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Hybrid, vaccine-induced and natural immunity against SARS-CoV-2 in traditional food markets in Bolivia (2020–2022): A cross-sectional analysis of a serological survey

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ABSTRACT

Background: In low-and middle-income countries, market vendors played a crucial role in food security during the coronavirus pandemic. High numbers of contacts, combined with social, political and health system upheaval in Bolivia, meant they were highly exposed to SARS-CoV-2 infections.

Methods: Demographic, clinical and serological data were collected at survey rounds between 2020 and 2022 from a cohort of market vendors in two purposively selected markets where the community and researchers co-promoted health and safety. We used these longitudinal data to examine SARS-CoV-2 anti-spike antibody levels between those vaccinated with and without previous infection and those unvaccinated. The association between antibody levels, and vaccine status, socio-demographic and health information was assessed using linear regression.

Findings: A total of 213 market vendors had repeated serological sampling in July, and November 2021, and again in May 2022. In November 2020, 105 (49.3 %) of this cohort had participated in a pre-vaccination municipal serological survey. Seroprevalence then was 45·7 % (95 %CI 36·3–55·4). By November 2021, 67·8 % of the full cohort had one vaccination and seroprevalence was 83·6 %. We showed IgG levels in those sero-positive were higher in participants with evidence of vaccination and prior infection compared to those unvaccinated. By May 2022, the majority of participants developed antibodies against SARS-CoV-2, and these differences were attenuated.

Interpretation: A substantial proportion of vendors were susceptible to SARS-CoV-2 in late 2020 when, nationally, excess mortality was high. Our analyses suggested a combination of natural infection and vaccination provided better protective antibody levels than natural infection alone at the peak of the pandemic. Future pandemic planning requires timely targeted serological surveys to understand pandemic dynamics and support prompt interventions. In addition, communication with organized communities can inform effectiveness of pandemic mitigation strategies including improved vaccination uptake. Timely quantitative IgG level monitoring can also inform waning immunity.

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1. Introduction

The COVID-19 pandemic has affected households and health systems worldwide. Despite their young populations, South American countries were disproportionally hit. The working-age population represent 52 %, 50 % and 44 % of the estimated COVID-related deaths in Bolivia, Peru, and Brazil, respectively, while they only amount to between 10 and 15 % in European countries [1]. After the first pandemic wave in September 2020, Bolivia ranked sixth worldwide in number of officially confirmed COVID-19 deaths per million despite strong indications of heavy underreporting [2]. Bolivia was after Bangladesh, the country with the highest COVID-19 excess deaths per 100,000 inhabitants worldwide [3].

Bolivia was struck by COVID-19 amid a political crisis. After the October 2019 elections, mass protests broke out leading to the installation of a transition government, distrusted by large segments of the public [4]. This government managed the pandemic response until October 2020. From March 26th to June 1st, 2020, a strict nationwide lockdown with a stringency index of 96 according to the Oxford Coronavirus Government Response Tracker (OxCGRT) project was imposed and maintained at 89·81 until the end of August 2020. The stringency index is a composite measure based on nine response indicators including school closures, workplace closures, and travel bans, rescaled to a value from 0 to 100 (100 = strictest) [5]. This strict lockdown failed to halt the rapid spread of COVID-19 in a context of political tension and stigmatization of infected people [6].

The health system response, traditionally managed at the local level, was taken over at the national level. Nearly one third of trusted primary health care providers were moved to hospitals for COVID-19 triage. No comprehensive national health plan was put in place. The response prioritized containment measures such as isolation centers, prolonged quarantine, and school closures. However, it lacked a structured approach for case detection, screening, and strengthening healthcare services for severe cases. The collapse of the healthcare system amid widespread transmission left a large portion of the population without medical care. Many patients lacked access to treatment, with some dying at home without receiving medical attention [7].

Taken together, lack of social protection for close to 75·6 % of the working population active in the informal sector [1], the political tension, and a weak health system response [6] hindered contact tracing, timely COVID-19 case isolation and treatment leading to a massive infection rate. This was confirmed in a pre-vaccine serology study in January 2021 wherein 43 % of health care workers from a tertiary care hospital in Cochabamba, Bolivia, had SARS-CoV-2 IgG antibodies [9]. Vaccines were available in March 2021 for high-risk groups and from July 2021 onwards for the whole population. Vaccination uptake was however amongst the lowest in the South American region. By January 1st, 2022, only 46·26 % of the Bolivian population had received at least one dose of the vaccine, the average for the South American region was 75·71 % [10].

During this pandemic period, informal market vendors were essential for food security, offering affordable, accessible, and fresh food, as well as infection prevention by default with decentralized markets for communities. These market vendors were however disproportionally exposed to SARS-CoV-2 through a combination of many contacts, shared transport, and limited access to protective equipment [11]. Their vulnerability was further increased by their sedentary lifestyle with a higher prevalence of cardiovascular risk factors like obesity, high blood pressure and diabetes compared to available data for this same region [12].

To address this challenge, an interdisciplinary team of researchers collaborated with the local authorities and market vendors of the municipality of Sacaba in Bolivia to reduce the impact of the pandemic by promoting health and safety in markets. Quarterly follow-up of a cohort of market vendors from November 2020 to May 2022 in a setting with high pre-vaccination seroprevalence of anti-SARS-CoV-2 antibodies combined with the late vaccine availability and low vaccination uptake [13] allowed examination of the evolution of natural immunity, vaccine induced immunity and hybrid (both natural and vaccine derived) immunity. Variations in the immune response related to sociodemographic and cardiovascular risk indicators were also explored. A report of the findings is provided here to help to draw lessons about the role of seroprevalence monitoring on pandemic management and vaccination roll out in high contact settings in low-and-middle income countries.

2. Material and methods

2.1. Study design and data collection

This study is part of a participatory action research project to mitigate the impact of COVID-19 in the Municipality of Sacaba, a mixed rural peri-urban municipality in Cochabamba, Bolivia. A multidisciplinary research team co-created and coordinated through alliances with the municipal authorities, the health network, and the federation of market vendors established health posts in two separate markets as hubs for research and clinical care [12]. These markets were purposively chosen to represent a range of organizational structures. The Quintanilla market is a small market with a closed defined space, about 100 market vendors that belong to a single association or governing body, and a low number of mostly middle- or higher-class customers. The Abasto market is the largest municipal market with a busy but physically open and well-ventilated structure, close to 1000 market vendors belonging to many associations grouped in two different federations, and a high number of diverse, mostly lower- or middle -class customers.

