Supplementary Appendix

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Section A. Supplementary Methods Material

Supplementary Section S1. Description of data sources and study period by country

While a standardized protocol was used, the data sources and study period varied slightly by country.

Data sources and other study aspects	Argentina	Brazil	Chile	Colombia
Case and control ascertainment source data	Electronic and paper-based hospital information systems from 3 hospital sites: (i) Hospital Posadas, Buenos Aires; (ii) Hospital Rawson, Cordoba; and (iii) Public Sector Hospitals, Tierra del Fuego. Additional controls were identified from the subset of suspected COVID-19 hospitalizations reported to the National Health Surveillance System (SNVS 2.0[1]) from the municipalities that correspond to each hospital site.	SIVEP-Gripe (source for cases and controls in primary analysis using the TN design) from the states of the 5 hospitals used for SN design: Amazonas, Ceará, Distrito Federal, Paraná, Rio de Janeiro Electronic and paper-based hospital information systems from 5 hospital sites (source for cases and controls in secondary analysis using the SN design): (i) Hospital Universitário Antônio Pedro,	Electronic hospital information systems from 3 hospital sites: (i) Hospital Davila, Santiago; (ii) Hospital Rancagua, OHiggins; and (iii) Hospital Antofagasta, Antofagasta. Additional controls were identified from the subset of suspected COVID-19 hospitalizations reported to the National Epidemiological Surveillance System (EPIVIGILA[2]).	Electronic hospital information systems from hospitals affiliated with MutualSer insurer, located in the Caribbean region, and others affiliated with the Secretary of Health, Bogota.

		Niterói; (ii) Complexo Hospital de Clínicas da Universidade Federal do Paraná, Curitiba; (iii) Fundação de Medicina Tropical Doutor Heitor Vieira Dourado (FMT) with Hospital Delphina Rinaldi Abdel Aziz, Manaus; (iv) Hospital Estadual Leonardo Da Vinci (HELV) do Instituto de Saúde e Gestão Hospitalar (ISGH), Fortaleza and (v) Hospital Universitário de Brasília, Brasília		
Testing and symptom data	SNVS 2.0	SIVEP Gripe	EPIVGILA	SIVIGILA
Vaccination data	Federal Nominal Vaccination Registry (NOMIVAC)	Rede Nacional de Dados em Saúde (RNDS)	National Immunization Registry (RNI)	PAI-Web
Other covariates available	SNVS 2.0 and hospital information	SIVEP Gripe	EPIVGILA and hospital information	SIVIGILA and hospital information

	systems		systems	systems
Time period	03-10/2021	02-12/2021	03-08/2021	02-12/2021
Vaccines	ChAdOx1, Sputnik V, Sinopharm	ChAdOx1, CoronaVac, Ad26.COV2.S, BNT162b2	BNT162b2, ChAdOx1, CoronaVac, Sinopharm	ChAdOx1, CoronaVac, BNT162b2, mRNA-1273

Supplementary Section S2. Description of GISAID individual-level genomic sequencing data used in the study to derive dominant variant periods

Metadata from a total of 14,627 SARS-CoV-2 genomes collected from Argentina, 102,688 from Brazil, 18,992 from Chile and 13,219 from Colombia were included and compiled into datasets. For each sample, the GISAID lineage classification (based on Pangolin nomenclature) was used for its categorization into WHO's variants of concern (VOCs) or variants of interest (VOIs) (https://www.who.int/activities/tracking-SARS-CoV-2-variants, https://cov-lineages.org/index.html).

Supplementary Section S3. Sample size calculations

Sample size calculations for study planning were derived using the Sample Size Calculator for Evaluation of COVID-19 Vaccine Effectiveness (https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement_tool-2021.1).[3] We created lower and upper bound ranges for sample sizes proposed in the study protocol by assuming a 50% and 20% combined multi-product vaccination coverage at the national level (as a proxy for controls) for each country. Desired precision width was fixed at $\pm$ 15% and a type 1 error of 0.05; and the predicted vaccine product specific effectiveness was informed by the literature. As vaccine effectiveness varies by product and age, we calculated sample sizes for each vaccine product and each age group, and then applied these minimum sample size recommendations depending on use of the vaccine product in each country. Initially, a case-control ratio of 1:1 to was proposed. However, there were a limited number of controls identified in all country settings due to the minimal circulation of respiratory viruses other than SARS-CoV-2 during the study period.

Supplementary Section S4. COVID-like symptom criteria

Symptom criteria eligibility were based on the WHO COVID-19 surveillance case definition guidance detailed below.[4] Each study site screened patients using hospital records and/or surveillance system data to ascertain each patient met these criteria:

1) *Acute onset of fever AND cough (influenza-like illness) OR*
2) *Acute onset of ANY THREE OR MORE of the following signs or symptoms: fever, cough, general weakness/fatigue1 , headache, myalgia, sore throat, coryza, dyspnoea, nausea, diarrhea, anorexia.*

Supplementary Section S5. comorbidities

The comorbidity variable was categorized as a binary variable, with presence of at least one of the following comorbidities coded as 1 and absence of any reported as 0.

- Cardiovascular disease
- Neurologic disease
- Pulmonary disease
- Gastrointestinal disease
- Endocrine disease
- Renal disease
- Hematologic disease
- Malignancy
- Immunosuppression
- Psychiatric
- Obesity
- Other

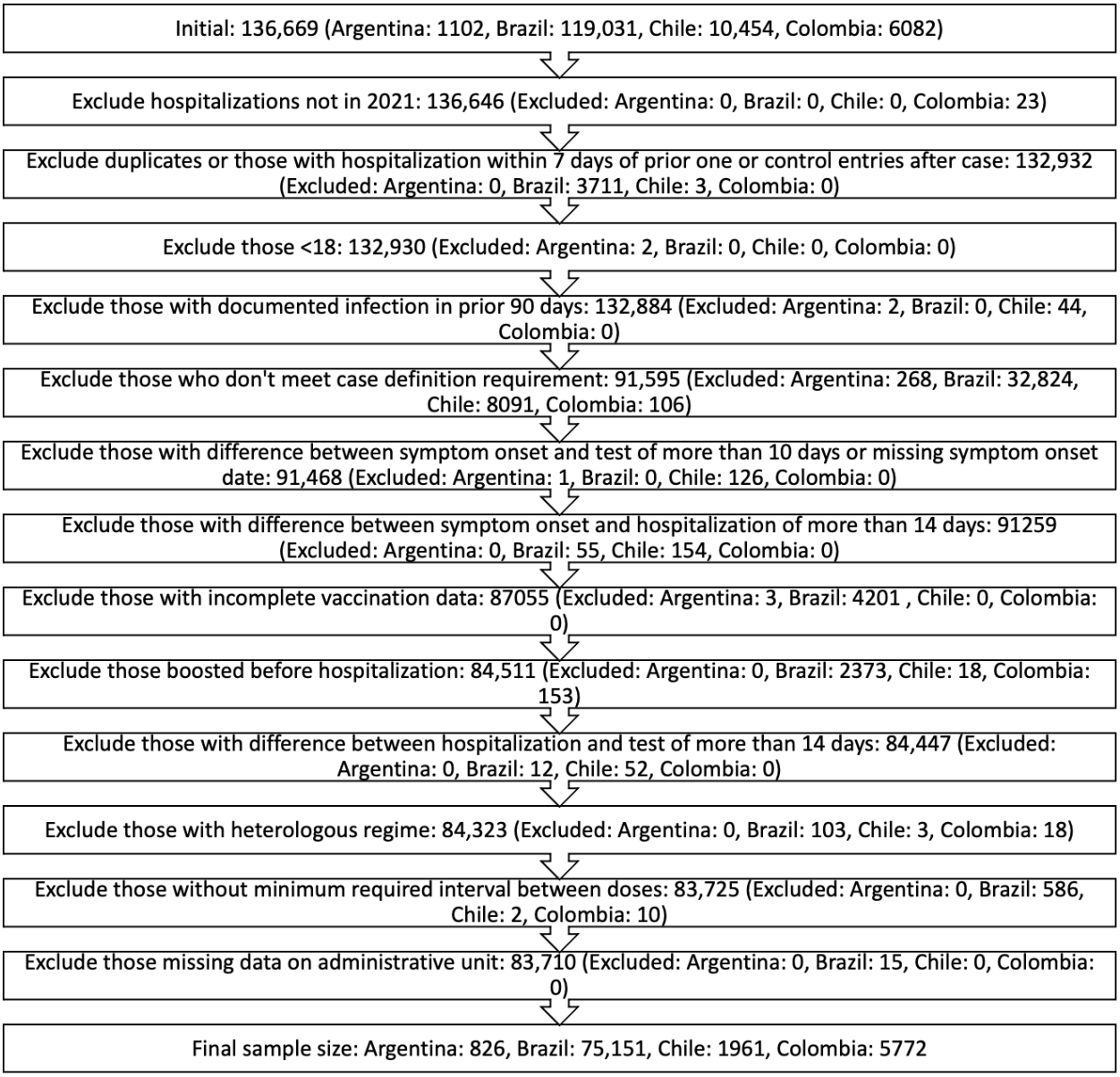
Section B. Supplementary figures and tables

