# Effectiveness of Naturally Acquired and Vaccine-Induced Immune Responses to SARS-CoV-2 Mu Variant

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SARS-CoV-2 Mu variant emerged in Colombia in 2021 and spread globally. In 49 serum samples from vaccinees and COVID-19 survivors in Colombia, neutralization was significantly lower ($p<0.0001$) for Mu than a parental strain and variants of concern. Only the Omicron variant of concern demonstrated higher immune evasion.

Diverse SARS-CoV-2 variants have arisen during the pandemic. As of May 4, 2022, there had been 2 recognized variants of concern (VOC), Delta and Omicron, in addition to earlier emerging VOCs Alpha, Beta, and Gamma and strains previously categorized as variants of interest (VOI). Many VOIs have been understudied in terms of pathogenesis, transmissibility, and potential for immune escape. Delta and Omicron illustrate how variants emerging in tropical settings can spread globally.

Mu was first reported as a VOI in early January 2021 in northern Colombia. While outcompeting other locally circulating variants, Mu spread to additional countries, such as Ecuador, United States, Mexico, and Spain; as of early 2022, it was still circulating at low levels in Colombia (*1*). Mu caused 70% of all COVID-19 cases in Colombia during May–July 2021 (Figure 1), a period which also accounted for the highest number of deaths in Colombia during the pandemic, suggesting substantial pathogenicity of Mu (*1*). Mu was later outcompeted by Delta and Omicron, and the number of Mu-related cases gradually decreased through the end of 2021 (Figure 1).

Recent studies relying on data from spike-based pseudovirus testing suggested substantially lower neutralization of Mu compared with the parental B.1 virus in antiserum samples from persons in Japan and China who had received either the BNT162b2 (Pfizer-BioNTech, https://www.pfizer.com) or Sinovac (http://www.sinovac.com) vaccines or recovered from COVID-19 (*2*,*3*). Because of inherent limitations in pseudovirus-based systems for reproducing response variations based on natural infection (*4*), regional differences of immune responses (*5*), and different vaccines used in Colombia, we comparatively characterized the neutralization of Mu and VOCs using fully infectious viruses and serum samples from persons in Colombia. The study was approved by the Ethics Committee of the Universidad Industrial de Santander (protocol 4110) and by the Ethics Committee of the Charité-Universitätsmedizin Berlin (protocol EA2/031/22). All participants provided written informed consent.

## The Study

By March 2022, ≈68% of the population of Colombia had been vaccinated, predominantly with spike-based mRNA (BNT162b2), vectored (AZD1222; AstraZeneca, https://www.astrazeneca.com), and chemically inactivated whole virus–based vaccines (CoronaVac) (Appendix Figure 1, https://wwwnc.cdc.gov/EID/article/28/8/22-0584-App1.pdf). To investigate the potency of natural and vaccine-derived immunity, we tested and compared the

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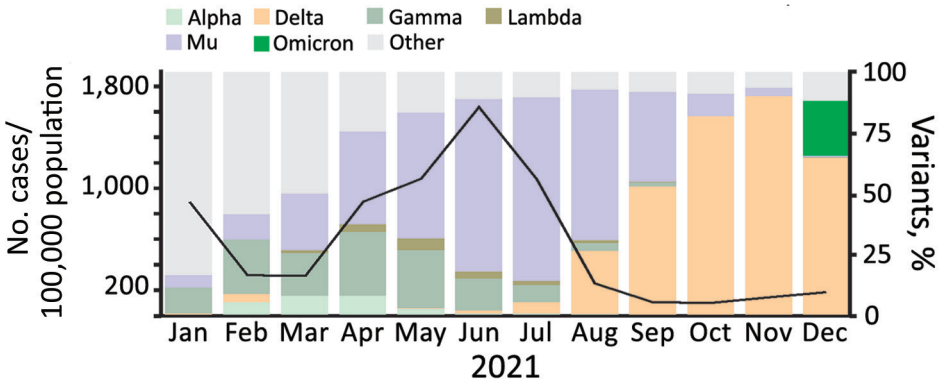


**Figure 1.** Incidence of SARS-CoV-2 and circulation of variants, by month, Colombia, 2021. Data on variant circulation was obtained from GISAID (https://www.gisaid.org) and data on the number of cases in Colombia from the Our World in Data database (https://www.ourworldindata.org).