We carried out a longitudinal study in these two markets to report on descriptive characteristics and to examine seroprevalence, infection and vaccine-induced immunity. In both markets, demographic and clinical information was collected in 213 vendors in July 2021, and three rounds of serological sampling were carried out in July 2021, November 2021, and May 2022, see *Fig. 1*. Researchers asked the board of directors of the largest market federation of Sacaba, the overarching governing body of the Quintanilla market association and 80 % of the associations of the Abasto market, to select up to 100 participants from each of the selected markets. For the Abasto market, stratification across the 11 different associations belonging to this federation was requested. Criteria for participation were age over 18 years, and actively trading during the study period. In the Quintanilla market, all 75 actively trading vendors took part, whereas in the Abasto market, a sample of 138 vendors, trading various commodities, were recruited from the different associations by their governing body. Response rates were not collected or available to the researchers. A subset of the sample, 105 (49·3 %) of the 213 participants included in July 2021, had participated in a municipal serological surveillance cross sectional study performed with the same serological assay in November 2020.

Samples at each round were taken within 4 weeks of the round start date. Sociologists used questionnaires to gather data on age, sex, educational level, family composition and living conditions. Medical staff collected clinical information, access to health care, COVID-19 history, cardiovascular risk, height, weight, blood pressure, capillary blood sugar and cholesterol levels.

2.2. Serological survey, July 2021 to May 2022

During all rounds, samples were taken for SARS-CoV-2 serology and qt-PCR irrespective of symptoms. Our primary outcome of interest was serum IgG antibody levels reported in binding antibody units per millilitre (BAU/ml) units. Serology data from all participants were collected in ratio units using the EUROIMMUN Anti-SARS-CoV-2 S1 Curve ELISA (IgG), a commercially available quantitative immunoassay test system [14]. We obtained BAU/ml by multiplying with the conversion factor of 3·2 as detailed in a WHO standardisation of serological tests to allow comparison with other studies [15]. IgG values were truncated at 384 BAU/ml corresponding to the validated linearity range. The threshold for being categorised seropositive was 25·6 BAU/ml.

2.3. Population characteristics and covariates

Vaccination status and dates vaccine doses received were verified through national COVID-19 vaccination registers. Evidence of prior SARS-CoV-2 infection was defined as having a seropositive IgG result in a survey round and not having received any dose of a vaccine or only having received the first vaccine less than 14 days before the round. In each of the rounds the primary exposure of interest was a composite variable based on vaccination status and prior infection, formed of three categories: unvaccinated, vaccinated without evidence of prior infection, and vaccinated with evidence of prior infection.

Obesity was defined as having a body mass index (BMI) of ≥30 according to WHO thresholds. A cardiovascular risk score (see *Supplementary table 1*) was calculated using BMI groupings, blood pressure, glycaemic values, total and HDL cholesterol levels, and smoking status.

2.4. Local COVID-19 data

To put the study data into context, the chronology of COVID-19 waves respective to the sampling rounds and official data related to the pandemic behaviour in Bolivia included in *Table 1*. Data related to officially registered COVID-19 cases, number of people vaccinated and excess mortality at the country level are presented. Excess mortality is presented as the additional proportion of people that died that month compared to what would be expected based on the prior years [10].

2.5. Statistical analysis

Demographic, clinical, vaccination and seropositivity were presented for each survey round and market. Differences in IgG levels across characteristic subgroups of interest were compared within unvaccinated and vaccinated groups using Mann-Whitney *U* test and Kruskal-Wallis's test as appropriate and presented in scatter box plots (*Figs. 2–3*).

To assess factors affecting IgG antibody levels we focused our analysis on serology testing round 2 since by this round over half of the participants had received at least one dose of the vaccine (67·8 %) while a significant number still had not received a vaccine. We used multiple linear regression to estimate the association between being vaccinated (with and without prior infection) and IgG antibody levels amongst seropositive participants compared with being unvaccinated, while adjusting for potential confounders. Confounders were selected a priori based on the research objectives and data sparsity (sex was not adjusted for due to low numbers of males in the cohort). We minimally adjusted for age (model 0), then additionally adjusted for market (to account for difference between market profiles) and educational attainment (as a proxy for socioeconomic status) (model 1), and finally for obesity and cardiovascular risk score (model 2). The multiple linear regression models with the same specifications for round 3 in May 2022 were also conducted. The evidence used to define prior infection for a subgroup of participants came from the additional serological data from the pre-study municipal survey and included in a sensitivity analysis. All analyses were carried out using Stata 17.