Supplementary Table S1. Characteristics of study participants

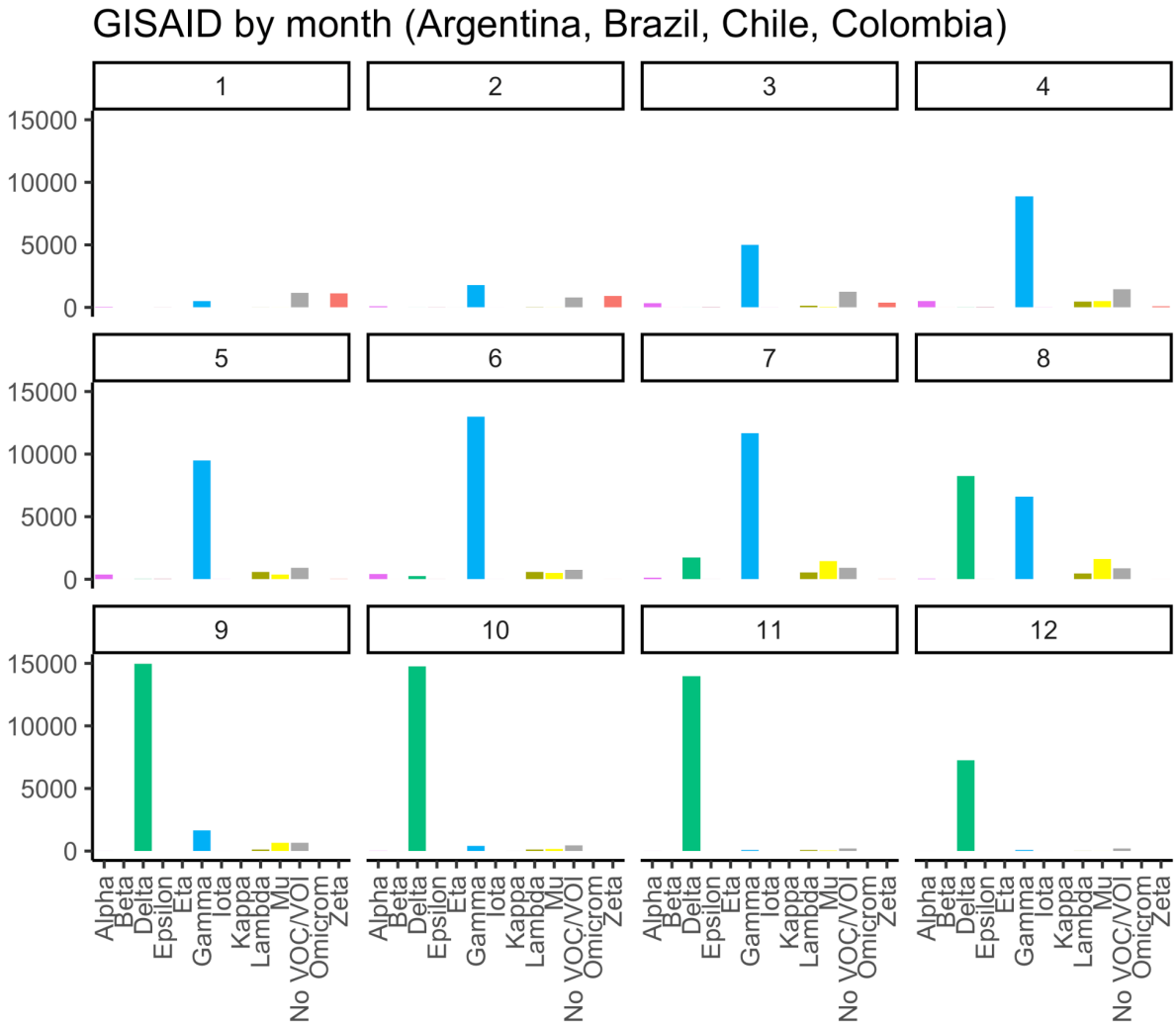
Study participant characteristic	Cases N (%)	Controls N (%)
Country		
Argentina	491 (0.8%) (101 deaths)	335 (1.7%) (21 deaths)
Brazil	60,406 (94.1%) (14,772 deaths)	14,745 (75.5%) (3189 deaths)
Chile	1,608 (2.5%) (160 deaths)	353 (1.8%) (19 deaths)
Colombia	1,673 (2.6%) (360 deaths)	4,097 (21%) (160 deaths)
Sex		
Male	36,129 (56.3%)	9,765 (50%)
Female	28,049 (43.7%)	9,765 (50%)
Age		
18-49y	24,124 (37.6%)	5726 (29.3%)
50-64y	20,287 (31.6%)	4519 (23.1%)
65-79y	14,402 (22.4%)	5411 (27.7%)
80+y	5365 (8.4%)	3874 (19.8%)
Comorbidities		
One or more	38,385 (59.8%)	13,242 (67.8%)
None	25,793 (40.2%)	6288 (32.2%)
Variant period during hospitalization		
Gamma	53,476 (90.3%)	10,033 (58.5%)
Delta	5,726 (9.7%)	7,111 (41.5%)
Vaccine series completion		

None	46,431 (72.3%)	8,743 (44.8%)
Partially	9,385 (14.6%)	3,520 (18.0%)
Fully	8,362 (13.0%)	7,267 (37.2%)
Type of vaccine administered		
Sputnik V	67 (0.4%)	78 (0.7%)
mRNA-1273	10 (0.1%)	104 (1.0%)
CoronaVac	9,692 (54.6%)	5,205 (48.3%)
ChAdOx1	6905 (38.9%)	3,979 (36.9%)
BNT162b2	936 (5.3%)	1,326 (12.3%)
Ad26.COV2.S	92 (0.5%)	58 (0.5%)
Other (not analyzed)	45 (0.3%)	37 (0.4%)

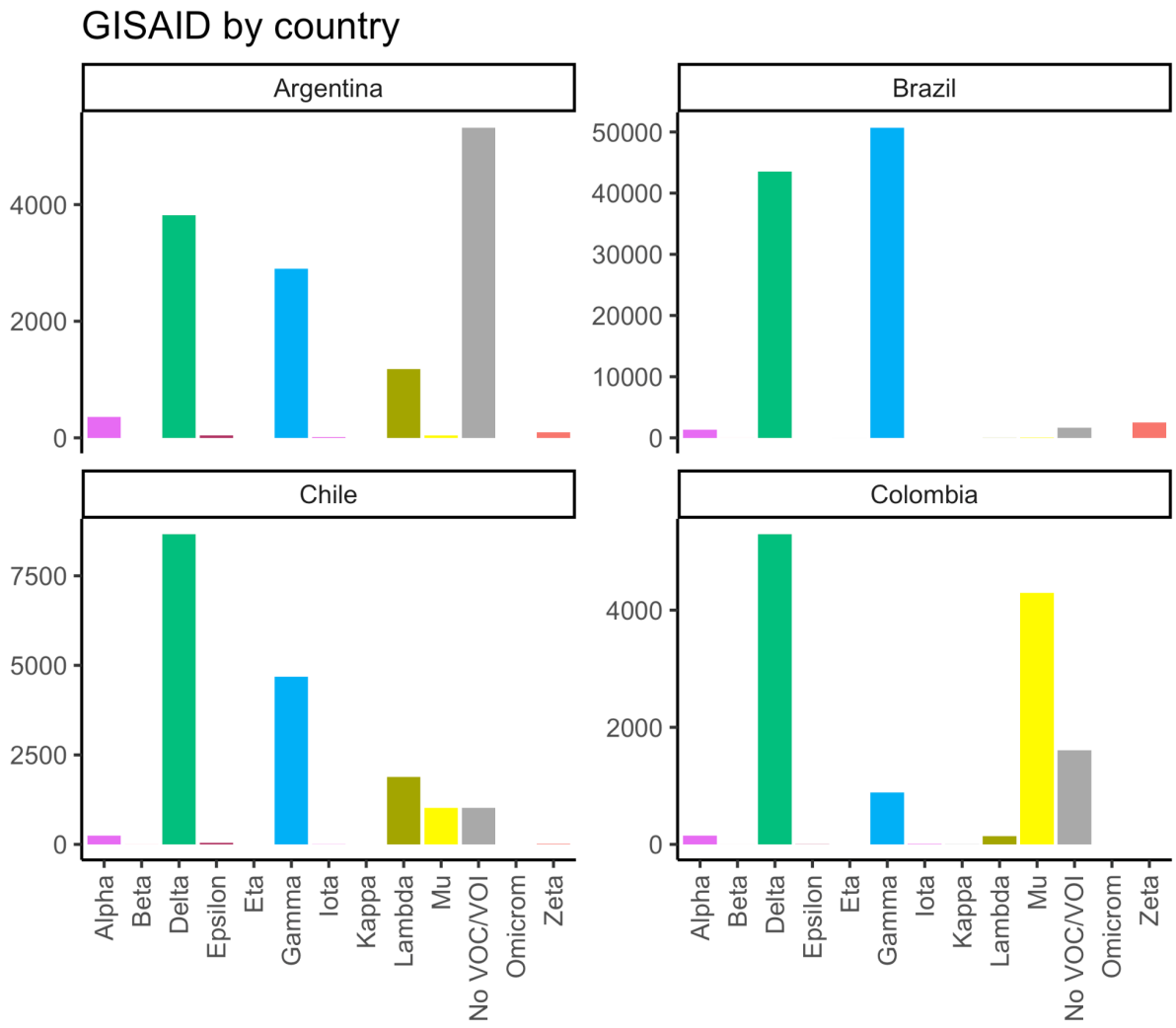
Supplementary Figure S1. Study participant exclusion/inclusion flow chart



