Post-vaccination SARS-CoV-2 infections and incidence of presumptive B.1.427/B.1.429 variant among healthcare personnel at a northern California academic medical center

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Summary: In this retrospective report, 189 of 660 SARS-CoV-2 cases detected in healthcare personnel at an academic medical center occurred post-vaccination. Incidence of the L452R mutation, consistent with the B.1.427/B.1.429 variant of concern, did not vary by vaccination status.

Abstract

Background:

Although mRNA-based SARS-CoV-2 vaccines report ≥90% efficacy, breakthrough infections occur. Little is known about the effectiveness of these vaccines against SARS-CoV-2 variants, including the highly-prevalent B.1.427/B.1.429 variant in California..

Methods:

In this quality improvement project, we collected demographic and clinical information from post-vaccine SARS-CoV-2 cases (PVSCs), defined as health care personnel (HCP) with positive SARS-CoV-2 NAAT after receiving ≥1 vaccine dose. Available specimens were tested for L452R, N501Y and E484K mutations by RT-PCR. Mutation prevalence was compared among unvaccinated, early post-vaccinated (<=14 days after dose 1), partially vaccinated (positive test >14 days after dose 1 and ≤14 days after dose 2) and fully vaccinated (>14 days after dose 2) PVSCs.

Results:

From December 2020-April 2021, >=23,090 HCPS received at least 1 dose of an mRNA-based SARS-CoV-2 vaccine, and 660 HCP cases of SARS-CoV-2 occurred of which 189 were PVSCs. Among the PVSCs, 114 (60.3%), 49 (25.9%) and 26 (13.8%) were early post-vaccination, partially vaccinated, and fully vaccinated, respectively. Of 261 available samples from vaccinated and unvaccinated HCP, 103 (39.5%), including 42 PVSCs (36.5%), had L452R mutation presumed to be B.1.427/B.1.429,. When adjusted for community prevalence of B.1.427/B.1.429, PVSCs did not have significantly elevated risk for infection with B.1.427/B.1.429 compared with unvaccinated HCP.

Conclusions:

Most PVSCs occurred prior to expected onset of full, vaccine-derived immunity. Presumptive B.1.427/B.1.429 was not more prevalent in post-vaccine cases than in unvaccinated SARS-CoV-2 HCP. Continued infection control measures, particularly ≤14 days post-vaccination, and continued variant surveillance in PVSCs is imperative to control future SARS-CoV-2 surges.

Keywords: post-vaccination SARS-CoV-2, post-vaccination COVID-19, B.1.427/B.1.429, L452R, SARS-CoV-2 variant

Introduction

SARS-CoV-2 has infected 120 million people worldwide, causing at least 2.6 million deaths since December 2019.(1) mRNA-based vaccines developed by Pfizer and Moderna obtained emergency use authorization approval in the United States in December 2020. Vaccine administration to elderly individuals, healthcare workers and other first responders began shortly thereafter. In clinical trials and observational studies after vaccine rollout, both mRNA vaccines proved effective in preventing symptomatic and severe disease.(2-4) In clinical trials, the vaccines demonstrated 52-95% efficacy against symptomatic disease 14 days after the first dose, and 95% efficacy seven days after the second dose.(3, 4) Early observational reports in vaccinated health care personnel suggest 80% effectiveness >14 days after first dose and 90% >14 days after second dose.(5-7) Emerging evidence indicates that the vaccines may also prevent asymptomatic infection(8), a potential source of transmission.

Concerns about emergence of SARS-CoV-2 variants, including variants first reported in the UK (B.1.1.7), South Africa (B.1.351), Brazil (P.1), California (B.1.427/B.1.429), and India (B.1.617)(9, 10), have dampened hopes for a rapid end to the COVID-19 pandemic through vaccination. The B.1.427/B.1.429 variant, which carries a L452R substitution mutation in the spike protein(11), was first detected in the spring of 2020 and by January 2021 accounted for 35-50% of all SARS-CoV-2 cases detected in California.(9, 12) Studies indicate reduced neutralizing activity of naturally-, vaccine-acquired and monoclonal antibodies against these variants including B.1.427/B.1.429(13-18), and possibly increased transmissibility(11, 19) and virulence. Humoral immunity, however, is not the only factor in determining protection against infection(20) and more real-world data is needed to determine effectiveness of the available SARS-CoV-2 vaccines against SARS-CoV-2 and its variants.

Stanford Health Care (SHC) began vaccinating healthcare personnel (HCP) against SARS-CoV-2 on December 18, 2020, during a surge in COVID-19 cases when the B.1.427/B.1.429 variant was rapidly spreading.(9) We performed a retrospective, quality-improvement project of post-vaccine SARS-CoV-2 cases (PVSCs) to help inform infection control recommendations for vaccinated HCP. Our aims were to: 1) define and characterize post-vaccine SARS-CoV-2 infections in HCP, 2) evaluate our HCP vaccination program, and 3) determine the role of variants in causing PVSCs.

