SARS-CoV-2 seroprevalence, cumulative infections, and immunity to symptomatic infection – A multistage national household survey and modelling study, Dominican Republic, June–October 2021

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Summary

Background Population-level SARS-CoV-2 immunological protection is poorly understood but can guide vaccination and non-pharmaceutical intervention priorities. Our objective was to characterise cumulative infections and immunological protection in the Dominican Republic.

Methods Household members ≥5 years were enrolled in a three-stage national household cluster serosurvey in the Dominican Republic. We measured pan-immunoglobulin antibodies against the SARS-CoV-2 spike (anti-S) and nucleocapsid glycoproteins, and pseudovirus neutralising activity against the ancestral and B.1.617.2 (Delta) strains. Seroprevalence and cumulative prior infections were weighted and adjusted for assay performance and seroreversion. Binary classification machine learning methods and pseudovirus neutralising correlates of protection were used to estimate 50% and 80% protection against symptomatic infection.

Findings Between 30 Jun and 12 Oct 2021 we enrolled 6683 individuals from 3832 households. We estimate that 85.0% (CI 82.1–88.0) of the ≥5 years population had been immunologically exposed and 77.5% (CI 71.3–83) had been previously infected. Protective immunity sufficient to provide at least 50% protection against symptomatic SARS-CoV-2 infection was estimated in 78.1% (CI 74.3–82) and 66.3% (CI 62.8–70) of the population for the ancestral and Delta strains respectively. Younger (5–14 years, OR 0.47 [CI 0.36–0.61]) and older (≥75-years, 0.40 [CI 0.28–0.56]) age, working outdoors (0.53 [0.39–0.73]), smoking (0.66 [0.52–0.84]), urban setting (1.30 [1.14–1.49]), and three vs no vaccine doses (18.41 [10.69–35.04]) were associated with 50% protection against the ancestral strain.

Interpretation Cumulative infections substantially exceeded prior estimates and overall immunological exposure was high. After controlling for confounders, markedly lower immunological protection was observed to the ancestral and Delta strains across certain subgroups, findings that can guide public health interventions and may be generalisable to other settings and viral strains.

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Research in context

Evidence before this study

Given asymptomatic and paucisymptomatic SARS-CoV-2 infections are common, serology-based studies that can detect prior infection regardless of the presence of symptoms have proven to be important tools for characterizing transmission and prior cumulative infections. Yet, few national level serological studies have been performed more than 18-months into the pandemic, and none have aimed to translate findings to estimate population-level immunological protection. We searched MEDLINE, Embase, and Web of Science, using the following search terms through April 2022: SARS-COV-2, COVID-19, infections, seroprevalence, serology, and immunological protection. A World Health Organisation led meta-analysis estimated that global seroprevalence was 26% (95% CI 25–28) by April 2021, with seroprevalence of 21% (20–22) in lower and middle-income countries in the Americas. A modelling analysis of global, regional, and national infections estimated that by November 2021 44% (40–47) of the global population, 57% (52–63) of the Caribbean and Latin American population, and 33% (14–51) the Dominican Republic population had been previously infected. A large US-based study of blood donation samples from December 2021 estimated that national infection induced seroprevalence was 29% (28–29) and combined seroprevalence from vaccination and infection was 95% (95%–95%). We did not identify any serology-based studies that aimed to assess immunological protection. Only one study, using estimates of prior infection and COVID-19 vaccines administered in the United States and reported on a preprint server assessed population level immunological protection and estimated that by January 2021, 54% (51–59) of the population had effective protection against pre-Omicron strains.

Added value of this study

This is the first study in any setting to combine traditional seroepidemiological methods with estimates of immunological protection. Overall, there are four discrete areas of added value. First, we conducted the first nationally household seroepidemiological study from the heavily impacted Latin American region and generate directly measured, rather than modelled, estimates of SARS-CoV-2 seroprevalence and prior infections. Despite the value of mathematical modelling to estimate key epidemiological parameters, direct measurement is invaluable to assess, validate and parameterize these models. As observed, our findings diverge markedly from modelled estimates. Second, we developed novel methods to estimate immunological protection against symptomatic infection and generate the first estimates of population level protection using measured immunological markers, and only the second using any approach. Our methods provide a framework for expanding the insights gained through population-based serological survey and may be used in other settings (and for other pathogens) to predict future transmission scenarios and guide policy makers when considering restrictive control measures. Third, we assessed immunological protection across groups at high risk for severe COVID-19, providing key data to inform targeted public health interventions. Fourth, we identified factors associated with variable immune protection and, for example, identified markedly lower immunological protection among active smokers, young children, and older adults, even after controlling for prior infection and number of COVID-19 vaccination doses received, again providing population level data to guide public health interventions and policy both in the Dominican Republic and more widely.

Implications of all the available evidence

Much of the global population have been exposed to SARS-CoV-2 antigens through infection, vaccination, or both. However, translating these data to understand future risks is challenging given the limited understanding of population level immunological protection, particularly across low- and middle-income countries. The immunological landscape to SARS-CoV-2 has become increasingly complex with widespread undetected infections, multiple COVID-19 vaccines with variable immunogenicity, poorly understood hybrid immunity (conferred by a combination of infection and vaccination) and waning or contracting immunological protection. The need to directly measure immunological markers to understand population level immunological protection will become increasingly important to guide targeted public health action.

Introduction

Controlling the coronavirus disease 2019 (COVID-19) pandemic will require robust population immunity conferred by repeated exposures to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigens through vaccinations, infections, or both. Much is known about individual-level immunity after SARS-CoV-2 infection, vaccination, and to a lesser extent a combination of the two. Yet, given non-sterilising immunity, variable immune response across vaccines and viral strains, heterogenous and often unrecognised transmission and infections, and a relatively rapid decline in protective immunity, at least to symptomatic infection, the global immunological landscape is largely unknown.

Serological surveys have proven to be valuable tools to characterise key epidemiological parameters during the COVID-19 pandemic. Yet, leveraging these tools to define immunological protection has been challenging

given limited understanding of how to define immunological protection, and because seroepidemiological studies typically measure binding antibodies rather than functional markers of protection. Recently, however, neutralising antibodies, either measured with live or pseudoviral SARS-CoV-2 assays, have been identified as robust measures of immune protection,[1] providing an opportunity to reframe these tools to estimate population level protective immunity.[2–6] Characterising population level immunological protection can help identify susceptible and high risk populations, parameterise transmission models to inform national and global health authorities on future transmission, healthcare utilisation scenarios and vaccine requirements, and more precisely define the impact of non-pharmaceutical interventions.