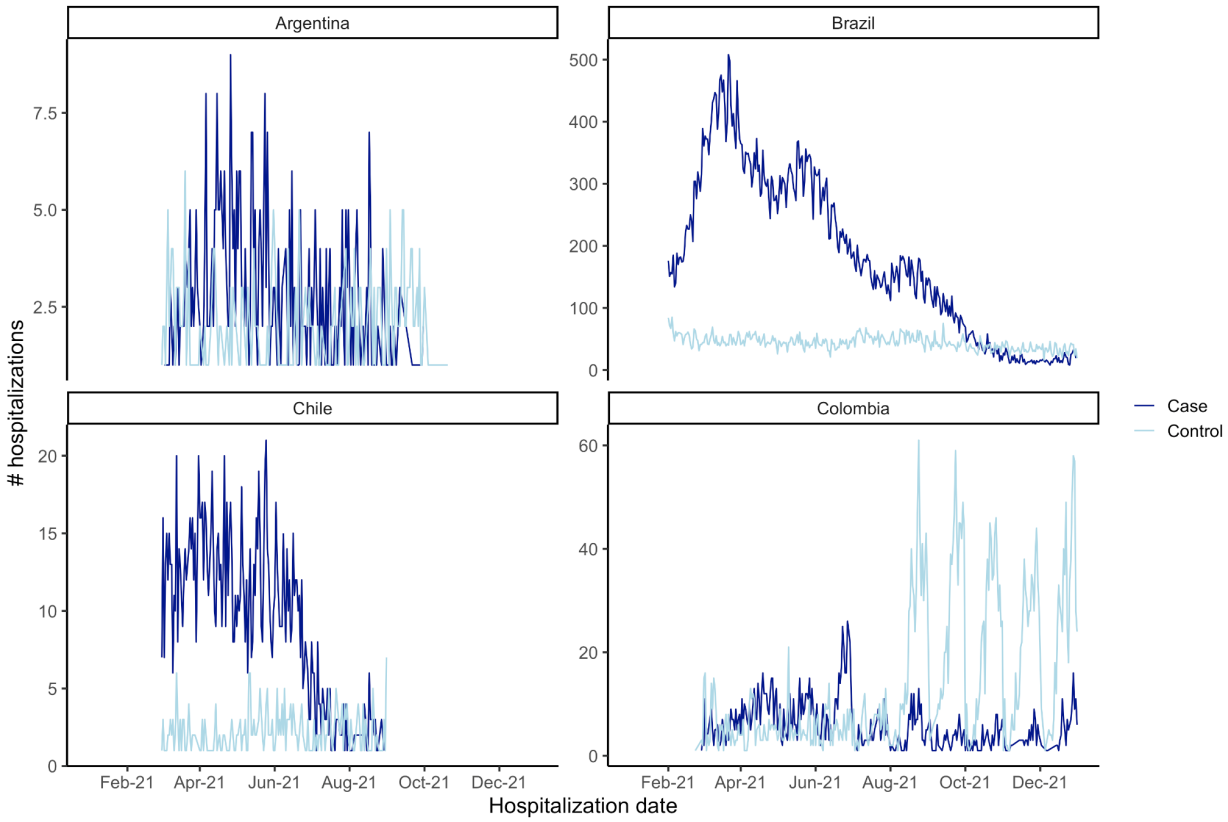
Supplementary Figure S2a. SARS-CoV-2 variants detection over time available at the EpiCoV database on GISAID, pooled from Argentina, Brazil, Chile, Colombia.



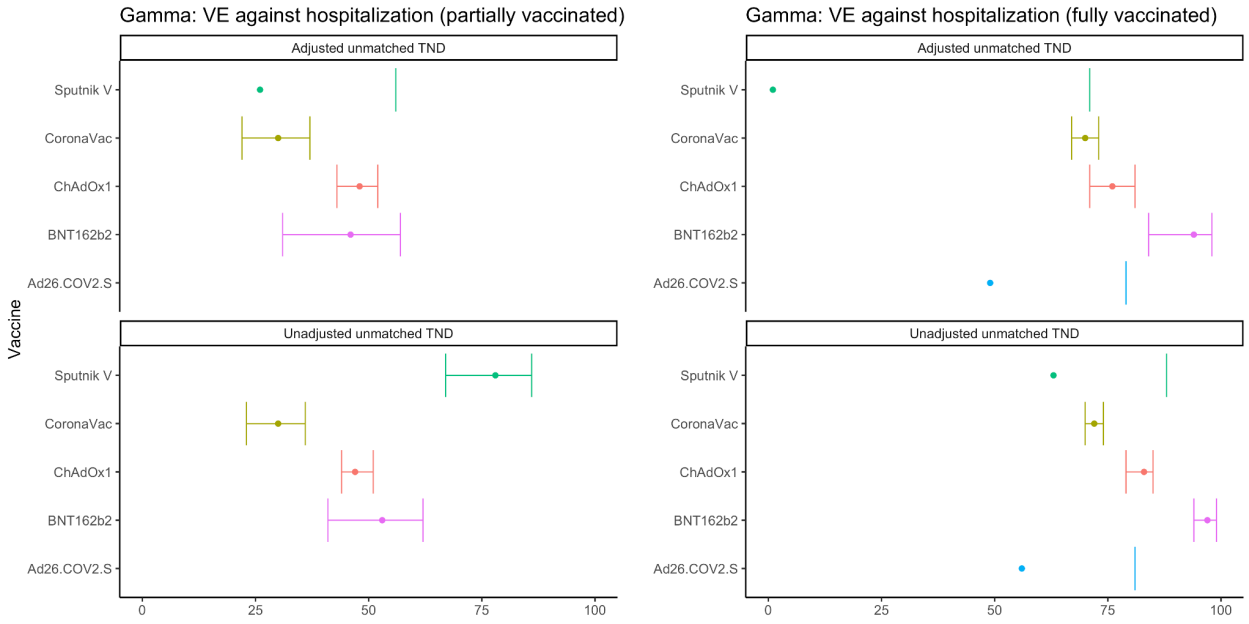
Supplementary Figure S2b. SARS-CoV-2 variants detection over time available at the EpiCoV database on GISAID, Argentina, Brazil, Chile, Colombia.



Supplementary Figure S3. Hospitalizations among eligible cases and controls in the test-negative primary analysis over time by country



Supplementary Figure S4a. VE against lab-confirmed COVID-19 hospitalization, by vaccine product use during Gamma predominant period



Adjusted for continuous age, sex, secondary administrative unit location of residence, date of hospitalization grouped into categorical epiweeks, presence of 1 or more comorbidities, and study site country. Some estimates and/or 95% confidence intervals fall outside of the range 0-100% shown on the graph. These values can be found in Table S2a. TND = test-negative design.

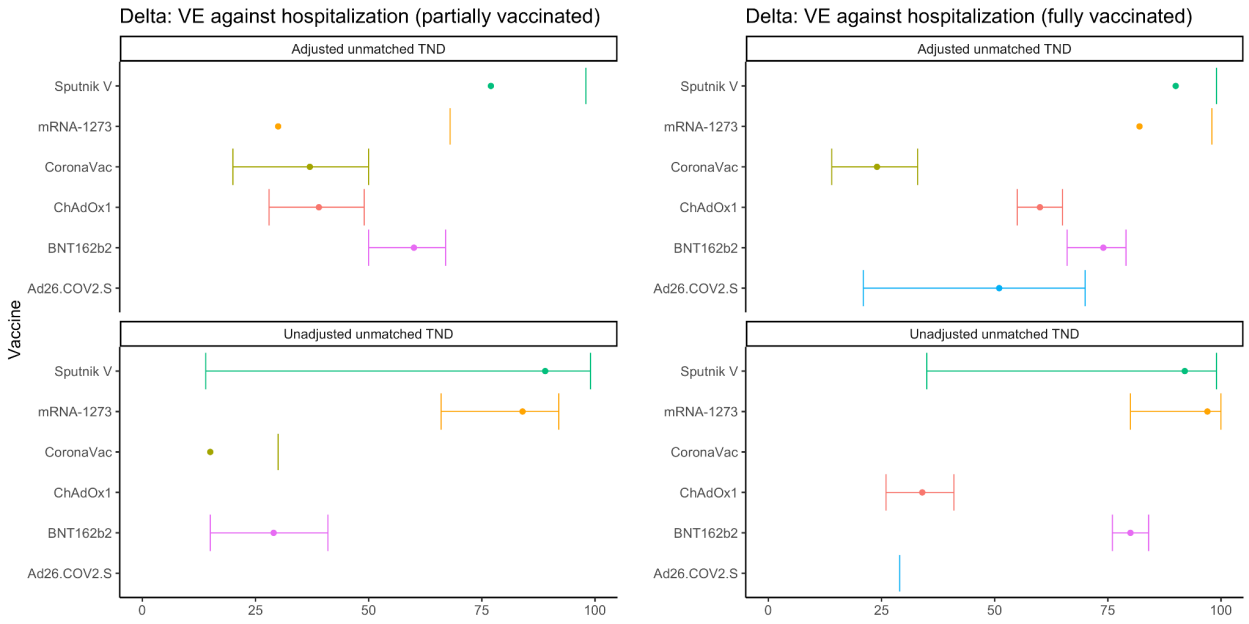
Supplementary Table S2a. VE against lab-confirmed COVID-19 hospitalization, by vaccine product use during Gamma predominant period

