



Use of Whole-Genome Sequencing to Estimate the Contribution of Immune Evasion and Waning Immunity on Decreasing COVID-19 Vaccine Effectiveness

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Background. The impact variant-specific immune evasion and waning protection have on declining coronavirus disease 2019 (COVID-19) vaccine effectiveness (VE) remains unclear. Using whole-genome sequencing (WGS), we examined the contribution these factors had on the decline that followed the introduction of the Delta variant. Furthermore, we evaluated calendar-period-based classification as a WGS alternative.

Methods. We conducted a test-negative case-control study among people tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between 1 April and 24 August 2021. Variants were classified using WGS and calendar period.

Results. We included 2029 cases (positive, sequenced samples) and 343 727 controls (negative tests). VE 14–89 days after second dose was significantly higher against Alpha (84.4%; 95% confidence interval [CI], 75.6%–90.0%) than Delta infection (68.9%; 95% CI, 58.0%–77.1%). The odds of Delta infection were significantly higher 90–149 than 14–89 days after second dose (P value = .003). Calendar-period-classified VE estimates approximated WGS-classified estimates; however, calendar-period-based classification was subject to misclassification (35% Alpha, 4% Delta).

Conclusions. Both waning protection and variant-specific immune evasion contributed to the lower effectiveness. While calendar-period-classified VE estimates mirrored WGS-classified estimates, our analysis highlights the need for WGS when variants are cocirculating and misclassification is likely.

Keywords. COVID-19; vaccine effectiveness; variant-specific immune evasion; waning; whole-genome sequencing.

As the number of cases and deaths among vaccinated and unvaccinated people rose following the introduction of the Delta variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the summer of 2021, concerns regarding variant-specific immune evasion surfaced [1, 2]. While some studies found vaccine effectiveness against Delta was lower than previously circulating variants (such as Alpha) [3–11], other studies found the differences were likely driven by waning levels of protection, not variant-specific immune evasion [12–17].

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However, interpreting and comparing studies of vaccine effectiveness is challenging due to the use of inconsistent variant-specific outcome definitions. In the absence of whole-genome sequencing (WGS), studies commonly rely on calendar-period-based variant classification [6, 8, 10, 11, 15, 18, 19]. Although studies reliant on this approach have incorporated sensitivity analyses with varying time periods, this approach remains subject to unaccountable outcome (variant) misclassification. Despite its frequent use, a comparison of vaccine effectiveness resulting from WGS and calendar-period-based variant classification has not been completed. As a result, the reliability of calendar-period-based estimates remains uncertain.

In this retrospective analysis, we leveraged data from a large cohort of individuals enrolled in the Yale New Haven Health System (YNHH) who underwent reverse transcription polymerase chain reaction (RT-PCR) testing to estimate and compare the effectiveness of mRNA vaccines (mRNA-1273-Moderna and BNT162b2-Pfizer) against infection, symptomatic infection, and coronavirus disease 2019

(COVID-19)-associated hospitalization with WGS-classified Alpha, Delta, and other cocirculating variants. Furthermore, we examined whether protection conferred by primary series vaccination declined over time since series completion (second dose receipt). Finally, to examine the reliability of calendar-period-based variant classification, we compared estimates of vaccine effectiveness during the calendar period of Alpha and Delta variant predominance with those obtained from WGS.

METHODS

Study Design and Setting

We conducted a test-negative-case-control (TNCC) analysis using RT-PCR tests collected between 1 April and 24 August 2021, as part of the larger Studying COVID-19 Outcomes after SARS-CoV-2 Infection and Vaccination (SUCCESS) Study at YNHH. The YNHH is a large academic health system comprising 4 delivery networks in Connecticut, southeastern New York, and western Rhode Island. We chose a TNCC design because it mitigates the risk of confounding introduced by care-seeking and testing access and has been shown to provide estimates of vaccine effectiveness consistent with those from randomized control trials [20–24].

RT-PCR Collection and Sequencing

SARS-CoV-2 RT-PCR testing was broadly implemented at YNHH to screen people with suspected SARS-CoV-2 exposure and patients who underwent procedures or were admitted for hospitalization. Specimens were collected using nasopharyngeal/oropharyngeal swabs and primarily evaluated with QuantStudio 7 Flex Real-Time PCR System (Applied Biosystems), BHG Probe Panther (Hologic), and Cobas 6800 System (Roche Diagnostics). Excess positive nasopharyngeal/oropharyngeal swabs were stored at -80°C prior to processing for WGS.

Specimens were processed using custom NEB/Roche reagents the SARS-CoV-2 v2 SNAP kit + Omicron spike-in from IDT/Swift and were sequenced on the Illumina NovaSeq 6000 platform on SP or S2 flow cells. Variant calls were made for each specimen based on the proportion of variant-defining mutations present in the specimen (cutoff, $\geq 40\%$). Specimens that did not meet a variant-defining criterion were classified as an “unidentified variant.” Specimens with $\leq 65\%$ of targeted bases covered at $100\times$ were considered to have failed quality control and excluded. This cutoff was selected internally as it corresponded with the inclusion of 5% of unclassifiable samples ([Supplementary Table 1](#)).

Data Access

Demographic, comorbidity, COVID-19 vaccination, SARS-CoV-2 testing, and hospitalization data were extracted

from the electronic health records using the Yale Computational Health Platform [25]. Records for vaccinations that occurred outside of YNHH were obtained from the state vaccination registry and extracted using the same platform. COVID-19 symptom data were collected from medical notes using a natural language processor [26]. This study was approved by the Yale Institutional Review Board (ID No. 2000030222).

Study Sample

We identified all SARS-CoV-2 RT-PCRs collected among vaccine-eligible people (aged ≥ 16 years) in the YNHH EHR between 1 April and 24 August 2021. We excluded tests from people who received a vaccine prior to state distribution (14 December 2020), had a previous positive SARS-CoV-2 RT-PCR or rapid antigen test, or had missing covariate information (see “Statistical Analysis”). Additionally, we excluded tests that were performed after receiving a booster (third) dose or an Ad26.COV2 vaccine dose.

Outcome (Case) Definition and Control Selection

Our primary outcomes of interest were WGS-classified Alpha-, Delta-, and other-variants infection, symptomatic infection, and COVID-19-associated hospitalizations. We defined infection as positive, sequenced specimens that passed quality control. Infections were categorized as Alpha, Delta, or other-variant based on their WGS classification, where the other-variant category comprised all non-Alpha, non-Delta samples. Controls were defined as negative RT-PCRs. We selected up to 3 negative tests (controls) per person. If an individual had more than 1 negative test within a 7-day period, 1 random test was selected.