To better understand prior infections and transmission, high risk susceptible populations, and population-level immunological protection to symptomatic SARS-CoV-2 infection, we conducted a national cross-sectional seroepidemiological and modelling study in the Dominican Republic.

Methods

Setting

The Dominican Republic is an upper middle income Latin American country that shares the island of Hispaniola with Haiti. With almost 11 million residents, it is the second most populous country in the Caribbean.[7,8] Latin America emerged as a global SARS-CoV-2 hotspot during the first year of the COVID-19 pandemic, with model estimates suggesting cumulative attack rates of 30–50% in many countries by late 2020.[9,10] The first laboratory confirmed case of SARS-CoV-2 was reported in the Dominican Republic on 1 March 2020, and strict public health measures commensurate with most regional countries were implemented.[11] By August 21, 2021, the survey midpoint, 347,637 and 3989 cumulative cases and deaths were reported, respectively, with a mean virological test positivity rate of 18.0% (Fig. 1).[11] A national COVID-19 vaccination campaign was launched in February 2021 and the Dominican Republic was the first country in the Americas to authorise third doses for high-risk individuals. By the survey midpoint, 52.3% of the population had received at least one dose of a COVID-19 vaccine, 36.2% had received a two dose primary vaccine series and 5.3% a third dose.[11] The principal COVID-19 vaccines administered included the inactivated viral CoronaVac (Sinovac), the adenovirus vector ChAdOx1-S (Oxford/AstraZeneca) and mRNA BNT162b2 (Pfizer/BioNTech) vaccines, with CoronaVac accounting for approximately 90% of doses administered. The B.1.617.2 (Delta) SARS-CoV-2 variant was first detected in the Dominican Republic in July 2021 and B.1.1.529 (Omicron) in December 2022 (Fig. 1).

Study design, participant selection, and ethical considerations

We conducted a three-stage cross-sectional national household serological survey and selected 134 clusters from 12,565 communities, representing one of every 93 communities. First, after dividing the country into five regions, we assigned the number of clusters to each of the 31 provinces plus the Santo Domingo National district by proportion of the national population, while also considering spatial distribution and urban vs rural environments. Second, clusters were selected by province using grid methods designed to maximize spatial dispersion of clusters.[12] A total of 23 households per cluster were selected for enrolment using similar methods. Two provinces where longitudinal enhanced acute febrile infection surveillance is conducted were oversampled with 60 households per cluster enrolled. Third, households were selected using satellite images and grid methods.[12] For full description of sampling methods see Supplementary methods. Household members aged ≥5 years old present in the home at the time of the serosurvey were invited to participate.

Written consent was obtained for all participants. For children <18 years old, except emancipated minors, consent was obtained from the legal guardian. Written assent was provided by adolescents 14–17 years old, and verbal assent by children 7–13 years old. The study protocol was approved by the National Council of Bioethics in Health, Santo Domingo (013-2019), the Institutional Review Board of Pedro Henríquez Ureña National University, Santo Domingo, and the Mass General Brigham Human Research Committee, Boston, USA (2019P000094). Study procedures and reporting adhered to STROBE criteria for observational studies.

Study procedures

Questionnaires were administered to all study participants using the KoBo Toolbox data collection platform (www.kobotoolbox.org) on electronic tablets to collect self-reported demographics individual-level covariates including self-reported demographics (age, gender, race-ethnicity); comorbid medical conditions (high blood pressure, coronary heart disease, diabetes, cancer, kidney disease, stroke, asthma, chronic obstructive pulmonary disease, other disease of the immune system); weight and height; primary occupation; if the work location was primarily indoors, outdoors, or a mix of the two; smoking status; and number, date, and type of COVID-19 vaccine received. Venous blood was collected from all study participants processed as sera, and frozen at –80°C.

Immunoassay characteristics

Pan-immunoglobulin antibodies against SARS-CoV-2 spike (anti-S) and nucleocapsid (anti-NC) glycoproteins