Methods

On December 18, 2020, SHC began vaccinating HCP with Pfizer mRNA SARS-CoV-2 vaccine, initially to patient-facing frontline HCP in high acuity settings, expanding to all patient-facing frontline HCP on December 28, and finally to all health system employees beginning January 8, 2021. Moderna mRNA vaccine was available as of January 22, 2021. All HCP were required to self-monitor for COVID-related symptoms and attest to the absence of those symptoms every day when they entered the medical campus using a mandatory digital application. If any symptoms were reported, HCP underwent testing through Occupational Health. Asymptomatic HCP with high risk occupational or community exposures (e.g. household contacts, part of contact tracing effort after a work-related exposure) also were tested by Occupational Health. In addition, all HCP working on campus were strongly encouraged to participate in voluntary weekly asymptomatic testing using self-collected swabs that were processed using the Color platform.(21) HCPs tested at non-SHC facilities were required to report any positive tests to Occupational Health.

Data Collection

Post-vaccine SARS-CoV-2 cases (PVSCs) were defined as individuals identified by occupational health case notification and chart extraction with a positive SARS-CoV-2 nucleic acid amplification testing (NAAT) after receiving at least one dose of a SARS-CoV-2 vaccine. Initial respiratory SARS-CoV-2 NAAT was conducted on a variety of platforms(22-24) including: 1) a previously-described laboratory-developed reverse transcription quantitative polymerase chain reaction (RT-qPCR) targeting the envelope gene (*E* gene) on the Rotor-Gene Q (Qiagen, Germantown, MD); 2) a laboratory-developed RT-qPCR assay utilizing a PerkinElmer kit targeting the ORF1ab and nucleocapsid gene ([*N* gene] PerkinElmer, San Jose, CA); 3) Panther Fusion SARS-CoV-2 (Hologic, Marlborough, MA), a high-throughput RT-qPCR method targeting open reading frame 1ab (ORF1ab); 4) Aptima SARS-CoV-2 (Panther System, Hologic), a transcription mediated amplification method targeting ORF1ab; 5) GeneXpert Xpress SARS-CoV-2 (Cepheid, Sunnyvale, CA), a rapid RT-qPCR method targeting both *E* and *N* genes; 6) cobas Liat SARS-CoV-2 & Influenza A/B (Roche, Indianapolis, IN), a point-of-care RT-PCR method targeting ORF1ab and *N* gene; 7) e-Plex SARS-CoV-2 (Genmark, Carlsbad, CA), a rapid RT-PCR method targeting the *N* gene. Screening tests performed on at Color used a SARS-CoV-2 RT-LAMP Diagnostic Assay.(21)

All HCP with positive SARS-CoV-2 tests were contacted within 24 hours of their result by an Occupational Health provider who documented demographic information as well as presence and date of onset of COVID-19 symptoms in a standardized note. For PVSCs, data collected also included dates of reported vaccine doses, household exposures to SARS-CoV-2, previous history of a COVID-19 diagnosis prior to vaccination, and immunocompromising conditions or medications.

Between December 1, 2020 and February 28, 2021 all available specimens testing positive for SARS-CoV-2 by NAAT with RT-qPCR cycle threshold (C_t) ≤ 30 or transcription-mediated amplification relative light units (RLU) ≥ 1,100 were subject to multiplex allele-specific genotyping RT-qPCR targeting three spike mutations associated with known variants of concern, including N501Y (B.1.1.7, B.1.351, P.1), E484K (B.1.351, P.1), and L452R (B.1.427/B.1.429).(25) The screening threshold was changed to C_t ≤ 34 for specimens collected after February 28th.

Weekly variant prevalence from positive samples in the surrounding community was provided to us by the Stanford Clinical Virology Laboratory, which serves patients throughout the Bay Area and surrounding locales.

Available samples underwent SARS-CoV-2 whole-genome amplicon-based sequencing as previously described.(25) In brief, long range PCR was used for target enrichment, followed by NEBNext library preparation (New England BioLabs, Ipswich, MA), and single-end 150-cycle sequencing on an Illumina MiSeq using MiSeq reagent kit V3 (Illumina, San Diego, CA). Whole-genome sequences with at least 90% genome coverage to a depth of at least 10 reads were accepted. Mutation calling required a depth of at least 12 reads with a minimum variant frequency of 20%. Genomes were assembled using NCBI NC_045512.2 as reference, and pangolin was used for PANGO lineage assignment.(26)

Data collection for this quality improvement project was approved by hospital privacy compliance and deemed to not be human subjects research by the Stanford University School of Medicine Panel on Human Subjects in Medical Research.

Exposures and outcomes

The primary exposure was vaccination status at time of positive test, defined as unvaccinated, early post-vaccination (positive test ≤14 days after first vaccine dose), partially vaccinated (positive test >14 days after first vaccine dose to ≤14 days after the second vaccine dose), and fully vaccinated (positive test >14 days after second vaccine dose).

The primary outcome was the presence of isolated L452R mutation consistent with presumptive B.1.427/B.1.429.(27) If no L452R, N501Y, or E484K mutations were identified, the infection was designated as wild-type SARS-CoV-2.

