Avni, A. Huppert, E. Kepten, R. D. Balicer, D. Netzer, S. Ben-Shachar, A. Stern, Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2-mRNA-vaccinated individuals. *Nat. Med.* **27**, 1379–1384 (2021).
9. G. Corrao, M. Franchi, F. Rea, D. Cereda, A. Barone, C. R. Borriello, P. G. Della Valle, M. Ercolanoni, I. Fortino, J. Jara, O. Leoni, F. Mazziotta, E. Pierini, G. Preziosi, M. Tirani, M. Galli, G. Bertolaso, G. Pavesi, F. Bortolan, Protective action of natural and induced

immunization against the occurrence of delta or alpha variants of SARS-CoV-2 infection: A test-negative case-control study. *BMC Med.* **20**, 52 (2022).
10. M. S. Graham, C. H. Sudre, A. May, M. Antonelli, B. Murray, T. Varsavsky, K. Kläser, L. S. Canas, E. Molteni, M. Modat, D. A. Drew, L. H. Nguyen, L. Polidori, S. Selvachandran, C. Hu, J. Capdevila; COVID-19 Genomics UK (COG-UK) Consortium, A. Hammers, A. T. Chan, J. Wolf, T. D. Spector, C. J. Steves, S. Ourselin, Changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: An ecological study. *Lancet Public Heal.* **6**, e335–e345 (2021).
11. D. Eggink, S. P. Andeweg, H. Vennema, N. van Maarseveen, K. Vermaas, B. Vlaemynck, R. Schepers, A. B. van Gageldonk-Lafeber, S. van den Hof, C. B. E. M. Reusken, M. J. Knol, Increased risk of infection with SARS-CoV-2 Omicron BA.1 compared with Delta in vaccinated and previously infected individuals, the Netherlands, 22 November 2021 to 19 January 2022. *Eurosurveillance* **27**, 2101196 (2022).
12. L. Dai, G. F. Gao, Viral targets for vaccines against COVID-19. *Nat. Rev. Immunol.* **21**, 73–82 (2021).
13. M. J. van Gils, A. H. A. Lavell, K. van der Straten, B. Appelman, I. Bontjer, M. Poniman, J. A. Burger, M. Oomen, J. H. Bouhuijs, L. A. van Vught, M. A. Slim, M. Schinkel, E. Wynberg, H. D. G. van Willigen, M. Grobben, K. Tejjani, J. Snitselaar, T. G. Caniels, A. P. J. Vlaar, M. Prins, M. D. de Jong, G. J. de Bree, J. J. Sikkens, M. K. Bomers, R. W. Sanders, D. van de Beek, M. C. Brouwer, D. T. P. Buis, N. Chekrouni, N. van Mourik, S. E. Olie, E. J. G. Peters, Y. M. Smulders, W. J. Wiersinga, Antibody responses against SARS-CoV-2 variants induced by four different SARS-CoV-2 vaccines in health care workers in the Netherlands: A prospective cohort study. *PLOS Med.* **19**, e1003991 (2022).
14. RIVM, Deelname COVID-19-vaccinatie in Nederland (2022); https://rivm.nl/sites/default/files/2022-05/COVID-19_Vaccinatie_Schattingen_WebSite_rapport_20220502_1100_def.pdf.
15. VWS, COVID-19 vaccinations (2021); coronadashboard.government.nl/landelijk/vaccinaties.
16. T. Harder, J. Koch, S. Vygen-Bonnet, W. Külper-Schiek, A. Pilic, S. Reda, S. Scholz, O. Wichmann, Efficacy and effectiveness of COVID-19 vaccines against SARS-CoV-2 infection: Interim results of a living systematic review, 1 January to 14 May 2021. *Euro Surveill.* **26**, 2100563 (2021).
17. B. de Gier, S. Andeweg, R. Joosten, R. ter Schegget, N. Smorenburg, J. van de Kassteele, S. J. Hahné, S. van den Hof, H. E. de Melker, M. J. Knol, A. Hofhuis, A. Teirlinck, A. van Lier, B. Boudewijns, C. Verstraten, G. Willekens, I. Veldhuijzen, J. Polman, J. Alblas, J. van Heereveld, J. Heijne, K. Bulsink, L. Wielders, L. van Asten, L. Jenniskens, L. Soetens, M. Mulder, M. Schipper, M. de Lange, N. Neppelenbroek, P. van den Berg, P. de Oliveira Bressane Lima, R. van Gaalen, S. Wijburg, S. van Iersel, S. de Bruijn, S. Wierenga, S. Lanooij, S. Keijser, T. Smit, D. Klinkenberg, J. Backer, P. de Boer, S. McDonald, A. Maxwell, A. Niessen, D. Berry, D. van Wees, D. van Meijeren, E. R. A. Vos, F. Dijkstra, J. Kemmeren, K. Ainslie, M. Middeldorp, M. Kooijman, S. A. Zadeh, T. Faber, A. J. van Hoek, E. Geubbels, J. Wallinga, R. van Gageldonk-Lafeber, Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021, *Eurosurveillance* **26**, 2100640 (2021).