2.6. Ethics statement

This study was approved by the Ethics Committee of the Universidad

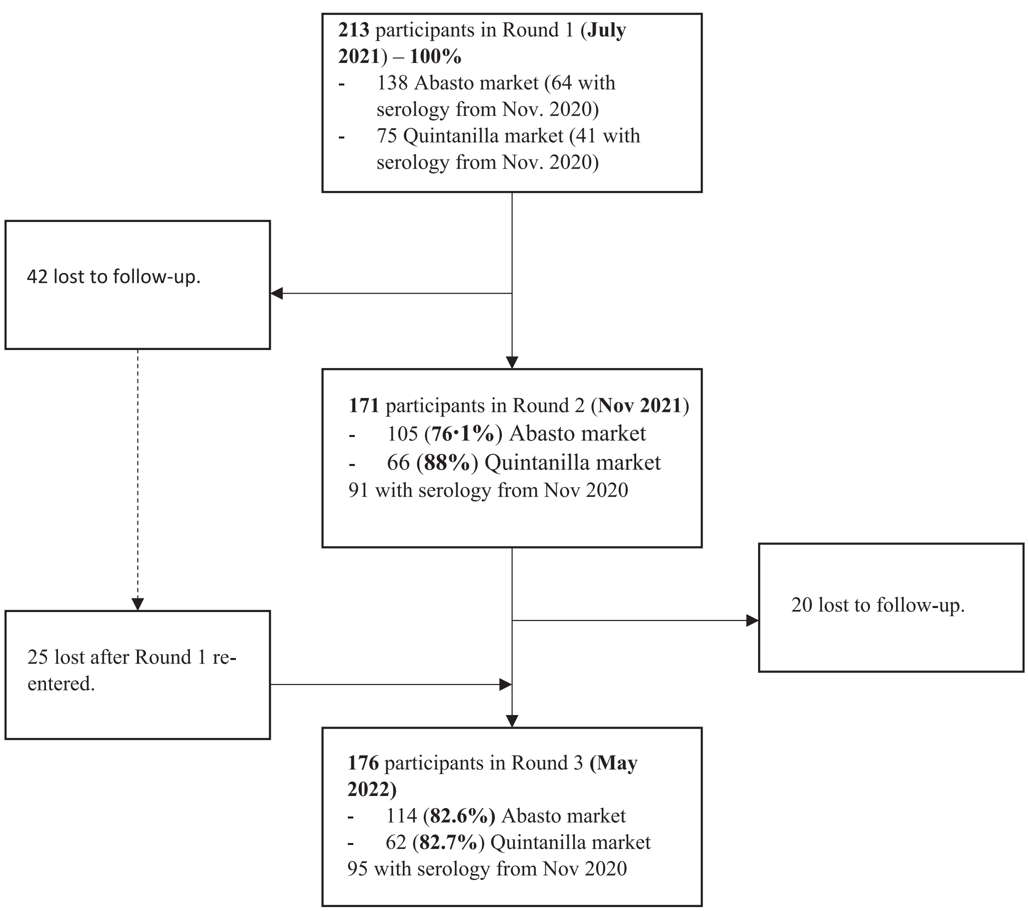

Fig. 1. Flow diagram for the market vendors' cohort

Table. 1
National COVID-19 Cases, Excess Mortality, and Vaccination Rates Compared to Seropositivity and Vaccination Uptake Amongst Market Vendors in Sacaba, Cochabamba Across Pandemic Waves

	July 20	Nov 20	Jan 21	June 21	July 21	Nov 21	Jan 22	May 22
Event	First Wuhan wave	Municipal surveillance	Gamma wave	Delta wave	Round 1 sampling	Round 2 sampling	Omicron wave	Round 3 sampling
Excess mortality*	245·4 %	10.9 %	119.8 %	127.3 %	62.8 %	22.6 %	112.7 %	NA
Registered COVID-19 cases (as % of the population nationally) **	0.6 % (6154 per 1 million people)	1.2 % (11,830 per 1 million people)	1.8 % (17,620 per 1 million people)	3.5 % (35,800 per 1 million people)	3.8 % (37.678 per 1 million people)	4.4 % (44,155 per 1 million people)	7.0 % (69,551 per 1 million people)	7.4 % (74,322 per 1 million people)
vaccination uptake national**	0 %	0 %	0 %	15.4 %	25.4 %	41.5 %	55.1 %	58.9 %
Positive IgG serology in market vendors cohort***		45.7 % (48/105) 95 %CI (36.3–55.4)			81.7 % (174/213) 95 %CI (75.9–86.4)	83.6 % (143/171) 95 %CI (77.3–88.5)		97.2 % (171/176) 95 %CI (93.3–98.8)
Vaccination uptake in market vendors cohort***		0 %	0 %		19.7 %	67.8 %		80.7 %

* Excess mortality in Bolivia: monthly deaths from all causes compared to projection based on previous years for the same month (https://ourworldindata.org/) [10]. NA = not available.
** Cumulative data from Bolivia for the last day of that month (https://ourworldindata.org/) [10].
*** Data from the 213 market vendors followed in this study. Seropositivity threshold was 25·6 BAU/ml. See Methods for information on serological assay.

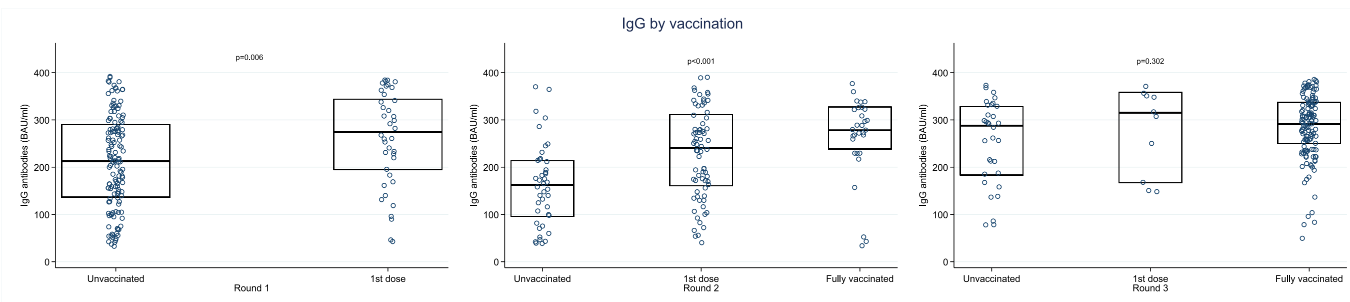

Fig. 2. Box and scatter plots showing IgG antibodies (BAU/ml) by vaccination status amongst seropositive participants in each of serology rounds 1–3.

