Evaluation of the effectiveness of COVID-19 vaccines in Latin America and the Caribbean

Generic Protocol

May 2021

ACRONYMS

95% CI	95% confidence interval
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease 2019
EPI	Expanded Program on Immunization
IPC	Infection prevention and control
NAA	Nucleic acid amplification
NIC	National Influenza Centre
OR	Odds ratio
PAHO	Pan American Health Organization
REVELAC-i	Network for the Evaluation of Vaccine Effectiveness in Latin America and the Caribbean - influenza
RT-PCR	Reverse transcriptase - Polymerase chain reaction
SARI	Severe acute respiratory infection
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VE	Vaccine effectiveness
WHO	World Health Organization

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The following professionals actively contributed to the review of this protocol: Minal Patel (WHO), Marc Rondy and Nathalie El Omeiri (PAHO), Rafael Chacón and Sofía Arriola (CDC), Marta Valenciano (Epiconcept), Amparo Larrauri and Clara Mazagatos (*Instituto de Salud Carlos III*), Isabel Martínez Pino (*Servicio de Epidemiología de la Junta de Castilla y León*) and Sergio Loayza (PAHO consultant).

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1. BACKGROUND

Coronaviruses are a large family of viruses that can cause diseases in animals and humans. In humans, it is known that several coronaviruses cause respiratory infections with symptoms that range from the common cold to more severe diseases, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), identified in 2003 and 2012, respectively. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease (COVID-19) and was identified for the first time in Wuhan, China in December 2019. By the end of March 2020, more than 400,000 COVID-19 cases were reported in over 150 countries. As of April 2021, more than 132 million cases and 2.9 million deaths had been reported throughout the world. In the Region of the Americas, more than 57 million cases and 1.4 million deaths have been reported since the onset of the pandemic. Brazil, Colombia, Argentina, and Mexico are the most affected countries [1].

COVID-19 immunization is considered an essential public health intervention for controlling the pandemic, together with other social and public health measures. COVID-19 vaccines can play a critical role in reducing mortality and severe morbidity due to COVID-19 and the spread of SARS-CoV-2. As of April 2021, more than 200 COVID-19 vaccine candidates are in the clinical development phase.* Of these, nine vaccines were recently authorized by regulatory agencies for use in Latin America and the Caribbean. A total of 49 countries and territories have initiated vaccination against COVID-19 in the Region†. Clinical trials conducted by the manufacturing laboratories have shown a favorable safety profile and high efficacy for these vaccines, ranging from 70 to 95% against cases of symptomatic disease [2-4].

Evaluation of vaccine effectiveness (VE) under operational conditions is essential for guiding decisions and evaluating the impact of the immunization program. Post-authorization studies (or phase IV studies) are observational studies that attempt to respond to questions about effectiveness that have not been answered in clinical trials. These include evaluating the effectiveness of vaccines when they are applied to vaccination groups, geographic areas, or population subgroups that are different from those included during the pre-authorization clinical research phases. Effectiveness studies evaluate the protection that vaccines confer for different levels of disease severity and different intervals between doses, as well as to measure the effectiveness of incomplete vaccination and the duration of long-term protection.

*World Health Organization. Draft landscape and tracker of COVID-19 candidate vaccines. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

†https://ais.paho.org/imm/IM_DosisAdmin-Vacunacion.asp

Furthermore, effectiveness evaluations help to understand the effectiveness of the vaccines in preventing infections, modifying the clinical course, producing less severe conditions, and reducing transmissibility.

This document presents a generic protocol for evaluating the effectiveness of COVID-19 vaccines based on the sentinel surveillance strategy for severe acute respiratory infections (SARI) [5], using existing regional platforms such as the Severe Acute Respiratory Infections Network (SARInet) and the Network for the Evaluation of Vaccine Effectiveness in Latin America and the Caribbean - influenza (REVELAC-i) [6, 7].

It is important to note that, since patients with COVID-19 can present symptoms compatible with influenza infection, countries can simultaneously evaluate the effectiveness of COVID-19 and influenza vaccines, using the same methodology described in the generic REVELAC-i protocol [8]. Similarly, WHO recommends maintaining and adapting the existing influenza surveillance systems to monitor SARS-CoV-2 [9].

This document has been developed in line with WHO protocols [10, 11] and aims to guide countries in the preparation of their national protocols. Participating countries should adapt and update this guidance according to their objectives, information sources, and COVID-19 vaccination policies and strategies (vaccination target groups, type of vaccine used, number of doses, vaccination schedule, etc.).

2. OBJECTIVES

2.1. Main objective

Estimate the effectiveness of COVID-19 vaccines in preventing SARI among patients with confirmed SARS-CoV-2 infection who are admitted at sentinel surveillance hospitals in participating countries in Latin America and the Caribbean.

