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Indirect effectiveness of COVID-19 vaccines in the pre-omicron and omicron periods: A nation-wide test-negative case-control study in Brazil

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ABSTRACT

Objectives: Mass COVID-19 immunization campaigns altered the pandemic's progress by protecting the vaccine recipient and reducing transmission. However, evidence for indirect vaccine effectiveness (IVE) is limited due to the difficulties of ascertaining this type of protection.
Methods: Using linked national Brazilian databases, we adapted the test-negative design to evaluate the IVE against symptomatic infection. We analyzed data from January 1 to December 1, 2021 (pre-omicron) and January 1 to April 30, 2022 (omicron BA.1 and BA.2). We compared the probability of testing positive across various levels of second ancestral-strain monovalent COVID-19 vaccine dose coverage, including only unvaccinated individuals in the main analysis and both vaccinated and unvaccinated individuals in additional analyses. Sensitivity analysis focused on children younger than 12 years who did not have access to COVID-19 vaccines during the pre-omicron period.
Results: We included 11,039,315 unvaccinated individuals tested during the pre-omicron study period. IVE was minimal until 30% vaccination coverage (<10%), then it followed a dose-dependent pattern, peaking at 37.7 (95% confidence interval 32-42.8) at 70% coverage. For children younger than 12 years, IVE peaked at 59.8% (95% confidence interval 52.7-65.9) at 70% coverage. During the omicron period, IVE remained constant at about 5% across all comparisons.
Conclusions: Our findings confirm that high vaccination coverage using vaccines that prevent infection indirectly protects the community. However, IVE was substantially higher during the pre-omicron period.

Introduction

Mass immunization campaigns against COVID-19 altered the pandemic's progress by protecting the vaccine recipient and lowering the risk of transmission [1]. The direct vaccine effectiveness of COVID-19 vaccines has been well demonstrated through several observational studies [2–4]. However, indirect vaccine effectiveness (IVE), the reduction in the intensity of transmission of the pathogen by vaccinated individuals protecting unvaccinated community members, remains less understood and more challenging to measure [5].

Brazil started the COVID-19 vaccination campaign in January 2021, with approximately 8 million confirmed COVID-19 cases and 208,000 confirmed deaths. By May of 2024, Brazil ranked fifth in the number of confirmed COVID-19 cases (37.51 M) and second in the number of deaths, with 702,116 behind only the United States with 1.19 million. With a vast amount of literature modeling the death averted by the vaccination [6].

The literature about IVE relies primarily on mathematical modeling and household contact data. The mathematical models provide evidence comparing different vaccination coverage scenarios and their reduction in the force of infection [7,8]. The biggest problem is that they rely heavily on assumptions and parameter estimates that may not reflect real-world complexities [9]. The second approach of evaluating household data provides empirical evidence of IVE by observing infection rates among unvaccinated individuals in households with vaccinated members; these studies do not compare different coverage scenarios [10].

In this study, we estimated the indirect effects of vaccines in Brazil, a large country with more than 200 million inhabitants across 5570 cities and with different rates of vaccination rollout. We adopted the test-negative design (TND) approach [11], leverag-

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ing its ability to control health-seeking behavior and exploiting the differences in the vaccination rollout across the country.

Methods

Study design and data sources

We adapted the TND to estimate the indirect effects of COVID-19 vaccination [12]. The advantage of the TND is that in situations where not everyone in a population is being tested, the factors that influence being tested (health-seeking behavior, access to health care, availability of testing, etc.) will apply to both those who test positive and those who test negative. Therefore, we conducted a TND case-control, initially with only unvaccinated individuals, to assess the IVE. The Brazilian Ministry of Health began the COVID-19 immunization campaign on January 18, 2021, for all people older than 18 years; on June 11, 2021, for those older than 12 years; on December 16, 2021, for those older than 5 years; and on July 13, 2022, for those older than 3 years. On September 06, 2021, the Ministry of Health started to recommend a third dose 6 months after the second dose, changing to 4 months after the second dose in December 2021.

We analyzed a deterministically linked dataset comprised the *Programa Nacional de Imunizações* (PNI), which holds records of all vaccines administered in Brazil (BNT162b2, ChAdOx1, Ad26.COV2.S, or CoronaVac); the *e-SUS Notifica*, which contains records of suspected and confirmed COVID-19 in outpatient clinics; and the *Sistema de Informação da Vigilância Epidemiológica da Gripe* (SIVEP-Gripe), which holds records of all COVID-19 hospitalizations and deaths. All data were pseudo-anonymized with a common unique identifier provided by the Brazilian Ministry of Health. The research protocol was approved by the Brazilian National Commission in Research Ethics (CONEP) (approval number 4.921.308).