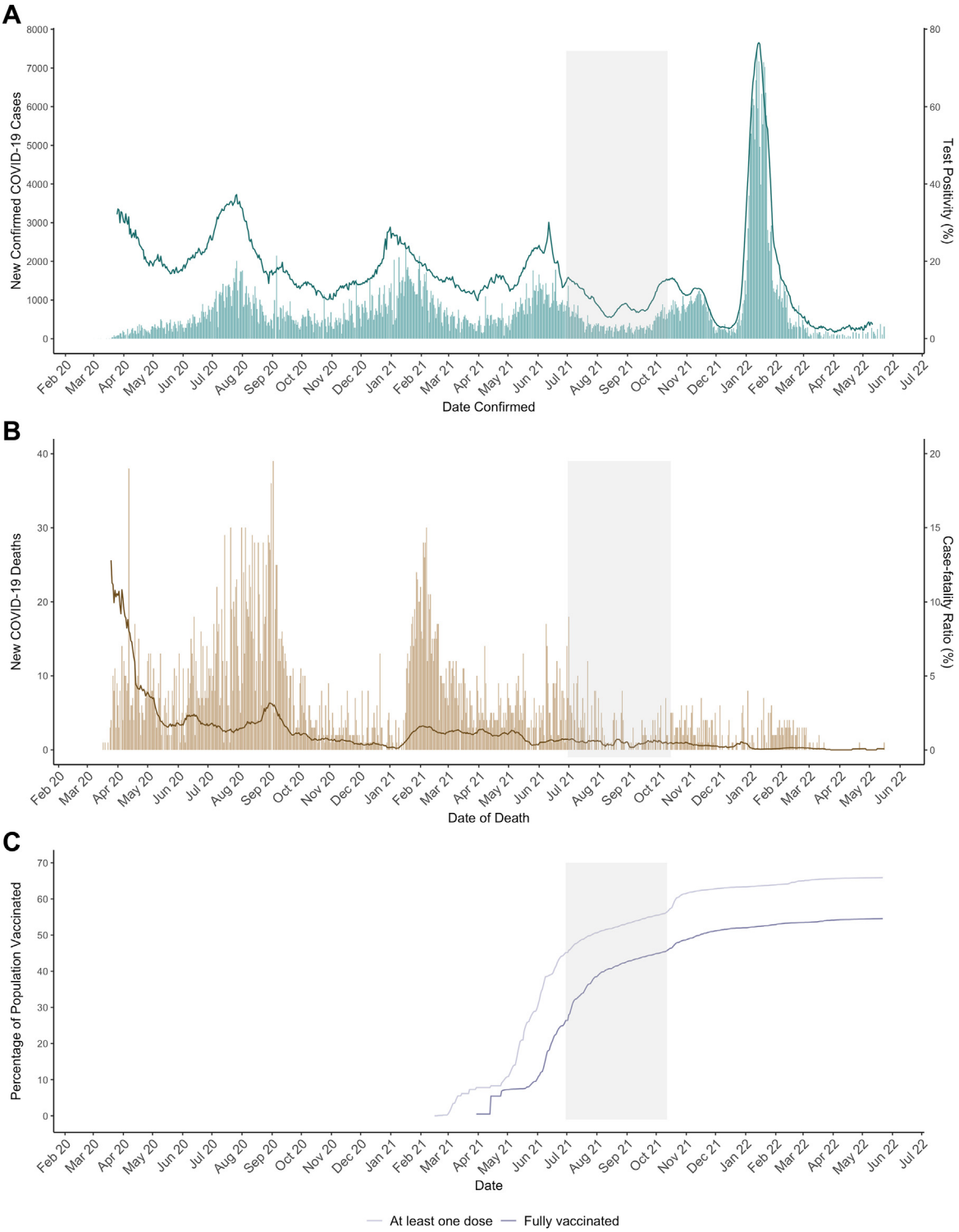

Fig. 1: **Reported SARS-CoV-2 cases, deaths, cumulative COVID-19 vaccination coverage, and timing of national household serological survey, Dominican Republic, March 2020–December 2021. Gray shading indicates the timing of the field survey (30 June–12 October 2021). (A)** Vertical light green bars indicate daily reported SARS-CoV-2 cases (y-axis, left) with solid line representing the test-positivity calculated using 14-day moving averages of daily cases reported and tests performed (y-axis, right). **(B)** Vertical tan bars indicate daily reported COVID-19 deaths, with the solid line representing the case fatality ratio. The case fatality ratio was calculated incorporating the delay

were measured on Roche Elecsys SARS-CoV-2 electrochemiluminescence immunoassays that use a recombinant protein modified double-antigen sandwich format (Roche Diagnostics, Indianapolis, USA). Assay performance measures were based on large non-manufacture-sponsored studies with specificities and sensitivities of 99.8% (CI 99.3–100) and 98.2% (CI 96.5–99.2) for the Elecsys anti-SARS-CoV-2 S assay and 99.6% (CI 98.9–100) and 90.8% (CI 81.3–95.7) for the anti-NC assay.[13,14] Ancestral Wuhan (WA1/2020) and Delta (B.1.617.2) pseudovirus neutralization assays were performed using methods previously described.[15] SARS-CoV-2 neutralization titers were defined as the sample dilution at which a 50% reduction (NT_{50}) in relative light units was observed relative to the average of the virus control wells. 300 samples included for neutralization were randomly selected from within three age categories (5–14, 15–65, >65 years), stratified by vaccination status, with anti-S-negative samples excluded given neutralising activity is rarely detectable among seronegative samples.[3] The mean convalescent titer, previously assessed for this assay and a measure intended to allow standardization across neutralization assays is 106 (95% confidence interval [CI] 87–129).[15]

Classification and statistical analysis

Prevalence of anti-S antibodies

Given anti-S antibodies are less prone to seroreversion than anti-NC antibodies,[16] anti-S values above the manufacturer cutoff index (COI) were used as the primary measure of seropositivity to SARS-COV-2. Seroprevalence estimates were weighted for sampling design (selection probability, clustering), corrected for finite population, and post-stratified for age group and sex.

Estimates of prior infection

The widely employed CoronaVac inactivated virus vaccine generates anti-S and to a lesser degree anti-NC antibodies. In contrast, other COVID-19 vaccines authorized in the Dominican Republic only generate anti-S antibodies. Therefore, to calculate the proportion of participants with prior infection, we used anti-NC prevalence, stratified by age and gender, among the population that received anti-S-only generating COVID-19 vaccines to estimate anti-NC prevalence among the overall vaccinated population. Estimates of prior infection were adjusted for assay performance and seroreversion. Given the 0- to 4-year age group were not enrolled in this study, we used infection rates among the 5- to 9-year age group as a proxy for this age group to generate national infection-to-fatality ratios (IFR) and infection-to-case (ICR) ratios. To calculate IFR, we divided the number of deaths reported through the survey mid-point by the estimated number of cumulative infections.[11] To calculated ICR we divided estimated cumulative infections by cases reported through the survey mid-point.

Correlates of protective immunity against symptomatic infection

We used pseudovirus correlates of protection against symptomatic SARS-CoV-2 infection, based on data from eight vaccine trials,[1] to define immunological protection. Accordingly, pseudoviral neutralization titers (PVNT) of approximately 20% and 80% of mean convalescent titers are estimated to provide 50% and 80% protection against symptomatic infection (PT_{50} and PT_{80}, respectively), with mean convalescent titers used to control across platforms. Conversion of convalescent titers for the pseudoviral neutralization assay used in this study equated to PVNT of 21 for PT_{50} and 84 for PT_{80}. Random forest binary classification machine learning algorithms were used to predict individual-level PVNT above or below PT_{50} and PT_{80} thresholds for both ancestral and Delta strains, with model features selected using recursive feature elimination from among covariates independently associated with anti-S serostatus. Models were trained and tested using non-overlapping training and testing datasets drawn from a 75:25 ratio of study participants with pseudoviral neutralization data. Random forest classification models were then applied to all study participants. Estimates of population immunological protection were weighted, corrected, and post-stratified for age group and sex.

ArcGIS software (v 10.7.1)[17] was used to generate spatial grids with Google Earth Pro maps (v 7.3.4.8642) to select sampling locations. All other analyses and data visualization were performed using the R statistical programming language (R version 4.1.3, 2022-03-10).[18] See Appendix for full details of methods and statistical analyses.

from case confirmation to death in the Dominican Republic using the 'datadelay' package at https://github.com/epiverse-trace/datadelay/. CFR estimates are shown from 24th March 2020, the first day when more than 1 COVID-19 death was reported, as few deaths prior to this date make interpretation of the CFR unreliable. (C) Percentage of the population that have received at least one COVID-19 vaccine dose (light purple line), and two or more COVID-19 vaccines doses (dark purple line). 52.8% and 41.9% of the population had received at least one and at least two doses, respectively, of a COVID-19 vaccine by the survey mid-point (August 21, 2021). The fourth (October–November, 2021) and fifth (January–February, 2022) waves of infection were predominantly due to the B.1.617.2 (Delta) and B.1.1.529 (Omicron) variants respectively with limited sequencing data available for earlier time points (data source: DR MOH). Data for reported cases and deaths are collected by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University and are available from https://github.com/CSSEGISandData/COVID-19. Data on COVID-19 vaccinations and testing are available from https://ourworldindata.org/coronavirus.