2.2. Secondary objectives

- Estimate the effectiveness of COVID-19 vaccines in preventing SARI among patients with confirmed SARS-CoV-2 infection who are admitted at sentinel surveillance hospitals by:
    - participating country, sub-region and for the entire Region
    - age group (according to vaccination target groups)
    - sex
    - risk groups
    - time since vaccination
    - number of vaccine doses received

- genetic variant of the virus

- Evaluate the effectiveness of COVID-19 vaccines in preventing severe disease caused by SARS-CoV-2 (e.g., ICU admission, in-hospital death, etc.) among patients with SARI who are admitted at the sentinel surveillance hospitals in participating countries.
- Identify factors that may modify VE: age, sex, chronic diseases, role of influenza vaccination, role of chronic medication, risk behaviors, etc.

Note: For the secondary objectives, the sample size needs to be sufficiently large to evaluate the effectiveness of the different variables. Aggregate data analysis at the regional level will make it possible to obtain these estimates.

3. METHODS

3.1. Evaluation design

Case control test-negative design: an observational study in which cases and controls are drawn from the network of SARI sentinel surveillance hospitals.

The data contributed by each sentinel hospital can be aggregated to obtain national and regional estimates.

3.2. Study population

Any individual who is included in the vaccination target groups, has no contraindication to COVID-19 vaccination, and is hospitalized for SARI in any hospital or service of the network of SARI sentinel surveillance.

3.3. Evaluation period

The evaluation will start when COVID-19 vaccination begins in the participating country, with a minimum duration of six months. Periodic analyses of the data collected will be run to obtain partial estimates. If there is no community circulation of the SARS-CoV-2 virus, which would limit the recruitment of cases, the evaluation may be interrupted.

3.4. Outcome variable

Hospitalized patients with SARI with a positive SARS-CoV-2 RT-PCR molecular test at admission or during the 14 days prior to hospitalization.

3.5. Disease severity

In addition to confirmation by RT-PCR, VE against different levels of severity associated with COVID-19 disease will be measured. The WHO guidance for the clinical management of COVID-19 patients defines a patient with severe COVID-19 as an adolescent or adult with clinical signs of severe pneumonia (fever, cough, dyspnea, or tachypnea) in addition to one of the following: respiratory rate > 30 breaths/minute; severe respiratory distress; SpO2 < 90% (without requiring supplemental oxygen). The critical COVID-19 patient is defined as a person with acute respiratory distress syndrome, sepsis, septic shock, or death [12].

Other outcome variables include disease severity indicators such as the duration of hospitalization, ICU admission, need for mechanical ventilation, and death during hospitalization. Sensitivity analyses (see section 3.20) will evaluate VE against severe COVID-19 cases based on different definitions of severity criteria collected in the patients' clinical information.

3.6. Definitions

3.6.1. Hospitalized patient

A patient who is hospitalized with SARI at one of the hospital or centers that is part of the network of SARI sentinel surveillance during the evaluation period. Hospitalization is considered as a minimum hospital stay of 24 hours.

3.6.2. Patient with SARI

A patient with SARI will be defined as a person who presents all these criteria [2]:

- History of fever or a measured fever of ≥38 °C,
- And cough,
- And symptom onset within the last 10 days,
- And who requires hospitalization.

Note: PAHO proposes this case definition for surveillance of severe acute respiratory illness due to influenza and COVID-19 [2, 13]. If countries use a different definition for SARI patient, it should be documented and reported so that it can be considered in the regional analysis of aggregate data.

3.6.3. SARI patient with confirmed COVID-19 (cases)

A confirmed COVID-19 case is defined as a patient who meets the SARI case definition with positive SARS-CoV-2 results by RT-PCR at admission. Patients with a positive RT-PCR result for SARS-CoV-2 in the previous 14 days prior to hospitalization will also be considered as cases.

SARI patients with a positive RT-PCR result for SARS-CoV-2 before the onset of symptoms will not be considered as cases.

Note: Based on current evidence, SARI patients with positive results only by SARS-CoV-2 antigen-detecting rapid diagnostic test will not be considered as cases (see section 3.10. Laboratory diagnosis).

3.6.4. SARI patient who tests negative for SARS-CoV-2 (controls)

A control is defined as a patient who meets the SARI case definition and presents a respiratory sample with a negative SARS-CoV-2 RT-PCR result at admission. Controls should not have received a positive SARS-CoV-2 result during the 14 days prior to hospitalization. A control can have a positive sample for other respiratory viruses.

In case of SARI patients testing negative by RT-PCR for SARS-CoV-2 but being found to have recent onset of anosmia or ageusia, or with chest imaging showing findings suggestive of COVID-19, a second RT-PCR could be considered (see section 3.10.1).

Note: Based on current evidence, SARI patients with negative results only by SARS-CoV-2 antigen-detecting rapid diagnostic test will not be considered as controls (see section 3.10).

For both cases and controls, respiratory specimens should be taken within 10 days from the onset of symptoms.