Statistical analysis

Statistical analyses were performed in SPSS Version 27. Chi square, Fisher's exact test, independent samples T tests, and a modified Poisson regression model (log-Poisson generalized linear model with robust standard errors)(28) was used to compare individuals with and without presumptive B.1.427/B.1.429 by vaccination status while adjusting for variant prevalence in the general population.

Results

Of approximately 30,000 eligibile HCPs, at least 23,090 received >=1 dose of the Pfizer (n=20,559) or Moderna (n=2,170) vaccines and at least 22,271 completed the 2-shot series between December 18, 2020 and April 2, 2021. In that same period, 51,638 SARS-CoV-2 NAATs were performed among 15,103 HCPs within the SHC system; 15,759 of these tests were performed by Occupational Health and 35,879 through the Color screening platform,

with 6,029 individuals testing once, 2,587 testing twice and 6,487 testing three or more times.

Between December 18, 2020 to April 2, 2021, Occupational Health identified 660 HCPs with SARS-CoV-2 (Table 1), 189 of whom were PVSCs (<1% of HCPs who received at least one dose of vaccine). Of these 189 PVSCs, 173 (91.5%) received at least one dose of the Pfizer and 15 (7.9%) the Moderna vaccine; one PVSC vaccinated outside of the SHC system had no documentation of vaccine brand (Table 2).

The median age of PVSCs was 38 years (IQR 32-48) and 125 (66.1%) were female; 42 (22.2%) were nurses (Table 2). Few individuals had immunocompromising conditions (n=7, 3.7%). Seventy-six (41.8%) reported a household contact with SARS-CoV-2 infection at the time of their positive NAAT.

The majority (n=114, 60.3%) of PVSCs occurred early post-vaccination (Figure 1A); 49 (25.9%) occurred while partially vaccinated, and 26 (13.8%) occurred in the fully vaccinated (Figure 1B). Of the 183 PVSCs, 157 (85.8%) experienced symptoms and 151 reported date of symptom onset; of these, 104 (68.9%) developed symptoms in the early post-vaccination period within 14 days of the first dose.

The majority of PVSCs (n=140, 74.1%) received their first vaccine in December 2020 with the greatest number vaccinated on December 22-23, 2020 (n=46, 24.3%), corresponding with the highest daily administration of vaccines (1940 doses given on 12/22/20 and 1934 given on 12/23/20). Of the PVSCs vaccinated on these dates, 21 (45.7%) tested positive

>14 days after their vaccination. The majority of positive tests in PVSCs occurred in December 2020 and early January 2021, when most PVSCs were ≤14 days from their first vaccine dose, coincident with the winter surge in COVID-19 in northern California. The B.1.427/B.1.429 variant rose in prevalence from representing 24.8%% of SARS-CoV-2 cases detected by Stanford laboratory in December 2020 to 62.5% of cases by March 2021.(27)

Symptoms in the 157 symptomatic PVSC's began a median of 8 days (IQR 3-18 days) after the first vaccination dose. Eighteen PVSCs developed symptoms of COVID-19 prior to or on the day of their first vaccine dose. Two PVSCs—both of whom tested positive <14 days after their first vaccine dose—were hospitalized with wild-type virus; there were no deaths. Of the 26 patients with no symptoms, 7 PVSCs (26.9%) had at least one repeat negative NAAT within 48 hours of their positive test. PVSCs who reported symptoms of COVID-19 had lower mean C_t value (24.2 vs 30.9, p=0.011) than those without symptoms but did not differ in terms of age (40.7 vs 40.3 years, p=0.879) or time from first vaccine dose to positive test (19.3 vs 21.8 days, p=0.572).

Four PVSCs (2.2%) had previous documentation of SARS-CoV-2 infection between 22-98 days before their vaccinations; two of these reported new onset of symptoms at the time of their positive post-vaccination test. Two of the four with prior infections had specimens available for mutation screening, and neither had evidence of a variant of concern.

Of the seven immunocompromised PVSCs, three were positive for SARS-CoV-2 early post-vaccination, two were partially vaccinated, and two were fully vaccinated; six were symptomatic and none required hospitalization.

Partially and fully vaccinated PVSCs had higher mean C_t values than unvaccinated or early post vaccination individuals (27.9 vs 22.9, p<0.001, of n=283 individuals with known C_t value) and were older (mean age 42.3 versus 36.8, p<0.001)(Table 3).

Tests for novel variant-associated mutations were performed on samples from 261 infected HCPs including 115 PVSCs (Table 1). Sixteen HCPs (6.1%) were found to have N501Y mutation, including two partially and one fully vaccinated PVSCs. Three E484K mutations were found in unvaccinated individuals. Samples with isolated L452R mutations, presumed to be B.1.427/B.1.429 lineage, were found in 103 (39.5%) HCP samples including 42 (36.5%) of PVSCs.

In unadjusted analysis, PVSCs infected with L452R-containing viruses were more likely than those with no identified mutations to have tested positive after the second vaccine dose, or to be partially- or fully-vaccinated at time of positive test (Table 2); this variant was not associated with age, gender, job role, brand of vaccine received, immunocompromised status, or symptomatic infection. In multivariate analysis, when controlling for community prevalence of L452R mutation the week prior to positive test (when exposure likely occurred), vaccination status at time of positive test was not significantly associated with presumptive B.1.427/B.1.429 (Table 4).