Symptomatic SARS-CoV-2 infection was defined as the subset of SARS-CoV-2 infections identified among symptomatic people (people with at least 1 natural language processor-captured COVID-19-related symptom recorded within 0–14 days prior to or following testing). We defined COVID-19-associated hospitalizations as the subset of symptomatic SARS-CoV-2 infections collected in the 21 days prior to or 3 days following hospitalization. Controls for these outcomes were selected among negative RT-PCR test results from symptomatic people.

Our secondary outcomes were calendar-period-classified Alpha and Delta infections. Specifically, we defined Alpha and Delta infections as positive RT-PCR tests collected during periods when the variant comprised $\geq 50\%$ of sequenced samples from Connecticut deposited in the global initiative on sharing all influenza data (GISAID; <https://www.gisaid.org>) [27, 28]. Alpha accounted for $\geq 50\%$ of sequenced samples from the beginning of the study (1 April) through 28 May 2021 [27, 28]. Delta contributed $\geq 50\%$ of the sequenced samples beginning on 27 June 2021 [27, 28]. Controls were then

limited to negative RT-PCRs collected during the period used for variant classification.

Statistical Analysis

We visually summarized the number of infections, or positive RT-PCRs, collected in the absence of a positive test in the previous 90 days, recorded in the YNHH between 1 April and 24 August 2021, and vaccine coverage among selected cases and controls by day. The number of sequenced samples that passed quality control were visually summarized by day and variant classification.

Vaccine Effectiveness Against WGS-Classified SARS-CoV-2 Outcomes

We estimated the association between mRNA COVID-19 vaccination (<14 days, 14–89 days, 90–149 days, and ≥150 days since second dose) and WGS-classified Alpha, Delta, and other-variant infection, symptomatic infection, and COVID-19-associated hospitalization using generalized additive multinomial, logistic regressions. We selected these categories of time since vaccination to account for the time prior to full effectiveness (<14 days), to match the booster dose eligibility timeline at the time of the analysis (≥150 days [29]), and stratified the remaining time by months since second dose while minimizing differences in duration of the categories (14–89 days and 90–149 days [difference 16 days]). We included the following a priori selected covariates: date of test (continuous), age (continuous), sex, race/ethnicity, Charlson comorbidity score [30] (continuous), number of nonemergent YNHH encounters in the year prior to vaccine rollout in Connecticut (December 2020; categorized as 0, 1–2, 3–4, 5+), insurance group (uninsured, Medicaid, Medicare, other), social vulnerability index (SVI) of residential zip code (continuous), and residential county. Continuous factors were modeled using a natural spline with 3 knots [31, 32]. From the model we estimated vaccine effectiveness as 1 minus the odds ratio (OR) of infection comparing vaccinated to unvaccinated people.

Duration of Protection From Primary Vaccination

We tested for declines in the level of protection over time by comparing the odds of infection among recently vaccinated people (14–89 days since second dose) to the odds of infection among people who received their second dose 90–149 and ≥150 days prior to testing [33]. We evaluated this association using a generalized additive logistic regression and accounted for the same confounders as in the WGS-classified vaccine effectiveness analysis.

Calendar Period-Classified, Variant-Specific Vaccine Effectiveness

We estimated period-defined variant-specific vaccine effectiveness using generalized additive logistic regressions and included the same confounders as in the WGS-classified vaccine

effectiveness analysis. All analyses were conducted in R, version 4.1.2 [34].

Sensitivity Analyses

We performed multiple sensitivity analyses testing the robustness of our findings to alternative study design, data cleaning, and modeling assumptions. Specifically, we examined the following scenarios: matched analysis (1:4 matching with replacement) and various quality control definitions. Additionally, we estimated vaccine effectiveness and tested for differences in the level of protection during periods when variants were cocirculating. Furthermore, to ensure that any differences observed between the period-classified and WGS-classified effectiveness estimates were not the result of bias introduced through the selection of sequenced samples, we performed the period-classified analysis among sequenced samples. Finally, to ensure the results from our variant comparison analysis were not driven by residual waning, we conducted a sensitivity analysis where we further stratified the 14–89 days after the second dose vaccine category into 14–59 days and 60–89 days after the second dose. For a detailed description, see [Supplementary Material](#), Sensitivity Analyses.

RESULTS

The regions served by YNHH experienced 2 successive waves of SARS-CoV-2 infections (or positive RT-PCRs) between 1 April and 24 August 2021 ([Figure 1A](#)). According to the 4125 samples available for sequencing during this period (1076 of which failed quality control and were omitted), the first wave comprised Alpha and other-variant (non-Alpha/Delta) infections and the second predominantly comprised Delta infections ([Figure 1B](#)). The proportion of tests collected among vaccinated people increased during April but remained around 50% for the rest of the study period ([Figure 1C](#)).

Population and Sample

Between 1 April and 24 August 2021, 502 618 RT-PCRs were collected among 268 045 vaccine-eligible people. Following the restriction to RT-PCRs that met the inclusion criteria ($n = 441\,356$ tests among 241 654 people), the sample contained 10 349 positives (cases), 2565 (25%) of which were sequenced (1560 sequenced samples did not meet our studies inclusion criteria) and 2029 passed quality control. From the 431 007 negative RT-PCRs that met our inclusion criteria, we randomly selected up to 3 per person, resulting in the inclusion of 343 727 negative RT-PCRs as controls ([Figure 2](#)).