3.6.5. Patients without SARI (additional controls)

Participating hospitals and centers should also consider a second set of controls (e.g., persons admitted at the hospital for non-respiratory illnesses or community controls). This additional control group would be useful to validate the test-negative design approach in hospital settings. Furthermore, given the current burden of COVID-19 and the low levels of other circulating respiratory viruses, it might be challenging to enroll enough controls who have a negative RT-PCR test result for SARS-CoV-2.

However, inclusion of controls that are not representative of the population from which the cases have arisen can introduce biases since vaccination coverage in those groups may be different. Possible

differences in vaccination between the controls and cases should be considered, since they could be very different and introduce biases, affecting the estimate of VE. It is recommended that non-SARI controls should have similar exposure to the virus and probability of vaccination as the cases. The process for selecting those controls should be documented in the national protocol.

3.7. Inclusion criteria

A patient with SARI is eligible for the evaluation of COVID-19 VE if the patient:

- Meets the SARI case definition (see section 3.5.2.)
- Has been hospitalized for at least 24 hours at the participating hospital
- Is eligible for COVID-19 vaccination
- Belongs in the group or sub-group for which vaccination has started (e.g., age group, area, professional group, etc.)
- Has provided a respiratory specimen within the framework of SARI surveillance
- Has specimen that was taken within a maximum of 10 days after the onset of symptoms

3.8. Exclusion criteria

A patient will be excluded from the evaluation of COVID-19 VE if the patient:

- Has a contraindication to the COVID-19 vaccine
- Has a contraindication to or difficulty providing the respiratory specimen
- Has been hospitalized during the 14 days prior to their admission for SARI, including hospital transfers
- Has symptoms that began after being hospitalized
- Has a vaccination status that cannot be determined

The reasons for excluding identified patients with SARI must be documented.

The eligibility verification form for SARI patients is in annex 1.

3.9. Recruitment of patients with SARI

Patients with SARI will be identified among the patients who present at participating hospitals during the evaluation period. Ideally, surveillance personnel will conduct daily active case-finding of patients admitted at the hospital with respiratory symptoms to identify patients who meet the SARI case definition and are eligible for the evaluation according to the inclusion and exclusion criteria (Annex 1).

Personnel may review the hospital admission records (for example, ICD-10 admission codes J00 to J22, corresponding to respiratory tract diseases, see Annex 2) and consult clinical personnel to identify patients with SARI. Laboratory records can also be reviewed to identify other patients who provided a respiratory specimen and were not included in the admission records. Case-finding can be implemented prospectively during admission or retrospectively once the respiratory specimen result is obtained.

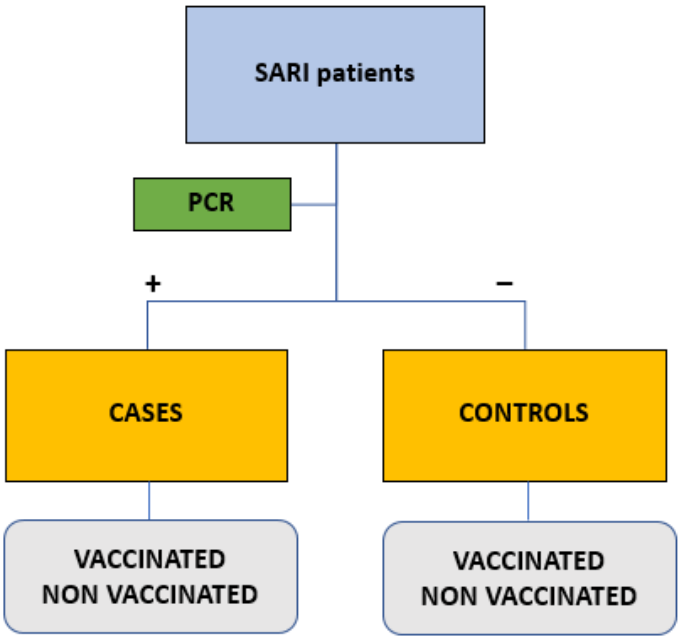
For the evaluation, only patients meeting all the inclusion criteria (see section 3.7) and not meeting any of the exclusion criteria (see section 3.8) will be considered. All SARI patients should have provided a respiratory specimen within 10 days following the onset of symptoms and a RT-PCR will be performed upon admission to confirm SARS-CoV-2 infection. If the RT-PCR test result is positive (or have a RT-PCR positive result in the 14 days prior to hospitalization), the patient will be considered as a case. If the RT-PCR test result is negative for SARS-CoV-2 (and the patient does not have any positive RT-PCR result in the last 14 days prior to hospitalization), the patient will be considered as a control. Cases and controls will be matched by date of admission and by site to minimize potential bias related with the exposure to the virus and to the vaccine.

Annex 3 presents the flowchart for SARI patients for REVELAC-COVID-19.

For both cases and controls, COVID-19 vaccination status prior to symptom onset will be recorded along with other information.