Next generation sequencing was available for 134 infected HCPs, including 87 of the 189 PVSCs (Table 1). Of 31 individuals with L452R mutation and available sequencing results, 30 (96.8%) were confirmed to be B.1.427/B.1.429 variant and one was the B.1.617 variant (Table 5).(29)

Discussion

In this cohort of HCP at an academic medical center in Northern California, similar to other reports elsewhere (5, 6), we found that SARS-CoV2 infection post-vaccination is uncommon despite widespread community disease. We identified only 189 such cases out of a total of >23,000 vaccinated HCP.(30) Not surprisingly, most of these cases occurred in the first 2 weeks after vaccination, before immunity is expected to develop. Whether these individuals were exposed before or after their vaccine dose cannot be known, although the dates of symptom onset combined with the typical incubation period of 5-9 days(31) suggests that some early cases were acquired prior to the first vaccine dose. In contrast, 26 PVSCs occurred >14 days after the second dose, when full immunity is expected. Although >85% of PVSC infections were symptomatic, only 2 PVSCs required hospitalization; both developed symptoms and tested positive within 14 days of the first vaccine dose. These findings are consistent with other real-world reports of excellent vaccine effectiveness >14 days after the first and second doses(5, 6, 32) particularly in preventing severe disease, and highlights the need to observe strict precautions until full immunity is achieved >14 days after the second vaccine dose.

Isolated L452R mutation presumptive of infection with B.1.427/B.1.429 variant was associated with partially- and fully-vaccinated status on univariate analysis of PVSCs. This finding appears to be attributable to the timing of most vaccinations early in December and the subsequent rising prevalence of B.1.427/B.1.429 from December 2020 to March 2021, rather than to reduced vaccine effectiveness against B.1.427/B.1.429. On multivariate analysis controlling for overall community prevalence of the variant, infection with presumptive B.1.427/B.1.429 was not significantly more common in PVSCs compared with unvaccinated HCPs. Although this finding is reassuring, case numbers were small and further vigilance is warranted. Reduced in vitro neutralizing activity of naturally- and vaccine-

acquired antibodies against the B.1.427/B.1.429 compared with wild-type S protein has been reported.(11, 18) As more people become fully vaccinated, careful surveillance will be needed to determine if variants such as B.1.427/B.1.429 can escape vaccine-derived protection in vivo, and continued caution is needed especially as states begin to relax restrictions intended to curb transmission.

Higher C_t values, which correspond with lower viral load, were identified in PVSCs positive >14 days after first vaccine dose compared to unvaccinated and early post-vaccination cases, suggesting that lower levels of viral replication may afford some protection and reduction in transmissibility in people who contract SARS-CoV-2 post vaccination. This finding is consistent with reports from a mass vaccination campaign in Israel.(33) Lower C_t values were seen in PVSCs who reported symptoms consistent with COVID-19 compared with the few who remained asymptomatic.

The peak in post-vaccine positive SARS-CoV-2 cases in late December 2020 to early January 2021 corresponds with a rise in county-wide cases and HCP cases at that time. We did not find any evidence to support transmission clusters or superspreading events contributing to post-vaccination SARS-CoV-2 infections within the health care system. Although several PVSCs had been vaccinated on the same two days in December, nearly half of these infections occurred more than two weeks after vaccination, suggesting that exposure occurred sometime after the date of vaccination. Further, 41.8% reported household contacts with known SARS-CoV-2 infection at the time of their positive test, suggesting community transmission was driving these cases rather than workplace exposure; the multiple cases in late December and early January may have been related to holiday celebrations. This highlights the importance of maintaining social distancing and diligent mask wearing at work in the setting of increased prevalence of variants. Describing

the phenomenon of PVSCs in this quality improvement project has allowed us to more effectively promote these measures within our system at a time when many are tempted to loosen precautions due to "pandemic fatigue" and a sense of security after being vaccinated.

We do note several limitations in this report. We did not obtain detailed demographic and clinical information from the comparison group of unvaccinated SARS-CoV-2-infected HCP so we are unable to comment on differences in clinical course between vaccinated and unvaccinated SARS-CoV-2 positive HCP. Morevoer, we cannot state with certainty that the 26 asymptomatic PVSCs remained asymptomatic since this information was only obtained on two occasions: within 24 hours of positive test and at the end of the quarantine period. If symptoms developed in the interim period, they would not have been captured. We cannot estimate vaccine efficacy since some HCPs may not have reported infections detected outside the SHC system and, since asymptomatic screening was not required, asymptomatic and mildly symptomatic cases may have been missed. Finally, although presence of L452R mutation in the absence of N501Y and E484K has been shown to be highly correlative with B.1.427/B.1.429 by sequencing during this time period(25), these mutations are occasionally detected sporadically in non-variant of concern/interest lineages, and it is not possible to know the variant definitively in unsequenced samples. The identification of the B.1.617 variant in one sample with an L452R mutation is illustrative of the need for ongoing surveillance with sequencing in post-vaccine cases. Nevertheless, we believe our findings are an important contribution to the understanding of PVSCs in the context of rising prevalence of new SARS-CoV-2 variants.