Cases (positive RT-PCRs), sequenced cases, and controls were similar with respect to age, sex, SVI of residential zip code, and Charlson comorbidity score. However, a larger proportion of controls occurred among non-Hispanic white people (61% of controls vs 40% of Alpha infections, 49% of Delta

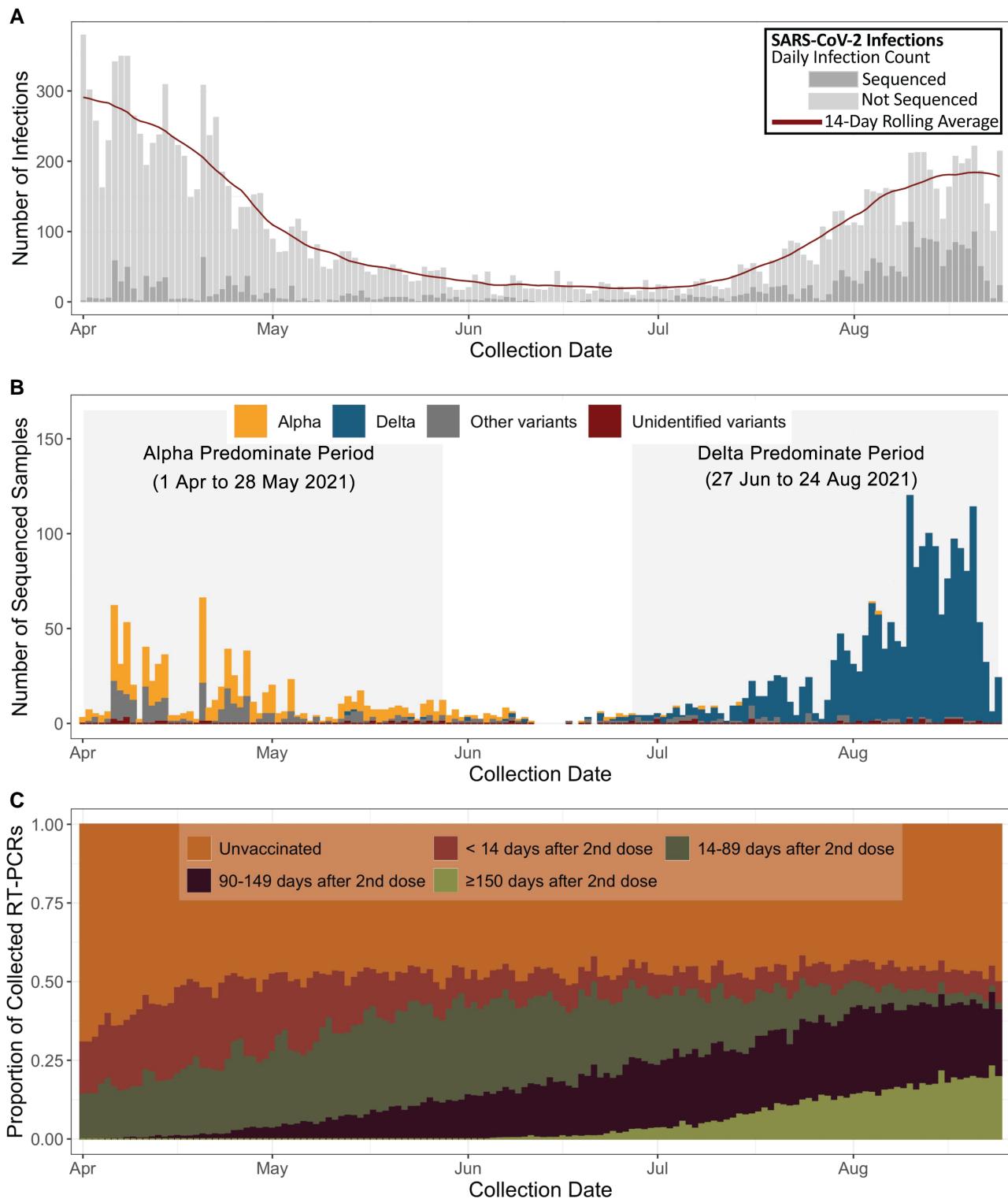


Figure 1. Trends in SARS-CoV-2 infection frequency and vaccination status at the Yale New Haven Health System between 1 April 2021 and 24 August 2021. The trends in (A) SARS-CoV-2 infections; (B) whole-genome-sequence-defined infections that passed quality control overlaid on the Alpha- and Delta-predominant periods (Alpha, 1 April 1 to 28 May 2021; Delta, 27 June 27 to 24 August 2021); and (C) mRNA vaccination status over the study period (1 April 2021 through 24 August 2021). SARS-CoV-2 infections were defined as positive RT-PCRs collected among people without a prior positive SARS-CoV-2 RT-PCR recorded in the Yale New Haven Health System. Infections were stratified by if they were sequenced (lower bars) or not (upper bars). Variant-predominant periods were defined as periods where the variant comprised at least 50% of Connecticut samples in GISAID. Abbreviations: RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