Data sources

National and provincial demographic data and cluster population and classification (urban versus rural) were provided by the Dominican Republic National Statistics Office and the United National Statistics Division.[7,8] SARS-CoV-2 cases and deaths were obtained from COVID-19 GitHub repository.[11] Data on COVID-19 vaccinations are available from https://ourworldindata.org/coronavirus. Other data were enumerated during the study.

Role of the funding source

This study was funded through a US Centers for Disease Control and Prevention (CDC) U01 Cooperative Agreement and CDC staff supported the design, interpretation, and manuscript editing. The first nine and last four authors had full access to all the data. E.J.N., R.C.M., E.Z.G., C.L.L. had final responsibility for the decision to submit for publication.

Results

Enrolment, demographics, and seroprevalence

Between 30 June and 12 October, 2021, 6683 study participants aged ≥5 years were enrolled from 3832 households in 134 clusters across all provinces. This comprised 84.4% (6683/7916) of eligible individuals present at the time of household visit and 49.6% (6683/13,487) of the total eligible household members (Fig. 2).

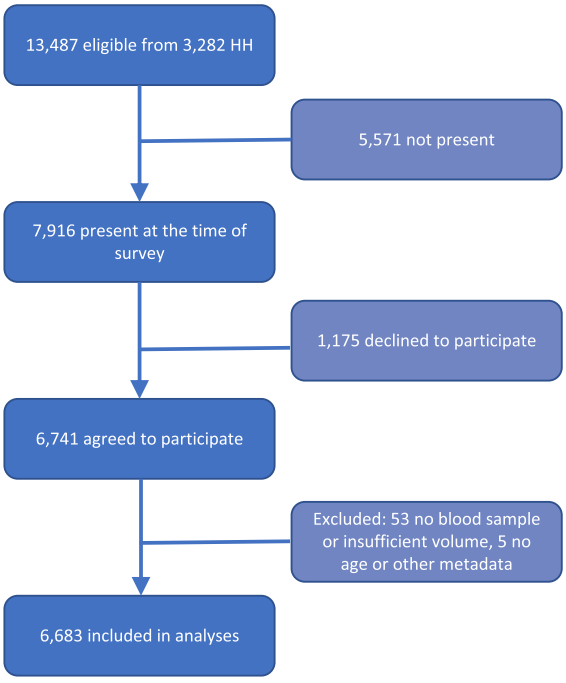

Fig. 2: **Study participant enrolment.**

4171/6683 (62.4%) were female with a median and mean age of 40 (interquartile range [IQR] 23–58) and 41.4 years (standard deviation [SD] 20.5), respectively. Additional demographics of study participants are described in Table 1 and a flowchart of participant enrolment is provided in Fig. 2. Study enrolment relative to national reported cases, deaths, and COVID-19 vaccination status is shown in Fig. 1. The adjusted national prevalence of anti-S and anti-NC antibodies among individuals aged ≥5 years was 85.0% (CI 82.1–88.0) and 74.3% (CI 70.2–78.0), respectively, with anti-S prevalence by demographic variables and vaccination status shown in Table 1.

Factors associated with SARS-CoV-2 seropositivity

Univariable odds ratios (ORs) for the presence of anti-S antibodies were lower among younger age groups (5- to 14- and 15- to 24-year-olds), working outdoor versus indoors, living in rural vs urban areas, and unvaccinated versus vaccinated (Table 2). Multivariable analyses identified young age (5–14 years), living in rural areas, smaller household size (fewer than five residents), work outdoors, and being unvaccinated as independently associated with lower odds of anti-S seropositivity (Table 2). Predictors of anti-NC seropositivity are reported in Supplementary Table S5. Findings largely align with anti-S seropositivity but with progressively lower ORs with increasing age above the reference 35- to 44-year age group and markedly lower ORs for recipients of COVID-19 vaccines when compared to anti-S ORs.

Cumulative infections, infection-to-case ratio, and infection-to-fatality ratio

We estimate that 77.6% (CI 71.1–83.4) of the population aged ≥5 years were previously infected with SARS-CoV-2 by the study midpoint and that 76.7% (CI 70.1–82.5) of the total population, including all age groups, were previously infected, translating to 8,080,604 (CI 7,384,610–8,695,536) individuals infected at least once. Age stratified estimates of prior cumulative infection were 70.8% (CI 64.7–76.8) for the 5- to 14-year-old, 80.0% (CI 75.0–84.6) for the 15- to 64-year-old, and 74.4% (CI 52.6–89.8) for the ≥65-year-old age groups. Among the study population ineligible for COVID-19 vaccines (5- to 11-years, n = 401), 69.3% (CI 63.6–74.9) were estimated to have been previously infected. We estimate that 79.3% (CI 75.6–83.0) of the unvaccinated and 75.8% (CI 66.5–83.6) of the vaccinated population (one or more doses of a COVID-19 vaccine) were previously infected. Collectively our data suggests about 37.5% (CI 32.9–41.3) of the ≥5-year-old population were previously infected and vaccinated, 40.1% (CI 38.2–42.0) were previously infected but not vaccinated, 11.9% (CI 8.1–16.5) had been vaccinated but not infected, and

Covariate	Participants, n	Seropositive participants, n	Unadjusted seroprevalence, % (95% CI)	Adjusted seroprevalence, % (95% CI)
Overall	6683	5958	89.2 (88.4–89.9)	85.0 (82.1–88.0)
Gender				
Female	4144	3712	89.6 (88.6–90.5)	86 (81.7–89.4)
Male	2494	2205	88.4 (87.1–89.6)	84 (80.8–86.8)
Other	45	41	91.2 (78.4–96.7)	87.5 (63.9–96.5)
Age, years				
5–14	661	446	67.5 (63.8–70.9	66.7 (59.7–73)
15–24	1133	1009	89.1 (87.1–90.8)	86.5 (80.5–90.9)
25–34	1010	928	91.9 (90.0–93.4)	89.6 (80.9–94.6)
35–44	950	879	92.5 (90.7–94.0)	92.3 (86.4–95.7)
45–54	953	873	91.6 (89.7–93.2)	91.3 (88–93.8)
55–64	913	846	92.7 (90.8–94.2	93.6 (90.2–95.9)
65–74	673	624	92.7 (90.5–94.5)	93.5 (90.2–95.8)
≥75	390	353	90.5 (87.2–93.1)	94.2 (86–97.8)
Area of residence				
Rural	3086	2682	86.9 (85.7–88.1)	82.5 (72.7–89.3)
Urban	3597	3276	91.1 (90.1–92.0)	85.8 (82.1–88.8)
No. HH residents				
1–2	1427	1275	89.3 (87.6–90.9)	88.3 (80.6–93.2)
3–4	2776	2462	88.7 (87.46–89.8)	85.2 (82.2–87.8)
5–6	1768	1583	89.5 (88.0–90.9)	83.2 (77.9–87.4)
≥7	712	638	89.6 (87.1–91.7)	85.2 (81.9–88)
Occupation				
Active worker	2061	1878	91.1 (89.8–92.3)	90.6 (86.5–93.6)
Houseperson	1764	1616	91.6 (90.2–92.8)	89.9 (85.6–93)
Retired	237	221	93.2 (89.3–95.8)	95.4 (86.6–98.5)
Student	1208	952	78.8 (76.4–81)	71.2 (66.8–75.3)
Unemployed	1370	1258	91.8 (90.3–93.2)	93.6 (90.5–95.8)
Work environment				
Indoor	664	631	95.0 (93.1–96.5)	96.2 (94.2–97.6)
Mix indoor/outdoor	868	802	92.4 (90.4–94.0)	89.2 (80.9–94.2)
Outdoor	527	443	84.1 (80.7–86.9)	82.9 (68.1–91.7)
Vaccine doses				
None	2576	1966	76.3 (74.6–77.9)	73.3 (68.7–77.6)
One	952	873	91.7 (89.8–93.3)	92.5 (89.4–94.8)
Two	2700	2665	98.7 (98.2–99.1)	99.1 (98.1–99.6)
Three	455	454	99.8 (98.5–100)	98.5 (86.3–99.9)