18. B. De Gier, S. Andeweg, J. A. Backer, S. J. Hahné, S. van den Hof, H. E. de Melker, M. J. Knol, Vaccine effectiveness against SARS-CoV-2 transmission to household contacts during dominance of Delta variant (B.1.617.2), the Netherlands, August to September 2021. *Eurosurveillance* **26**, 2100977 (2021).
19. B. de Gier, M. Kooijman, J. Kemmeren, N. de Keizer, D. Dongelmans, S. C. J. L. van Iersel, J. van de Kassteele, S. P. Andeweg, the R. C.-19 epidemiology and surveillance Team, H. E. de Melker, S. J. M. Hahné, M. J. Knol, S. van den Hof, COVID-19 vaccine effectiveness against hospitalizations and ICU admissions in the Netherlands, April–August 2021. *medRxiv* 2021.09.15.21263613 (2021). https://doi.org/10.1101/2021.09.15.21263613.
20. M. M. Higdon, B. Wahl, C. B. Jones, J. G. Rosen, S. A. Truelove, A. Baidya, A. A. Nande, P. A. ShamaeiZadeh, K. K. Walter, D. R. Feikin, M. K. Patel, M. Deloria Knoll, A. L. Hill, A systematic review of coronavirus disease 2019 vaccine efficacy and effectiveness against severe acute respiratory syndrome coronavirus 2 infection and disease. *Open Forum Infect. Dis.* **9**, ofac138 (2022).
21. C. H. Hansen, D. Michlmayr, S. M. Gubbels, K. Mølbak, S. Ethelberg, Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: A population-level observational study. *Lancet* **397**, 1204–1212 (2021).
22. S. Pilz, A. Chakeri, J. P. Ioannidis, L. Richter, V. Theiler-Schwetz, C. Trummer, R. Krause, F. Allerberger, SARS-CoV-2 re-infection risk in Austria. *Eur. J. Clin. Invest.* **51**, e13520 (2021).
23. A. Leidi, F. Koegler, R. Dumont, R. Dubos, M. E. Zaballa, G. Piumatti, M. Coen, A. Berner, P. Darbellay Farhoumand, P. Vetter, N. Vuilleumier, L. Kaiser, D. Courvoisier, A. S. Azman, I. Guessous, S. Stringhini, Risk of reinfection after seroconversion to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): A population-based propensity-score matched cohort study. *Clin. Infect. Dis.* **74**, 622–629 (2022).
24. V. J. Hall, S. Foulkes, A. Charlett, A. Atti, E. J. M. Monk, R. Simmons, E. Wellington, M. J. Cole, A. Saei, B. Oguti, K. Munro, S. Wallace, P. D. Kirwan, M. Shrotri, A. Vusirikala, S. Rokadiya, M. Kall, M. Zambon, M. Ramsay, T. Brooks, C. S. Brown, M. A. Chand, S. Hopkins, N. Andrews, A. Atti, H. Aziz, T. Brooks, C. S. Brown, D. Camero, C. Carr, M. A. Chand, A. Charlett, H. Crawford, M. Cole, J. Conneely, S. D'Arcangelo, J. Ellis, S. Evans, S. Foulkes, N. Gillson, R. Gopal, L. Hall, V. J. Hall, P. Harrington, S. Hopkins, J. Hewson, K. Hoschler, D. Ironmonger, J. Islam, M. Kall, I. Karagiannis, O. Kay, J. Khawam, E. King, P. Kirwan, R. Kyffin, A. Lackenby, M. Lattimore, E. Linley, J. Lopez-Bernal, L. Mabey, R. McGregor, S. Miah, E. M. J. Monk, K. Munro, Z. Naheed, A. Nissr, A. M. O'Connell, B. Oguti, H. Okafor, S. Organ, J. Osbourne, A. Otter, M. Patel, S. Platt, D. Pople, K. Potts, M. Ramsay, J. Robotham, S. Rokadiya, C. Rowe, A. Saei, G. Sebbage, A. Semper, M. Shrotri, R. Simmons, A. Soriano, P. Staves, S. Taylor, A. Taylor, A. Tengbe, S. Tonge, A. Vusirikala, S. Wallace, E. Wellington, M. Zambon, D. Corrigan, M. Sartaj, L. Cromey, S. Campbell, K. Braithwaite, L. Price, L. Haahr, S. Stewart, E. D. Lacey, L. Partridge, G. Stevens, Y. Ellis, H. Hodgson, C. Norman, B. Larru, S. Mcwilliam, S. Winchester, P. Cieciwa, A. Pai, C. Loughrey, A. Watt, F. Adair, A. Hawkins, A. Grant, R. Temple-Purcell, J. Howard, N. Slawson, C. Subudhi, S. Davies, A. Bexley, R. Penn, N. Wong, G. Boyd, A. Rajgopal, A. Arenas-Pinto, R. Matthews, A. Whileman, R. Laugharne, J. Ledger, T. Barnes, C. Jones, D. Botes, N. Chitalia, S. Akhtar, G. Harrison, S. Horne, N. Walker, K. Agwuh, V. Maxwell, J. Graves, S. Williams, A. O'Kelly, P. Ridley, A. Cowley, H. Johnstone, P. Swift, J. Democratis, M. Meda, C. Callens, S. Beazer, S. Hams, V. Irvine, B. Chandrasekaran, C. Forsyth, J. Radmore, C. Thomas, K. Brown, S. Roberts, P. Burns, K. Gajee, T. M. Byrne, F. Sanderson, S. Knight, E. Macnaughton, B. J. L. Burton, H. Smith, R. Chaudhuri, K. Hollinshead, R. J. Shorten, A. Swan, C. Favager, J. Murira, S. Baillon, S. Hamer, K. Gantert, J. Russell, D. Brennan, A. Dave, A. Chawla, F. Westell, D. Adeboyeku, P. Papineni, C. Pegg, M. Williams, S. Ahmad, S. Ingram, C. Gabriel, K. Pagget, G. Maloney, J. Ashcroft, I. Del