neutralization activity in 49 serum samples from vaccinated and naturally infected persons in Colombia. Among vaccinated persons, we tested serum from 32 persons sampled in October 2021. Of those, 10 vaccinated with BioNTech-Pfizer were tested a median 99.5 d (range 65–170) after completing vaccination, 7 vaccinated with AstraZeneca were tested a median 146.0 d (range 129–173) after completing vaccination, and 15 vaccinated with Sinovac were tested a median 46.0 d (range 28–131) after completing vaccination. We tested serum samples from 17 persons who tested positive for SARS-CoV-2 antibodies (MAGLUMI 2019-nCoV IgG; Snibe Diagnostic, https://www.snibe.com) (Table 1; Appendix Table 1) during a seroprevalence study conducted in November 2020. To control whether persons vaccinated with spike-based vaccines were not previously infected, serum samples were tested against the SARS-CoV-2 IgG nucleocapsid protein by ELISA (SARS-CoV-2 NCP kit; Euroimmun, https://www.euroimmun.com) (Table 2). We used 50% plaque reduction neutralization tests to obtain neutralizing titers against an early isolate and the Alpha, Beta, Delta, Gamma, Omicron BA.1, and Mu variants (Appendix).

Neutralizing antibody titers against Mu were significantly lower than those against the parental isolate ($p<0.0001$ by Wilcoxon matched-pairs signed-rank test) in all serum samples tested in this study, irrespective of whether immune responses were elicited by vaccination or by natural infection. Vaccine-derived antibodies neutralized Mu on average 8.1-fold ($p<0.0001$ by Wilcoxon test) less than the parental strain resembling the vaccine backbones (Figure 2, panels A–C; Appendix Figure 2). We found a similar 8.0-fold reduced neutralization of Mu ($p<0.0001$ by Wilcoxon test) for the group of naturally infected persons (Figure 2, panel D). Despite the relatively lower neutralization potency observed in serum samples from persons immunized with the inactivated full virus-based vaccine Sinovac, observed differences in the ability to neutralize Mu compared with the parental strain among the 3 vaccine groups were not statistically significant (range 7.7–11.4-fold; $p = 0.8298$ by Kruskal-Wallis test) (Figure 2).

Compared with other variants, neutralizing antibody titers from serum samples of both naturally infected persons and vaccinees were lower against Mu than against all VOCs except for Omicron (Figure 2, panels A and B). Therefore, our results provide strong evidence for immune evasion of the Mu VOI on the basis of results from robust neutralization testing using full viral isolates. Neutralization of Mu by vaccine-induced antibodies was significantly lower than for Beta ($p = 0.0083$ by Wilcoxon text), for which immune evasion properties led to the suspension of AstraZeneca usage in South Africa (*6*), and Gamma, which resulted in breakthrough infections in Latin America (*7*). Immune evasion of Mu is consistent with shared mutations in spike protein residues associated with immune evasion in Beta and Gamma, such as E484K (*8*). In addition, the mutation leading to the amino acid exchange R346K in Mu is known to be involved in the evasion of monoclonal antibody–mediated neutralization (*9*), and genomic exchanges occurring at 3 adjacent sites (Y144T, Y145S, and insertion of the amino acid asparagine [N] between spike residues 145 and 146) have been associated with the immune escape properties of Mu (*10*,*11*).

**Table 1.** Median age and days after the second dose of vaccinated persons, by vaccine type, at time of sampling among persons in Colombia*

| Vaccine groups | Days after second dose (range) | Age, y (range) |
|---|---|---|
| AstraZeneca | 146 (129–173) | 66.0 (61–72) |
| Pfizer-BioNTech | 99.5 (65–170) | 44.6 (27–65) |
| Sinovac | 46.0 (23–131) | 44.5 (23–92) |

*AstraZeneca (AZD1222), https://www.astrazeneca.com; Pfizer-BioNTech (BNT162b2), https://www.pfizer.com; Sinovac (CoronaVac), http://www.sinovac.com.

Antigenic cartography was recently employed to map the antigenic relationship between the SARS-CoV-2 Omicron and Delta VOCs and other previously circulating VOCs and VOIs (S.H. Wilks et al., unpub. data, https://www.biorxiv.org/content/10.1101/2022.01.28.477987v1). Among the serum samples from Colombia vaccinees, there was a high antigenic distance between Mu and most variants from other serum samples, which clustered together with the parental strain and Alpha (Appendix Figure 3). Of note, antibody responses in naturally infected persons supported past infection with strains bearing similarities to early SARS-CoV-2 isolates and the Gamma variant (Figure 2, panel D). Antibody reactivity in naturally