Vaccine	Analytic method	# Vaccinated	# Unvaccinated	Partially vaccinated	Fully vaccinated
Sputnik V	Adjusted** unmatched TND	98	49434	26 (-24, 56)	1 (-232, 71)
Sputnik V	Unadjusted unmatched TND	98	49434	78 (67, 86)	63 (-17, 88)
CoronaVac	Adjusted unmatched TND	7683	49434	30 (22, 37)	70 (67, 73)
CoronaVac	Unadjusted unmatched TND	7683	49434	30 (23, 36)	72 (70, 74)
ChAdOx1	Adjusted unmatched TND	5743	49434	48 (43, 52)	76 (71, 81)

ChAdOx1	Unadjusted unmatched TND	5743	49434	47 (44, 51)	83 (79, 85)
BNT162b2	Adjusted unmatched TND	479	49434	46 (31, 57)	94 (84, 98)
BNT162b2	Unadjusted unmatched TND	479	49434	53 (41, 62)	97 (94, 99)
Ad26.COV2.S	Adjusted unmatched TND	28	49434		49 (-21, 79)
Ad26.COV2.S	Unadjusted unmatched TND	28	49434		56 (-4, 81)

**Adjusted for continuous age, sex, secondary administrative unit location of residence, date of hospitalization grouped into categorical epiweeks, presence of 1 or more comorbidities, and study site country

Supplementary Figure S4b. VE against lab-confirmed COVID-19 hospitalization, by vaccine product use during Delta predominant period



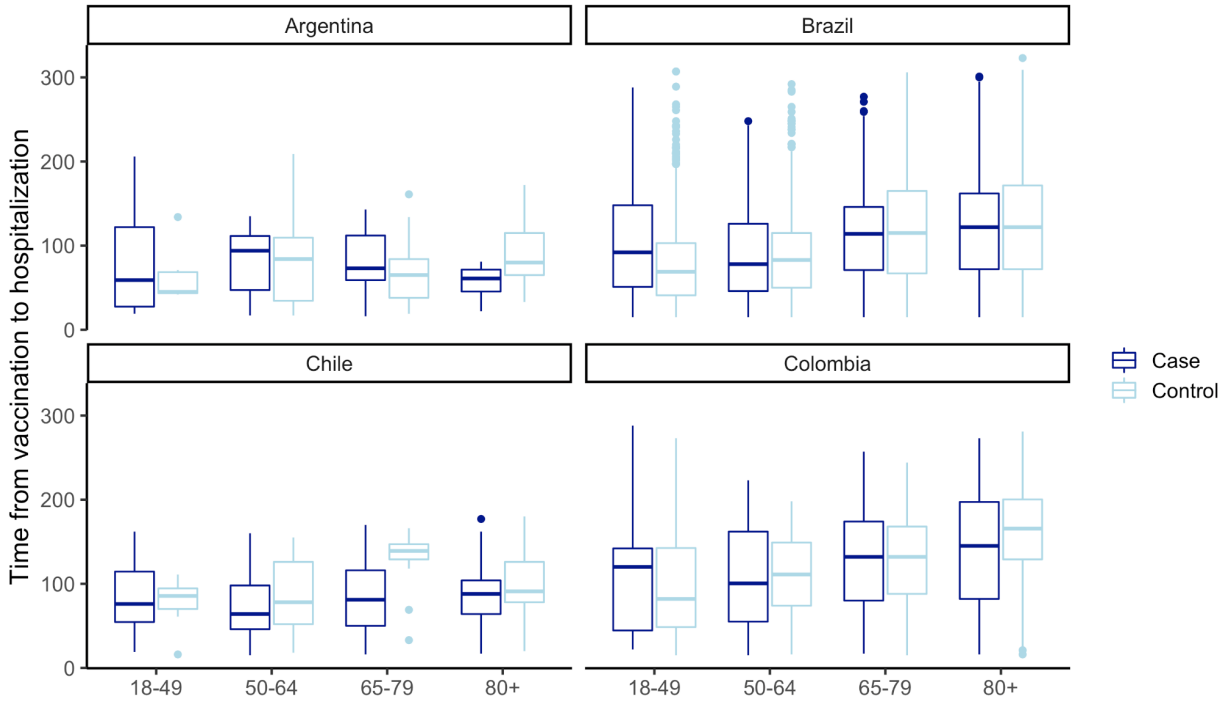
***Adjusted for continuous age, sex, secondary administrative unit location of residence, date of hospitalization grouped into categorical epiweeks, presence of 1 or more comorbidities, and study site country Some estimates and/or 95% confidence intervals fall outside of the range 0-100% shown on the graph. These values can be found in Table S2b. TND = test-negative design.*

Supplementary Table S2b. VE against lab-confirmed COVID-19 hospitalization, by vaccine product use during Delta predominant period

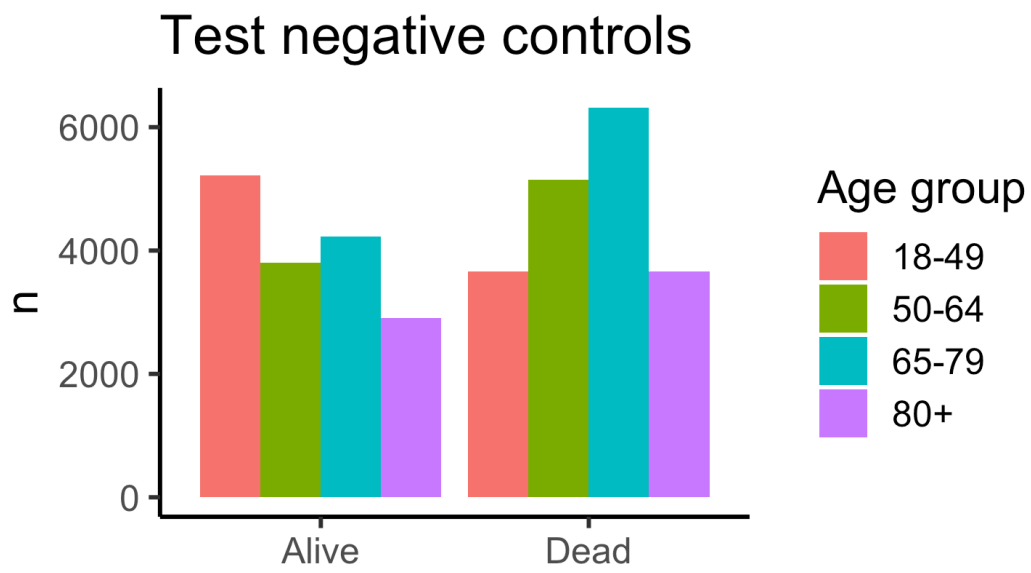
Vaccine	Analytic method	# Vaccinated	# Unvaccinated	Partially vaccinated	Fully vaccinated
Sputnik V	Adjusted** unmatched TND	25	3275	77 (-133, 98)	90 (-12, 99)
Sputnik V	Unadjusted unmatched TND	25	3275	89 (14, 99)	92 (35, 99)
mRNA-1273	Adjusted unmatched TND	102	3275	30 (-52, 68)	82 (-30, 98)
mRNA-1273	Unadjusted unmatched TND	102	3275	84 (66, 92)	97 (80, 100)
CoronaVac	Adjusted unmatched TND	4684	3275	37 (20, 50)	24 (14, 33)
CoronaVac	Unadjusted unmatched TND	4684	3275	15 (-4, 30)	-19 (-31, -9)
ChAdOx1	Adjusted unmatched TND	3338	3275	39 (28, 49)	60 (55, 65)
ChAdOx1	Unadjusted unmatched TND	3338	3275	-20 (-40, -4)	34 (26, 41)
BNT162b2	Adjusted unmatched TND	1311	3275	60 (50, 67)	74 (66, 79)
BNT162b2	Unadjusted unmatched TND	1311	3275	29 (15, 41)	80 (76, 84)
Ad26.COV2.S	Adjusted unmatched TND	80	3275		51 (21, 70)
Ad26.COV2.S	Unadjusted unmatched TND	80	3275		-10 (-72, 29)