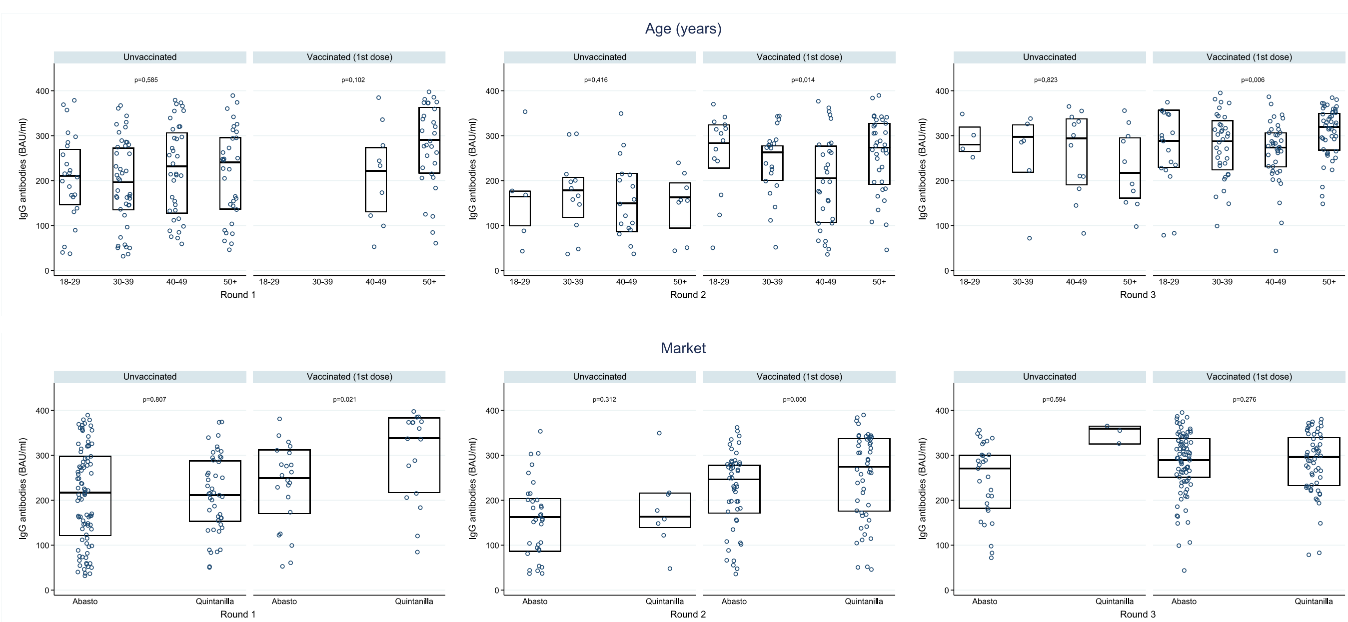

Fig. 3. Box and scatter plots showing IgG antibodies (BAU/ml) stratified by vaccination status and by age and market amongst seropositive participants across Rounds 1–3.

Peruana Cayetano Heredia, Peru, with institutional registration number: CIE IORG0000671 and international registration number: IRB00001014. Ethics approvals were also obtained from the RVC and LSHTM.

3. Results

The timing and seroprevalence at each sampling round compared to the course of the COVID-19 pandemic in Bolivia is described in *Table 1*. Excess mortality in Cochabamba was high and highest during the circulation of the Wuhan strain, although the number of registered COVID-19 cases was low. Excess mortality and a rise in registered cases were documented for the month with the highest excess mortality during every subsequent wave and for the months the serologic surveys were performed [10]. Pre-vaccination seropositivity in the study market vendors was 45·7 % (95 %CI 36·3–55·4) after the first wave and before the second Gamma wave. This was seen in the municipal surveillance in Nov 2020, which included nearly half the cohort participants (46·4 % (64/138) of the Abasto market and 54·7 % (41/75) of the Quintanilla market).

3.1. Study cohort with three rounds of sampling

In July 2021, 213 market vendors were included in round 1 of the cohort, this was 100 % of the participants invited for the Quintanilla market and 13 more than those originally registered by their governing body for the Abasto market. In round 2, 171 participants remained and underwent serology testing, in round 3 this were 176 (see *Fig. 1*). Twenty-four participants lost to follow up after round 1 returned to the cohort for round 3. The proportion of individuals with anti-spike antibody levels of at least 25.6 BAU/ml increased with each sampling round during the COVID-19 pandemic in Bolivia, alongside the rise in vaccination coverage (*Table 1*).

Data collected related to health and socio-demographics are summarised in *Table 2*. Vaccination uptake was lower in the larger Abasto market (57·1 %) compared to the closed, smaller Quintanilla market, with 84·8 % of participants receiving at least one dose vaccination 14 days or more before round 2 testing. By round 3, 18.1 % of Abasto market participants had been fully vaccinated compared with 27.3 % of Quintanilla market participants (*Table 2*). Distribution of the six vaccination types offered was broadly similar in both markets, the most common being the Sinopharm vaccine (*Supplementary table 3*). In the Abasto market nearly 2 in 5 (37·7 %) had none or incomplete primary education, while this was the case for 1 in 5 (22·7 %) in the Quintanilla market. Obesity was also slightly less common in the latter but amongst the cohort overall, most (84·0 %) participants BMIs were categorised as overweight, obese, or severely obese.

Seropositivity was similar in both sets of market vendors. During the municipal serology surveillance in November 2020, when no vaccination was available yet, (29/64) 45·3 % (95 %CI 33·4–57·8) and (19/41) 46·3 % (95 %CI 31·4–61·9) of the market vendors tested in the Abasto market and the Quintanilla market respectively were seropositive for SARS-Cov-2. In July 2021 (round 1), seropositivity amongst market vendors went up to 81·2 % (95 %CI 73·7–86·9) in Abasto and 82·7 % (95 %CI 72·2–89·8) in Quintanilla, increasing to 97·4 % (95 %CI 92·1–99·2) and 96.8 % (95 %CI 87·7–99·2) respectively by round 3.

Thirty-nine of the 105 (37·1 %) participants tested in the municipal round in Nov 2020 had seroconverted by July 2021 (round 1). Between November 2021 (round 2) and May 2022 (round 3) however 14·6 % seroconverted in Abasto compared with only 1·8 % in Quintanilla, where market vendors had higher vaccine uptake levels (*Table 2*).

Supplementary table 4 summarises the percentage seropositive amongst vaccinated participants compared with unvaccinated with some evidence of a higher percentage amongst vaccinated in the first survey round. There was little evidence of a difference by market and several sociodemographic factors apart from weak evidence of an inverse association with education and smoking status only in the first round.