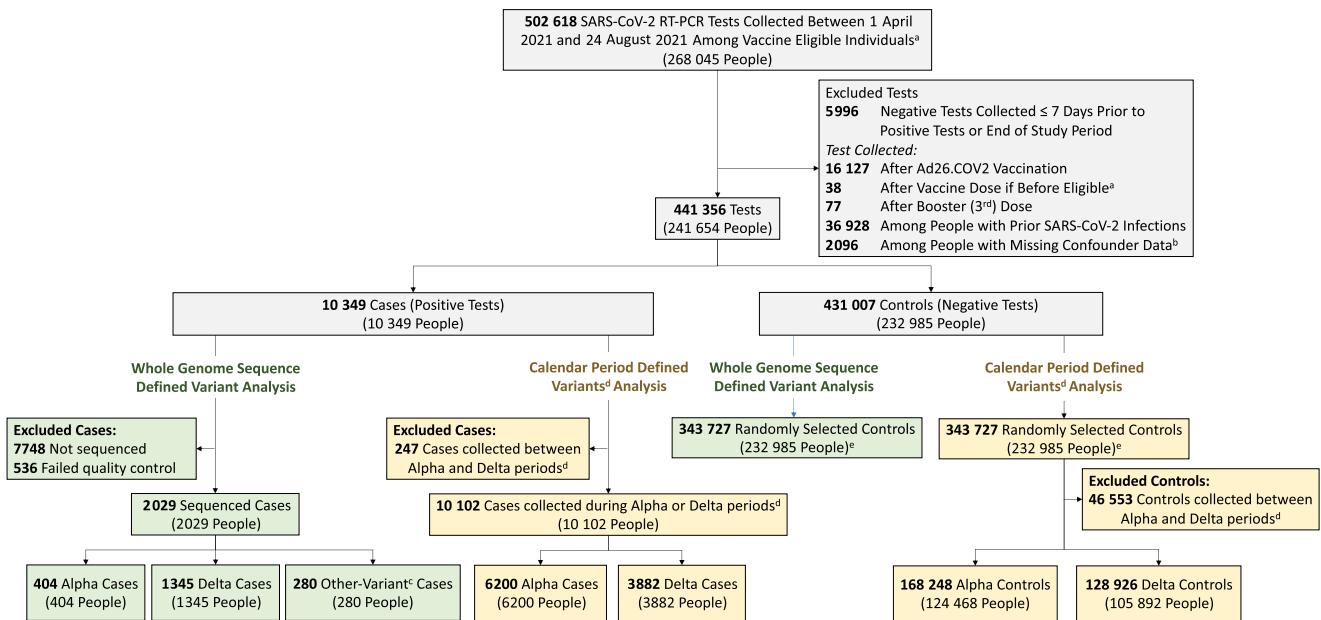


Figure 2. Selection of tests for the case control analysis. The sample was limited to viral RNA samples collected between 1 April and 24 August 2021, among vaccine-eligible individuals (people aged 16 years or older^a) with recorded confounder data (2032 and 64 tests were collected among people without social vulnerability index and sex data, respectively). Whole-genome sequencing was performed on available specimens and variant calls were made based on the frequency of variant-defining mutations. The other-variant classification incorporated all non-Alpha/Delta samples^c. Period-based variant classifications were defined as cases collected during variant-dominant periods, or periods when at least 50% of sequenced samples deposited in GISAID were that variant [28]. The Alpha-dominate period was 1 April through 28 May 2021 and the Delta-dominate period was 10 July through 24 August 2021^d. People were allowed to contribute up to 3 negative tests to the control sample^e. Abbreviations: RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

infections, and 41% of other-variant infections). Among vaccinated people, the median time between second dose administration and testing was shorter for Alpha cases (55 days; first-third quartile, 25–66 days) than other-variant cases (85 days; first-third quartile, 54–127 days) and Delta cases (135 days; first-third quartile, 110–169 days; *Table 1*).

Vaccine Effectiveness Against WGS-Classified SARS-CoV-2 Outcomes

The effectiveness of primary mRNA vaccination 14–89 days after second dose administration was 84.4% (95% confidence Interval [CI], 75.6%–90.0%) and 68.9% (95% CI, 58.0%–77.1%) against Alpha and Delta infection, respectively, and 85.5% (95% CI, 65.5%–93.9%) and 85.4% (95% CI, 60.2%–94.6%) against Alpha- and Delta-associated hospitalizations, respectively (*Figure 3A* and *3C*). The effectiveness of primary vaccination did not differ between Alpha-, Delta-, and other-variant classified infections for people who received their second dose <14 days prior to testing. However, the level of protection offered against Alpha infection was significantly higher than that offered against Delta infection for people who received their second dose 14–89 days prior to testing (*P* value = .013). Only 1 Alpha infection was recorded among people vaccinated ≥90 days prior to testing and we were unable to reliably compare the level of protection ≥90 days after second dose receipt. The level of protection offered against other-

variant infection was lower than against Alpha infection and higher than Delta infection but was not significantly different from either. The level of protection did not vary significantly by variant for symptomatic infection or COVID-19-associated hospitalization (*Figure 3B* and *3C*).

Duration of Protection From Primary Vaccination

The odds of Delta infection and symptomatic infection were significantly higher 90–149 and ≥150 days after second dose administration than 14–89 days after administration (*Table 2*). However, the odds of Delta-associated hospitalization, as well as Alpha and other-variant infection, symptomatic infection, or COVID-19-associated hospitalization, did not increase significantly. The precision around these estimates was, however, low.

Calendar Period-Classified, Variant-Specific Vaccine Effectiveness

A total of 6200 cases and 168,248 controls were collected during the Alpha-predominant period (1 April to 28 May 2021). During the Delta-predominant period (27 June to 24 August 2021), 3882 cases and 128,926 controls were collected (*Figure 2*). Cases collected during the variant-predominant periods were similar to sequenced cases with respect to demographic and clinical factors. However, the median time between second dose receipt and calendar-period-classified

Table 1. Characteristics of SARS-CoV-2 RT-PCR Tests Analyzed Between 1 April 2021 and 24 August 2021 and Included as Cases or Controls

Characteristic	Sequenced Cases				
	Control ^a (n = 343727)	Case ^a (n = 10349)	Alpha ^b (n = 404)	Delta ^b (n = 1345)	Other ^b (n = 280)
Age, y, median (p25–p75)	48 (31–65)	40 (28–55)	38 (27–54)	41 (29–58)	41 (28–59)
Sex, No. (%)					
Female	201 942 (58.8)	5651 (54.6)	224 (55.4)	695 (51.7)	160 (57.1)
Male	141 785 (41.2)	4698 (45.4)	180 (44.6)	650 (48.3)	120 (42.9)
Race/ethnicity, No. (%)					
Black or African American	40 524 (11.8)	1854 (17.9)	97 (24.0)	249 (18.5)	59 (21.1)
Hispanic or Latino	44 327 (12.9)	2316 (22.4)	104 (25.7)	264 (19.6)	66 (23.6)
Other/unknown	49 575 (14.4)	1270 (12.3)	43 (10.6)	169 (12.6)	39 (13.9)
White	209 301 (60.9)	4909 (47.4)	160 (39.6)	663 (49.3)	116 (41.4)
Charlson Score, ^c median (p25–p75)	0 (0–1.00)	0 (0–1.00)	0 (0–1.00)	0 (0–1.00)	0 (0–1.00)
SVI, median (p25–p75)	0.52 (0.45–0.52)	0.52 (0.45–0.52)	0.52 (0.52–0.52)	0.52 (0.45–0.52)	0.52 (0.45–0.52)
Insurance group, No. (%)					
Uninsured	19 168 (5.6)	858 (8.3)	31 (7.7)	130 (9.7)	31 (11.1)
Medicaid	49 306 (14.3)	2559 (24.7)	135 (33.4)	279 (20.7)	60 (21.4)
Medicare	36 640 (10.7)	554 (5.4)	23 (5.7)	99 (7.4)	13 (4.6)
Other	238 613 (69.4)	6378 (61.6)	215 (53.2)	837 (62.2)	176 (62.9)
No. of nonemergent visits, ^d median (p25–p75)	1.00 (0–8.00)	0 (0–5.00)	1.00 (0–8.00)	0 (0–5.00)	1.00 (0–7.00)
Vaccination status at time of test, No. (%)					
Unvaccinated	171 149 (49.8)	7966 (77.0)	340 (84.2)	873 (64.9)	223 (79.6)
Incomplete primary vaccination (<14 d after 2nd dose)	47 505 (13.8)	988 (9.5)	41 (10.1)	59 (4.4)	28 (10.0)
Complete primary vaccination					
14–89 d after 2nd dose	63 296 (18.4)	369 (3.6)	22 (5.4)	45 (3.3)	14 (5.0)
90–149 d after 2nd dose	44 475 (12.9)	633 (6.1)	1 (0.2)	217 (16.1)	10 (3.6)
≥ 150 d after 2nd dose	17 302 (5.0)	393 (3.8)	0	151 (11.2)	5 (1.8)
Interval between 2nd dose and testing, median (p25–p75)	83 (45–121)	115 (78–152)	55 (25–66)	135 (110–169)	85 (54–127)