Conclusion

Post-vaccination SARS-CoV2 infection occurred in <1% of vaccinated HCP with the great majority occurring prior to full, vaccine-derived immunity. Presumptive B.1.427/B.1.429 did not represent a significantly higher proportion of cases in vaccinated versus unvaccinated SARS-CoV-2-infected HCP, but the number of fully vaccinated PVSCs was small. Continued infection control measures in the workplace and in the community including social distancing and masking, particularly in the early days post-vaccination, as well as continued variant surveillance in PVSCs, is imperative in order to anticipate and control future surges of infection.

NOTES

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References

1. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) Baltimore, MD: Johns Hopkins University; 2021 [Available from: https://coronavirus.jhu.edu/map.html.
2. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2021;384(5):403-16.
3. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383(27):2603-15.
4. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med. 2021.
5. Keehner J, Horton LE, Pfeffer MA, Longhurst CA, Schooley RT, Currier JS, et al. SARS-CoV-2 Infection after Vaccination in Health Care Workers in California. N Engl J Med. 2021.
6. Daniel W, Nivet M, Warner J, Podolsky DK. Early Evidence of the Effect of SARS-CoV-2 Vaccine at One Medical Center. N Engl J Med. 2021.
7. Thompson MG BJ, Naleway AL, et al. . Interim Estimates of Vaccine Effectiveness of BNT162b2 and mRNA-1273 COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Health Care Personnel, First Responders, and Other Essential and Frontline Workers — Eight U.S. Locations, December 2020–March 2021. MMWR Morb Mortal Wkly Rep. 2021.
8. Tande AJ, Pollock BD, Shah ND, Farrugia G, Virk A, Swift M, et al. Impact of the COVID-19 Vaccine on Asymptomatic Infection Among Patients Undergoing Pre-Procedural COVID-19 Molecular Screening. Clin Infect Dis. 2021.
9. Zhang W, Davis BD, Chen SS, Sincuir Martinez JM, Plummer JT, Vail E. Emergence of a Novel SARS-CoV-2 Variant in Southern California. JAMA. 2021.
10. Yadav PD, Sapkal GN, Abraham P, Ella R, Deshpande G, Patil DY, et al. Neutralization of variant under investigation B.1.617 with sera of BBV152 vaccinees. Clin Infect Dis. 2021.
11. Deng X, Garcia-Knight MA, Khalid MM, Servellita V, Wang C, Morris MK, et al. Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. medRxiv. 2021.
12. Shu Y, McCauley J. GISAID: Global initiative on sharing all influenza data - from vision to reality. Euro Surveill. 2017;22(13).
13. Collier DA, De Marco A, Ferreira I, Meng B, Datir R, Walls AC, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. Nature. 2021.
14. Wibmer CK, Ayres F, Hermanus T, Madzivhandila M, Kgagudi P, Oosthuysen B, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nat Med. 2021.
15. Wang P, Wang M, Yu J, Cerutti G, Nair MS, Huang Y, et al. Increased Resistance of SARS-CoV-2 Variant P.1 to Antibody Neutralization. bioRxiv. 2021.
16. Starr TN, Greaney AJ, Dingens AS, Bloom JD. Complete map of SARS-CoV-2 RBD mutations that escape the monoclonal antibody LY-CoV555 and its cocktail with LY-CoV016. bioRxiv. 2021.
17. Li Q, Wu J, Nie J, Zhang L, Hao H, Liu S, et al. The Impact of Mutations in SARS-CoV-2 Spike on Viral Infectivity and Antigenicity. Cell. 2020;182(5):1284-94 e9.
18. McCallum M, Bassi J, Marco A, Chen A, Walls AC, Iulio JD, et al. SARS-CoV-2 immune evasion by variant B.1.427/B.1.429. bioRxiv. 2021.