3.2. Association between characteristics and IgG antibody levels in seropositive participants

IgG antibody levels in BAUs/ml in those who were seropositive stratified by vaccine status in each round are noted in *Fig. 2*. In round 2 (November 2021), vaccinated participants had higher crude IgG levels compared to unvaccinated ones, regardless of previous infection. The levels were higher compared to unvaccinated individuals after the first dose and increased even more in those receiving full vaccination more than 14 days before the round ($p < 0{\cdot}001$). The IgG levels were similar for unvaccinated and vaccinated participants in May 2022, round 3 ($p = 0{\cdot}302$) (*Fig. 2*).

In all rounds there was some suggestion at the crude level of higher IgG levels in those who received at least a first vaccination dose with the unvaccinated only for the participants aged ≥50 years (*Fig. 3*). We observed higher IgG levels for vaccinated participants in Quintanilla market ($p < 0{\cdot}001$) compared with Abasto in round 2, and a similar trend in round 1. There was limited evidence of variation in IgG levels amongst both unvaccinated and vaccinated across educational attainment, obesity, and cardiovascular risk, though there was some suggestion of higher IgG levels amongst unvaccinated obese participants in round 3 (*Supplementary fig. 1*).

In the multiple regression analysis of the IgG antibody levels in round 2 we found that amongst seropositive participants, there was evidence of increased mean IgG levels in those vaccinated with a prior infection (62·04 BAU/ml (95 %CI 18·27–105·80 $p = 0{\cdot}017$)) compared with unvaccinated participants while minimally adjusting for age, and this association remained when adjusting for other potential confounders (49·81 BAU/ml (95 %CI 4·75–94·88 $p = 0{\cdot}049$)) (Table 3). Adjusted IgG antibodies in Quintanilla market were higher (41·20 (95 %CI 7·86–74·55 $p = 0{\cdot}016$) than in Abasto market vendors despite the application of a similar mix of vaccines. We found no evidence of an association between increased IgG levels and age, obesity, cardiovascular risk score or educational status. See Table 3 for estimates.

A sensitivity analysis that included prior infections from the municipal serology survey in the linear regression analysis, found slightly more evidence of higher mean IgG antibody levels in people vaccinated with prior infection compared with vaccinated without prior infection and unvaccinated amongst seropositive participants (*Supplementary table 2*).

In round 3, May 2022, mean IgG levels no longer differed in those vaccinated with prior infection compared with those without prior infection after adjusting for confounders. There was also no difference by market. There was some evidence for an association between increased mean IgG levels amongst those vaccinated with no prior infection (37·08 (95 %CI 4·64–69·51 $p = 0{\cdot}077$)) versus unvaccinated controlling for age only. However, the latter association becomes less clear when adjusting for the full set of confounders (*Supplementary table 3*).

4. Discussion

Monitoring the IgG antibody prevalence and levels over time in a high contact population of market vendors in Bolivia provided additional insights into the pandemic evolution, the vaccine induced immunity, immunity waning and the impact of market organization. The results show the relevance of IgG antibody level measurements to monitor the SARS-CoV-2 presence and immunity over time and if it had been available early on may have supported decisions on timely mitigation strategies like vaccination. Vaccination strategies, including the identification of risk groups, can be better planned, and coordinated when data on antibody levels and seroconversion are available.

Table. 2
Infection-related, vaccination-related and sociodemographic characteristics of the cohort of market vendors stratified by market (Abasto and Quintanilla) across the three serology survey rounds (total $N = 213$).