All individuals, independent of age, who reported COVID-19-like symptoms and were tested within 10 days for SARS-CoV-2 between January 1, 2021 and December 1, 2021 (pre-omicron) and between January 1, 2022 and April 30, 2022 (omicron BA.1 – BA.2) were eligible for the study. We excluded: (i) tests with missing information of age, sex, and city of residence or sample collection date; (ii) negative test within 14 days of a previous negative test; (iii) negative test followed by a positive test up to 7 days; (iv) any test up to 90 days after a positive test; and (v) any vaccinated individual, according to the status at the time of testing. Cases were defined as those who tested positive for SARS-CoV-2 reverse transcriptase-polymerase chain reaction or rapid antigen test and controls were those who tested negative, both from samples collected within 10 days of symptoms onset.

Exposure

The primary exposure is the COVID-19 vaccination coverage for the second dose at the city level. The coverage was estimated based on the municipality of residence where the first dose of the individual was administered. The COVID-19 vaccines administered in Brazil during the study period were BNT162b2 (messenger RNA), ChAdOx1 (adenoviral vector), Ad26.COV2.S (adenoviral vector), and CoronaVac (inactivated virus); all of them were ancestral-strain monovalent vaccines. The vaccination coverage for each day was determined by calculating the ratio of the number of individuals who received a second dose, with a 14-day lag, to the total population of the city. A 14-day delay was implemented, considering the time required for full protection after receiving the dose. The vaccination coverage was bound to 95%; if the final first dose vaccine coverage (evaluated on April 30, 2022) exceeded 95%, the corresponding population for the city was resized to maintain coverage bounded at 95% [13].

Statistical analysis

The risk ratio (RR) comparing the probability of positive test between different levels of vaccination coverage and its associated 95% confidence interval (CI) were derived using generalized additive logistic regression and the delta method to derive standard errors. Vaccine coverage was modeled as a spline. We controlled for potential confounding factors at both the individual and city levels. At the individual level, we adjusted for age, sex, previous infection, number of previous tests, and comorbidities such as cardiac disease, diabetes mellitus, obesity, immunosuppression, and chronic kidney disease (categorized as none, one, or at least two). At the city level, we accounted for confounders such as temporal trend, population (based on the 2022 census), municipality human development index (based on the 2010 census), and gross domestic product per capita (based on 2021, Instituto Brasileiro de Geografia e Estatística) [14]. The temporal trend was determined by estimating the number of days from the start of the study and the date when symptoms first appeared. We modeled the temporal trend as a spline and allowed it to vary between different states of residency. In addition, we incorporated a random intercept for the specific geographic area. This method involves comparing the likelihood of receiving a positive test result in cities that are in the same immediate region (510 immediate regions; Supplementary Table 1) and share similar characteristics such as human development index, population, and gross domestic product per capita. To prevent the occurrence of imprecise estimates, we excluded the records from coverage (rounded to the closest 0.01) with a low number of cases and controls (less than 4000 records). Analysis code available at https://github.com/csthiago/ive_brazil.

The IVE was calculated as 1-RR, using the predefined contrasts in percentage: 10, 20, 30, 40, 50, 60, 70 vs 0, and 50, 60, 70 vs 40.

Average marginal contrasts are computationally expensive to estimate, as it is needed to predict the dataset for each combination of variables. To manage this, we fitted the models retaining the categoric variables at the reference level and the numerical (age and temporal trend) at the minimum, maximum and first, second and third quantile.

We conducted multiple sensitivity analyses to test the robustness of our study results. (i) To assess if the vaccination coverage also offers additional protection for vaccinated individuals, we included vaccinated individuals classified as first dose (14 days or more after the first dose) and second dose (14 days or more after the second dose). (ii) To assess if depletion bias could affect the results, we restricted the analysis to the population without vaccine availability. We then restricted the analysis only to children younger than 12 years. (iii) We then restricted the analysis only to children younger than 5 years. (iv) To assess if the IVE effect is dependent on the level of individual protection, we repeated the main analysis using the coverage of the first dose instead of the second dose. (v) To assess the degree of model dependency, we used a simpler logistic model (generalized linear model). We repeated the main analysis, categorizing the coverage by 10% intervals, and the temporal trend was controlled using the week of symptom onset instead of a spline by immediate region. In the analysis including unvaccinated and vaccinated individuals, the model included an interaction term between the vaccination status of the individual and vaccination coverage.