19. Peng J, Mann SA, Mitchell AM, Liu J, Laurie MT, Sunshine S, et al. Estimation of secondary household attack rates for emergent SARS-CoV-2 variants detected by genomic surveillance at a community-based testing site in San Francisco. medRxiv. 2021.
20. Tarke A, Sidney J, Methot N, Zhang Y, Dan JM, Goodwin B, et al. Negligible impact of SARS-CoV-2 variants on CD4 (+) and CD8 (+) T cell reactivity in COVID-19 exposed donors and vaccinees. bioRxiv. 2021.
21. SARS-CoV-2 LAMP Diagnostic Assay Burlingame, CA: Color; [updated May 21, 2020. Version 1.2:[Available from: https://www.color.com/wp-content/uploads/2020/05/Color-LAMP-Diagnostic-Assay_v1-2_Updated-052120.pdf.
22. Bulterys PL, Garamani N, Stevens B, Sahoo MK, Huang C, Hogan CA, et al. Comparison of a laboratory-developed test targeting the envelope gene with three nucleic acid amplification tests for detection of SARS-CoV-2. J Clin Virol. 2020;129:104427.
23. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020;25(3).
24. Hogan CA, Sahoo MK, Pinsky BA. Sample Pooling as a Strategy to Detect Community Transmission of SARS-CoV-2. JAMA. 2020;323(19):1967-9.
25. Wang H, Miller J, Verghese M, Sibai M, Solis D, Mfuh KO, et al. Multiplex SARS-CoV-2 Genotyping PCR for Population-Level Variant Screening and Epidemiologic Surveillance. medRxiv. 2021:2021.04.20.21255480.
26. Pangolin: lineage assignment in an emerging pandemic as an epidemiological tool. [Internet]. [cited May 10, 2021]. Available from: github.com/cov-lineages/pangolin.
27. Wang H, Miller JA, Verghese M, Sibai M, Solis D, Mfuh KO, et al. Multiplex SARS-CoV-2 Genotyping PCR for Population-Level Variant Screening and Epidemiologic Surveillance. [Unpublished work]. In press 2021.
28. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702-6.
29. Verghese M, Jiang B, Iwai N, Mar M, Sahoo MK, Yamamoto F, et al. Identification of a SARS-CoV-2 Variant with L452R and E484Q Neutralization Resistance Mutations. J Clin Microbiol. 2021.
30. Novel Coronavirus (COVID-19) [Internet]. Santa Clara County Public Health. 2021 [cited 3/30/21]. Available from: https://www.sccgov.org/sites/covid19/Pages/home.aspx.
31. Alene M, Yismaw L, Assemie MA, Ketema DB, Gietaneh W, Birhan TY. Serial interval and incubation period of COVID-19: a systematic review and meta-analysis. BMC Infect Dis. 2021;21(1):257.
32. Amit S, Beni SA, Biber A, Grinberg A, Leshem E, Regev-Yochay G. Post-Vaccination COVID-19 among Healthcare Workers, Israel. Emerg Infect Dis. 2021;27(4).
33. Petter E, Mor O, Zuckerman N, Oz-Levi D, Younger A, Aran D, et al. Initial real world evidence for lower viral load of individuals who have been vaccinated by BNT162b2. medRxiv. 2021:2021.02.08.21251329.

TABLES

Table 1. SARS-CoV-2 cases among healthcare personnel, December 18, 2020 to April 2, 2021

	Total n=660	Unvaccinated n=471	Early post-vaccination n=114	Partially Vaccinated n=49	Fully Vaccinated n=26
Age (mean in years, SD)	37.5 (10.6)	36.1 (10.0)	39.8 (10.8)	44.0 (12.6)	39.1 (9.5)
Sex					
Female	461 (69.8%)	336 (71.3%)	75 (65.8%)	32 (65.3%)	18 (69.2%)
Male	199 (30.2%)	135 (28.7%)	39 (34.2%)	17 (34.7%)	8 (30.8%)
Mutation identified by RT-qPCR*					
E484K	3 (1.1%)	3 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
L452R	103 (39.5%)	61 (41.8%)	22 (29.7%)	10 (43.5%)	10 (55.6%)
N501Y	16 (6.1%)	13 (8.9%)	0 (0.0%)	2 (8.7%)	1 (5.6%)
No mutation	139 (53.3%)	69 (47.3%)	52 (70.3%)	11 (47.8%)	7 (38.9%)
PANGO Lineage**					
B.1.1.7	10 (7.5%)	8 (17.0%)	0 (0.0%)	2 (10.5%)	1 (11.1%)
B.1.427	26 (19.4%)	5 (10.6%)	13 (22.0%)	5 (26.3%)	3 (33.3%)
B.1.429	9 (6.7%)	2 (4.3%)	4 (6.8%)	1 (5.3%)	2 (22.2%)
B.1.617	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)
Not variant of concern/interest	88 (65.7%)	32 (68.0%)	42 (71.2%)	11 (57.9%)	2 (22.2%)
Ct value*** (mean, SD)	23.5 (7.6)	23.0 (7.4)	22.6 (7.0)	27.7 (8.7)	28.5 (7.4)

*Mutation analysis was performed on n=261 HCPs. Mutation analysis was not available for 149 (22.6%) who were tested outside the SHC laboratory, 43 (6.5%) did not meet C_t or RLU value criteria, 114 (17.3%) with insufficient quantity, 6 (0.9%) that failed amplification, and 87 (13.2%) that were discarded or otherwise unavailable.

**PANGO lineage as determined by next generation sequencing (NGS) was available for n=134 samples; NGS was unavailable for n=148 HCP who were tested by Color or outside of Stanford lab, n=43 with high Ct values, n=13 samples with low TMA RLU, n=6 samples with PCR amplification failure, n=114 with insufficient quantity, and n=215 that were otherwise unavailable.