Rosario, R. Crosby-Nwaobi, C. Reeks, S. Fowler, L. Prentice, M. Spears, G. McKerron, K. McLelland-Brooks, J. Anderson, S. Donaldson, K. Templeton, L. Coke, N. Elumogo, J. Elliott, D. Padgett, A. Cross, J. Price, S. Joyce, I. Sinanovic, M. Howard, T. Lewis, P. Cowling, D. Potoczna, S. Brand, L. Sheridan, B. Wadams, A. Lloyd, J. Mouland, J. Giles, G. Pottinger, H. Coles, M. Joseph, M. Lee, S. Orr, H. Chenoweth, C. Auckland, R. Lear, T. Mahungu, A. Rodger, K. Penny-Thomas, S. Pai, J. Zamikula, E. Smith, S. Stone, E. Boldock, D. Howcroft, C. Thompson, M. Aga, P. Domingos, S. Gormley, C. Kerrison, L. Marsh, S. Tazzyman, L. Allsop, S. Ambalkar, M. Beekes, S. Jose, J. Tomlinson, A. Jones, C. Price, J. Pepperell, M. Schultz, J. Day, A. Boulos, E. Defever, D. McCracken, K. Gray, A. Houston, T. Planche, R. P. Jones, D. Wycherley, S. Bennett, J. Marrs, K. Nimako, B. Stewart, N. Kalakonda, S. Khanduri, A. Ashby, M. Holden, N. Mahabir, J. Harwood, B. Payne, K. Court, N. Staines, R. Longfellow, M. E. Green, L. E. Hughes, M. Halkes, P. Mercer, A. Roebuck, E. Wilson-Davies, L. Gallego, R. Lazarus, N. Aldridge, L. Berry, F. Game, T. Reynolds, C. Holmes, M. Wiselka, A. Higham, M. Booth, C. Duff, J. Alderton, H. Jory, E. Virgilio, T. Chin, M. Z. Qazzafi, A. M. Moody, R. Tilley, T. Donaghy, K. Shipman, R. Sierra, N. Jones, G. Mills, D. Harvey, Y. W. J. Huang, J. Birch, L. Robinson, S. Board, A. Broadley, C. Laven, N. Todd, D. W. Eyre, K. Jeffery, S. Dunachie, C. Duncan, P. Klenerman, L. Turtle, H. Baxendale, J. L. Heeney, SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: A large, multicentre, prospective cohort study (SIREN). *Lancet* **397**, 1459–1469 (2021).
25. Variants of the coronavirus SARS-CoV-2|RIVM; https://rivm.nl/en/coronavirus-covid-19/virus-sars-cov-2/variants.
26. WHO, Guidance on conducting vaccine effectiveness evaluations in the setting of new SARS-CoV-2 variants: Interim guidance, 22 July 2021. Addendum to Evaluation of COVID-19 vaccine effectiveness (WHO, 2021); https://who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-variants-2021.1.
27. J. Lopez Bernal, N. Andrews, C. Gower, E. Gallagher, R. Simmons, S. Thelwall, J. Stowe, E. Tessier, N. Groves, G. Dabrera, R. Myers, C. N. J. Campbell, G. Amirthalingam, M. Edmunds, M. Zambon, K. E. Brown, S. Hopkins, M. Chand, M. Ramsay, Effectiveness of covid-19 vaccines against the B.1.617.2 (Delta) variant. *N. Engl. J. Med.* **385**, 585–594 (2021).
28. A. Sheikh, J. McMenamin, B. Taylor, C. Robertson, SARS-CoV-2 Delta VOC in Scotland: Demographics, risk of hospital admission, and vaccine effectiveness. *Lancet* **397**, 2461–2462 (2021).
29. D. Geers, M. C. Shamier, S. Bogers, G. den Hartog, L. Gommers, N. N. Nieuwkoop, K. S. Schmitz, L. C. Rijsbergen, J. A. T. van Osch, E. Dijkhuizen, G. Smits, A. Comvalius, D. van Mourik, T. G. Caniels, M. J. van Gils, R. W. Sanders, B. B. Oude Munnink, R. Molenkamp, H. J. de Jager, B. L. Haagmans, R. L. de Swart, M. P. G. Koopmans, R. S. van Binnendijk, R. D. de Vries, C. H. GeurtsvanKessel, SARS-CoV-2 variants of concern partially escape humoral but not T-cell responses in COVID-19 convalescent donors and vaccinees. *Sci. Immunol.* **6**, eabj1750 (2021).
30. D. R. Feikin, M. M. Higdon, L. J. Abu-Raddad, N. Andrews, R. Araos, Y. Goldberg, M. Groome, A. Huppert, K. O'Brien, P. G. Smith, A. Wilder-Smith, S. L. Zeger, M. D. Knoll, M. Patel, Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: Results of a systematic review and meta-regression. *Lancet* **399**, 924–944 (2022).