All data processing and analyses were performed in R (version 4.1.1) using the following packages: marginaleffects, mgcv.

Results

Between January 1, 2021 and December 1, 2021, 11,039,315 unvaccinated individuals were tested for SARS-CoV-2 (Supplementary Figure 1). The median age was 34 years (interquartile range 24,

Table 1
Clinical and sociodemographic characteristics of individuals included in a test-negative design analysis by test positivity.

Characteristic	Control, N = 6,380,102	Case, N = 5,258,406	Overall, N = 11,638,508
Number of individuals	**6,015,039**	**5,252,672**	**11,267,711**
Age, years - median (interquartile range)	32 (22, 43)	37 (27, 49)	34 (24, 46)
Age group - years			
0-17	1,006,479 (15.8%)	392,861 (7.5%)	1,399,340 (12.0%)
18-49	4,376,389 (68.6%)	3,585,148 (68.2%)	7,961,537 (68.4%)
50-64	781,704 (12.3%)	971,602 (18.5%)	1,753,306 (15.1%)
≥65	215,530 (3.4%)	308,795 (5.9%)	524,325 (4.5%)
Sex - Female	3,429,217 (53.7%)	2,661,592 (50.6%)	6,090,809 (52.3%)
Region			
North	308,634 (4.8%)	260,590 (5.0%)	569,224 (4.9%)
Northeast	917,418 (14.4%)	955,600 (18.2%)	1,873,018 (16.1%)
Southeast	3,092,397 (48.5%)	2,494,571 (47.4%)	5,586,968 (48.0%)
South	1,526,334 (23.9%)	1,035,706 (19.7%)	2,562,040 (22.0%)
Central-west	535,319 (8.4%)	511,939 (9.7%)	1,047,258 (9.0%)
Race			
White	3,059,084 (47.9%)	2,311,726 (44.0%)	5,370,810 (46.1%)
Black	269,021 (4.2%)	209,855 (4.0%)	478,876 (4.1%)
Asian	78,928 (1.2%)	66,746 (1.3%)	145,674 (1.3%)
Mixed	2,041,621 (32.0%)	1,759,440 (33.5%)	3,801,061 (32.7%)
Indigenous	5,408 (0.1%)	2,807 (0.1%)	8,215 (0.1%)
Missing	926,040 (14.5%)	907,832 (17.3%)	1,833,872 (15.8%)
Number of previous tests			
0	5,409,027 (84.8%)	4,754,122 (90.4%)	10,163,149 (87.3%)
1	778,337 (12.2%)	428,318 (8.1%)	1,206,655 (10.4%)
2	143,765 (2.3%)	60,540 (1.2%)	204,305 (1.8%)
≥3	48,973 (0.8%)	15,426 (0.3%)	64,399 (0.6%)
Type of test			
Rapid antigen	2,791,706 (43.8%)	2,172,477 (41.3%)	4,964,183 (42.7%)
Reverse transcription-polymerase chain reaction	3,588,396 (56.2%)	3,085,929 (58.7%)	6,674,325 (57.3%)
Number of medical comorbidities			
0	5,749,408 (90.1%)	4,602,872 (87.5%)	10,352,280 (88.9%)
1	513,036 (8.0%)	484,223 (9.2%)	997,259 (8.6%)
2	96,601 (1.5%)	139,898 (2.7%)	236,499 (2.0%)
≥3	21,057 (0.3%)	31,413 (0.6%)	52,470 (0.5%)

46), and 52.1% were women (Table 1). Overall, cases and controls had similar characteristics, except for a higher proportion of individuals younger than 18 years in the control group (Table 1). The vaccination campaign progressed more rapidly in the southern and southeastern regions compared with the rest of the country. By April 30, 2022, over half of the cities in the south and southeast had administered the second dosage to more than 80% of their population, whereas in the north region, less than 5% of cities achieved this coverage (Figure 1 and Supplementary Figure 2). The number of tests conducted per COVID-19 case in Brazil remained consistently low throughout the research period, peaking around 9 in 2021 and 14 by the end of April 2022 (Figure 2).