**Adjusted for continuous age, sex, secondary administrative unit location of residence, date of hospitalization grouped into categorical epiweeks, presence of 1 or more comorbidities, and study site country

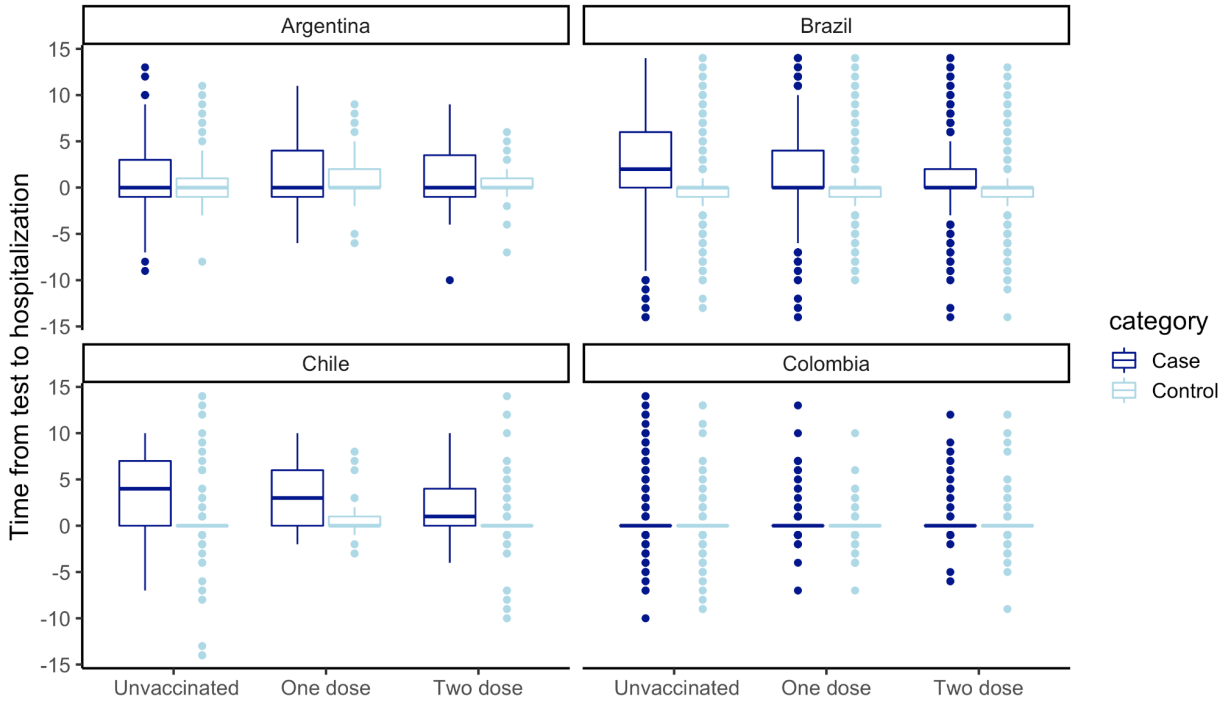
Supplementary Figure S5. Time between vaccination and hospitalization among fully vaccinated cases and controls by age group and country



Supplementary Figure S6. Death by age group



Supplementary Figure S7. Time from test to hospitalization among cases and controls by country



Supplementary Table S3. Bias indicator analysis

Comparison	Estimate	Lower bound	Upper bound
0-13 days	18.69	9.69	26.8
0-6 days	63.14	56.18	68.99
7-13 days	-16.01	-32.25	-1.77

Supplementary Table S4. Description of Sinopharm and Sputnik V + Moderna recipients

Vaccine regimen	Case	Control
Sinopharm	45	31
Sputnik V + mRNA-1273	0	6

Section C. Protocol

COVID-19 Vaccine Effectiveness Study: a multicenter regional evaluation

PROTOCOL
Version: 3

September 1st , 2021

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1. Background

The World Health Organization (WHO) declared a public health emergency of international concern (PHEIC) on January 30, 2020 in response to the identification of a novel coronavirus (SARS-CoV-2) in China (1). In March 2020, as lab-confirmed SARS-CoV-2 cases exponentially grew in China and newly identified transmission was reported in other countries, WHO declared the outbreak a global pandemic and called on countries to rapidly respond with control and mitigation plans to slow the virus' spread. In the ensuing months, countries worldwide have faced challenges to keep a responsive pace with the spread of the virus, which has led to substantial health loss and socioeconomic consequences worldwide (2,3). By late July 2021, there were over 191 million confirmed cases and 4.13 million deaths globally due to COVID-19, the disease caused by viral transmission of SARS-CoV-2 (2).

Countries in the Americas have been among the hardest hit by the pandemic. Approximately 48% of all COVID-19 deaths have occurred in the region, reaching 1.98 million deaths as of July 22, 2021 (4). Since January 2021, South America has continued to surpass North America as the sub-region contributing the highest proportions of cases and deaths per month (4). Although most COVID-19 deaths occur among the elderly and individuals living with health comorbidities, deaths have occurred in all ages including young children, even though younger ages appear to be less susceptible to severe disease (4–6).

As of July 2021, eight COVID-19 vaccines have received Emergency Use Listing (EUL) by the WHO pre-qualification process (7), upon meeting predefined criteria for safety and efficacy (8), and at least several dozen more are under investigation in phase 2 and 3 clinical trials (9). Additionally, other vaccines that are still under review by the WHO pre-qualification process have been authorized for use in some countries in Latin America and the Caribbean following approval from national regulatory agencies (10).

The rapid deployment of vaccines is critical to halting the pandemic's toll in the region. To facilitate this critical need, PAHO's Revolving Fund, a technical cooperation mechanism that consolidates forecasted vaccine demand from PAHO Member States to improve purchasing power for National Immunization Programs and access to affordable vaccines, is actively collaborating with the COVAX Facility (11). This global initiative is working with governments and manufacturers to accelerate equitable access to COVID-19 vaccines. As of October 2020, various countries and territories in Latin America and the Caribbean have signed self-financing

commitment agreements to participate in the mechanism and others will benefit from the Advanced Market Commitment (AMC) that aims to provide cost-sharing for COVID-19 vaccines in eligible countries, 10 of which are in the Region (11). To date, all Member States in the WHO Region of the Americas (PAHO/Pan American Health Organization Region) have initiated COVID-19 vaccination and more than 587 million doses of COVID-19 vaccines have been administered. There are a total of 13 vaccine products in use, or with plans for use, to target specific priority groups, which vary by country (12). Excluding the US and Canada, the products with the most doses administered in the region include AstraZeneca (29% of all doses administered), CoronaVac (27%), and Pfizer (14%). Additionally, Gamaleya, Sinopharm, among others, are widely used (12). Despite the initial availability of COVID-19 vaccines across the region, wide inter- and intra-country variation in access and availability to vaccines at the local level remains, resulting in only 15% of eligible individuals being fully vaccinated in the region (12,13). As global supply increases and lower prices are negotiated, it is anticipated that there will be widespread use of COVID-19 vaccines in Latin America and the Caribbean as the main mechanism for bringing regional outbreaks under control (14,15).

In clinical trials, COVID-19 vaccines have shown high efficacy against symptomatic illness, ranging from 50-95% (16–21). Generally, the conditions under which vaccine efficacy trials are conducted do not entirely reflect real-world conditions (22,23). The differential effects of SARS-CoV-2 vaccine products against severe disease states, across age groups, and in special populations remain poorly documented and, in some cases, understood (24). Additionally, the emergence of genomic variations of SARS-CoV-2 characterized by higher levels of transmission or fatality have resulted in questions about the effectiveness and sustained protection of the available vaccine products against symptomatic disease associated with these Variants of Concern (VOC) (24). This is a particular concern for the region, where at least one VOC has been detected in 47 countries and territories and 11 have detected all four VOCs – including alpha, beta, gamma, and delta (13).

Prior real-world observational studies to estimate the effectiveness of COVID-19 vaccines have largely been conducted in early vaccine adopter/access settings, such as the UK, USA, Israel, and Denmark (25). The findings from these studies have been largely consistent with the results from RCTs. However, most of these countries have adopted mRNA vaccines. There is limited evidence on the real-world effect of the mix of vaccines currently in use in Latin America, including many non-mRNA vaccines. Further, data on the direct vaccine effects against severe disease and deaths associated with COVID-19, particularly in the elderly, and in the presence of

the continued spread of SARS-CoV-2 virus variants of concern (VOC) is only available in the non-peer-reviewed and a few recently peer-reviewed publications (26–29). Determining the effectiveness of vaccines in use specifically against gamma and delta VOCs is a priority.