The TND has several advantages. First, all cases and controls have sought care at the same facilities. Hence, cases and controls will generally have come from the same communities, reducing bias due to community-level variations in vaccine access and disease risk. Second, cases and controls have all sought care and been tested for a similar set of symptoms. This reduces confounding due to differences in health care-seeking behavior or access between cases and controls, which is often a source of bias in traditional case-control studies, particularly in outpatient settings where care seeking can be more variable. Figure 1 shows the selection of cases and controls using the test-negative design.

Figure 1. Selection of cases and controls for an evaluation with a test-negative design.



Note: All patients who meet the inclusion criteria and do not have any exclusion criterion will be included in the study (see Annex 1). In high-incidence situations with a high number of patients with SARI (community transmission level 3 or 4) or in situations with a lack of human or laboratory resources to include all patients with SARI, participating centers can randomly select patients (for example, systematic random selection of one patient for every certain number of patients or selection of the first patient admitted on a given day, etc.). The country should define the modality for selecting patients when it is not possible to implement the exhaustive inclusion of all SARI cases that present at the sentinel hospital or service.

3.10. Laboratory diagnosis

Skilled health personnel will take respiratory specimens from the patients who are eligible for the evaluation, respecting the safety standards for infection prevention and control (IPC) and COVID-19 biosafety standards [14-16].

3.10.1. Type of respiratory specimens

Upper respiratory tract specimens are adequate for analyzing early phase infections, especially in asymptomatic or mild cases. It has been demonstrated that tests with combined nasopharyngeal and oropharyngeal swabs from a single patient increase the sensitivity for detecting respiratory viruses and

improve the reliability of the result. Two swabs from a single person can be combined in a sample collection tube or a nasopharyngeal/oropharyngeal combination swab can be obtained. Collection of lower respiratory tract specimens is advised if the samples are collected later during COVID-19 or from patients with negative results on the upper respiratory tract sample and clinical suspicion of COVID-19 (e.g., presence of anosmia and/or ageusia). Lower respiratory tract specimens include sputum (if produced, spontaneously induced sputum is not recommended since this increases the risk of aerosol transmission), or endotracheal aspirate or bronchoalveolar lavage in patients with more serious respiratory conditions. Caution should be used due to the high risk of aerosolization; therefore, strict monitoring of IPC procedures is required during sample collection. A physician should evaluate the need for an invasive procedure.

3.10.2. Specimen transport

Specimens for virus detection should reach the laboratory as soon as possible after their collection. Correct specimen handling during transport and in the laboratory is essential.

Participating hospitals or services that do not have a laboratory for RT-PCR diagnosis should ensure adequate specimen transport to the reference laboratory for diagnosis.

In-country specimen transport should be done according to the applicable national regulation. International transport of specimens that may contain SARS-CoV-2 should comply with the United Nations Model Regulations, Biological Substance, Category B (UN 3373) and any other applicable regulation related to mode of transport.

3.10.3. Biosafety practices in the laboratory

Tests on clinical specimens that may contain SARS-CoV-2 should be carried out in laboratories that are duly equipped with personnel trained in pertinent technical and safety procedures. National laboratory biosafety directives should be met in all circumstances. Handling of specimens for standard RT-PCR molecular tests requires biosafety level (BSL) 2 or equivalent installations that use a biological safety chamber or primary containment device that is recommended for sample handing before inactivation.

3.10.4. SARS-CoV-2 diagnostic tests

Specimens from patients with SARI should be analyzed using nucleic acid amplification (NAA) tests like RT-PCR. The nucleic acid amplification tests should target the SARS-CoV-2 genome.

Diagnostic test results should be interpreted correctly based on clinical suspicion. In the case of high clinical suspicion with a negative RT-PCR result, the test will be repeated. Collection of lower respiratory tract specimens could be considered.

Several factors can lead to a negative result in an infected person, including:

- Poor quality of the specimen, if it contains very low quantity of patient material
- Specimen was collected during a late phase of the disease or was taken from a body compartment that did not contain the virus at that time
- Specimen was not handled or sent in the appropriate conditions
- Technical reasons implicit in the test, for example, inhibition of the PCR
- Mutation of the virus: changes in the viral genome can reduce the sensitivity of NAA tests.

Note: Rapid antigen-based diagnostic tests are not currently recommended since they are not meeting the minimum performance requirements of sensitivity ≥80% and specificity ≥97% [17].

3.10.5. Diagnostic tests for influenza virus and other respiratory viruses

According to the WHO recommendations for influenza surveillance and SARS-CoV-2 monitoring [9] and within the framework of the evaluation of influenza VE carried out through REVELAC-i, it is recommended that participating countries conduct diagnostic tests for COVID-19, influenza, and other respiratory viruses on respiratory specimens collected from patients with SARI. If this is not possible, diagnostic tests for influenza and other respiratory viruses should be done on the respiratory specimens that are negative for SARS-CoV-2. Each participating country should determine the diagnostic strategy used.