31. S. Y. Tartof, J. M. Slezak, H. Fischer, V. Hong, B. K. Ackerson, O. N. Ranasinghe, T. B. Frankland, O. A. Ogun, J. M. Zamparo, S. Gray, S. R. Valluri, K. Pan, F. J. Angulo, L. Jodar, J. M. McLaughlin, Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: A retrospective cohort study. *Lancet* **398**, 1407–1416 (2021).
32. T. M. León, V. Dorabawila, L. Nelson, E. Lutterloh, U. E. Bauer, B. Backenson, M. T. Bassett, H. Henry, B. Bregman, C. M. Midgley, J. F. Myers, I. D. Plumb, H. E. Reese, R. Zhao, M. Briggs-Hagen, D. Hoefer, J. P. Watt, B. J. Silk, S. Jain, E. S. Rosenberg, COVID-19 cases and hospitalizations by COVID-19 vaccination status and previous COVID-19 diagnosis—California and New York, May–November 2021. *MMWR Recomm. Rep.* **71**, 125–131 (2022).
33. R. Grant, T. Charmet, L. Schaeffer, S. Galmiche, Y. Madec, C. Von Platen, O. Chény, F. Omar, C. David, A. Rogoff, J. Paireau, S. Cauchemez, F. Carrat, A. Septfons, D. Levy-Bruhl, A. Mailles, A. Fontanet, Impact of SARS-CoV-2 Delta variant on incubation, transmission settings and vaccine effectiveness: Results from a nationwide case-control study in France. *Lancet Reg. Heal. Eur.* **13**, 100278 (2022).
34. A. Singanayagam, S. Hakki, J. Dunning, K. J. Madon, M. A. Crone, A. Koycheva, N. Derqui-Fernandez, J. L. Barnett, M. G. Whitfield, R. Varro, A. Charlett, R. Kundu, J. Fenn, J. Cutajar, V. Quinn, E. Conibear, W. Barclay, P. S. Freemont, G. P. Taylor, S. Ahmad, M. Zambon, N. M. Ferguson, A. Lalvani, A. Badhan, S. Dustan, C. Tejpal, A. V. Ketkar, J. S. Narean, S. Hammett, E. McDermott, T. Pillay, H. Houston, C. Luca, J. Samuel, S. Bremang, S. Evetts, J. Poh, C. Anderson, D. Jackson, S. Miah, J. Ellis, A. Lackenby, Community transmission and viral load kinetics of the SARS-CoV-2 Delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: A prospective, longitudinal, cohort study. *Lancet Infect. Dis.* **22**, 183–195 (2022).
35. M. Levine-Tiefenbrun, I. Yelin, H. Alapi, R. Katz, E. Herzel, J. Kuint, G. Chodick, S. Gazit, T. Patalon, R. Kishony, Viral loads of Delta-variant SARS-CoV-2 breakthrough infections after vaccination and booster with BNT162b2. *Nat. Med.* **27**, 2108–2110 (2021).
36. C. H. Luo, C. P. Morris, J. Sachithanandham, A. Amadi, D. Gaston, M. Li, N. J. Swanson, M. Schwartz, E. Y. Klein, A. Pekosz, H. H. Mostafa, Infection with the SARS-CoV-2 delta variant is associated with higher infectious virus loads compared to the alpha variant in both unvaccinated and vaccinated individuals. *medRxiv* 2021.08.15.21262077 (2021). https://doi.org/10.1101/2021.08.15.21262077.
37. Coronavirus variants; https://coronadashboard.government.nl/landelijk/varianten.
38. nCoV-2019 sequencing protocol v2 (GunIt); https://protocols.io/view/ncov-2019-sequencing-protocol-v2-bdp7i5rn?version_warning=no.
39. GitHub-RIVM-bioinformatics/SARS2seq: SARS2seq is a pipeline designed to process raw FastQ data from targeted SARS-CoV-2 sequencing and generate biologically correct consensus sequences of the SARS-CoV-2 genome; https://github.com/RIVM-bioinformatics/SARS2seq.
40. I. Aksamentov, C. Roemer, E. Hodcroft, R. Neher, Nextclade: Clade assignment, mutation calling and quality control for viral genomes. *J. Open Source Softw.* **6**, 3773 (2021).
41. A. Rambaut, E. C. Holmes, Á. O'Toole, V. Hill, J. T. McCrone, C. Ruis, L. du Plessis, O. G. Pybus, A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. *Nat. Microbiol.* **5**, 1403–1407 (2020).