**Table 2.** ELISA results and endpoint titers for vaccinee and naturally infected individual serum samples from persons in Colombia*

| Group | Patient ID | Nucleocapsid IgG ELISA† | Neutralizing titer by $PRNT_{50}$ | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | WT | Mu | Alpha | Beta | Gamma | Delta | Omicron |
| AstraZeneca | AZ2 | 0.15 | 204 | 41 | 154 | 79 | 64 | 77 | 13 |
| | AZ3 | 0.07 | 453 | 123 | 381 | 305 | 306 | 470 | 25 |
| | AZ4 | 0.11 | 75 | 3 | 91 | 16 | 20 | 24 | 6 |
| | AZ5 | 0.12 | 76 | 9 | 104 | 3 | 13 | 29 | 2 |
| | AZ6 | 0.13 | 34 | 4 | 45 | 3 | 23 | 15 | 0 |
| | AZ9 | 0.08 | 179 | 35 | 189 | 75 | 128 | 84 | 10 |
| | AZ10 | 0.07 | 319 | 9 | 153 | 47 | 55 | 26 | 8 |
| Pfizer-BioNTech | PF1 | 0.14 | 119 | 9 | 85 | 1 | 18 | 38 | 3 |
| | PF2 | 0.04 | 28 | 3 | 43 | 35 | 15 | 17 | 3 |
| | PF3 | 0.15 | 262 | 62 | 158 | 130 | 101 | 149 | 19 |
| | PF4 | 0.06 | 754 | 121 | 715 | 204 | 226 | 187 | 43 |
| | PF5 | 0.05 | 501 | 87 | 320 | 48 | 91 | 259 | 9 |
| | PF6 | 0.07 | 123 | 10 | 119 | 52 | 15 | 11 | 3 |
| | PF7 | 0.19 | 214 | 9 | 70 | 5 | 0 | 125 | 3 |
| | PF8 | 0.05 | 207 | 18 | 167 | 28 | 25 | 66 | 3 |
| | PF9 | 0.09 | 715 | 10 | 273 | 0 | 46 | 108 | 2 |
| | PF10 | 0.62 | 1043 | 132 | 1036 | 343 | 333 | 799 | 47 |
| Sinovac | SVN1 | 2.96 | 51 | 54 | 72 | 36 | 66 | 83 | 0 |
| | SVN2 | 1.68 | 47 | 9 | 24 | 23 | 21 | 22 | 0 |
| | SVN3 | 0.46 | 41 | 6 | 1 | 1 | 18 | 1 | 0 |
| | SVN4 | 2.43 | 118 | 61 | 151 | 111 | 89 | 87 | 25 |
| | SVN7 | 0.97 | 363 | 162 | 347 | 407 | 188 | 259 | 56 |
| | SVN8 | 0.81 | 303 | 5 | 93 | 26 | 30 | 61 | 5 |
| | SVN9 | 0.69 | 53 | 0 | 32 | 3 | 15 | 35 | 0 |
| | SVN10 | 1.61 | 65 | 4 | 27 | 0 | 10 | 66 | 1 |
| | SVN12 | 0.29 | 52 | 8 | 52 | 1 | 20 | 21 | 0 |
| | SVN13 | 0.39 | 387 | 24 | 126 | 126 | 35 | 130 | 7 |
| | SVN15 | 2.81 | 145 | 175 | 168 | 197 | 147 | 133 | 19 |
| | SVN16 | 0.40 | 67 | 2 | 6 | 25 | 10 | 21 | 3 |
| | SVN17 | 0.07 | 24 | 1 | 1 | 5 | 0 | 15 | 3 |
| | SVN18 | 0.37 | 65 | 0 | 3 | 4 | 0 | 24 | 7 |
| | SVN20 | 1.88 | 686 | 464 | 612 | 155 | 131 | 503 | 16 |
| Naturally infected | EA210 | ND | 696 | 146 | 825 | 595 | 167 | 177 | 2 |
| | EA234 | ND | 142 | 4 | 86 | 83 | 67 | 9 | 0 |
| | EA238 | ND | 1,080 | 48 | 1080 | 314 | 541 | 79 | 5 |
| | EA245 | ND | 70 | 2 | 61 | 154 | 44 | 0 | 0 |
| | EA332 | ND | 93 | 10 | 43 | 94 | 1 | 20 | 0 |
| | EA334 | ND | 140 | 6 | 74 | 115 | 7 | 16 | 3 |
| | EA340 | ND | 77 | 2 | 24 | 61 | 0 | 14 | 2 |
| | EA352 | ND | 1,080 | 113 | 1,080 | 578 | 870 | 59 | 3 |
| | EA354 | ND | 336 | 119 | 423 | 972 | 90 | 628 | 0 |
| | EA380 | ND | 918 | 43 | 281 | 630 | 151 | 63 | 17 |
| | EA396 | ND | 139 | 24 | 98 | 88 | 14 | 21 | 0 |
| | EA413 | ND | 1,080 | 18 | 864 | 1,080 | 260 | 17 | 11 |
| | EA422 | ND | 2 | 20 | 28 | 6 | 123 | 100 | 0 |
| | EA439 | ND | 398 | 171 | 283 | 812 | 79 | 62 | 9 |
| | EA485 | ND | 357 | 87 | 531 | 206 | 114 | 14 | 0 |
| | EA501 | ND | 17 | 13 | 86 | 80 | 1 | 0 | 2 |
| | EA520 | ND | 166 | 36 | 154 | 211 | 16 | 141 | 1 |