3.11. Genomic sequencing

The VE could be altered by the concordance between the circulating strains of the virus and the vaccine. New genomic variants of SARS-CoV-2 could therefore have a potential impact on VE. Genomic sequencing of positive specimens for SARS-CoV-2 aims to identify the circulating variants of the virus and study the effectiveness of vaccines against these variants [18, 19].

3.11.1. Specimen selection for genomic sequencing

Genomic sequencing will ideally be carried out on specimens that are positive for SARS-CoV-2 and feasible for sequencing. Ideally, sequencing will be performed on all positive specimens or, when not possible, on a random selection of a specific number of representative specimens (from vaccinated and non-

vaccinated, for different age groups and geographic locations; from different time periods; and in cases with different clinical presentation). The criteria for representativeness and the virologic characteristics of clinical specimens for genomic sequencing are described in the document developed by PAHO [20].

The number of specimens to select will be determined by the laboratory capacity to conduct sequencing. The positive specimens will be selected using simple random or systematic sampling. The sampling fraction (proportion of specimens selected for sequencing out of all specimens eligible for sequencing) will be documented to estimate the probability of selection and the sampling weights.

3.11.2. Virologic characteristic of the clinical samples

Good quality clinical specimens with high viral loads are crucial for retrieving full genome sequences with high quality. Selected clinical specimens for genomic sequencing should fulfill the following requirements:

- Samples with Ct values ≤ 30;
- Samples transported through an unbroken cold chain and stored under ultra-low temperature conditions;
- Avoid multiple freeze-thaw cycles of the sample.

3.11.3. Analysis of the specimens for genomic sequencing

The genomic sequencing of the virus will be conducted by designated laboratories with the required capacity. When there is no in-country capacity for sequencing, laboratories can facilitate shipment to reference laboratories through the COVID-19 Genomic Surveillance Regional Network.[‡]

3.11.4. Report of genomic sequence

All specimens sequenced will be identified and the genomic sequence will be linked with the case report form that contains other individual information, including the vaccination status of the cases. The result of the sequence (lineage, clade, or name of the variant) will be recorded in the case report. The sequence will also be shared through the Global Initiative on Sharing All Influenza Data (GISAID) to contribute to the global monitoring of genetic variants and study the effectiveness of vaccines against these variants [21]. In case the sequencing was unable to be conducted this should be documented.

[‡] PAHO. COVID-19 Genomic Surveillance Regional Network. https://www.paho.org/en/topics/influenza/covid-19-genomic-surveillance-regional-network

3.12. Exposure (COVID-19 vaccination)

3.12.1. Definition of vaccination status

The periods for defining vaccination status will be determined for each type of vaccine according to available information and evidence. For most vaccines, protection begins 14 days after administration of both the first and second doses.

Partial vaccination will refer to an individual who received a single dose of the vaccine (for vaccines that require two doses) at least 14 days before the onset of symptoms.

Complete vaccination will refer to an individual who received one vaccine dose (for vaccines that require only one dose) or two vaccine doses (for vaccines that require two doses) at least 14 days before the onset of symptoms.

An individual will be considered unvaccinated if the person has not received any dose of the vaccine or received the vaccine after the onset of symptoms.

Note: VE for the different types of vaccines will be evaluated for one and two doses (if applicable) and for the time elapsed since the vaccination date. The classification of vaccinated/unvaccinated will be made based on available evidence about the time elapsed between vaccination and the appearance of antibodies for each vaccine type. Furthermore, sensitivity analyses will evaluate the effectiveness for different vaccination intervals. Therefore, it is especially important to obtain precise vaccination dates and the date of the onset of symptoms.

3.12.2. Verification of vaccination status

If available, national electronic or paper-based nominal records, such as the daily registry or vaccination logs, can be reviewed. In countries where there is no national electronic or paper-based nominal registry, verification of vaccination status will be based on the reviews of vaccination cards during patient hospitalizations. If this verification is not possible at that time, the surveillance personnel can review the medical record or ask the Expanded Program on Immunization (EPI) personnel to identify the patient in the program records using the person's name, date of birth, and residence information. Only vaccination status with documented proof (nonverbal) will be considered.

- An individual will be considered as vaccinated against COVID-19 if the person has documented vaccination evidence, such as:
  - Vaccination card with the vaccination date

- SARI surveillance form that shows that the person is vaccinated (using the vaccination card, not a verbal report, as the source)
- Registration as vaccinated in national EPI vaccination registry

- An individual will be considered as unvaccinated against COVID-19 if:
  - The patient's SARI surveillance form states that the person is unvaccinated (based on the vaccination card, on which COVID-19 vaccination does not appear)
  - The patient appears as unvaccinated in the national EPI vaccination registry
  - There is no vaccination recorded for COVID-19 on the patient's vaccination card, but there is information for other vaccines
- An individual will be excluded if the person's vaccination status cannot be determined

Note: Countries that use other sources or consider other factors to define vaccination status (for example, absence of a vaccination record or absence of a vaccination date as "unvaccinated") will have to document and report this information when sending the data so that it can be considered in the regional analysis of grouped data.