Infection- and vaccination-related characteristics	Round 1 (July 2021)			Round 2 (Nov. 2021)			Round 3 (May 2022)		
	Overall	Abasto	Quint.	Overall	Abasto	Quint.	Overall	Abasto	Quint.
Participants in each round (n/N (%))	213/213 (100)	138/138 (100)	75/75 (100)	171/213 (80·3)	105/138 (76·1)	66/75 (88)	176/213 (82·6)	114/138 (82·6)	62/75 (82·7)
	$N = 213$	$N = 138$	$N = 75$	$N = 171$	$N = 105$	$N = 66$	$N = 176$	$N = 114$	$N = 62$
Seropositivity: Positive (≥25·6 BAU/ml) n (%)	174 (81·7)	112 (81·2)	62 (82·7)	143 (83·6)	85 (81·0)	58 (87·9)	171 (97·2)	111 (97·4)	60 (96·8)
95 % Confidence Interval (%)	(75·9–86·4)	(73·7–86·9)	(72·2–89·8)	(77·3–88·5)	(72·2–87·4)	(77·3–93·9)	(93·3–98·8)	(92·1–99·2)	(87·7–99·2)
Seroconversion from previous round (n/n (%))	39/105 (37·1) *	24/64 (37·5) *	15/41 (36·6) *	9/171 (5·3)	6/105 (5·7)	3/66 (4·5)	15/151 (9·9)	14/96 (14·6)	1/55 (1·8)
Seroreversion from previous round (n/N (%))	1/105 (1·0)	0/64 (0·0)	1/41 (2·4)	7/171 (4·1)	6/105 (5·7)	1/66 (1·5)	0/151 (0·0)	0/96 (0·0)	0/55 (0·0)
Vaccination (n (%))	N = 213	N = 138	N = 75	N = 171	N = 105	N = 66	N = 176	N = 114	N = 62
1st dose >14 days before round date	42 (19·7)	23 (16·7)	19 (25·3)	116(67·8)	60 (57·1)	56 (84·8)	142/ (80·7)	84/ (73·7)	58(93·5)
1–6 month before	38 (17·8)	21 (15·2)	17 (22·7)	96 (56·1)	50 (47·6)	46 (69·7)	22 (12·5)	16 (14·0)	6 (9·7)
Fully vaccinated[1]2 >14 days before round date	0 (0·0)	0 (0·0)	0 (0·0)	37 (21·6)	19 (18·1)	18 (27·3)	131 (74·4)	76 (66·7)	55 (88·7)
1–6 month before	0 (0·0)	0 (0·0)	0 (0·0)	37 (21·6)	19 (18·1)	18 (27·3)	95 (54·0)	56 (49·1)	39 (62·9)
PCR/LAMP Positive	10 (4·7)	10 (7·2)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Table 2b: Sociodemographic characteristics (n (%))	Round 1 (July 2021)			Round 2 (Nov. 2021)			Round 3 (May 2022)		
	Overall N = 213	Abasto N = 138	Quint. N = 75	Overall N = 171	Abasto N = 105	Quint. N = 66	Overall N = 176	Abasto N = 114	Quint. N = 62
Age[2]									
18–29	32 (15·0)	20 (14·5)	12 (16·0)	21 (12·3)	10 (9·5)	11 (16·7)	24 (13·6)	13 (11·4)	11 (17·7)
30–39	50 (23·5)	31 (22·5)	19 (25·3)	40 (23·4)	23 (21·9)	17 (25·8)	42 (23·9)	26 (22·8)	16 (25·8)
40–49	59 (27·7)	43 (31·2)	16 (21·3)	55 (32·2)	40 (38·1)	15 (22·7)	52 (29·5)	38 (33·3)	14 (22·6)
50+	72 (33·8)	44 (31·9)	28 (37·3)	55 (32·2)	32 (30·5)	23 (34·8)	58 (33·0)	37 (32·5)	21 (33·9)
Sex									
Female	183 (85·9)	126 (91·3)	57 (76·0)	146 (85·4)	96 (91·4)	50 (75·8)	151 (85·8)	104 (91·2)	47 (75·8)
Male	30 (14·1)	12 (8·7)	18 (24·0)	25 (14·6)	9 (8·6)	16 (24·2)	25 (14·2)	10 (8·8)	15 (24·2)
Education level									
None or incomplete primary	69 (32·4)	52 (37·7)	17 (22·7)	52 (30·4)	36 (34·3)	16 (24·2)	58 (33·0)	44 (38·6)	14 (22·6)
Primary or some secondary	64 (30·0)	42 (30·4)	22 (29·3)	55 (32·2)	34 (32·4)	21 (31·8)	52 (29·5)	33 (28·9)	19 (30·6)
Secondary	55 (25·8)	23 (16·7)	32 (42·7)	44 (25·7)	18 (17·1)	26 (39·4)	48 (27·3)	22 (19·3)	26 (41·9)
Technical or university	25 (11·7)	21 (15·2)	4 (5·3)	20 (11·7)	17 (16·2)	3 (4·5)	18 (10·2)	15 (13·2)	3 (4·8)
HH size									
1–3	50 (23·5)	34 (24·6)	16 (21·3)	37 (21·6)	24 (22·9)	13 (19·7)	44 (25·0)	29 (25·4)	15 (24·2)
4–7	140 (65·7)	89 (64·5)	51 (68·0)	118 (69·0)	72 (68·6)	46 (69·7)	112 (63·6)	72 (63·2)	40 (64·5)
8+	23 (10·8)	15 (10·9)	8 (10·7)	16 (9·4)	9 (8·6)	7 (10·6)	20 (11·4)	13 (11·4)	7 (11·3)
Clinical characteristics									
Diabetes[3]									
Prediabetic	88 (41·3)	57 (41·3)	31 (41·3)	81 (47·4)	51 (48·6)	30 (45·5)	81 (46·0)	53 (46·5)	28 (45·2)
Diabetic	25 (11·7)	17 (12·3)	8 (10·7)	19 (11·1)	11 (10·5)	8 (12·1)	21 (11·9)	15 (13·2)	6 (9·7)
Hypertension[4]									
Prehypertensive	85 (39·9)	51 (37·0)	34 (45·3)	71 (41·5)	40 (38·1)	31 (47·0)	72 (40·9)	45 (39·5)	27 (43·5)
Hypertensive	22 (10·3)	11 (8·0)	11 (14·7)	17 (9·9)	9 (8·6)	8 (12·1)	17 (9·7)	9 (7·9)	8 (12·9)
BMI									
18·5–24·9 (Healthy)	34 (16·0)	15 (10·9)	19 (25·3)	28 (16·4)	10 (9·5)	18 (27·3)	27 (15·3)	11 (9·6)	16 (25·8)
25–29·9 (Overweight)	81 (38·0)	57 (41·3)	24 (32·0)	60 (35·1)	35 (33·3)	25 (37·9)	61 (34·7)	43 (37·7)	18 (29·0)

(*continued on next page*)

Table. 2 (*continued*)

Infection- and vaccination-related characteristics	Round 1 (July 2021)			Round 2 (Nov. 2021)			Round 3 (May 2022)		
	Overall	Abasto	Quint.	Overall	Abasto	Quint.	Overall	Abasto	Quint.
30–39·9 (Obese)	88 (41·3)	58 (42·0)	30 (40·0)	74 (43·3)	53 (50·5)	21 (31·8)	77 (43·8)	51 (44·7)	26 (41·9)
40+ ("Severe" obese)	10 (4·7)	8 (5·8)	2 (2·7)	9 (5·3)	7 (6·7)	2 (3·0)	11 (6·3)	9 (7·9)	2 (3·2)
Smoking status									
No	193 (90·6)	130 (94·2)	63 (84·0)	157 (91·8)	101 (96·2)	56 (84·8)	158 (89·8)	107 (93·9)	51 (82·3)
Yes	19 (8·9)	7 (5·1)	12 (16·0)	13 (7·6)	3 (2·9)	10 (15·2)	17 (9·7)	6 (5·3)	11 (17·7)

Proportions for characteristics are calculated from the number participating in each round. Proportions of missing values and first row are calculated from cohort total ($N = 138$ for Abasto, $N = 75$ for Quintanilla). Proportions for seroconversion and seroreversion from previous rounds are calculated from the total with serology results in the current and previous round.

[*] Seroconversion from the municipal pre-study serology survey in Nov. 2020. During this pre-study survey 29 (45·3) in Abasto and 19 (46·3) in Quintanilla were seropositive.

[1] fully vaccinated is defined here as two doses given for Astrazeneca, Pfizer, Moderna, Sinopharm and Sputnik-V. One dose for Johnson & Johnson. 41 participants had a discordant combination of multiple vaccine types, 39 of which were given a different type for their booster doses only (i.e., the full dose regimen was with the same vaccine)

[2] Age on 1st of July 2021

[3] Normal: fasting <100 mg/ dl; non-fasting <140 mg/dl. Pre-diabetes: fasting: 100–125 mg/dl; non-fasting: 140–199 mg/dl. Diabetes: fasting ≥126 mg/dl; non-fasting ≥200 mg/dl (glycaemic values).