*AstraZeneca (AZD1222), https://www.astrazeneca.com; Pfizer-BioNTech (BNT162b2), https://www.pfizer.com; Sinovac (CoronaVac), http://www.sinovac.com. ND, not determined; $PRNT_{50}$, 50% plaque reduction neutralization test; WT, wild-type.
†Cut-off ≥0.8 was considered positive.

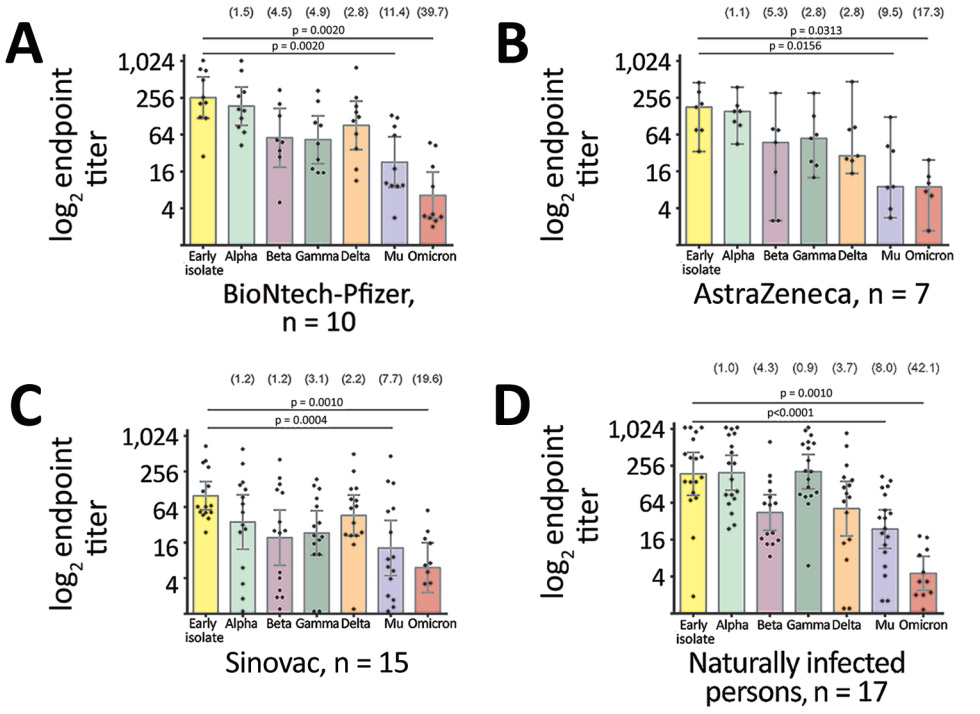


**Figure 2.** Comparative neutralization of the Mu SARS-CoV-2 variant in Colombia. A–C) Neutralization of SARS-CoV-2 variants from serum samples from persons fully immunized with BNT162b2 (Pfizer-BioNTech, https://www.pfizer.com) (A), AZD1222 (AstraZeneca, https://www.astrazeneca.com) (B), or CoronaVac (Sinovac, http://www.sinovac.com) (C). D) Neutralization of SARS-CoV-2 variants by serum samples from naturally infected persons who tested positive for SARS-CoV-2 antibodies during a seroprevalence study in November 2020. For all panels, each point represents the reciprocal plaque reduction neutralization test endpoint titer of 1 tested serum sample for different SARS-CoV-2 variants; colored bars indicate geometric mean titers, and error bars represent 95% CIs. Values in parentheses above bars represent reduction compared to the parental strain. Statistical significance was determined by the Wilcoxon matched signed-rank test; p values are indicated. For clarity of presentation, only significant values between the early isolate and the Mu variant are shown.

infected persons was thus in concordance with the circulation of SARS-CoV-2 variants in South America during the time of sampling in late 2020 (*12*), supporting the robustness of our data.