3.13. Confounding factors and effect modifiers

The measure of VE can be affected by confounding factors or effect modifiers. These may emerge when the observed effect distorts the real effect due to an unequal distribution of a third variable in the groups studied (confounding). The observation of an unexpected effect, although real, is also possible due to the simultaneous interrelationship between two or more factors that contribute to the effect studied (effect modification or interaction). Countries should define and evaluate potential confounding factors or effect modifiers that may alter the evaluation of effectiveness.

The list below presents potential confounding factors or effect modifiers:

- Age and sex
- Preexisting conditions: asthma, immunodeficiency, HIV and organ transplantation, cancer, diabetes, heart disease, hypertension, pulmonary disease, and obesity
- Other conditions: anemia, asplenia, dementia, liver disease, neuromuscular disease, renal disease, rheumatic disease, stroke, tuberculosis, etc.

- Severity of preexisting condition: number of medical visits and hospitalizations for the preexisting condition
- Use of medication prior to vaccination, illness, and hospitalization
- Smoking
- Use of antiviral drugs
- Health personnel and other risky professions
- Vaccination against influenza and pneumococcus
- Infection due to influenza and other respiratory viruses
- Residency in a long-term facility (for example, residences, homes, prisons)
- Educational level
- Ethnic group or race
- Fragility and belonging to minority or disadvantaged groups
- Risk behaviors: mask use, hand hygiene, social distancing, and perceptions about the pandemic
- Previous SARS-CoV-2 infection (confirmed by laboratory or through clinical criteria)

3.14. Information to collect

For each patient with SARI included in the evaluation, the patient's characteristics, clinical data, laboratory data, and vaccination history will be collected based on the variables in the national SARI surveillance forms. Annex 4 presents the detailed list of variables to collect.

Patient characteristics

- Age
- Sex
- Smoking
- Pregnancy
- Health worker
- Occupation
- Educational level
- Residency in a long-term facility (for example, residences, homes, prisons)
- Fragility and belonging to minority or disadvantaged groups
- Ethnic group or race

- Risk behaviors: rejection of prevention measures (mask use, hand hygiene, social distancing, perceptions about the pandemic, etc.)

Clinical information

- Signs and symptoms
- Symptom onset date
- Dates of admission and discharge (to calculate hospitalization duration)
- Hospitalization in intensive care
- Oxygen use
- Mechanical ventilation
- Discharge condition: dead/alive
- Preexisting conditions: asthma, immunodeficiency, HIV and organ transplantation, cancer, diabetes, heart disease, hypertension, pulmonary disease, and obesity
- Other conditions (optional): anemia, asplenia, dementia, liver disease, neuromuscular disease, renal disease, rheumatic disease, stroke, tuberculosis, etc.
- Severity of preexisting conditions (number of medical visits and hospitalizations in the last 12 months)

Laboratory data

- Type of sample (nasopharyngeal, oropharyngeal, sputum, endotracheal aspirate, or bronchoalveolar lavage)
- Specimen collection date
- Result of RT-PCR for SARS-CoV-2
- Genomic sequencing (if done)
- Result of RT-PCR for influenza, virus type, influenza A subtype, influenza B lineage
- Results of RT-PCR for other coronaviruses and other respiratory viruses

COVID-19 vaccination

- COVID-19 vaccination
- COVID-19 vaccine (brand) used for each dose
- Number of doses
- Vaccination date for each dose
- Information source used to determine the vaccination status (surveillance form, clinical records, nominal vaccination registry, vaccination card, other EPI documents or records)

Vaccination against influenza and pneumococcal disease and use of antiviral drugs

- Influenza vaccination
- Type of influenza vaccine: type and brand
- Influenza vaccination date
- Pneumococcal vaccination
- Type of pneumococcal vaccine used (polysaccharide vaccine, 23-valent and conjugate vaccine, 7/10/13-valent)
- Pneumococcal vaccination date
- Information source used to determine the vaccination status for influenza and pneumococcus
- Antiviral treatment: drug and dose received
- Antiviral treatment administration date (start and end dates)

The following variables are considered critical to estimating effectiveness and should be collected in a complete, compulsory manner for all included patients. Patients with missing information for at least one of these variables will be excluded from the analysis:

- Country
- Hospital or service
- Age
- Sex
- Pregnancy and gestational age
- Presence of preexisting conditions
- Symptom onset date
- Hospital admission date
- Discharge date (discharge or death)
- Specimen collection date
- Type of specimen collected
- Result of RT-PCR for COVID-19
- Result of RT-PCR for influenza
- Vaccination against COVID-19
- Number of doses received
- Type (brand) of vaccine received (first dose)
- Type (brand) of vaccine received (second dose)
- COVID-19 vaccination date (first dose)

- COVID-19 vaccination date (second dose)
- Information sources to confirm the vaccination status for COVID-19
- Vaccination against influenza in the current season
- Date of vaccination against influenza in the current season
- Vaccination against influenza with second dose (if applicable)
- Date of vaccination against influenza with second dose (if applicable)
- Information sources to confirm vaccination status for influenza

3.15. Sample size

The minimum sample size estimated for each country should consider several factors, such as the proportion of the population that is vaccinated (coverage) in the target group, expected VE, desired precision of the VE estimates, and case to control ratio. The minimum sample size can be calculated following the methodology described by Robert T. O'Neill [22].