NC = not calculated. Gender values representing other (n = 28) and preferred not to respond (n = 17) aggregated and reported as other. 43 occupation values not included (anti-S prevalence 76.7 (61.7–87.1). Work environment enumerated for active workers and excluded students, housepersons, retirees and unemployed. No values were missing for other covariates. Adjusted seroprevalence weighted for study design (selection probability, clustering), finite population correction, and post-stratified for age and sex.

Table 1: **National SARS-CoV-2 anti-spike antibody prevalence by demographics and COVID-19 vaccination status, Dominican Republic, June–October 2021.**

10.5% (CI 8.6–12.3) neither vaccinated nor infected. The overall national ICR and IFR were estimated to be 23.2 (CI 21.2–25.0) and 0.049% (CI 0.046–0.054), respectively.

Population-level protective immunity against symptomatic infection

The adjusted proportion of the Dominican Republic population aged ≥5 years estimated to have at least 50% (PT_{50}) and 80% (PT_{80}) protection against symptomatic infection was 78.1% (CI 74.3–82) and 67.1% (CI 62.6–71) to the ancestral strain, and 66.3% (CI 62.8–70.0) and 37.1% (33.5–41.0) to the Delta strain. Lower PT_{50} and PT_{80} levels were consistently observed for Delta versus the ancestral strain across all variables. Lower values were observed across the 5–14-year-old age group across viral strains and levels of protection, and higher point estimates observed among the oldest age group (≥75 years) against the Delta strain, but with

Variable	Univariable odds ratios (95% CI)	p-value	Multivariable odds ratios (95% CI)	p-value
Gender				
Female	*Ref*		*Ref*	
Male	0.89 (0.76–1.04)	0.14	1.17 (0.97–1.43)	0.11
Other	1.19 (0.48–3.98)	0.74	0.81 (0.29–2.92)	0.72
Age, years				
5–14	0.17 (0.12–0.22)	**<0.001**	0.30 (0.21–0.42)	**<0.001**
15–24	0.66 (0.48–0.89)	**0.01**	0.78 (0.55–1.08)	0.14
25–34	0.91 (0.66–1.27)	0.60	0.96 (0.67–1.36)	0.81
35–44	*Ref*		*Ref*	
45–54	0.88 (0.63–1.23)	0.46	0.81 (0.56–1.15)	0.23
55–64	1.02 (0.72–1.44)	0.91	0.98 (0.68–1.43)	0.93
65–74	1.03 (0.71–1.51)	0.88	0.97 (0.62–1.53)	0.90
≥75	0.77 (0.51–1.18)	0.22	0.70 (0.43–1.16)	0.16
Residential setting				
Rural	*Ref*		*Ref*	
Urban	1.54 (1.32–1.80)	**<0.001**	1.31 (1.11–1.56)	**0.002**
No. household members				
1–2	*Ref*		*Ref*	
3–4	0.93 (0.76–1.15)	0.52	1.13 (0.90–1.42)	0.30
5–6	1.02 (0.81–1.28)	0.86	1.39 (1.07–1.79)	**0.01**
≥7	1.03 (0.77–1.38)	0.86	1.71 (1.23–2.38)	**<0.001**
Work environment				
Indoor	*Ref*		*Ref*	
Mix indoor/outdoor	0.63 (0.41–0.97)	**0.04**	0.67 (0.42–1.04)	0.08
Outdoor	0.28 (0.18–0.42)	**<0.001**	0.39 (0.24–0.60)	**<0.001**
NE	0.39 (0.27–0.56)	**<0.001**	0.74 (0.49–1.07)	0.13
Smoking status				
Non–smoker	*Ref*		*Ref*	
Current smoker	0.82 (0.62–1.09)	0.16	0.74 (0.55–1.03)	0.07
COVID-19 vaccine doses				
None	*Ref*		*Ref*	
One	3.43 (2.69–4.42)	**<0.001**	2.87 (2.24–3.72)	**<0.001**
Two	23.63 (16.99–33.98)	**<0.001**	18.95 (13.53–27.40)	**<0.001**
Three	140.86 (31.79–2475.08)	**<0.001**	111.00 (24.91–1953.13)	**<0.001**

Ref = reference group. Work environment enumerated only for active workers and excluded students, housepersons, retirees and unemployed (aggregated as NE = not enumerated). All study participants included (n = 6683). From survey data collected from 30 June to 12 October 2021, with August 21 the survey midpoint. Model estimates calculated with glm logistic regression and performance measures reported in Supplementary Table S9. Boldface indicates values below 0.05.

Table 2: **Univariable and multivariable predictors of anti-S seropositive status.**

overlapping confidence intervals (Fig. 3A, F, K and P). Protection was similar between males and females. The most important covariate associated with protection, particularly to the Delta strain, was receipt of a third dose of a COVID-19 vaccine (Fig. 3N and S).

Covariates associated with protective immunity

Findings from the multivariable logistic regression models for protective immunity against symptomatic SARS-CoV-2 infection are detailed in Table 3. These data provide estimates of the influence of covariates on PT_{50} and PT_{80} status after controlling for other factors. In summary, the number of vaccine doses was most strongly and consistently associated with protection against symptomatic infection, with the highest ORs for those receiving three vaccine doses. Being a current smoker was consistently associated with about one-third lower ORs and residing in an urban versus rural setting was associated with about 20–30% higher ORs. Residing in households with ≥5 residents versus 1–2 residents was associated with higher ORs against the ancestral strain. Working primarily in an outdoor versus indoor setting was associated with 40–50% lower ORs for protective immunity against the ancestral strain, but less so against the Delta strain. Younger age (5–14 years) and older age (≥65 years) were associated with or trended to lower ORs against the ancestral strain, with overall similar but less pronounced trends against the Delta strain.