***Ct value available for n=283 samples

Table 2. Characteristics of post-vaccine SARS-CoV-2 cases among healthcare personnel

	Total N=189	No Mutation Identified (Wild-type) N=70* (62.5%)	L452R (Presumptive B.1.427/B.1.429) N=42* (37.5%)	p value
Age in years				
Mean (SD)	40.8 (11.2)	42.5 (11.6)	40.8 (10.1)	0.424
Median (IQR)	38 (32-48)			
Sex				
Male	64 (33.9%)	18 (25.7%)	13 (31.0%)	0.549
Female	125 (66.1%)	52 (74.3%)	29 (69.0%)	
Professional Role**				
Patient facing	129 (68.3%)	45 (66.2%)	31 (73.8%)	0.400
Non-patient facing	55 (29.1%)	23 (33.8%)	11 (26.2%)	
Unknown	5 (2.6%)			
Immunocompromised				
Yes	7 (3.7%)	3 (4.5%)	2 (5.4%)	
No	166 (87.8%)	63 (95.5%)	35 (94.6%)	0.846
Unknown	16 (8.5%)			
Tested positive after second vaccine dose				
Yes	39 (20.6%)	10 (14.3%)	14 (33.3%)	0.017
No	150 (79.4%)	60 (85.7%)	28 (66.7%)	
Days from dose 1 to symptom onset (n=151)[a]				
Mean (SD)	16.8 (23.3)	11.6 (17.4)[a1]	24.2 (29.0)[a2]	0.008
Median (IQR)	8 (3-18)			
Days from dose 1 to positive NAAT				
Mean (SD)	19.4 (22.0)	14.7 (17.7)	25.8 (28.0)	0.011
Median (IQR)	11 (7-22)			

Days from dose 2 to symptom onset (n=31)[b]				
Mean (SD)	30.0 (27.8)	25.0 (22.0)[b1]	36.6 (32.0)[b2]	0.350
Median (IQR)	24 (4-60)			
Days from dose 2 to positive NAAT (n=39)[c]				
Mean (SD)	31.3 (25.5)	29.6 (22.2)[c1]	35.5 (28.2)[c2]	0.573
Median (IQR)	24 (7-55)			
Vaccination status at time of positive NAAT				
Early post-vaccination	114 (60.3%)	52 (74.3%)	22 (52.4%)	0.020[†]
Partially vaccinated	49 (25.9%)	11 (15.7%)	10 (23.8%)	
Fully vaccinated	26 (13.8%)	7 (10.0%)	10 (23.8%)	
Vaccine brand				
Pfizer	173 (91.5%)	66 (94.3%)	39 (92.9%)	0.762
Moderna	15 (7.9%)	4 (5.7%)	3 (7.1%)	
Unknown	1 (0.5%)			
C_t value (n=101)[a]				
Mean (SD)	24.9 (8.0)	21.1 (4.5)[d1]	19.3 (4.4)[d2]	0.133
Median (IQR)	22 (17-31)			
Experienced SARS-CoV-2 Symptoms				
Yes	157 (83.1%)	63 (92.6%)	38 (95.0%)	0.631
No	26 (13.8%)	5 (7.4%)	2 (5.0%)	
Unknown	6 (3.2%)			
Household Contact				
Yes	79 (41.8%)	32 (50.0%)	21 (55.3%)	0.607
No	94 (49.7%)	32 (50.0%)	17 (44.7%)	
Unknown	16 (8.5%)			
Previously positive for SARS-CoV-2				
Yes	4 (2.1%)	2 (3.1%)	0	0.533
No	167 (88.4%)	63 (96.9%)	37 (100%)	
Unknown	18 (9.5%)			

*Mutation data available for n=115 PVSC; 70 with no mutation, 42 with isolated L452R mutation presumptive of B.1.427/B.1.429 variant, and 3 with isolated N501Y mutation. Only samples with L452R and no other mutations are compared here due to few N501Y mutations. Mutation data not available for n=32 with C_t values not meeting criteria, n=27 with SARS-CoV-2 test done outside SHC system, n=15 with samples otherwise not available for mutation testing

**Patient facing roles = Physician/APP (n=22, 11.7%); nursing (n=42, 22.2%); MA (n=17, 9.0%), RT/PT/OT (n=5, 2.6%), other (n=43, 22.8%). Non-patient facing roles = housekeeping/food services (n=22, 11.7%); other (33, 17.4%).

[†]p-value reflects Extended Mantel-Haenszel chi square for linear trend, univariate analysis unadjusted for rising prevalence of B.1.427/B.1.429 from December 2020 to March 2021

[a]n=151 includes symptomatic PVSC with known date of symptom onset; [a1]n=62; [a2]n=37

[b]n=31 includes symptomatic PVSC who tested positive after dose 2 and had known date of symptom onset; [b1]n=9; [b2]n=11

[c]n=39 includes all PVSC who tested positive after dose 2; [c2]n=10; [c2]n=14

[d] C_t values not available for individuals tested outside SHC system or by transcription mediated amplification (TMA); only samples with $C_t \leq 30$ (before March 1, 2021) or $C_t \leq 34$ (after March 1, 2021) included in variant analysis; [d1]n=45; [d2]n=19

Table 3. Age and C_t value by vaccination status

	Unvaccinated+Early post-vaccination	Partially+Fully vaccinated	P value
Age in years **Mean (SD)**	36.8 (10.2)	42.3 (11.8)	<0.001
C_t value (n=98) **Mean (SD)**	22.9 (7.3)	27.9 (8.2)	<0.001

T tests comparing age and Ct value by vaccination status. Early post-vaccination = Positive SARS-CoV-2 NAAT ≤14 days from vaccine dose 1; Partially vaccinated = >14 days from vaccine dose 1 and ≤14 days from vaccine dose 2; Fully vaccinated = >14 days from vaccine dose 2.