Our study was limited by different time points for sampling of vaccinees and the lack of information on natural infections altering immune responses in vaccinees. However, lack of detectable N-protein antibody responses and the absence of clinical records suggestive of COVID-19 infection in vaccinees immunized with spike-based vaccines supports the robustness of our data despite the vaccinees' unclear infection histories.

## Conclusions

Our data highlight the importance of continuous monitoring for the emergence of new SARS-CoV-2 variants and strains and the timely identification of those variants with potential to evade naturally elicited and vaccine-derived immune responses, using local sampling specimens in the context of regional epidemiologic conditions. Moreover, our data confirmed the potential of Mu to partially evade immune responses, which may affect the efficacy of vaccination programs in southern America and other areas (*7*,*13*). Further studies are warranted to evaluate the pathogenicity of and cell-mediated immunity against Mu and the ability of immune responses associated with Mu to neutralize other SARS-CoV-2 variants. However, because vaccination boosters still provide some degree of protection against severe disease from Omicron (*3*,*14*), which shows more immunity evasion than Mu, vaccination will likely still provide protection against severe disease from Mu.

## Acknowledgments

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## About the Author

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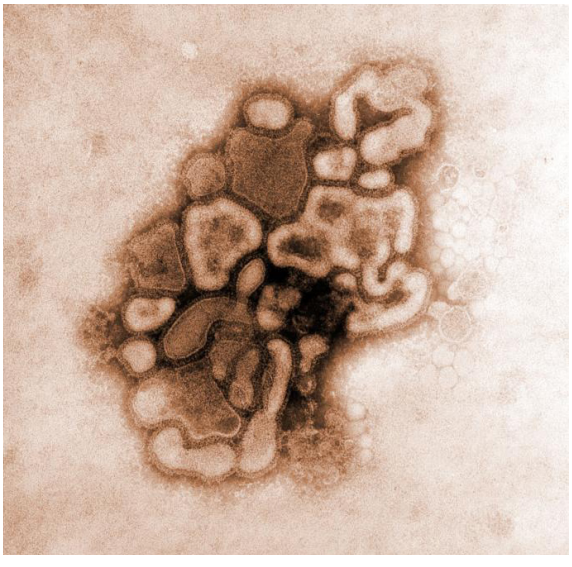
## Farmer Infected with Avian-Like Swine Influenza



Viruses are constantly mutating, and with those mutations can come shifts in their abilities to infect different hosts. Sometimes these mutations allow a virus to "jump" from one species to another, such as an avian influenza virus adapting to pigs.

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# Effectiveness of Naturally Acquired and Vaccine-Induced Immune Responses to SARS-CoV-2 Mu Variant

## Appendix

## Participant Recruitment and Sampling

The study was approved by the Ethics Committee of the Universidad Industrial de Santander (protocol 4110) and by the Ethics Committee of the Charité Universitätsmedizin-Berlin (Protocol EA2/031/22). All patients provided written informed consent. To control whether the vaccinated persons also had been naturally infected, subjects were followed up and did not report clinical symptoms or direct contact with persons who tested positive until sampling. In addition to that, all persons vaccinated with the spike-based vaccines from Pfizer and AstraZeneca tested negative for antibodies against the SARS-CoV-2 N protein, suggesting lack of natural infection and consistent with recording of clinical symptoms.

### 50% Plaque Reduction Neutralization Tests

We used a parental SARS-CoV-2 B.1 lineage strain (Pango version 3.1.17) sampled in January 2020 (Munich/ChVir929/2020 strain, GISAID accession: EPI_ISL_406862), containing one mutation (D614G) in the spike-encoding gene only compared to the SARS-CoV-2 reference sequence used for vaccine production (Isolate Wuhan-Hu-1 GenBank accession number: NC045512). We used the following SARS-CoV-2 variants: Alpha (ChVir21652/2020, GISAID accession: EPI_ISL_802995), Beta (ChVir22131/2021, GISAID accession: EPI_ISL_862149), Gamma (NH-RIVM_10915/2021, GISAID accession: EPI_ISL_943045), Delta (454236/2021, GISAID accession: EPI_ISL_4566914), Mu (H3/2021, GISAID accession: EPI_ISL_6665693) and Omicron (hCoV-19/Netherlands/NH-RIVM-71076/2021, GISAID accession: EPI_ISL_6841611.2; Pango lineage: BA.1.17.2). A total of 60 plaque-forming units were incubated with serum dilutions of 1:40, 1:120,1:360, and 1:1080 for 1 h, and afterwards added onto a monolayer containing $1.8x10^5$ Vero E6 cells per well in a 12-well plate. After 1 h of

incubation, an overlay containing DMEM with 1% FCS and 2% Avicell was added, and cells were further incubated for 3 d for Mu and 2 d for the other variants. The overlay medium was removed, and cells were fixated with 6% paraformaldehyde and stained with crystal violet. PRNT50endpoint titers were calculated using a logistic regression function in GraphPad prism6 (www.graphpad.com).