The protection conferred by IVE remained low until 30% of second dose vaccination coverage, with values of IVE ranging from 0-5%. After reaching 30% coverage, the IVE shows a dose-response pattern, peaking at 37.7% (95% CI 32-42.8) when comparing 70% coverage to 0% coverage (Figure 3a and Supplementary Table 2). In the analysis including vaccinated individuals, the results were similar to the principal analysis, with IVE for the unvaccinated group ranging from 2-7% up to 30% of coverage, peaking at 44.6 (95% CI 41.9-47.2) in the 70 vs 0% of second dose coverage (Figure 3b and Supplementary Table 2). The vaccinated groups, first and second dose past 2 weeks, also exhibited protection with the increase of vaccination coverage, with IVE peaking at 54.0% (95% CI 51.3-56.5) for the first dose group and at 46.8% (95% CI 44.5-49.0) for the second dose group (Figure 3b and Supplementary Table 2).

Analyses of children up to 11 years old only, an age group that did not have vaccines available during 2021, showed a pattern similar to that in the main analysis but showed a greater IVE when comparing 70% vs 0% of second dose vaccination coverage (59.8% [95% CI 52.7-65.9]) (Figure 3c and Supplementary Table 3).

The simpler logistic model categorizing the coverage by 10% and including the temporal trend as week of the yielded results consistent with the main analysis. The odds ratio comparing the group 20-30% vs 0% vaccination coverage was 0.97 (95% CI 0.95-0.99), and the odds ratio comparing 60-70% vs 0% vaccination coverage was 0.36 (95% CI 0.34-0.37) (Supplementary Table 4).

The analysis using the first dose vaccination coverage exhibited a different pattern than in the main analysis, with IVE ranging between 10 and 16% up to 60% coverage and reaching an IVE of 26.9 (95% CI 23.3-30.3) at 80% of vaccination coverage (Supplementary Table 5).

The analysis during the omicron period (January 1, 2022 to April 30, 2022) evaluating only unvaccinated individuals and then also including vaccinated individuals showed small and constant IVE (approximately 5%) in the comparisons of 50%, 60%, 70%, and 80% vs 40% second dose coverage (Figures 4a, 4b and Supplementary Table 6).

We further examined the IVE in children younger than 4 years, an age group that did not have vaccines available in 2021 and early 2022. During the pre-omicron period, the IVE gradually increased, starting at 19.7% (95% CI 14.8-43.3) for the comparison 50% vs 40% second dose vaccine coverage and peaking at 53.8% (95% CI 45.6-60.8) for the comparison 70% vs 40% coverage. In the omicron period, the IVE for the 50% vs 40% coverage comparison was 2.9% (95% CI −6.0 to 11.1), and for the 70% vs 40% comparison, it was −4.6% (95% CI −13.5 to 3.7) (Supplementary Table 6).

Discussion

The findings of this study support the potential for IVE of COVID-19 vaccines. During the pre-omicron period, the vaccination coverage with ancestral-strain monovalent vaccines provided