Abbreviations: RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SVI, social vulnerability index; p25–p75, 25th to 75th percentile.

^aParticipants allowed to contribute both cases (positive RT-PCRs) and up to 3 controls (negative RT-PCRs) tests.

^bSARS-CoV-2 variants defined based on whole-genome sequencing.

^cScore as of December 2020.

^dNumber of nonemergent visits in the year prior to the vaccination period within Yale New Haven Health System (2 December 2019 to 1 December 2020).

Alpha infections was shorter (37 days) than WGS-classified Alpha infections (55 days; *Supplementary Table 2*).

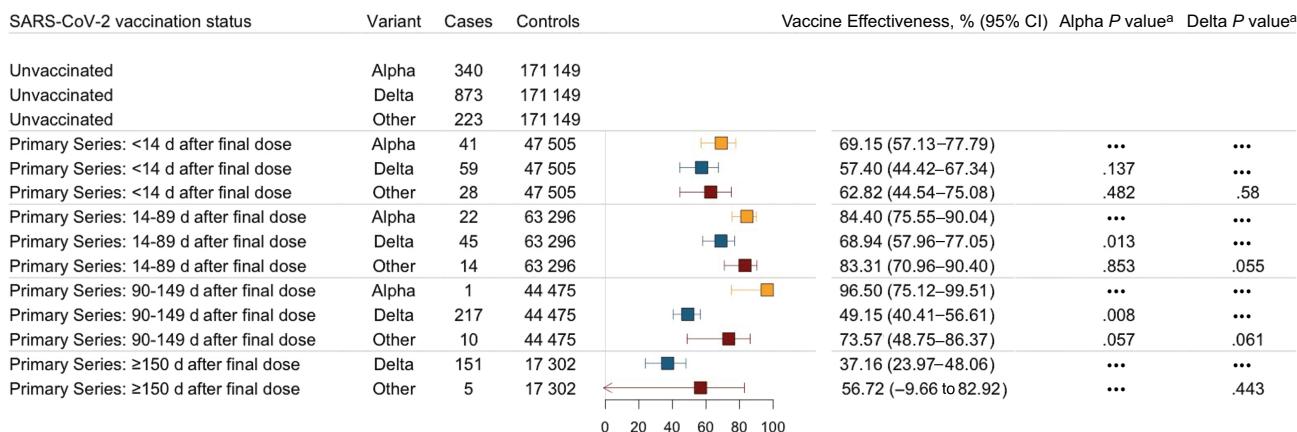
Among the samples collected during the Alpha-predominant period, 65% were Alpha, 0.9% were Delta, and 34.5% were other-variant. Conversely, during the Delta period, 95% of sequenced samples were Delta (*Supplementary Table 3*). The effectiveness of primary vaccination 14–89 days after second dose administration was 88.2% (95% CI, 86.3%–89.8%) and 64.6% (95% CI, 58.0%–70.1%) during the period of Alpha and Delta predominance, respectively (*Figure 4*).

Sensitivity Analyses

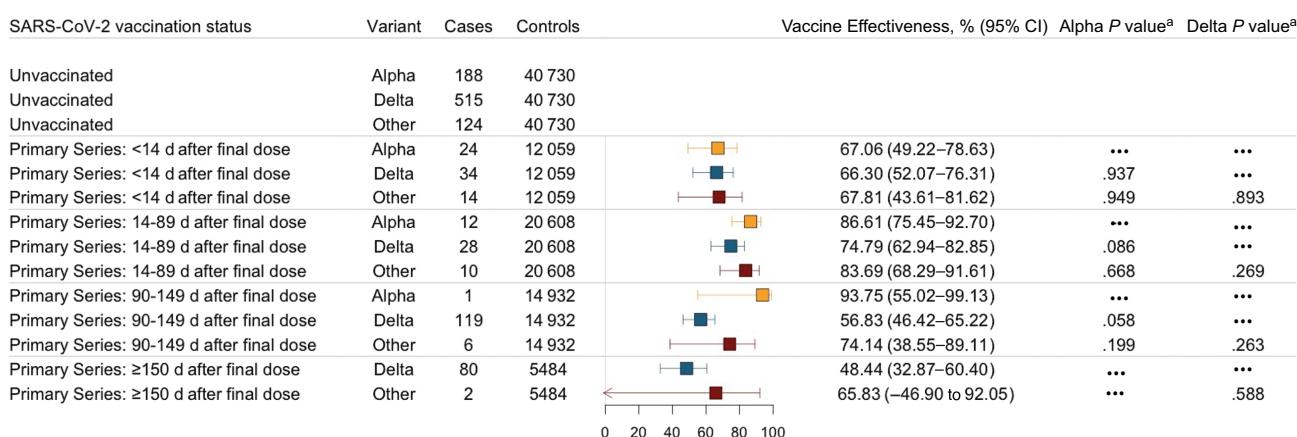
The effectiveness of primary vaccination (14–89 days after second dose administration) was 81.5%–89.9% against Alpha and 67.3%–70.4% against Delta in the sensitivity analyses (*Supplementary Figures 1–7, Supplementary Table 4*). Under each examined scenario, the level of protection ≥90 days after second dose administration was significantly higher against Alpha than against Delta. The effectiveness of vaccination

≥14 days after second dose administration was significantly higher against Alpha than Delta for all examined scenarios except when quality control was defined at 100% bases covered at 100× (*Supplementary Figure 2*). The level of protection offered against other-variant infection was higher than that offered against Delta infection for the matched and quality control defined as 50% bases covered at 100× analyses (*Supplementary Figures 1 and 3*). The effectiveness against calendar-period-classified infections were similar following the restriction to sequenced samples (14–89 days Alpha, 84.4% [95% CI, 77.1%–89.4%]; Delta, 69.3% [95% CI, 58.6%–77.2%]; *Supplementary Table 4*) as the primary analysis (14–89 days Alpha, 88.2% [95% CI, 86.3%–89.8%]; Delta, 64.6% [95% CI, 58.0%–70.1%]; *Figure 4*). When we further stratified time since vaccination from 14–89 days to 14–59 days and 60–89 days after second dose, we continued to observe significant differences in the level of protection offered against Alpha and Delta infections (14–59 days *P* value, .049; 60–89 days *P* value, .017; *Supplementary Figure 8*).