### Antigenic Cartography

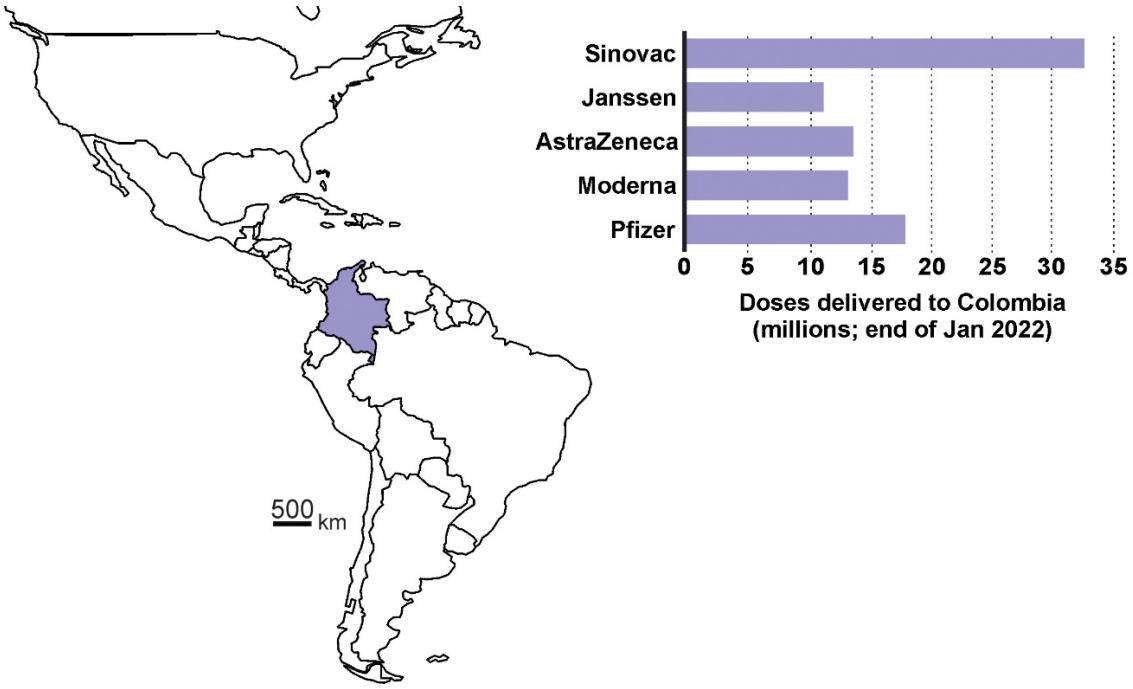
Antigenic cartography was done using the R package Racmacs (onhttps://acorg.github.io/Racmacs) as described elsewhere (S.H. Wilks; unpub. data, https://www.biorxiv.org/content/10.1101/2022.01.28.477987v1). Comparative neutralization of SARS-CoV-2 variants by serum samples from persons fully immunized with the different vaccines (BioNTech-Pfizer BNT162b2, AstraZeneca AZD1222, and CoronaVac).