2. Rationale for the research objectives, aims, and design of the study

Considering the vast geography and diverse composition of the population in Latin America and the Caribbean, it is imperative to conduct vaccine effectiveness (VE) studies that assess performance of COVID-19 vaccines in use for these populations, and especially against rarer outcomes such as hospitalizations and deaths for which trials were not sufficiently powered. Secondarily, the evaluation of COVID-19 VE will address pending programmatic questions such as dosing intervals and schedules, and eventually duration of protection from vaccination. This multi-center study protocol led by PAHO establishes a collaboration between a select number of Latin American countries to implement case-control and cohort studies to evaluate the effectiveness of COVID-19 vaccines against COVID-19 related hospitalizations and deaths, primarily among general population adults aged 50 years and older. Using existing hospital-based and/or population-based information systems, these studies will leverage secondary data sources to generate estimates of vaccine effectiveness, according to vaccine type and schedule and, where possible, in the context of diverse circulating virus types and levels of transmission intensity. A set of core (primary) research objectives will be addressed in each country when implementing this uniform protocol, with the aim of making it methodologically possible to draw comparative inferences based on the VE estimates generated from this study. Pooled analysis may be merited where sample sizes for estimating VE by specific stratifying variables (vaccine product, for example) are not adequate at the center-level. Additionally, country teams may choose to incorporate additional research aims into the country-adapted protocols, while continuing to prioritize response to the core questions.

Several study designs have been proposed and used to study the effectiveness of COVID-19 vaccines, including cohort and case-control studies (24,30). Cohort studies follow a population over time and can provide reliable and easily interpretable estimates of VE, especially if they are started (either prospectively or retrospectively) early on in vaccine rollout when the vaccinated and unvaccinated populations are more comparable and if data on potential confounders are available. However, cohort studies require a population-wide data source that allows for complete follow-up (e.g. from a national database) and a large sample size, particularly for rare outcomes such as severe disease, hospitalizations, or death. The test-negative design (TND), a

variant of the case-control study, is commonly used in evaluations of vaccines, historically for influenza and more recently for COVID-19 (31–34). TNDs select participants from healthcare facilities, often based on a defined set of symptoms; cases are those that test positive, and controls are those that test negative for the infection of interest. By restricting to those who seek care, TNDs minimize bias from health seeking behavior, although this bias is less of a concern with more severe outcomes. However, the TND can induce other biases from conditioning on a post vaccination event (i.e. testing), and control for predictors of both vaccination and disease remains critical for obtaining an unbiased effect estimate. Additionally, outcome misclassification can occur due to imperfect test sensitivity or specificity (35); this bias can be exacerbated in more severe cases who may be further from their date of infection and may no longer be shedding virus. Traditional case-control studies, in which controls are not restricted to the same set of symptoms as the cases, can help mitigate this bias, although they are more subject to bias from differential health seeking behavior; routine testing in the healthcare facility (not just symptom-based) is important for minimizing bias in selection of controls for this study design. Despite its limitations, the WHO recommends the TND for analysis of COVID-19 vaccines in many settings (24).

Recognizing the potential benefits of embedding an evaluation of methodological approaches to studying COVID-19 VE and taking advantage of the diverse set of data sources and systems in the countries selected for this study, this protocol proposes the use of three study designs to evaluate VE: following the methods of Tenforde et al (36), a case-control study with 1) “test-negative” controls and 2) “syndrome-negative” controls, and 3) a cohort study. All countries included in the multi-center study will implement a harmonized approach to evaluating COVID-19 VE using one or more of these study designs, depending on available data sources. Comparing results from these three distinct study designs will provide critical insight into VE and potential bias from different study designs.

Four countries have been invited to participate at this first stage of the project, including: Argentina, Brazil, Chile, and Colombia. Each country will identify an academic implementing partner to serve as the country principal investigator (PI) institution. The overall project aims are:

- Establish a collaborative network with biomedical research institutions in Latin America (LA) for the study of COVID-19 vaccine effectiveness (VE) studies

- Develop and adapt a harmonized study protocol to assess VE across a diverse set of LA countries and populations that addresses key evidence gaps about the use of vaccines for the prevention and control of severe COVID-19 disease and associated deaths in hospitalized patients
- Implement the study protocol simultaneously across the selected countries, with the aim of generating results that are methodologically comparable between countries and specific to the country evidence gaps
- Conduct a pooled or meta-analysis of VE against key outcomes across countries, including some that may not have sufficient sample to study at the country-level
- Facilitate collaborative exchange of timely information between LA countries participating in the network and others in the region

2.1 Primary research objectives

To estimate the effectiveness of COVID-19 vaccines (disaggregated by vaccine product) against lab-confirmed COVID-19 related hospitalizations and deaths among general population patients aged 50 and older in Argentina, Brazil Chile, and Colombia. Each country will define the sub-aims that support this overarching research aim which, depending on data availability, may consider stratification or sub-studies for the evaluation of vaccine effectiveness by:

1) other age strata: among vaccine eligible younger adults 18-49, and/or in other combinations of finer age strata such as 18-49, 50-59, 60-69, 70-79, 80+
2) circulating virus variant
3) vaccination schedule (dosing intervals and partial completions; heterologous schedules; booster doses, if introduced)
4) past SARS-CoV-2 infection history
5) comorbidities
6) time periods since vaccination (to assess waning over time)

Additionally, if data are available, countries may conduct an additional study focused specifically in pregnant women.

3. Methods

3.1 Study design and data sources

All details provided here are a starting point based on the best practices in VE study design. The harmonized protocol will need to be adapted to data availability in each country to guarantee a consistent approach that allows for pooled analysis.

2.1.1. Case-control

A case-control study with the option for two types of controls, test-negative and syndrome-negative (see 3.5), will be used for this multi-country evaluation of the effectiveness of COVID-19 vaccines against COVID-19 related hospitalizations and deaths among general population adults aged 50 and older and separately among pregnant women. For this protocol, disease cases will be identified through pre-existing hospital information systems that allows for collecting data on case patients and identifying appropriate controls, or non-cases. These systems could either:

1) serve as the (electronic) medical records system for an integrated hospital system or select hospitals, or
2) constitute a population-based hospital admission registry system.

Both data sources must also ideally collect information on hospital admission details (date and length of stay, symptom onset date, disease severity, level of care, etc.), vaccination status (type of vaccine, administration dates), individual patient characteristics (age, sex, municipality of residence), laboratory testing (rt-PCR SARS-CoV-2 testing results, test date), prior medical history (including past lab-confirmed COVID-19 diagnoses and/or related hospital admissions), among other covariates (health condition, prior vaccination history). These data may be available in separate data systems, which will require capability of linkage. If a country requires selecting a sample of hospitals for inclusion in the study, some criteria for selection may include:

1) Hospitals that have been involved in COVID-19 surge response i.e. sites that will have sufficient numbers of cases to meet the sample size considerations
2) Electronic information systems that have capability to integrate admission records with other public health systems
3) Storage of SARS-CoV-2 specimen aliquot samples for genomic sequencing (see note on storage specifications)
4) Capacity to perform genomic sequencing on SARS-CoV-2 specimen samples or has capability of collaborating with other laboratory networks to perform the sequencing

5) Hospital sites with broad testing protocols for SARS-CoV-2. This is not required but testing of non-SARI/suspect COVID patients is required for the syndrome negative case-control design. This is further discussed in section 3.5.

2.1.2. Cohort

In countries with population-based data sources, in addition to the case-control study, we also propose conducting a cohort study. Following the design of Dagan et al (37), we will use a "rolling cohort" design in which we match newly vaccinated individuals during the study period to unvaccinated controls on their day of vaccination. Individuals will be followed up until they experience the outcome(s) (i.e. COVID-19 related hospitalization or in-hospital death), die of other causes, or for vaccinated individuals when their matched control gets vaccinated, or until the end of the study period. In addition to date, age group, and sex, vaccinated and unvaccinated individuals should be individually matched on additional variables that are associated with both vaccination and infection, such as geography, (see section 3.6.2 for suggested variables), depending on data availability.

3.2 Study population

The study will identify general population adults aged 50 and older, and separately pregnant women where possible, who are eligible to receive COVID-19 vaccines according to the national recommendations. Depending on data availability, other age groups may be selected for the study population, and VE for specific age sub-groups may be sought. Likewise, exclusion criteria may possibly include history of a positive SARS-CoV-2 rt-PCR test in the 90 days prior to the index event (case or control) for this study[1], contraindication to receiving the available COVID-19 vaccines, or, in the case of hospital-based information sources, patients who were transferred from another hospital system.

3.3 Study period

The study period will vary by setting depending on country-specific timelines for COVID-19 vaccination roll-out and scale-up. Each country will determine the **retrospective** study period based on the dates when vaccine was readily available in the study population, which may vary by age sub-group.

[1] If this information is not readily available, alternative methods will need to be defined to apply this exclusion in order to avoid bias from patients who may experience prolonged viral shedding and/or have differentially opted out of vaccination due to having had natural infection.