A Vaccine Effectiveness Against SARS-CoV-2 Infection



B Vaccine Effectiveness Against Symptomatic SARS-CoV-2 Infection



C Vaccine Effectiveness Against COVID-19 Associated Hospitalization

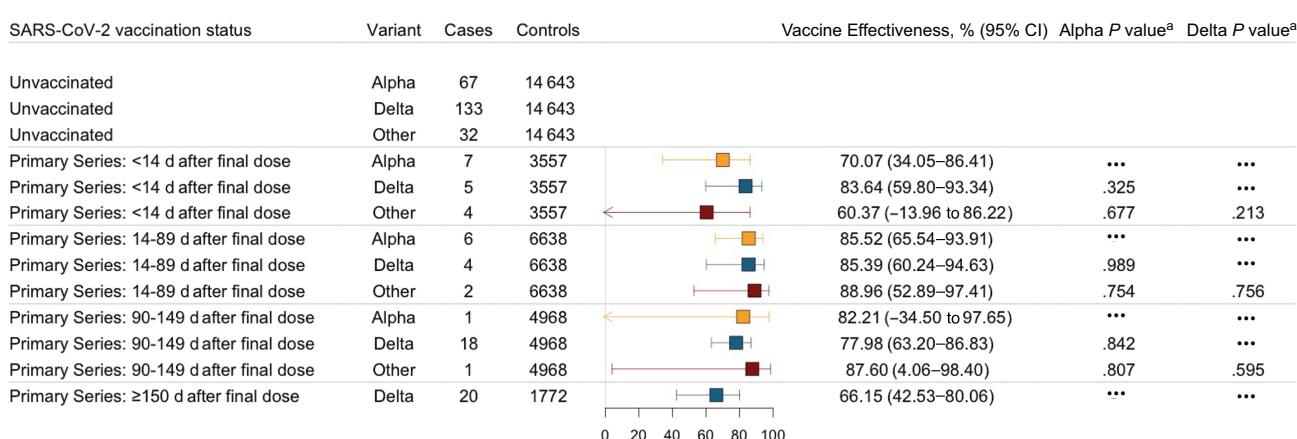


Figure 3. Forest plot of mRNA vaccine effectiveness against whole-genome-sequence-classified Alpha, Delta, and other-variant SARS-CoV-2 infection, symptomatic infection, and COVID-19-associated hospitalization identified at the Yale New Haven Hospital system between 1 April 2021 and 24 August 2021. The effectiveness of primary mRNA vaccination against variant-defined (A) SARS-CoV-2 infection, (B) symptomatic infection, and (C) COVID-19-associated hospitalization. A, SARS-CoV-2 infection was defined as a RT-PCR-positive, sequenced viral RNA samples collected among a vaccine-eligible persons (≥ 16 years old at testing) and passed quality control ($\geq 65\%$ bases covered at $100\times$). B, Symptomatic infection was defined as a SARS-CoV-2 infection collected within 12 days of a record of COVID-19 symptoms (captured using a natural language processor). C, COVID-19-associated hospitalization was defined as a symptomatic infection that was collected within the 21 days prior to 3 days after hospitalization. Cases were defined as Alpha, Delta, and other-variant based on whole-genome sequencing. The other-variant classification incorporated all non-Alpha/Delta infections. Rows containing no cases were omitted.^aThe levels of protection offered against the examined variants were compared and significance was defined with an α of .05. Error bars display the 95% confidence intervals. Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2. Risk of Variant-Specific SARS-CoV-2 Infection Among Vaccinated People, According to Time After Receiving a Second Primary Vaccine Dose

Vaccine Status at Testing	Case No.	Control No.	Alpha			Delta			Other Variant		
			Odds Ratio (95% Confidence Intervals) ^a	P Value ^a	Case	Odds Ratio (95% Confidence Intervals) ^a	P Value ^a	Case	Odds Ratio (95% Confidence Intervals) ^a	P Value ^a	
SARS-CoV-2 infection											
14–89 d after 2nd dose	22	63 296	45	63 296	14	63 296	...
90–149 d after 2nd dose	1	44 475	0.22 (0.03–1.65)	.141	217	44 475	1.64 (1.18–2.28)	.003	10	44 475	1.58 (0.69–3.62)
≥150 d after 2nd dose	0	17 302	0.00 (0.00–Infinity)	.940	151	17 302	2.04 (1.44–2.88)	.000	5	17 302	2.59 (0.90–7.47)
Symptomatic SARS-CoV-2 infection											
14–89 d after 2nd dose	12	20 608	28	20 608	10	20 608	...
90–149 d after 2nd dose	1	14 932	0.47 (0.06–3.65)	.471	119	14 932	1.71 (1.12–2.61)	.013	6	14 932	1.59 (0.56–4.48)
≥150 d after 2nd dose	0	5484	0.00 (0.00–Infinity)	.964	80	5484	2.02 (1.29–3.18)	.002	2	5484	2.09 (0.43–10.12)
COVID-19 hospital admission											
14–89 d after 2nd dose	6	6638	4	6638	2	6638	...
90–149 d after 2nd dose	1	4968	1.14 (0.13–9.88)	.903	18	4968	1.53 (0.51–4.57)	.449	1	4968	1.11 (0.10–12.88)
≥150 d after 2nd dose	0	1772	0.00 (0.00–Infinity)	1.000	20	1772	2.47 (0.81–7.52)	.111	0	1772	0.00 (0.00–Inf)

^aAdjusted for date of test, age (in years), sex, race/ethnicity, insurance, comorbidity (Charlson Score), social vulnerability index of zip code, presence of prior infection, county, and number of nonemergent visits during the year prior to vaccine rollout in Connecticut (2 December 2019 and 1 December 2020).