[4] Normal: ≤ 120 systolic and ≤ 80 diastolic. Pre-hypertension: 121–139 systolic or 81–89 diastolic. Hypertension: ≥ 140 systolic or ≥ 90 diastolic (blood pressure).

Table 3

Linear regression models for the association between vaccination status, prior infection and other covariates and IgG levels (in BAU/ml) in those who were seropositive in Round 2 (November 2021).

	Round 2								
Covariates	Model 0[1] ($N = 143$)			Model 1 (N = 143)			Model 2 (N = 143)		
	n (%)	Coefficients (95 % CI)	p-value	n (%)	Coefficients (95 % CI)	p-value	n (%)	Coefficients (95 % CI)	p-value
Constant term		144·32 (76·42–212·22)			134·46 (66·76–202·16)			136·43 (65·82–207·05)	
Unvaccinated	24 (16·8)	0·00 (ref)		24 (16·8)	0·00 (ref)		24 (16·8)	0·00 (ref)	
Vaccinated + no prior infection	37 (25·9)	31·64 (−18·53–81·81)	0·017	37 (25·9)	16·27 (−34·88–67·43)	0·048	37 (25·9)	14·81 (−37·13–66·75)	0·049
Vaccinated + prior infection[2]	82 (57·3)	62·04 (18·27–105·80)		82 (57·3)	49·67 (4·99–94·35)		82 (57·3)	49·81 (4·75–94·88)	
Age (years)		0·61 (−0·66–1·89)	0·344		0·74 (−0·52–2·00)	0·248		0·77 (−0·50–2·05)	0·232
Market									
Abasto				85 (59·4)	0·00 (ref)		85 (59·4)	0·00 (ref)	
Quintanilla				58 (40·6)	42·18 (9·30–75·05)	0·012	58 (40·6)	41·20 (7·86–74·55)	0·016
Education									
None/primary				90 (62·9)	0·00 (ref)		90 (62·9)	0·00 (ref)	
Secondary/university				53 (37·1)	−4·93 (−37·51–27·64)	0·765	53 (37·1)	−5·28 (−38·10–27·54)	0·751
Not obese							71 (49·7)	0·00 (ref)	
Obese							72 (50·3)	−10·99 (−54·13–32·14)	0·615
Cardiovascular risk									
6–14							61 (42·7)	0·00 (ref)	
15+							82 (57·3)	5·01 (−38·54–48·57)	0·820

P-values are Wald tests for heterogeneity. Coefficients are IgG levels in BAU/ml. Cell counts and proportion of total for categorical parameters are presented.

[1] Baseline model minimally adjusted for age in years (analysed as a continuous variable). Model 1 is adjusted for age, market, and education level. Model 2 is adjusted for age, market, education level, obesity, and cardiovascular risk score.

[2] Prior SARS-CoV-2 infection was defined as reporting a seropositive IgG result in a previous survey round and not having received the vaccine or having received the vaccine less than 14 days before the round.

4.1. Underreporting of SARS-CoV2 infection rate

The findings of this study confirm a high SARS-CoV-2 infection rate in Bolivia, with seroprevalence before vaccination was available similar to a study in healthcare workers in Cochabamba, Bolivia, in January 2021 (43.4 %, 95 % CI 38.8–48.0) [9]. Both studies suggest a massive underreporting of COVID-19 cases in Bolivia, reported as 3·8 % of the population in July 2021 [10]. In Bolivia, the very limited testing carried out, particularly during the first wave of the pandemic (average of 2 tests per case between May and August 2020), led to an underestimation of the infection rate and related deaths. The seroprevalence estimates in this study may help to validate the forecasts from an early modelling study published during the first wave with a suspected infection rate of over half of the population at some point during the pandemic [16].

4.2. Protective effect of the vaccine

Higher levels of IgG antibodies were observed in vaccinated participants with previous infection compared to those without prior infection, as in previous studies [17]. The level of IgG antibodies in unvaccinated seropositive market vendors was lower compared to vaccinated market vendors in July 2021, during the Delta wave, and in November 2021, before the Omicron wave. During the delta wave the average BAU/ml levels were above 264 in those vaccinated, inferring protection to the Wuhan variant [18], but less so to the Delta variant with an expected protective effect for BAU/ml above 500 [19]. Notwithstanding, none of the 10 participants who tested positive with qt-PCR in July 2021 had received a vaccine. This may suggest a protective effect of the vaccine even below the BAU/ml threshold, possibly due to hybrid immunity (immunity from both natural infection and vaccination) in those vaccinated.

4.3. Waning of natural immunity

A similar protective effect for those fully vaccinated was seen for the Omicron wave. Although the seroconversion due to the Omicron variant mount a relatively low antibody response, 46·4 BAU/ml, compared to 435·5 and 358 BAU/ml in average for the delta and Wuhan variant respectively [20,21], in this study the average IgG antibody levels in unvaccinated seropositive participants rose after the Omicron wave, from November 2021 to May 2022, while there was minimal change for the fully vaccinated. This suggests a protective effect against the Omicron wave for those fully vaccinated. In November 2021, we found the crude IgG levels were lower in the seropositive unvaccinated than in the seropositive vaccinated. These surveillance data could have informed timelier vaccine availability.

4.4. Hybrid immunity

High pre-vaccination seropositivity (78·9 %) in July 2021, the increase in IgG levels for those with a single dose vaccine and the seropositive unvaccinated from November 2021 to May 2022 (up from 78·9 % in July 2021 to 94·1 % by May 2022), indicate that most participants presented hybrid immunity, vaccination and infection, or had been infected more than once with different SARS-CoV-2 variants by May 2022. Studies suggest that antigen exposure from natural infection before or after vaccination substantially boosts the quantity, quality, and breadth of humoral immune response [22] Due to widespread natural infection in this study population, it is most probable that nearly all participants were exposed before or after vaccination, leading to high levels of hybrid as well as natural immunity in those vaccinated by the third serological survey round [6].