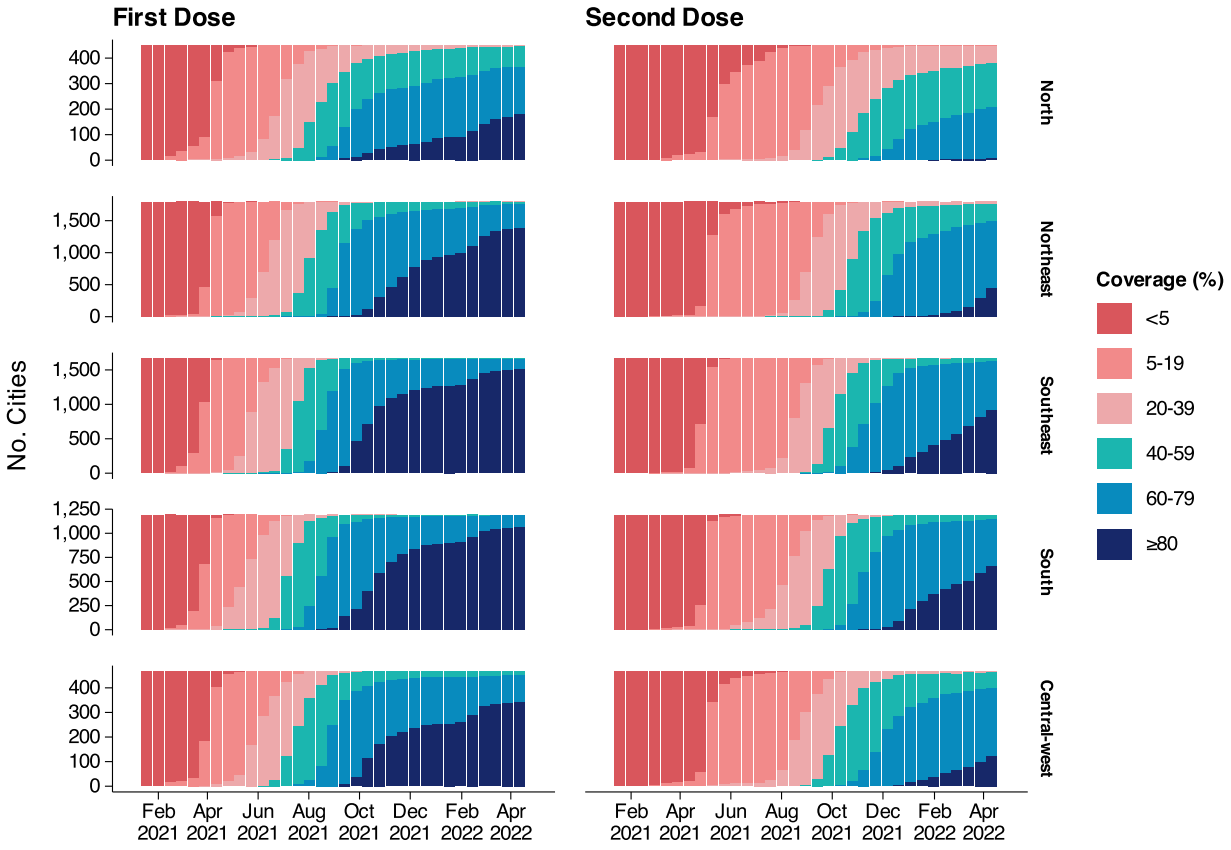

Figure 1. Vaccination coverage in cities by dose in Brazil by region.