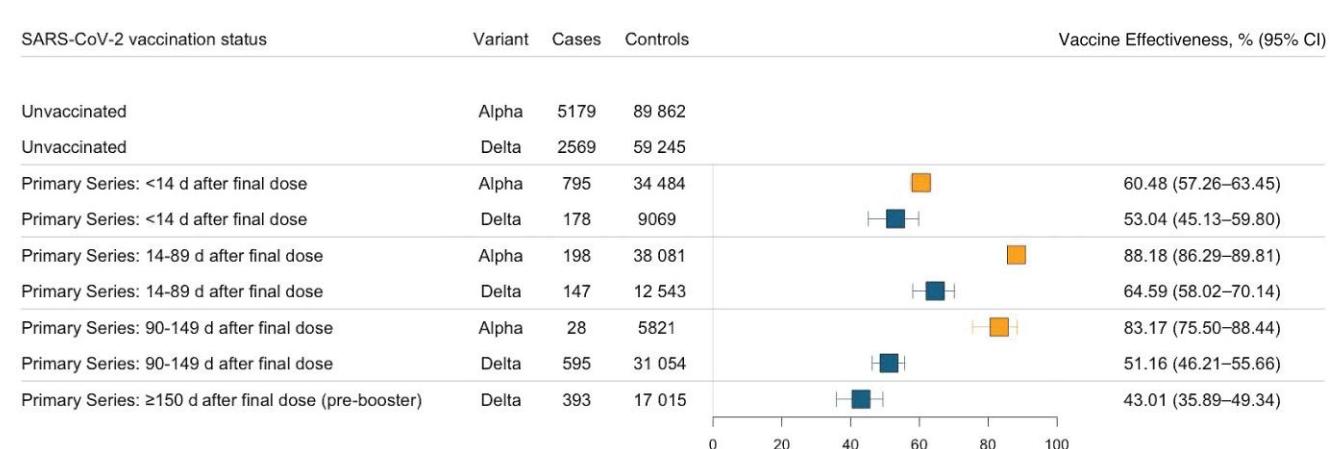


Figure 4. Forest plot of mRNA vaccine effectiveness against calendar-period-classified Alpha, Delta, and other-variant SARS-CoV-2 infection identified at the Yale New Haven Hospital system between 1 April 2021 and 24 August 2021. The effectiveness of primary mRNA vaccination against variant-defined SARS-CoV-2 infection. Infection was defined as a RT-PCR-positive samples collected among a vaccine-eligible persons (≥ 16 years old at testing). Infections were classified based on periods of variant predominance ($\geq 50\%$ of Connecticut samples deposited in GISAID). The Alpha-dominate period was 1 April through 28 May 2021 and the Delta dominate period was 10 July through 24 August 2021. Error bars display the 95% confidence intervals. Abbreviations: CI, confidence interval; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

DISCUSSION

In this retrospective analysis, we estimated the effectiveness of primary mRNA COVID-19 vaccination against WGS-classified, variant-specific SARS-CoV-2 infection, symptomatic infection, and COVID-19-associated hospitalization. We found that mRNA COVID-19 vaccines provided less protection against Delta infection than Alpha infection and that the level of protection offered against Delta infection declined significantly over time since vaccine administration. However, we did not observe a significant difference in the level of protection offered against variant-specific symptomatic infection or hospitalization.

These findings build upon existing literature suggesting that the increase in SARS-CoV-2 cases among vaccinated people during the Delta wave of fall 2021 was the result of variant-specific immune evasion and waning levels of vaccine protection [3–5, 10–17, 35–39]. However, while there is ample evidence of both phenomena during the Delta period [3–5, 10–17, 35–39], few studies have disentangled the 2 processes [3–5, 10–17, 35–39]. Furthermore, even when their cooccurrence was reported, the authors have typically concluded that 1 of the 2 phenomena was the primary driver of the reduced effectiveness [13, 14, 16]. In contrast, we, in alignment with Britton et al, observed strong evidence for both declining levels of protection and variant-specific immune evasion [18].

While many factors likely contribute to the variability of vaccine effectiveness estimates in the literature, differences in variant classification methodology are a potential component [40]. To examine how the vaccine effectiveness estimates from calendar-period-based variant classifications compares to WGS, we estimated the effectiveness of primary vaccination against Alpha and Delta cases defined by periods of variant predominance. We found that estimates of vaccine effectiveness against SARS-CoV-2 infection during periods of Alpha and Delta predominant were similar to those estimated using WGS.

These findings are not surprising. While there was a high degree (35% of sequenced samples) of misclassification during the Alpha-predominance period, effectiveness against Alpha and other-variant (the major variant category cocirculating during the Alpha-predominant period) infection did not vary significantly in the WGS analysis. Thus, we would not expect that this degree of misclassification would significantly alter vaccine effectiveness estimates. However, this finding is unlikely to hold under situations with similarly large amounts of misclassification and underlying differences in variant-specific vaccine effectiveness.

Unlike Alpha, data from the WGS analysis suggests that the effectiveness against Delta infection compared to other-variant infections may differ (differed significantly for multiple sensitivity analyses but not primary analysis). As a result, a large amount of variant misclassification during the Delta predominant period may impact vaccine effectiveness estimates.

However, Delta rapidly became the predominant variant accounting for 50% of samples from Connecticut in GISAID on 27 June 2021, 75% on 10 July 2021, and 100% on 6 September 2021 [27, 28]. It is, thus, unsurprising that the period-classified vaccine effectiveness estimates mirrored the WGS-classified estimates.

These findings suggest that, even when the effectiveness of the variants is expected to differ, calendar-period-based variant classification may yield reliable estimates, when there is limited superimposition of variant waves and the proportion of misclassified cases is expected to be low. However, under scenarios when variants or subvariants are cocirculating, as is the case with the Omicron subvariants, calendar-period-based classification provides limited utility. Not only would subvariant calendar-period-based classification result in meaningful amounts of misclassification, but it also prevents researchers from comparing the effectiveness of variants as they cocirculate. As a result, the need for WGS in future vaccine effectiveness and severity analysis has only increased.