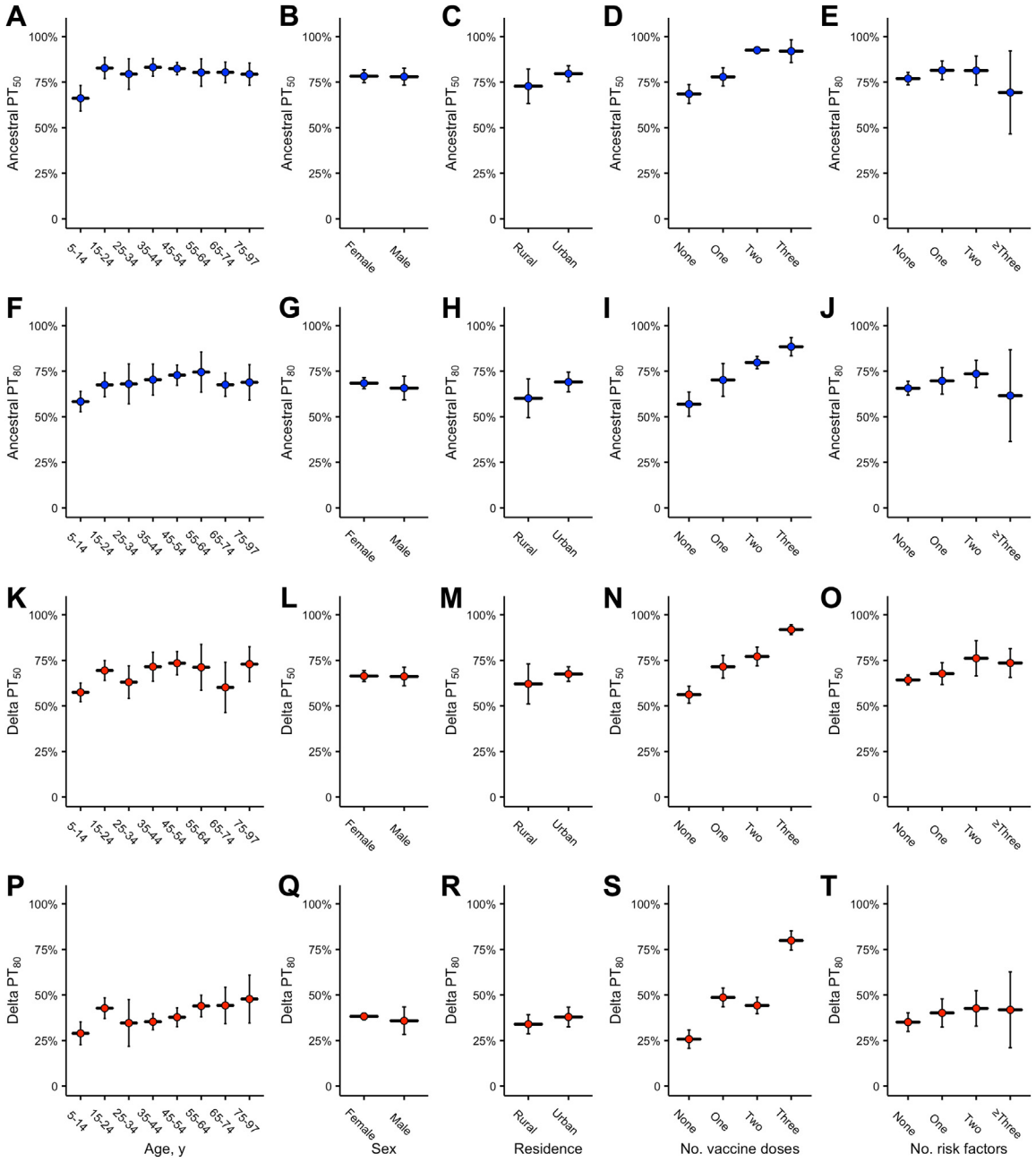

Fig. 3: **Estimated protective immunity sufficient to provide at least 50% (PT_{50}) and 80% (PT_{80}) protection against symptomatic SARS-CoV-2 infection by August 2021, Dominican Republic.** Data are weighted for study design and selection probability, corrected for finite populations, and post-stratified for age and gender (Supplementary Table S9). Upper panels show results for the ancestral Wuhan strain (blue), and lower panels Delta strain (red). Horizontal black bars with central-colored circles indicates point-estimates of the proportion with pseudovirus neutralising titers ≥21 NT_{50} and ≥84 NT_{50}, the titers estimated to provide at least 50% and 80% protection against symptomatic infection, with vertical lines indicating 95% CI. Risk factors for severe COVID-19 include age ≥65 years, obesity (BMI ≥ 30), cardiovascular disease, diabetes, active cancer, chronic kidney disease, immune deficiency conditions, cerebrovascular accident, and chronic obstructive pulmonary disease. Data collected from 30 June to 12 October 2021, with August 21, 2021, the survey midpoint.

Discussion

We report one of the few national SARS-CoV-2 serological studies conducted in 2021, and the first at any time to generate estimates of population-level immune protection. Our findings suggest that about 90% of the national population aged five years or older had been immunologically exposed to SARS-CoV-2 through infection, vaccination, or both, and about three-quarters had been infected during the prior 18-months. An estimated 78% and 66% of the population had sufficient SARS-CoV-2 neutralising activity to provide a minimum of 50% protection against symptomatic infection by the ancestral and Delta strains, respectively. The level of exposure and prior infection is striking, although as evidenced by the large subsequent waves of Delta and Omicron transmission (Fig. 1), substantial segments of the population remained susceptible to symptomatic infection, particularly against viral variants with immune evasion capabilities.