Acknowledgments: We would like to thank all personnel at the 25 Public Health Services for data collection in the national surveillance database and all laboratories for providing specimens for sequence analyses. **Funding:** This work was funded by the Ministry of Health, Welfare and Sports (VWS). **Author contributions:** M.J.K., I.V., A.B.v.G.-L., and D.E. designed the study. H.V., C.R., and D.E. supervised the laboratory analysis. D.S. and F.Z. analyzed the sequence data. S.P.A. and N.S. performed data analysis. S.P.A. performed statistical analysis, and M.J.K. supervised statistical analysis. H.V., S.J.M.H., and C.R. contributed analytically to the interpretation of the data. S.P.A., I.V., M.J.K., and D.E. drafted the manuscript with input from all authors. All authors reviewed the manuscript. **Competing interests:** The authors declare that they have no competing interests. **Data and materials availability:** All data associated with this study are present in the paper or the Supplementary Materials. Data to generate figures are in data file S1. SARS-CoV-2 sequences are deposited on GISAID, and the accession IDs are available in table S1. Code for sequencing data processing is publicly available at github.com/RIVM-bioinformatics/SARS2seq. Scripts for statistical analysis, figures, and tables can be found at github.com/Stijn-A/STM_SARS_CoV_2_genomic_epidemiology.