Our study was subject to several limitations. First, specimens available for sequencing were limited. However, the storage and sequencing of specimens was considered random and, while it reduced our power, this restriction was unlikely to have introduced bias. Furthermore, our sensitivity analysis limiting the calendar-period-classified infections to sequenced samples mirrored the main analysis. Second, to classify variants using WGS we had to exclude cases that did not meet our quality control definition. While this further reduced our sample, we show that this restriction was unlikely the driver of our results in sensitivity analyses. Third, sequenced samples have lower cycle threshold values than those for which sequencing is unsuccessful. For this reason, the vaccine effectiveness estimates against infection may be biased towards more severe illness, which in turn may impact the generalizability of our findings. Fourth, due to a limited number of Alpha infections ≥ 90 days after second dose receipt ($n = 1$), we were unable to reliably estimate the level of protection after 89 days or examine waning levels of protection against Alpha infection. Fifth, our calendar-period-based classification relied on samples deposited within GISAID, which may be biased [41]. Additionally, residual waning within our vaccination categories may exist. Given that the median time to testing differed between Alpha and Delta cases (Table 1), such waning could be driving the observed difference in protection against Alpha and Delta infection. However, when we further stratified our first fully vaccinated category from 14–89 days to 14–59 days and 60–89 days after the second dose, we continued to see a significant difference in the levels of protection (Supplementary Figure 8). Finally, we had few to no Alpha outcomes for the ≥ 90 days after second dose administration categories and were unable to provide reliable estimates.

CONCLUSION

In this study, the use of WGS revealed differences in variant-specific COVID-19 vaccine effectiveness, with the effectiveness of primary mRNA vaccination against Delta infection being significantly lower than that against Alpha infection. However, the effectiveness of vaccination was found to be moderate against symptomatic COVID-19 and high against COVID-19-associated hospitalization regardless of variant. Although we observed broad agreement between estimates of variant-specific vaccine effectiveness when WGS and calendar-period were used to define Alpha and Delta variants, there was a significant degree of misclassification associated with calendar-period classifications, which may limit its application in future SARS-CoV-2 epidemic waves and in settings with heterogeneity in variant-specific vaccine effectiveness.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copy-edited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. M. L. L., M. D. T. H., W. S., A. I. K., D. A. T. C., J. D. H., S. M., and A. C. contributed to the concept and design. M. L. L., F. W., A. C., C. D., and D. F. performed acquisition and interpretation of data. M. L. L., M. D. T. H., S. M., A. C., and A. I. K. drafted the manuscript. M. L. L. performed statistical analysis. C. D. and R. B. contributed administrative, technical, or material support. A. I. K., M. D. T. H., W. S., D. A. T. C., and J. D. H. contributed supervision. All authors performed critical revision of the results and of the manuscript for important intellectual content. M. L. L., A. I. K., and W. S. have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Potential conflicts of interest. A. I. K. serves as an expert panel member for Reckitt Global Hygiene Institute, scientific advisory board member for Revelar Biotherapeutics, and a

consultant for Tata Medical and Diagnostics and Regeneron Pharmaceuticals; and has received grants from Merck, Regeneron Pharmaceuticals, and Tata Medical and Diagnostics for research related to COVID-19. W. L. S. was an investigator for a research agreement, through Yale University, from the Shenzhen Center for Health Information for work to advance intelligent disease prevention and health promotion; collaborates with the National Center for Cardiovascular Diseases in Beijing; is a technical consultant to Hugo Health, a personal health information platform; co-founder of Refactor Health, an AI-augmented data management platform for health care; and has received grants from Merck and Regeneron Pharmaceutical for research related to COVID-19. J. D. H., R. C., S. M., D. F., S. H., and A. Z. are employees and shareholders of Regeneron Pharmaceuticals, Inc. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Data use agreement. Data cannot be shared publicly because of the presence of potentially identifiable health information. Requests for access can be directed to the corresponding author and Yale Human Research Protection Program (hrpp@yale.edu).

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CONFIDENCE IN DOVATO ACROSS TREATMENT SETTINGS⁴⁻⁹

Treatment-naïve resistance rates, with up to **3 years of evidence**⁵⁻⁷

0 %
(n=0/1,885)*⁴
REAL-WORLD EVIDENCE

0.1 %
(n=1/953)*^{1,2,5,6}
RANDOMISED CONTROLLED TRIALS

Treatment-experienced resistance rates, with up to **5 years of evidence**¹⁻³

0.03 %
(n=10/35,888)*⁴
REAL-WORLD EVIDENCE

0 %
(n=0/615)^{1,2,4,8,9}
RANDOMISED CONTROLLED TRIALS

>300,000 PEOPLE LIVING WITH HIV HAVE BEEN TREATED WITH DOVATO GLOBALLY¹⁰

DOVATO is supported by a wealth of evidence, with the outcomes of **>40,000** people living with HIV captured within clinical trials and real-world evidence, including those with:^{4-9,11,12}



NO PRIOR TREATMENT EXPERIENCE¹³



NO BASELINE RESISTANCE TESTING¹³

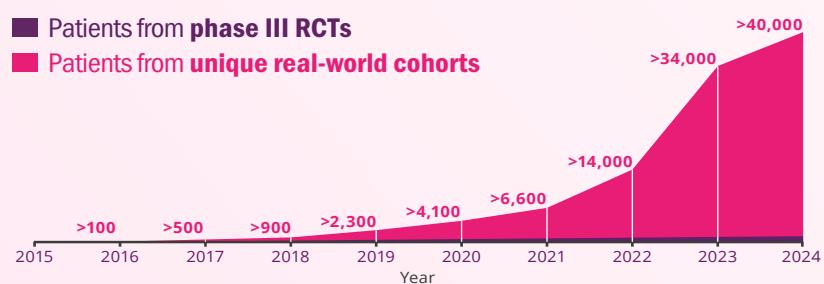


HIGH BASELINE VIRAL LOAD
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ABBREVIATIONS

3TC, lamivudine; CD4, cluster of differentiation 4; DTG, dolutegravir; FDA, United States Food and Drug Administration; FTC, emtricitabine; HIV, human immunodeficiency virus; ITT-E, intention-to-treat exposed; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; RCT, randomised controlled trial; RNA, ribonucleic acid; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; XTC, emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).⁵⁻⁷

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤50,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).¹³

‡STAT is a phase IIIB, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.⁸

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/ml at Week 48.⁷ Results at week 24 of the study.

|| The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).^{8,9}

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).^{8,13}

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).⁹