The sample size should be adjusted based on the expected participation rate in the evaluation, the stratifications, and the exclusions that may be applied for the different sensitivity analyses. When there are several types of vaccines, the sample size should be calculated separately for each type of vaccine.

The following sample size estimates focus on the precision of estimation of expected VE of 50-90%, with a precision of ±10%, a population vaccination coverage of 30-90%, a 1:1 case-control ratio, and a type I error (α) of 0.05 (table 1).

Note: For the size sample calculation, a precision of ±10% is considered appropriate since a more precise estimate would result in a larger sample size that may compromise the implementation of the study. However, these calculations can be adjusted based on local capacities and resources. Use of lower precision will result in a smaller required sample size, reduce certainty when interpreting the VE estimate, and make secondary analyses that use a sample subset more difficult.

Increasing the number of controls per case would increase the power of the study. However, a case-control ratio of 1:1 has been considered feasible since a limited number of controls (SARI patients who test negative for SARS-CoV-2) is anticipated given the high incidence of COVID-19 and the low incidence of influenza and other respiratory viruses.

An online tool for sample size calculation is available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement_tool-2021.1

Table 1. Minimum Sample Size Assuming VE of 50-90%, Precision of ±10%, Vaccination Coverage of 30-90%, a 1:1 Case-control Ratio, and a Type I Error (α) of 0.05

VE	Vaccination coverage	Number of cases	Number of controls
50%	0.3	1,133	1,133
	0.4	925	925
	0.5	828	828
	0.6	803	803
	0.7	855	855
	0.8	1,047	1,047
	0.9	1,736	1,736
60%	0.3	801	801
	0.4	639	639
	0.5	559	559
	0.6	530	530
	0.7	550	550
	0.8	658	658
	0.9	1,066	1,066
70%	0.3	526	526
	0.4	408	408
	0.5	346	346
	0.6	317	317
	0.7	319	319
	0.8	369	369
	0.9	580	580
80%	0.3	308	308
	0.4	229	229
	0.5	186	186
	0.6	163	163
	0.7	156	156
	0.8	171	171
	0.9	257	257
90%	0.3	150	150
	0.4	106	106
	0.5	80	80
	0.6	65	65
	0.7	56	56
	0.8	56	56
	0.9	75	75

3.16. Data collection and integration

The primary information source for the evaluation will be data obtained through the sentinel sites that participate in SARI surveillance. Each patient will be assigned a unique identifier that will identify the country, hospital, and patient. For each patient, data will be collected through a questionnaire in paper format (SARI surveillance forms) or electronic format (surveillance databases at the local or national level), or through a digital platform (national online system). Annex 4 details the variables that will be collected. Vaccination history will be completed, if necessary, through EPI records or documents (see verification of vaccination status in section 3.10.2). If the laboratory data are not systematically incorporated into the forms, they will be retrieved from the corresponding databases.

Data collected from the different hospitals and services that participate in the evaluation will be confirmed and validated by the services or units in charge of the evaluation (for example, the epidemiology service). Data will be entered through an online platform that is available for countries to enter data from paper forms or upload existing digital files.

3.17. Data manager

The data will be added through an online data import and management package that includes an interface to enter information from paper forms through the PAHO flu online system[§] or import data through existing digital information systems. The country will define the most adequate method and the regional team will provide any technical assistance needed to adapt the manager to the existing systems.

There are two proposed alternatives for information exchange between the national and regional levels:

1. **Countries that use the PAHO Flu online information system for sentinel surveillance of influenza and other respiratory viruses**

    a. They will have access to the REVELAC-i downloadable form for both influenza and COVID-19, which will contain the data entered into the PAHO flu online system for sentinel surveillance coded as indicated in the protocol.

    b. This form and the PAHO Flu system will be directly connected to the REVELAC-i data import and management module for influenza and COVID-19.