Younger age (5–14 years) and working in outdoor settings were independently associated with lower anti-S prevalence, while residing in an urban setting and number of household residents were associated with higher anti-S prevalence. These findings align with reports of lower seroconversion after laboratory confirmed infection among younger children vs adults[19] and SARS-CoV-2 population representative serological surveys in the pre-COVID-19 vaccine period reported markedly lower seroprevalence among younger children versus adults.[20,21] Lower transmission in outdoor settings is well documented[22] but this is the first study we are aware of that provides population-level estimates of the differences in risk between indoor and outdoor work environments. Living in urban settings and households with more residents increases the opportunity for SARS-CoV-2 transmission and higher seroprevalence in these settings has been previously reported.[20,23]

Our findings suggests that about 37% of the population had some form of hybrid immunity, defined as immunity elicited by a combination of infection and vaccination, 40% had been infected but not vaccinated, 12% had been vaccinated but not infected, and 11% neither vaccinated nor previously infected. With ongoing COVID-19 vaccination efforts and two waves of infection attributable to Delta and particularly Omicron that occurred after our study, current levels of hybrid immunity are likely to be substantially higher. Given SARS-CoV-2 infection prior to a primary vaccine series increases binding and neutralising level titers, broadens and sustains the B cell response with improved cross-neutralization of viral variants, and decreases the risk of subsequent infections, compared to infection-naive primary vaccine series recipients,[24–26] high levels of hybrid immunity in the Dominican Republic and immunologically comparable countries are likely to play a key role in future transmission dynamics.

To understand the immune landscape in the Dominican Republic and quantify how high levels of antigen exposure translate to immune protection, we developed a novel approach combining correlates of protection, functional markers of immunity, and machine learning methods. By testing approximately 5% of samples for SARS-CoV-2 neutralising activity and applying machine learning methods we generated the first estimates of population-level immunological protection for SARS-CoV-2. These findings and the application of these methods may provide calibration for predictive transmission models and identify populations who have been exposed to SARS-CoV-2 antigens through infection or vaccination but remain at high risk for infection and potentially poor clinical outcomes. For example, large segments of the population with two or more risk factors for severe COVID-19 remained susceptible to symptomatic infection, suggesting that these populations should be prioritized for future vaccination and other public health interventions.

We used outputs from the machine learning models to identify factors independently associated with levels of immunological protection against symptomatic infection (Table 3). As anticipated, the number of COVID-19 vaccine doses received was most strongly associated with protection. But, additional factors were identified, suggesting either differential risk of infection, variable immune response to antigen exposure, or both. By considering risks for prior infection, using independent measures of anti-S positivity (Table 2), we explored if differences in protection immunity were driven primarily by prior infection or biological differences in the immune response. For example, higher levels of immunological protection across urban dwellers, individuals working primarily in indoor settings, and among residents of larger households largely aligned with higher ORs for anti-S seropositivity across these variables, suggesting higher levels of prior infection was the primary driver of higher levels of protection. Conversely, lower levels of immunological protection were strongly and consistently observed among active smokers (with only a non-significant trend to lower ORs for anti-S seropositivity), suggesting differences in the immunogenic response among active smokers. This finding is supported by reports of lower SARS-CoV-2 antibody titers among smokers following COVID-19 vaccination.[27] Age appears to exert a similar biological role with lower protection above 64 years of age, a finding that aligns with reports of lower SARS-CoV-2 neutralising activity among elderly after a two-dose COVID-19 vaccine series.[28]

This study has multiple strengths. We used a rigorous multistage sampling method with final estimates carefully weighted for survey design and adjusted to reflect the national population demographics. Sera were tested with widely used and validated

Variable	Ancestral PT50		Ancestral PT80		Delta PT50		Delta PT80	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Gender								
Female	*Ref*		*Ref*		*Ref*		*Ref*	
Male	1.03 (0.89–1.20)	0.67	0.96 (0.84–1.09)	0.50	0.97 (0.85–1.1)	0.63	1.02 (0.90–1.1)	0.78
Age, y								
5–14	0.47 (0.36–0.61)	**<0.001**	0.81 (0.64–1.03)	0.08	0.83 (0.66–1.0)	0.12	0.91 (0.72–1.1)	0.43
15–24	1.00 (0.77–1.29)	0.98	1.20 (0.98–1.47)	0.08	1.32 (1.08–1.6)	**0.01**	1.09 (0.90–1.3)	0.37
25–34	0.98 (0.75–1.27)	0.87	1.06 (0.87–1.30)	0.55	1.00 (0.82–1.2)	0.98	0.88 (0.72–1.0)	0.19
35–44	*Ref*		*Ref*		*Ref*		*Ref*	
45–54	0.94 (0.72–1.22)	0.63	1.11 (0.90–1.37)	0.32	1.06 (0.87–1.3)	0.55	0.93 (0.76–1.1)	0.45
55–64	0.79 (0.61–1.03)	0.08	1.10 (0.89–1.36)	0.39	1.07 (0.86–1.3)	0.56	1.19 (0.97–1.4)	0.09
65–74	0.68 (0.49–0.92)	**0.01**	0.83 (0.64–1.08)	0.17	0.71 (0.55–0.9)	**0.01**	1.02 (0.80–1.3)	0.86
≥75	0.40 (0.28–0.56)	**<0.001**	0.61 (0.45–0.83)	**0.001**	0.69 (0.51–0.9)	**0.01**	0.88 (0.65–1.1)	0.39
Residence								
Rural	*Ref*		*Ref*		*Ref*		*Ref*	
Urban	1.30 (1.14–1.49)	**<0.001**	1.21 (1.08–1.35)	**0.001**	1.18 (1.05–1.3)	**0.004**	1.20 (1.08–1.3)	**0.001**
No. HH residents								
1–2	*Ref*		*Ref*		*Ref*		*Ref*	
3–4	1.10 (0.93–1.30)	0.28	1.00 (0.86–1.15)	0.96	1.03 (0.89–1.1)	0.67	1.03 (0.89–1.1)	0.71
5–6	1.79 (1.47–2.18)	**<0.001**	1.48 (1.26–1.75)	**<0.001**	1.13 (0.96–1.3)	0.14	1.11 (0.95–1.2)	0.21
≥7	1.53 (1.20–1.97)	**0.001**	1.36 (1.11–1.68)	**0.004**	1.21 (0.99–1.4)	0.07	1.23 (1.01–1.5)	**0.04**
Work environment								
Indoor	*Ref*		*Ref*		*Ref*		*Ref*	
Indoor and outdoor	0.84 (0.62–1.14)	0.26	0.83 (0.65–1.06)	0.13	0.90 (0.71–1.1)	0.38	1.03 (0.83–1.2)	0.79
Outdoor	0.53 (0.39–0.73)	**<0.001**	0.60 (0.46–0.79)	**<0.001**	0.71 (0.54–0.9)	**0.01**	0.86 (0.66–1.1)	0.27
NR	0.95 (0.73–1.22)	0.70	0.84 (0.69–1.03)	0.10	0.90 (0.73–1.0)	0.28	1.17 (0.98–1.4)	0.09
No. risk factors								
None	*Ref*		*Ref*		*Ref*		*Ref*	
One	1.02 (0.86–1.21)	0.84	1.01 (0.87–1.16)	0.92	1.02 (0.89–1.1)	0.75	0.95 (0.83–1.0)	0.45
Two	0.78 (0.61–1.01)	0.05	0.92 (0.74–1.13)	0.42	1.10 (0.89–1.3)	0.36	0.99 (0.81–1.2)	0.96
≥Three	0.78 (0.54–1.12)	0.18	0.93 (0.68–1.27)	0.63	1.05 (0.76–1.4)	0.78	0.87 (0.64–1.1)	0.37
Smoking history								
Nonsmoker	*Ref*		*Ref*		*Ref*		*Ref*	
Current smoker	0.66 (0.52–0.84)	**0.001**	0.62 (0.50–0.76)	**<0.001**	0.56 (0.46–0.6)	**<0.001**	0.69 (0.55–0.8)	**0.001**
No. vaccine doses								
None	*Ref*		*Ref*		*Ref*		*Ref*	
One	1.48 (1.23–1.78)	**<0.001**	1.77 (1.50–2.09)	**<0.001**	1.88 (1.60–2.2)	**<0.001**	1.89 (1.61–2.2)	**<0.001**
Two	3.73 (3.17–4.38)	**<0.001**	2.47 (2.18–2.81)	**<0.001**	2.62 (2.31–2.9)	**<0.001**	1.88 (1.66–2.1)	**<0.001**
Three	18.41 (10.69–35.04)	**<0.001**	13.97 (9.45–21.57)	**<0.001**	16.23 (10.85–25.4)	**<0.001**	18.25 (13.66–24.8)	**<0.001**