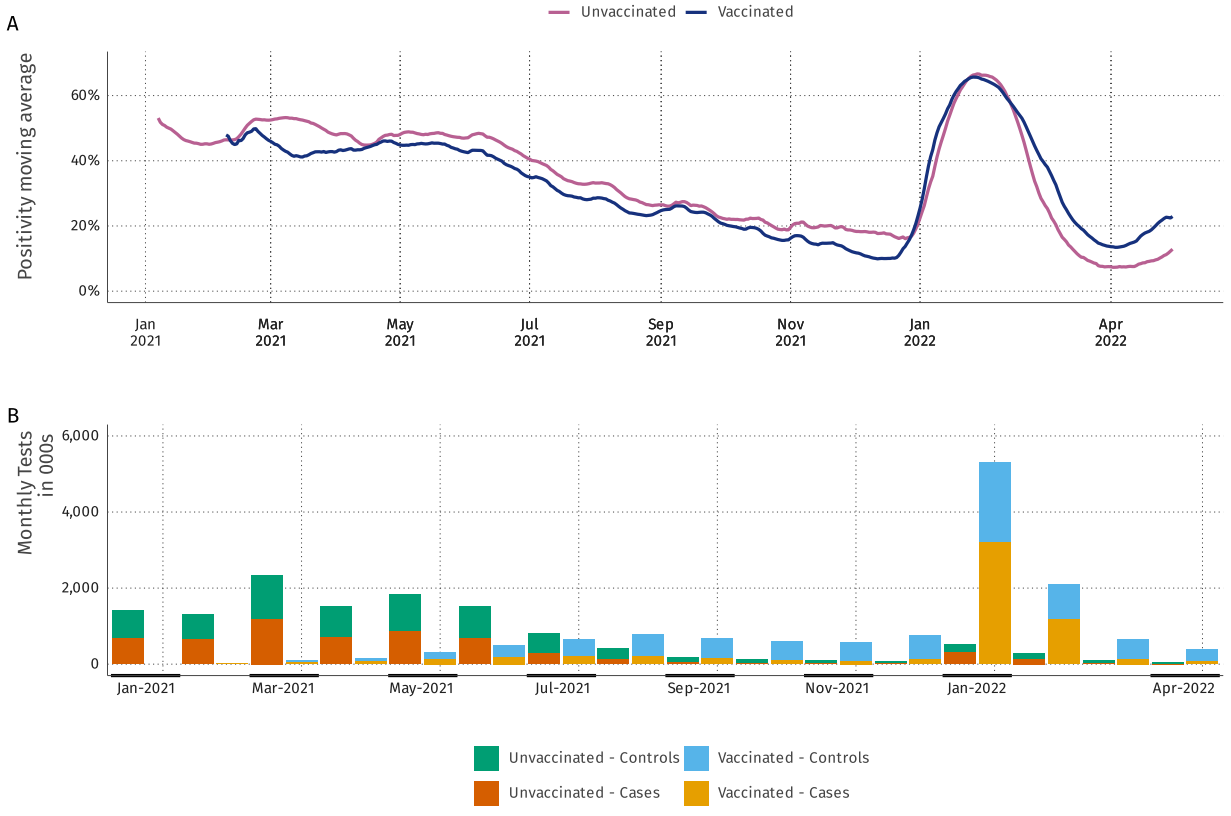

Figure 2. Weekly average test positivity (a) and the monthly number of tests by vaccination status (b). Vaccinated include individuals with one or two doses past 14 days of the dose.

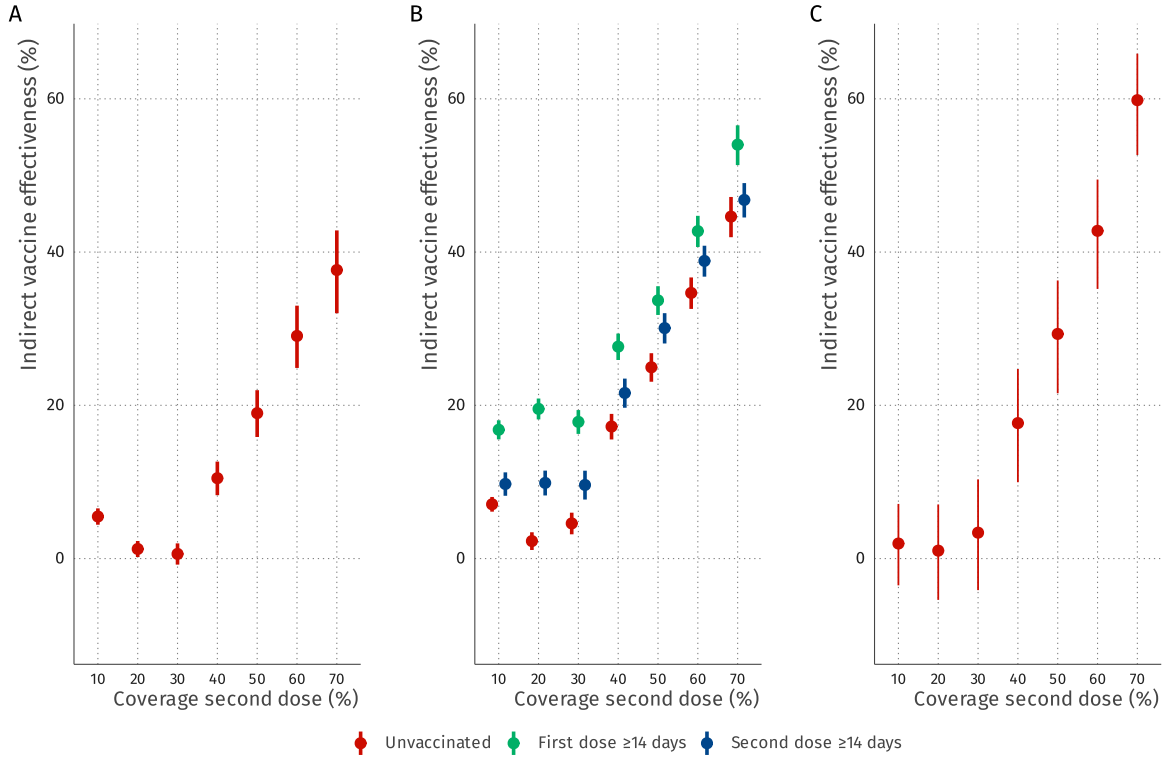

Figure 3. Estimated indirect vaccine effectiveness during 2021 (pre-omicron) with 0% of second dose coverage as the comparison group. (a) Estimates from the model including only unvaccinated individuals; (b) Estimates from the model including unvaccinated and vaccinated individuals; (c) Estimates from the model including only children younger than 12 years.