Table 4. Risk ratios for infection with presumptive B.1.427/B.1.429 among HCP by vaccination status and adjusted for community prevalence of L452R mutation at time of infection

Vaccination status at time of positive test	n	Presumptive B.1.427/B.1.429 n (%)	Concomitant Community Prevalence of L452R Median (quartiles)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Unvaccinated	130	61 (46.9%)	41.4% (32.8%, 47.4%)	Ref.	Ref.
Early post-vaccination	74	22 (29.7%)	36.2% (32.8%, 41.4%)	0.63 (0.43-0.94)	0.70 (0.47-1.05)
Partially Vaccinated	21	10 (47.6%)	41.4% (32.8%, 45.7%)	1.02 (0.63-1.65)	1.05 (0.65-1.70)
Fully Vaccinated	17	10 (58.8%)	51.8% (50.7%, 57.7%)	1.25 (0.81-1.94)	1.05 (0.65-1.68)

Modified Poisson regression model (log-Poisson generalized linear model with robust standard errors) comparing individuals with and without presumptive B.1.427/B.1.429 by vaccination status at time of positive SARS-CoV-2 NAAT and adjusted for percent of total positive SARS-CoV-2 tests with isolated L452R mutation presumptive of B.1.427/B.1.429 within Stanford Health Care during week of infection. Early post-vaccination = Positive SARS-CoV-2 NAAT ≤14 days from vaccine dose 1; Partially vaccinated = Positive SARS-CoV-2 NAAT >14 days from vaccine dose 1 and ≤14 days from vaccine dose 2; Fully vaccinated = Positive SARS-CoV-2 NAAT >14 days from vaccine dose 2.

Table 5. PANGO lineage identified by next generation sequencing compared with mutations identified by RT-PCR among SARS-CoV-2 infected HCP

PANGO lineage by next generation sequencing	***Mutation identified by RT-PCR***					
	L452R	N501Y	E484K	No mutation	Mutation data not available	**Total**
B.1.1.7	0	11	0	0	0	11
B.1.427	22	0	0	0	4	26
B.1.429	8	0	0	0	1	9
B.1.617	1*	0	0*	0	0	1
Not variant of concern/interest	0	0	1	57	29	87
Total	31	11	1	57	34	134

Next generation sequencing (NGS) available for n=134 HCP; NGS was unavailable for n=148 HCP who were tested by Color or outside of Stanford lab, n=43 with high Ct values, n=13 samples with low TMA RLU, n=6 samples with PCR amplification failure, n=114 with insufficient quantity, and n=215 that were otherwise unavailable.

*This specimen had a blunted E484K amplification curve which was revealed to represent an E484Q mutation by sequencing.(29)

FIGURE LEGEND

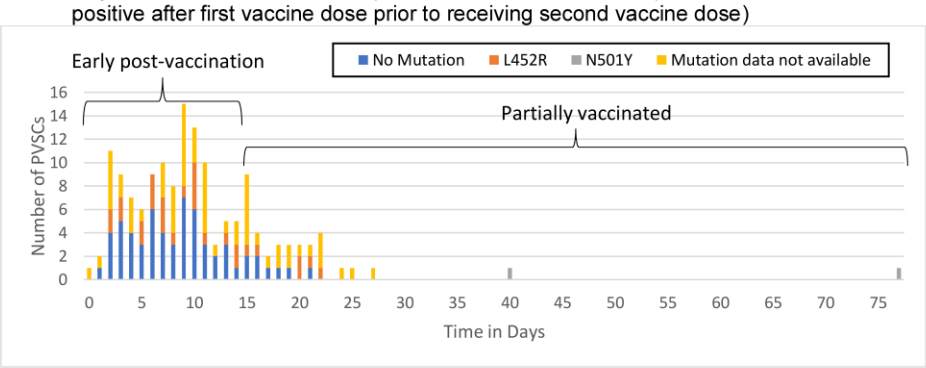
Figure 1. Time from vaccination to COVID-19 symptom onset and positive SARS-CoV-2 NAAT

A. Days from first vaccine dose to positive SARS-CoV-2 NAAT (n=150 PVSCs that tested positive after first vaccine dose prior to receiving second vaccine dose)

B. Days from second vaccine dose to positive SARS-CoV-2 NAAT (n=39 PVSC that tested positive after second vaccine dose)

Figure 1

A. Days from first vaccine dose to positive SARS-CoV-2 NAAT (n=150 PVSCs that tested positive after first vaccine dose prior to receiving second vaccine dose)



B. Days from second vaccine dose to positive SARS-CoV-2 NAAT (n=39 PVSC that tested positive after second vaccine dose)