Study participants will continue to be identified prospectively from the retrospective study period start date until the desired sample size has been achieved or a threshold of 80% vaccination coverage within the local source population has been reached, ensuring adequate sampling across all time periods of interest. For the case-control study, identifying a retrospective study period that aims to reduce bias associated with differential propensity for vaccination (i.e., exposure) among cases and controls is crucial, which may occur at very low or high levels of vaccination coverage (22).

3.4 Primary study endpoint

The main study endpoints of interest are COVID-19 related hospitalization and death, stratified by age group and time period. Clinical case management definitions plus virologic lab-confirmation with or without primary discharge ICD-10 codes for COVID-19 (U07.1) will be used (see case definitions). There will be discussion to harmonize the case definition across settings.

3.4.1 Other endpoints

Primary endpoints may also be stratified by disease severity using the WHO COVID-19 clinical progression scoring system (38) or respiratory vent use vs no respiratory vent use.

In the presence of a genomic sequencing programme, there may be interest in stratifying the study endpoints by genomic variant of SARS-CoV-2 with demonstrated variation in the circulating viral variants. The capacity to incorporate variant-specific stratification will be explored by each country.

For the sequencing analysis of the virus, it would be important that the collected specimens are properly stored and transported. Ideally, clinical specimens should be stored at -70°C. If there is no access to –70°C, storage at -20°C can be considered. Specimens should not be repeatedly frozen and thawed. In addition, samples should have a real time PCR positive result for the viral target gene with a cycle threshold (CT) < 30 and a minimum volume of 500 µL of the clinical specimen should be available. If the samples need to be transported to a distinct laboratory for performing the sequencing protocol, transportation should be done in a reverse-cold chain.

3.4.2 Case definitions

Following WHO/PAHO public health surveillance guidance for COVID-19, a case is defined as a hospitalized patient included in Severe Acute Respiratory Symptoms (SARI) surveillance systems (39) and rtPCR—confirmed SARS-CoV-2.

The second case definition for this study is a hospitalized patient included in SARI surveillance systems with rtPCR-confirmed SARS-COV-2 resulting in death.

Sensitivity analyses that include cases confirmed by antigen tests may be conducted.

If there is variation in definitions for case classification between countries involved in the study, the case definitions will be finalized following a discussion with country research teams on the best approach to harmonize across settings.

3.4.3 Case ascertainment

Cases ascertainment will depend on the type of data source and the study design. Starting from the retrospective study period initiation date, all cases that fulfill the case definition criteria will be identified through active case searches using hospital-based information systems or systematically in population-based hospital registry systems. For hospital-based information system sources, the study investigators should establish procedures with service provider staff to route information from in-patient records and/or laboratory records. In the case of population-based registries, study investigators will determine appropriate step-wise algorithms for the identification of cases based on the inclusion criteria defined by the case definitions. Depending on the available data, inclusion criteria might include:

- Identifiable in data source for having experienced a hospital admission or death associated with lab-confirmed SARS-CoV-2
- Have specimen collection dated within 10 days of symptoms onset and hospitalization within 14 days of symptom onset for the outcome of hospitalization or have COVID-19 associated death within 28 days of symptom onset for the outcome of death.
- Have no history of positive rt-PCR test for SARS-CoV-2 in prior 90 days (if this information is available or if linkage with testing data is feasible)

Case ascertainment date should be defined based on specimen collection date for the case-control study and hospitalization or death date for the cohort study.

Further, the feasibility of using primary discharge diagnosis ICD-10 code for COVID-19 (U07.1) will be explored. ICD-10 codes for pneumonia (J12.89), acute bronchitis (J20.8 or J40), LRI (J22 or J98.8), ARDS (J80) that are viral non-specified with a U07.1 code should also be reviewed.

3.5 Control sources, selection, and definitions

Hospital-based controls, or non-cases, will be selected from the same data source utilized for case ascertainment for the case-control study. For the hospitalization outcome, controls will be chosen from hospitalized patients with negative rt-PCR tests. (Note, while positive antigen tests may be considered for inclusion as cases, due to lower sensitivity of antigen tests, controls must have a negative rt-PCR test.) As described above, for the hospitalization outcome, we will have two control groups: 1) test-negative controls will include all patients with the same set of symptoms[2] as cases who test negative for SARS-CoV-2 and 2) syndrome-negative controls will be selected from patients without COVID-19 symptoms who test negative for SARS-CoV-2. Syndrome-negative controls should only be used where hospital infection control policy includes routine SARS-CoV-2 testing with rt-PCR of all hospitalized patients.

For the death outcome, only test-negative controls will be used, and they will be chosen from hospitalized individuals with the same set of symptoms as cases who died from non-COVID causes and had a negative rt-PCR test. Due to the lack of available data for the underlying population that gives rise to the in-hospital COVID-19 deaths, syndrome-negative controls should not be used for this outcome.

Given the expected time-dependent changes in disease risk during vaccination rollout, controls should be matched on specimen collection date (± 7 day period of case ascertainment). Controls should also be matched on age, sex, and hospital; other matching factors, that are associated with both vaccination and risk of the outcomes may be proposed depending on data availability.

Control selection must adhere to study inclusion criteria, including identifying non-cases who are eligible to receive COVID-19 vaccines, are identifiable in the selected data source, and have no history of a positive SARS-CoV-2 rt-PCR test in the 90 days prior to control selection. For the

[2] Using patients included in SARI surveillance systems (40)

test-negative controls, patients with a first negative test more than 10 days after symptom onset should be excluded.

Depending on how the study period is defined, disease risk may remain high in the population and therefore the typical difficulty in obtaining a sufficient number of cases and controls to achieve statistical power may not be a concern. In this scenario, a ratio of selecting one syndrome-negative control per one case is sufficient (*see sample size considerations*). In low incidence settings, increasing the ratio of controls to cases is possible; however, there should be consensus among the multi-country study sites. Required sample size should be considered when choosing the number of hospitals to include in the case-control studies.

3.6 Minimum set of variables and other information

Verification of vaccination status (exposure) and collection of other key characteristics for both cases and controls are critical for reducing exposure misclassification bias and assessing other biases due to potential confounding or selection issues. Standardized data collection templates for patient (cases and controls) variables will be defined for study investigators and applied harmoniously across country study sites, considering any necessary adjustments needed to accommodate the data sources selected for the study. At a minimum, cases and controls (or exposed and unexposed individuals for the cohort) must have sufficient details to ascertain classification and characterize the individuals in the study population which includes lab-confirmation result, testing date, symptom onset date, vaccine type administered, date for each vaccine dose administration, age, sex, and municipality of residence. Pregnancy status should also be available if a separate study in pregnant women will be conducted.

3.6.1 Exposure definition

All eligible study participants must have data available to verify vaccination status. Depending on the data source selected for the study, this may include linkage to national vaccination registry systems where nominal systems with unique identifiers are available. Information that should be collected for each study patient includes:

- COVID-19 vaccine any receipt (binary yes/no)
- Type of vaccine received
- Number of doses received
- Dates of vaccine administration

From this information, study investigators will derive two main types of exposure variables that define vaccination status for each product to compare to the unvaccinated group:

1) **Fully vaccinated**, defined as receipt of complete vaccination series (1 or 2 doses depending on the vaccine) according to the national schedule recommendations, at least 14 or more days prior to a reference date.
2) **Partially vaccinated**, defined as receipt of incomplete vaccination series (1 dose for 2 dose vaccine series) according to the national schedule recommendations, at least 14 or more days prior to a reference date or 2 doses less than 14 days before reference date.

For participants in the cohort study and for cases and test-negative controls in the case-control study, the reference date should be symptom onset date (if available), or specimen collection date. For the syndrome-negative controls, the reference date should be hospital admission date. If sample size permits, we may further stratify by one or two week periods within the partially vaccinated and fully vaccinated exposure levels.
In addition to the product specific analyses, an additional analysis across all products may be conducted using the above two exposure variables and an additional third status:

3) **Mixed product vaccinated**, defined as receipt of more than one type of vaccine in the fully vaccinated category.

Finally, if boosters are implemented over the course of the study period, additional exposure levels may be added to accommodate the additional doses.

3.6.2 Other covariates

Additional information to characterize and control for potential differences between the case and control groups in the case-control study and the vaccinated and unvaccinated groups in the cohort study should be collected and retained for each study patient. In addition to patient data on age, sex, municipality of residence, and case/control index date, the following variables should also be considered for data collection.