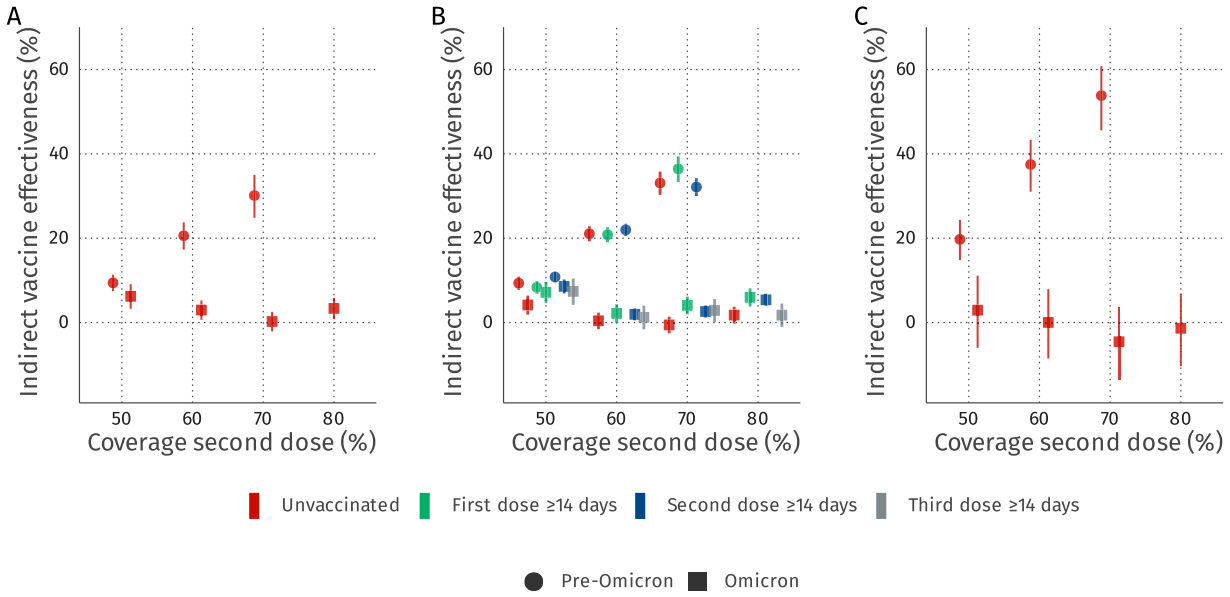

Figure 4. Estimated indirect vaccine effectiveness during 2021 (pre-omicron) and 2022 (Omicron) with 40% of second dose coverage as the comparison group. (a) Estimates from the models including only unvaccinated individuals; (b) Estimates from the models including unvaccinated and vaccinated individuals; (c) Estimates from the models including only children younger than 5 years.

IVE after reaching 30% for second dose coverage, peaking at 37.7% when comparing 70% to 0% coverage. This trend was also consistent among unvaccinated and vaccinated individuals. However, both unvaccinated and vaccinated groups exhibited a small IVE (approximately 5%) during the omicron period. These findings underscore the impact of the antigenic variation within SARS-CoV-2 strains on the indirect protection provided by vaccines.

Our findings are consistent with studies conducted during the pre-omicron period. An ecologic study that found a two-fold decrease in the positivity rate for each 20% additional vaccination coverage [15]. Furthermore, studies analyzing specific populations, such as inhabitants of long-term care institutions or prisons, found that vaccination coverage reduced the risk of COVID-19 by up to 80% [16,17]. However, due to the nature of their sample group,

those studies lack generalizability to the general population, as well as other concerns such as extraordinarily high vaccination coverage (92.6% within 3 months of vaccination campaign start) [16] or modeling issues (effects of vaccine coverage assumed to be monotonic) [17]. Our findings also accord with studies evaluating IVE through the impact of vaccination on individuals in the same household. A large study evaluating more than 100,000 households found an IVE of 39.0% after comparing vaccinated and unvaccinated individuals from the same household [18]. Similarly, children from vaccinated parents have a reduced risk between 21 and 72% compared with those from unvaccinated parents [19]. In addition, our study showed IVE benefits for vaccinated individuals.