The SeqNeth Molecular surveillance group and RIVM COVID-19 Molecular epidemiology group members have contributed to SARS-CoV-2 surveillance and sequence data analysis and interpretation.

SeqNeth Molecular surveillance group:

Janke Schinkel[2], Matthijs R.A. Welkers[2], Marcel Jonges[2], Jelle Koopsen[2], Menno D. de Jong[2], Richard Molenkamp[3], David F. Nieuwenhuijse[3], Reina S. Sikkema[3], Bas B. Oude Munnink[3], Marion Koopmans[3], Adri van der Zanden[4], Laura Manrho[4], Jessica de Beer[4], Stefan A. Boers[5], Erin Meijers[5], Tom Vreeswijk[5], Igor A. Sidorov[5], Djoo Dunk[6], Pieter W. Smit[6], Suzan D. Pas[7], Jaco J. Verweij[7], Joep J. J. M. Stohr[7], Jozef Dingemans[8], Brian van der Veer[8], Lieke van Alphen[8], Paul Savelkoul[8], Hubert G.M. Niesters[9], Erley F. Lizarazo Forero[9], Monika A Fliss[9], Lilli Gard[9], Anniek A.N. Tanja[10], Rob Schuurman[10], Annemarie M.J. Wensing[10], L. Marije Hofstra[10], Jordy P.M. Coolen[11], Janette C. Rahamat-Langendoen[11], Willem J. G. Melchers[11], Heiman F. L. Wertheim[11], Remco Dijkman[12], Manon M.C. Holstege[12], Cornelis J. Vermeulen[12], Sander Schuurman[12], Karin van Leeuwen[13], Nadia Keijzer[13], Lianne Koets[13], and Marco Koppelman[13]