**Appendix Table.** List of samples and reciprocal $PRNT_{50}$ endpoint titers of serum samples for vaccinated persons*†

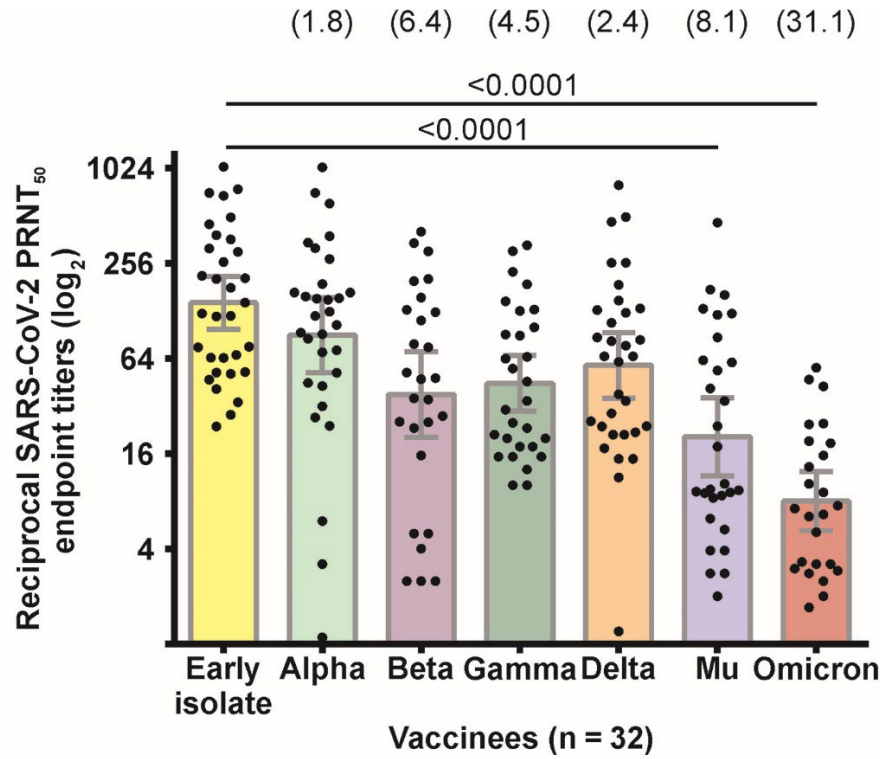
| Sample ID | Early isolate | Mu | Alpha | Beta | Gamma | Delta | Omicron | D after 2nd dose | Age | Vaccine |
|---|---|---|---|---|---|---|---|---|---|---|
| AZ2 | 204 | 41 | 154 | 79 | 64 | 77 | 13 | 129 | 64 | AstraZeneca |
| AZ3 | 453 | 123 | 381 | 305 | 306 | 470 | 25 | 173 | 69 | AstraZeneca |
| AZ4 | 75 | 3 | 91 | 16 | 20 | 24 | 6 | 173 | 72 | AstraZeneca |
| AZ5 | 76 | 9 | 104 | 3 | 13 | 29 | 2 | 146 | 61 | AstraZeneca |
| AZ6 | 34 | 4 | 45 | 3 | 23 | 15 | 0 | 165 | 72 | AstraZeneca |
| AZ9 | 179 | 35 | 189 | 75 | 128 | 84 | 10 | 142 | 61 | AstraZeneca |
| AZ10 | 319 | 9 | 153 | 47 | 55 | 26 | 8 | 142 | 63 | AstraZeneca |
| PF1 | 119 | 9 | 85 | 1 | 18 | 38 | 3 | 113 | 65 | BioNTech |
| PF2 | 28 | 3 | 43 | 35 | 15 | 17 | 3 | 170 | 42 | BioNTech |
| PF3 | 262 | 62 | 158 | 130 | 101 | 149 | 19 | 110 | 46 | BioNTech |
| PF4 | 754 | 121 | 715 | 204 | 226 | 187 | 43 | 110 | 27 | BioNTech |
| PF5 | 501 | 87 | 320 | 48 | 91 | 259 | 9 | 121 | 29 | BioNTech |
| PF6 | 123 | 10 | 119 | 52 | 15 | 11 | 3 | 80 | 46 | BioNTech |
| PF7 | 214 | 9 | 70 | 5 | 0 | 125 | 3 | 88 | 54 | BioNTech |
| PF8 | 207 | 18 | 167 | 28 | 25 | 66 | 3 | 66 | 35 | BioNTech |
| PF9 | 715 | 10 | 273 | 0 | 46 | 108 | 2 | 65 | 49 | BioNTech |
| PF10 | 1043 | 132 | 1,036 | 343 | 333 | 799 | 47 | 89 | 53 | BioNTech |
| SVN1 | 51 | 54 | 72 | 36 | 66 | 83 | 0 | 89 | 56 | CoronaVac |
| SVN2 | 47 | 9 | 24 | 23 | 21 | 22 | 0 | 33 | 23 | CoronaVac |
| SVN3 | 41 | 6 | 1 | 1 | 18 | 1 | 0 | 31 | 30 | CoronaVac |
| SVN4 | 118 | 61 | 151 | 111 | 89 | 87 | 25 | 27 | 28 | CoronaVac |
| SVN7 | 363 | 162 | 347 | 407 | 188 | 259 | 56 | 37 | 27 | CoronaVac |
| SVN8 | 303 | 5 | 93 | 26 | 30 | 61 | 5 | 37 | 54 | CoronaVac |
| SVN9 | 53 | 0 | 32 | 3 | 15 | 35 | 0 | 41 | 25 | CoronaVac |
| SVN10 | 65 | 4 | 27 | 0 | 10 | 66 | 1 | 46 | 26 | CoronaVac |
| SVN12 | 52 | 8 | 52 | 1 | 20 | 21 | 0 | 105 | 60 | CoronaVac |
| SVN13 | 387 | 24 | 126 | 126 | 35 | 130 | 7 | 90 | 57 | CoronaVac |
| SVN15 | 145 | 175 | 168 | 197 | 147 | 133 | 19 | 131 | 92 | CoronaVac |
| SVN16 | 67 | 2 | 6 | 25 | 10 | 21 | 3 | 90 | 54 | CoronaVac |
| SVN17 | 24 | 1 | 1 | 5 | 0 | 15 | 3 | 97 | 56 | CoronaVac |
| SVN18 | 65 | 0 | 3 | 4 | 0 | 24 | 7 | 81 | 52 | CoronaVac |
| SVN20 | 686 | 464 | 612 | 155 | 131 | 503 | 16 | 46 | 28 | CoronaVac |