Patient characteristics (for all study participants)

- Race/ethnicity
- Pregnancy status
- Presence of pre-existing and underlying chronic conditions, such as COPD, heart disease, chronic renal disease, diabetes, obesity

- Dates: initiation of symptoms, respiratory specimen collection for laboratory testing, hospital admission (or outpatient procedure for community controls), discharge
- Health behaviors, ie tobacco user, prior history of influenza or other adult vaccination record where applicable, other information about level of adherence to non-pharmaceutical interventions for the control of COVID-19
- Other demographics, where available, occupation, income, living situation, geographic location
- History of SARS-CoV-2 infection more than 90 days prior

Clinical characteristics (for cases)

- All metrics that compose clinical progression score, if using (i.e. pulse oximetry, respiratory rate, etc.)
- Other measures of care that signal severity (Vent use vs No ventilator use)

3.7 Analytic considerations

Considering the severity of the disease state defined for the primary study endpoint, there is less concern for confounding by health-seeking behaviors in the case group and hospital-based control group. However, evaluation of the covariate distribution by case disease status will help identify any potential measured confounding bias.

Sample size for the case-control study is determined by the prevalence of exposure (vaccination) in the study source population, the anticipated vaccine effectiveness for statistical detection at a precision of ±10%, considering a type 1 error of 0.05. Each country-setting will determine the minimum sample size, including the number of cases and controls, based on the status of vaccination rollout and the vaccines being studied. As vaccine effectiveness will be estimated separately for each vaccine product, the sample size should be estimated separately for each vaccine currently in use for each country. Additional sample will be required to ensure analyses can be conducted stratified by age group (<50, 50-59, 60-69, 70-79, 80+) and time period (every three months over course of the study). Therefore, if feasible, the sample size calculation described in section 3.7.1 should be repeated separately for each outcome and each combination of vaccine product, age-group, time period (e.g. Pfizer in 50-59 year olds from April – June 2021).

Attaining the minimum required sample size is an important consideration when choosing the hospital sites and number of hospitals to include in the case-control studies. Where there is

evidence of multiple SARS-CoV-2 variants of concern in circulation, additional sample may also be required to conduct stratified vaccine effectiveness analyses.

When matching is used, power depends on the number of discordant pairs in the analysis, which in turn depends on vaccine coverage and incidence, which are factors that are changing over time. As there is no sample size formula for this matched design, power and sample size can be simulated, following methods described in Hitchings et al. The sample size calculations described below can be used as a starting point, and the regional analysis support team will provide code and be available to support with simulations of power to determine the sample size needed to attain at least 80% power for the matched designs.

Sample size should be estimated separately for the analysis of pregnant women, with consideration of estimating vaccine product specific VE if multiple products are in use for this population.

3.7.1 Sample size

The following sample size guidance for informing the minimum number of cases and controls for each combination of outcome, vaccine product, age group, and time-period in each study site (country-level) may be used. To ensure adequate sample, the conservative effectiveness estimate of 50% for all groups and outcomes is recommended. The sample size will be dependent on vaccination coverage in each age-group and time period specified for analysis.

For the cohort study, all individuals who meet eligibility criteria should be included, allowing for a large sample size.

The WHO sample size calculator for cohort and case-control studies can be found: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement_tool-2021.1.

Table. Minimum number of cases and controls to detect hypothesized VE, considering the projected vaccination coverage in the population under evaluation, with 1-1 ratio of controls to cases, and a precision ±10%, considering a type 1 error of 0.05. A ratio of up to 4-1 may be considered.

Vaccine effectiveness	Vaccination coverage	Number Cases	Number Controls
50%	20%	1594	1594
	30%	1133	1133
	40%	925	925
	50%	828	828

	60%	803	803
	70%	855	855
60%	20%	1152	1152
	30%	801	801
	40%	639	639
	50%	559	559
	60%	530	530
	70%	550	550
70%	20%	776	776
	30%	526	526
	40%	408	408
	50%	346	346
	60%	317	317
	70%	319	319

Adapted from WHO's Guidance for the Evaluation of COVID-19 Vaccine Effectiveness

3.8 Analytic plan

Each country will implement their own analysis plan in line with the final country-specific adaptation of the protocol. Guidance will be provided to harmonize minimum datasets across countries to conduct the de-identified regional analysis. For the regional analysis, all analyses will be conducted separately for each country and also a pooled analysis will be conducted, ensuring that heterogeneity is appropriately accounted for in the analysis (40). If appropriate, we will conduct a two-staged pooled analysis, in which country specific estimates will be combined in a model with random effects. To ensure consistency between sites, hospitalizations may be restricted to a minimum clinical progression score before pooling.

3.8.1 Primary analysis

For the case-control study, conditional logistic regression will be conducted for each of the two primary outcomes to estimate the odds ratio (OR) of vaccination; vaccine effectiveness will equal 1-OR, and unvaccinated individuals (i.e. those who have not received any dose) will be the reference group. Separate analyses will be conducted for each of the two control groups. Analyses will be adjusted for key confounders, including calendar time, hospital, age, sex, and municipality of residence, and others depending on data availability (see 3.6.2). Missing data techniques, such as multiple imputation, will be implemented if necessary. Separate analyses will be conducted for each vaccine product. Upon data availability, the analyses will be repeated for the study of pregnant women.

For the cohort study, following Dagan et al (37), we will conduct a survival analysis, using the Kaplan-Meier estimator (41) for each of the two primary outcomes for three periods: (i) day 14 after the first dose through the day prior to the expected receipt of the second dose (per vaccine regimen), (ii) the expected day of the second dose through 13 days after expected receipt of the second dose, and (iii) day 14 after the expected day of the second dose through the end of the study period. For the latter two time periods, we will restrict analysis to matched pairs who survived until the start of the period. We will calculate the risk ratio (RR) comparing the different vaccination exposure levels to no vaccination for each period; vaccine effectiveness will equal 1-RR. Separate analyses will be conducted for each vaccine product.

If necessary for informing public health decisions prior to the conclusion of the study, interim analyses may be conducted. These analyses could be triggered by attaining certain vaccine coverage levels and estimated power (based on numbers of cases to date). Correction for multiple testing should be incorporated into the analysis if interim analyses are performed.

3.8.2 Secondary analysis

The primary analyses will be repeated for the secondary endpoints described in section 3.4.1. We will also conduct subgroup analyses, as described in section 2.1 and also compare different vaccine regimens (i.e. dosing intervals). If genomic data are available, we will also estimate strain specific vaccine effectiveness. In the absence of widespread genomic data, analyses could be stratified by time periods when different variants are most prevalent.

We will also conduct descriptive analyses of the study population's baseline characteristics. We will further conduct statistical tests to compare cases and controls in the case-control study and vaccinated and unvaccinated individuals in the cohort study.

We will also conduct an analysis using a composite outcome of hospitalization or death.

Analyses with mixed vaccine products as an additional exposure level may also be conducted.

3.8.3 Sensitivity analyses

To assess the success of matching in ensuring exchangeability between the vaccinated and unvaccinated in the cohort study, we will conduct an analysis for periods of 0-6 and 7-13 days after the first dose in which we would not expect there to be any vaccine effect.

Additionally, given that the outcomes of hospitalization and death are downstream effects of infection and symptom onset, we may conduct sensitivity analyses with the time periods used to define fully and partially vaccinated exposure levels relative to the reference dates.

We will also conduct additional analyses, varying the matching factors that are used.

Additional analyses including cases testing positive with antigen tests, in addition to those testing positive with rt-PCR, may also be conducted.

Due to different underlying populations, the cohort and case control studies may not be comparable. However, if possible (as a sensitivity analysis), countries may consider restricting the cohort analyses to the catchment areas of the hospitals used in the case-control study

4. Study limitations, risks, and benefits

Will be completed once the protocol is finalized.

5. Ethical clearance and considerations

This proposed study protocol leverages secondary data sources routinely collected via health information systems at the local-level or nationwide in the study countries. After obtaining adequate permissions, in collaboration with government authorities where necessary, the local study teams will remove all personally identifiable information linked to data sources required for this analysis (name, unique identifier numbers, date of birth). Any linking codes created for merging individual patient data across multiple information sources will be held solely by the local study team lead in each country. All other reasonable protections against breaches of data confidentially will be implemented both at the local and regional level. The team at PAHO will only have access to de-identified data.

Following discussion with the country study teams, the revised protocol will be submitted for ethical review by the PAHO Ethics Review Committee (PAHOERC). Each country study team will be responsible for adapting the protocol to their setting and submitting the country-specific iteration to their local institutional review board (IRB) or ethics clearance process.

6. Dissemination of results

Findings from each country study will be summarized and reported to national Ministries of Health. PAHO, in collaboration with the country study teams, will compile individual country study findings into a regional report that will be shared with all participating institutions and national Ministries of Health. Regional findings from the compiled reports, descriptive comparative analysis, and pooled analyses will be disseminated through presentations at relevant regional and international policy forum (PAHO TAG, WHO SAGE).

PAHO, with the involvement of the study teams and partners, will develop a regional peer-reviewed publication that will feature study background and methods, and a comparative analysis of study findings and methods. Each country can publish its own findings in local or international peer-reviewed journals after the Regional publication, which will be PAHO responsibility. Standardized criteria using ICMJE considerations will be developed by the project team to ensure appropriate designations of authorship. Additionally, group authorship details may be considered for inclusion where contributions from the project team as a whole should be mentioned in authorship or acknowledgements.

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