This study used a TND that integrated ecologic exposure data (population vaccine coverage) and individual-level data to assess IVE of vaccines. It offers a novel approach to evaluating vaccine protection while accounting for variations in health-seeking behavior that may affect those who get tested for COVID-19 [20–22]. Our sensitivity analysis including only children younger than 5 years, a group excluded from vaccination during the study period in 2021 and 2022, reinforces the robustness of our findings, and indicate that it is unlikely that there was depletion bias in the unvaccinated group due to vaccination [23].

We also evaluated the IVE during the circulation of omicron BA.1 and BA.2. This showed a very different pattern to the IVE during pre-omicron, with low levels of protection and no dose-dependence pattern according to vaccination coverage. This finding is in line with other evidence on the low levels of individual protection (direct vaccine effectiveness) against infection of the two-dose schema with monovalent vaccines against the omicron variant [24], which could not block the transmission of the virus despite the vaccines still providing a high level of protection against severe COVID-19 [24]. A household contact study conducted during the circulation of omicron variants (BA.1/2 and BA.4/5) also found no significant indirect protection after the emergence of the omicron variant [25].

Our findings have direct real-world implications, demonstrating that at least 30% of the population requires to have protection against infection to provide cross-protection to unvaccinated members of the community and that even when 70% coverage is reached, the population risk is only moderately reduced. In May 2024, 4 years after the emergence of COVID-19, Brazil had approximately 38 million COVID-19 confirmed cases, which represent less than 20% of the total population [6]. Thus, our findings highlight the impossibility of achieving herd immunity solely through natural infection without imposing a significant burden on the health system due to the large proportion of individuals required to be infected in a short period to reach the necessary threshold. Notably, the article from Lewis *et al.* [26] reported a 75% attack rate in Manaus in 2020 (pre-omicron period) through the analysis of blood bank samples. However, those results are likely overestimated as results from blood donors are unlikely to be generalizable for the whole population [26]. By the end of 2020, Manaus recorded only 82,218 COVID-19 cases [27]. Assuming that the actual number of cases is as high as five times the reported cases [28] (411,090), it still would only represent 19.9% of the population of Manaus, which, based on our results, is not enough to provide high indirect protection levels.

Our study has some significant limitations. First, our vaccine coverage calculation does not account for natural acquired immunity in the cities. Although the comparison was performed within each local geographic region, in which the incidence of infection should be relatively equal between the groups and time periods being compared, this cannot be guaranteed. Second, we assumed a homogenous effect of vaccine coverage, independent of time since the second dose or COVID-19 vaccine type; Brazil has used four COVID-19 vaccines, each offering different degrees of protection against infection and different levels of waning, making it difficult to isolate the individual effect of each vaccine. Third, Brazil had a lower number of tests per COVID-19 case, exemplified by the high positivity rate across all the study period, which could indicate differential access to testing; however, using the TND, our analysis is intended to correct this bias since both groups (cases and controls) have similar health-seeking behaviors and access to testing. In addition, we adjusted for variables that have previously been shown to effectively control for confounding in direct vaccine effectiveness studies [2,20].

Declarations of competing interest

The authors have no competing interests to declare.

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Author contributions

TC-S conceptualized the study and wrote the first draft of the manuscript. M.B.-N. secured funding and data access. NP supervised the data analysis. TC-S conducted the formal analysis. All authors contributed to the writing, reviewing, and editing of the manuscript. TC-S decided to submit the manuscript for publication.

Data availability statement

One of the study coordinators (MB-N) signed a term of responsibility for using each database made available by the Ministry of Health (MoH). Each member of the research team signed a term of confidentiality before accessing the data. Data was manipulated in a secure computing environment, ensuring protection against data leakage. The Brazilian National Commission in Research Ethics approved the research protocol (CONEP approval number 4.921.308). Our agreement with MoH for accessing the databases patently denies authorization of access to a third party. Any information for assessing the databases must be addressed to the Brazilian MoH at https://datasus.saude.gov.br/, and requests can be addressed to datasus@saude.gov.br. Herein, we used anonymized secondary data following the Brazilian Personal Data Protection General Law (LGPD), but it is vulnerable to re-identification by third parties, as they contain dates of relevant health events regarding the same person. To protect the research participants' privacy, the approved Research Protocol (CONEP approval number 4.921.308) authorizes only the dissemination of aggregated data, such as the data presented here.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107241.

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