Ref = reference. Bold face p-value signify p < 0.05. 45 individuals with missing data were excluded. All other study participants were included (n = 6638). Estimates are based on data collected from 30 June to 12 October 2021, with August 21, 2021, the survey midpoint. Risk factors are risk factors for severe COVID-19 and include age ≥65 years, obesity (BMI ≥ 30), cardiovascular disease, diabetes, active cancer, chronic kidney disease, immune deficiency conditions, prior cerebrovascular accident, and chronic obstructive pulmonary disease. Work environment enumerated for active workers and excluded students, housepersons, retirees and unemployed. Model performance measures are reported in Supplementary Table S9.

Table 3: **Multivariable logistic regression predictors of protective immunity sufficient to provide at least 50% (PT_{50}) and 80% (PT_{80}) protection against symptomatic SARS-CoV-2 infection by ancestral and Delta strains by August 2021, Dominican Republic.**

immunoassays so our findings can be compared across other settings. Estimates of prior infection were adjusted for assay performance and seroreversion, using the same immunoassay and based on the longest cohort of post-infection antibody kinetics reported to date. We developed novel methodological approaches to generate the first population level estimates of immunological protection using directly measured immunological markers, methods that may be applicable to other settings. Yet there are several limitations. Given ongoing community transmission and COVID-19 vaccination rollout during the study period, there may be variability across clusters based on interval exposure and time since the last vaccine dose that may impact our findings in either direction. Assay performance is based on symptomatic PCR-confirmed SARS-CoV-2 cases and

sensitivity may be lower across asymptomatic infections, resulting in higher seroprevalence and prior infection rates than we report. A higher proportion of females, older adults, and rural residents were enrolled than the national demographic profile, but we adjusted for these differences. We enrolled approximately 50% of eligible participants, with most non-enrolment due to absence from the household at the time of the serosurvey which would most likely lead to underestimating seroprevalence, prior infection, and immunological protection given socially active individuals are at higher risk of exposure. However, systematic differences between study participants vs those not present at the time of the survey or that refused to participate would not be accounted for by post-stratification, which may impact our findings in either direction. To provide national estimates of prior infections, we assumed similar rates of prior infection across individuals vaccinated with anti-S-only vaccines and those vaccinated with one or more doses of a whole inactivated viral vaccine, the implications of which are complex (for example lower efficacy of the whole virus vaccines would result in higher rates of prior infection) and may impact our estimates in either direction. To estimate ICR and IFR we assumed prior infection was similar between the 5- to 9-year-old and 0- to 4-year-old age groups, although any differences are unlikely to meaningfully affect our results. IFR estimates cover the entire period to the study midpoint and are likely lowered by vaccination and improvement in clinical management over time. Estimates of immunological protection do not account for cellular immunity or non-neutralising antibody-mediated effector functions that may provide additional immune protection.[29] Measures of immunological protection were assessed against the ancestral and Delta viral strains and are anticipated to be lower against strains with more effective immune evasion. Yet, differences in immunological protection across specific subgroups (such as active vs non-smokers) are anticipated to be similar for immune evading strains given similar findings between the ancestral and Delta strains, and given the Delta strain exhibits moderate immune evasion (i.e., 2–5 fold reduction in neutralising activity) compared to the ancestral strain.[30] Although random forest model accuracies were high, and misclassification was largely balanced between false negatives and false positives, misclassification may impact our estimates of immunological protection and regression model outputs in either direction. Uncertainty generated through machine learning prediction was not captured in logistic regression models but is reported in Supplementary Table S7. Given the immunological threshold for protection against severe COVID-19 is markedly lower than for symptomatic infection, we anticipate more of the population would be protected against severe outcomes than we report for symptomatic infection, an assumption supported by the low CFR during the post-study waves of infection.

In conclusion, cumulative infections substantially exceeded prior estimates and overall immunological exposure generated substantial population level protective immunity. After controlling for confounders, markedly lower immunological protection was observed across certain subgroups, findings that can guide public health interventions and may be generalizable to other settings and viral strains. Receipt of a third COVID-19 vaccine dose was the most important determinant of immunological protection against symptomatic infection and where possible should be prioritized for high-risk populations.

Disclaimer

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the U.S. Centers for Disease Control and Prevention.

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Data sharing statement

The data that support the findings of this study are available from the corresponding author, [E.J.N.], upon reasonable request.

Declaration of interests

E.J.N. is the PI on a US CDC funded U01 award that funded the study, and C.L.L., A.K., D.D., M.d.S.A., A.C.R., H.M., S.G., M.C.E., W.D., N.I., G.A., B.H., K.D., M.B., E.F., and L.I. have received salaries, consultancy fees, or travel paid through this award. E.Z.G., B.L., and A.E.-B. are employees of the US CDC. B.H., C.T., L.C., F.P., and R.S.-R. are employees of the Ministry of Ministry of Health and Social Assistance, Dominican Republic, that was subcontracted with funds from the US CDC award. A.K. and E.F. are supported by the Welcome Trust, UK. D.B. had a patent for COVID-19 vaccine licensed to Janssen. We declare no other competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2022.100390.

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