*AZ, AstraZeneca; PF, Pfizer; SVN, Sinovac

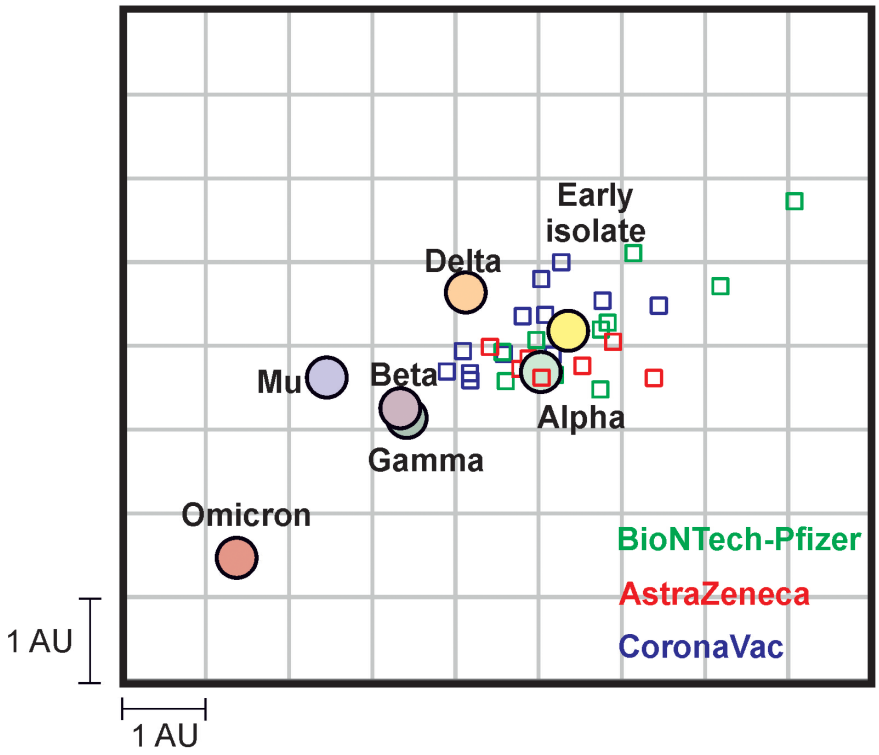
†Because we followed the Colombian vaccination program, it was not possible to collect samples the same time after completing the recommended vaccination scheme and the subjects' age were variable.




**Appendix Figure 1.** Vaccines doses delivered to Colombia as of January 2022 (https://www.minsalud.gov.co).




**Appendix Figure 2.** Comparative neutralization of SARS-CoV-2 variants by serum samples from persons fully immunized with the different vaccines (BioNTech-Pfizer BNT162b2, AstraZeneca AZD1222, and CoronaVac). Each point represents 50% plaque reduction neutralization test endpoint titers of 1 tested serum using different SARS-CoV-2 variants; the bars indicate the geometric mean titers, and the grey error bars represent 95% CI. Statistical significance was determined by the Wilcoxon matched signed-rank test and p-values are indicated on top. For clarity of presentation, only significant values between the early isolate and the Mu and the Omicron variants are shown.




**Appendix Figure 3.** Antigenic cartography of SARS-CoV-2 variants based on serum samples used in Figure 2 A–C. Each square corresponds to a serum sample tested. The colored circles indicate the tested SARS-CoV-2 variants. One grid square (1 antigenic unit) corresponds to a 2-fold serum dilution in the $PRNT_{50}$ assay. To decrease uncertainty in the antigenic cartography, $PRNT_{50}$ all endpoint titers <10 were considered as exactly <10. Antigenic mapping was not done for naturally infected persons because we could not rule out infection with multiple SARS-CoV-2 variants leading to heterogeneous antibody responses preventing a meaningful antigenic map.