4.5. Risk groups

The analysis showed no association between changes in mean IgG levels and obesity after adjusting for age in this cohort of market vendors, however the small sample size and high levels of obesity in the cohort may have reduced our ability to detect subgroup effects of the association between hybrid immunity and increased IgG response with respect to this characteristic. Previous research has found associations between obesity and COVID-19-related morbidity and mortality [23], and a recent study showed accelerated waning of vaccine-induced humoral immunity in individuals with severe obesity [24].

4.6. Infection risk and market type

Higher IgG levels ($p = 0{\cdot}016$) were observed amongst the market vendors in Quintanilla adjusting for vaccination uptake and other covariates. This is compatible with high SARS-CoV-2 circulation in the smaller closed Quintanilla market, higher than in the larger open, more ventilated, Abasto market. Additionally, the Quintanilla market offers a more diverse set of products, comparable to a grocery store, leading to contact with many different suppliers.

4.7. Massive vaccination campaign and the Delta wave

In Bolivia, the Delta wave led to a high death toll in young people with an excess mortality of 140% in June 2021 [25]. This took place just before the first round of this study, in July 2021, where 10/213 people swabbed had COVID-19 virus RNA on qt-PCR. High infection rates led to high mortality due to the lack of oxygen and health system capacity [26]. Much of the mortality can be associated with late access to vaccines for people under 40 Initiation of massive vaccination campaigns in June 2021, coincided with peak in mortality which led to some distrust in the vaccine in the population. Only by the end of 2021 vaccination uptake surged after installing a vaccine mandate (temporary in the end) that restricted unvaccinated people access to financial institutions and public offices [13].

4.8. Vaccination uptake and community organization

Similar to an experience with HPV vaccine uptake in Bolivia [27] the intersectoral collaboration and civil society engagement based on educating and empowering community leaders led to a high vaccination uptake in this cohort with 80.7 % compared to a national uptake of 58.9 % by May 2022 [10]. In November 2021, an important difference in vaccination uptake was seen between the two markets included in this study, 85 % in Quintanilla market versus 57 % in the Abasto market. As in other places in the Bolivian society, market vendors in this study were organized in associations and federations [28]. The Quintanilla market is a small market guided by a single governing body. In contrast, the Abasto market, unites close to 1000 market vendors, many associations and two different federations. Rumours on the risks of vaccination were spread in the Abasto market by the president of the federation that was not included in this study. Evidence on COVID-19 hesitancy in low-and middle-income countries suggest that misinformation may contribute to lower acceptance rates and that engaging communities through influencers can raise and reduce disparities in uptake [29].

4.9. Strengths and limitations

To our knowledge this is the first study to examine seroprevalence and associations between anti-spike IgG antibody levels and hybrid immunity for SARS-CoV-2 in a highly exposed population of market vendors in Bolivia and to compare infection with different SARS-CoV-2 variants with hybrid immunity. Strengths of this study include our detailed clinical dataset of a geographically homogenous and unique cohort, with reliable serological findings and vaccination data collected at four time periods during the COVID-19 pandemic. Limitations include specific population that were mainly female, the small sample size which limited the extent to which IgG levels could be studied over time and may affect generalisability to other populations in Bolivia, and in relation to other clinically relevant characteristics of interest and potential confounders, such as vaccine type. Thus, we could not explore the extent to which antibody levels waned over time in our multivariable analysis but rather cross-sectionally. Nor were the compounding effects of multiple vaccination doses on IgG levels analysed due to data sparsity issues. Recent studies have shown increased antibody levels resulting from multiple vaccination doses over time [30,31].

4.10. Conclusion and recommendations

Over the more than 2-year pandemic period the majority of our population of market vendors developed infection- and/or vaccine-induced antibodies against SARS-CoV-2. Serological testing can provide robust evidence of infection burden, risks of reinfection, and the effect of vaccination and hybrid immunity. It can play an important role in studying the need for vaccination or booster vaccination, still relevant for the current endemic phase of SARS-CoV-2, and in the identification of groups at risk for immunity waning. Better knowledge on levels of infection and immunity over time can orient timely and focused preventive measures and immunization. Acknowledging that some limitations in this study exist, such as small sample size disallowing adjustment for some potential confounders (e.g. vaccine type), this study population showed no significant difference in IgG antibody levels between those vaccinated and those with natural immunity by May 2022. Follow-up and further studies may identify the need for future vaccination or booster vaccination.

Low- and middle-income countries where most people work in the informal sector need a contextualized response to mitigate the impact of a health care crisis like a pandemic. Markets, although high contact places, can, if well-ventilated, well-informed, provided with the necessary personal protective equipment and with early access to vaccines, function as hubs to monitor infectious diseases, promote community engagement and guarantee food security. Closing markets would worsen the impact of a pandemic, hampering both food and income security for the population. An effective pandemic response takes advantage of a country's resources like existing community organizational structures to implement and promote public health strategies.

Serological testing to monitor a pandemic provide rich data on infection rates and immunity and is less time bound than qt-PCR or antigen virus identification tests. This study shows the potential of food markets in low- and middle-income countries as sentinel points to monitor a pandemic and promote an effective response. To be able to generalize this finding further studies in similar settings are recommended.

CRediT authorship contribution statement

Christine Leyns: Writing – review & editing, Writing – original draft, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization. **Elliot McClenaghan:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis. **Patricia Rodriguez:** Writing – review & editing, Resources, Investigation, Funding acquisition, Data curation, Conceptualization. **Patrick Nguipdop-Djomo:** Writing – review & editing, Validation, Methodology, Formal analysis. **Carla Ascarrunz:** Writing – review & editing, Investigation, Funding acquisition, Data curation, Conceptualization. **Daniel Eid Rodriguez:** Writing – review & editing, Funding acquisition, Data curation, Conceptualization. **Punam Mangtani:** Writing – review & editing, Validation, Formal analysis. **Javier Guitian:** Writing – review & editing, Project administration, Funding acquisition, Data curation, Conceptualization.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidad Peruana Cayetano Heredia, Peru, with institutional registration number: CIE IORG0000671 and international registration number: IRB00001014. Ethics approvals were also obtained from the RVC and LSHTM.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Javier Guitian reports financial support was provided by National Institute for Health and Care Research. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.127104.

Data availability

The authors do not have permission to share data.

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