RIVM COVID-19 Molecular epidemiology group:

Lynn Aarts[1], Jeroen Alblas[1], Birgit van Benthem[1], Sanne Bos[1], Annemarie van den Brandt[1], Sharon van den Brink[1], Jeroen Cremer[1], Timor Faber[1], Kim Freriks[1], Rolina van Gaalen[1], Brechje de Gier[1], Eveline Geubbels[1], Janneke van Heereveld[1], Karim Hajji[1], Susan van den Hof[1], Agnetha Hofhuis[1], Senna van Iersel[1], Ryanne Jaarsma[1], Jan van de Kassteele[1], Annelies Kroneman[1], Maarten Mulder[1], Priscila de Oliveira Bressane Lima[1], Jan Polman[1], Maarten Schipper[1], Euníce Then[1], Bas van der Veer[1], Ivo van Walle[1], Sara Wijburg[1], and Lisa Wijsman[1]

Affiliation 1 can be found on the first page of the paper. [2]Department of Medical Microbiology, Amsterdam University Medical Center, Amsterdam, Netherlands. [3]Department of Viroscience, Erasmus MC, Rotterdam, Netherlands. [4]Laboratory for Medical Microbiology and Public Health, Labmicta, Hengelo, Netherlands. [5]Department of Medical Microbiology, Leiden University Medical Center, Leiden, Netherlands. [6]Medical Microbiology Laboratory, Maasstad Hospital, Rotterdam, Netherlands. [7]Microvida Laboratory for Microbiology, Elisabeth-TweeSteden Hospital, Tilburg, Netherlands. [8]Department of Medical Microbiology, Maastricht University Medical Centre (MUMC+), Maastricht, Netherlands. [9]Department of Medical Microbiology, University Medical Center Groningen, Groningen, Netherlands. [10]Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, Netherlands. [11]Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, Netherlands. [12]Royal GD, Deventer, Netherlands. [13]Sanquin Diagnostics, Amsterdam, Netherlands

Submitted 26 November 2021
Resubmitted 9 March 2022
Accepted 8 July 2022
Published First Release 21 July 2022
Final published 22 February 2023
10.1126/scitranslmed.abn4338

Science Translational Medicine

Elevated risk of infection with SARS-CoV-2 Beta, Gamma, and Delta variants compared with Alpha variant in vaccinated individuals

Stijn P. Andeweg, Harry Vennema, Irene Veldhuijzen, Naomi Smorenburg, Dennis Schmitz, Florian Zwagemaker, Arianne B. van Gageldonk-Lafeber, Susan J. M. Hahn, Chantal Reusken, Mirjam J. Knol, Dirk Eggink, on behalf of the SeqNeth Molecular surveillance group and, and RIVM COVID-19 Molecular epidemiology group

Sci. Transl. Med., **15** (684), eabn4338.
DOI: 10.1126/scitranslmed.abn4338

Variants and vaccines

The emergence of SARS-CoV-2 variants has revealed that breakthrough infections can occur despite previous immunity caused by infection or vaccination. Andeweg *et al.* used SARS-CoV-2 sequence data collected during March to August 2021 through the national community testing program in the Netherlands to understand the relationship between immune status and breakthrough infection. They analyzed 28,578 samples and observed an increased risk of infection by the Beta (B.1.351), Gamma (P.1), or Delta (B.1.617.2) variants compared with the Alpha (B.1.1.7) variant after vaccination regardless of vaccine type. The risk of breakthrough infection with variants Beta, Gamma, or Delta was greatest 14 to 59 days after vaccination compared with >60 days, but no differences between variants were observed in unvaccinated individuals who had been previously infected with SARS-CoV-2. These findings highlight the effect viral variants have on vaccine efficacy. —CF

Science Translational Medicine (ISSN) is published by the American Association for the Advancement of Science. 1200 New York Avenue NW, Washington, DC 20005. The title *Science Translational Medicine* is a registered trademark of AAAS.