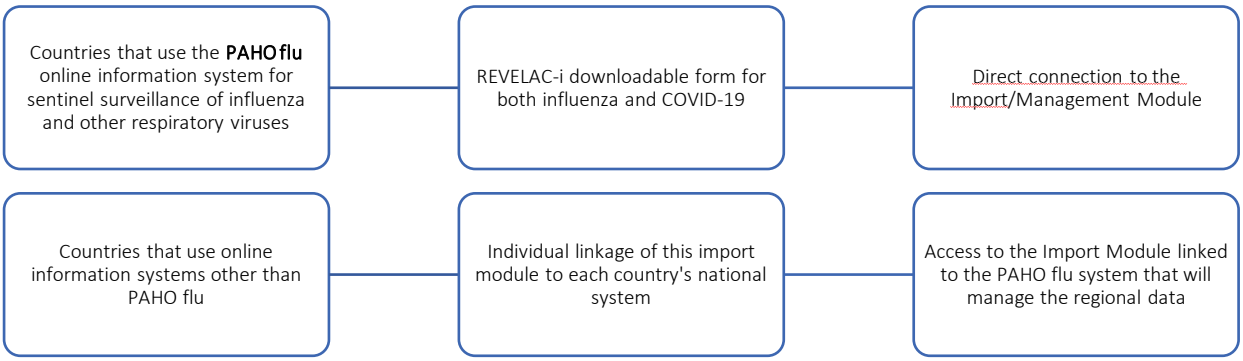
[§] https://vigilanciaflu.paho.org/Account/Login?ReturnUrl=%2F

2. Countries that use online information systems other than PAHO flu for sentinel surveillance of influenza and other respiratory viruses

    a. They will have access to an import module linked to the PAHO flu system that will manage the regional data. This import module will be linked to each country's national system. It will take the information from the national surveillance platform that should be recoded for entry into the REVELAC-i data form for both influenza and COVID-19, according to the protocol's variable dictionary.

The data import and management module will include the collected and shared data that is available for review at the regional level. Diagram 1 summarizes the flow of data collection and aggregation.

Diagram 1. Flow of Data Collection and Management to Evaluate COVID-19 Vaccine Effectiveness



3.18. Monitoring data quality

During the data collection process, the national team will be responsible for monitoring and verifying data completeness and quality. The national teams may implement activities to strengthen surveillance. Strategies will depend on each country and may include:

- Promoting active SARI case-finding, daily review of admission records, shipments of specimens to the reference laboratory, and visits to hospitalization services to detect new SARI cases, with support from medical personnel (*screening*).
- Raising the awareness of surveillance personnel regarding the importance of the completeness and quality of the critical variables on the case surveillance forms through training, supervision, periodic monitoring, and feedback.

- Promoting the daily review of case forms by surveillance personnel to identify errors or missing information and request it during the patient's hospitalization.
- Promoting the review of vaccination cards during hospitalization for timely, precise acquisition of vaccination statuses. This activity should be prioritized in countries that do not have national nominal registries.
- Establishing clear and timely mechanisms to link surveillance personnel with the EPI to retrieve vaccination histories.
- Facilitating information exchanges between ministries of health, PAHO country offices, and PAHO regional offices to implement joint analyses and obtain regional estimates.
- Other strategies can be documented in national protocols.

3.19. Data analysis

Data analysis will be conducted at the national level with the data obtained from sentinel sites participating in the evaluation. If necessary, the PAHO regional team will provide technical support for national data analyses. Pooled analyses can be conducted among the Region's participating countries to obtain regional estimates (see section 3.21. Pooled analysis). The possibility of contributing to a pooled analysis with other WHO regions will also be considered.

3.19.1. Data cleaning prior to analysis

The national team will review the data to detect possible errors, inconsistencies, or missing data, and will assure the quality and completeness of the data collected. If necessary, missing data will be retrieved and the necessary corrections will be made, together with documentation of any information that supports the interpretation of results. Any changes to the data will be documented and stored separately from the original database (raw data). Any recodes will also be documented.

3.19.2. Selection of patients for the analysis

The regional team will verify that the patients included in the evaluation meet the inclusion criteria (if not, they will be excluded) and will exclude those that meet the exclusion criteria (see section 3.6 and section 3.7 and annex 1). In addition, controls with symptom onset prior to the first confirmed COVID-19 case and two weeks after the last confirmed COVID-19 case in each country will be excluded.

3.19.3. Descriptive analysis

The cases and controls will be described by their sociodemographic, clinical, and laboratory characteristics and their COVID-19 vaccination history. Annex 5 presents an example of a descriptive table for cases and controls.

3.19.4. Measurement of effect (vaccine effectiveness)

VE will be calculated as 1 - odds ratio (OR) of vaccination in cases versus controls, with a 95% confidence interval [95% CI] around the estimate. An OR=1 indicates that there is no association between the exposure (vaccination) and the result (laboratory-confirmed COVID-19). An OR<1 indicates that the vaccination is a potential protective factor, considering the confidence interval around the OR for its interpretation. For vaccination as a preventive factor, VE can be calculated using formula 1. A 95% confidence interval around the point estimate can also be calculated.

Formula 1. Calculation of VE

$$VE = (1 - OR) \times 100$$

VE for complete and partial vaccination and the estimated VE for the days and weeks post-administration of each dose will be calculated, for each vaccine administered in each country (if sample size allows).

Univariate analysis will be conducted to measure VE against laboratory-confirmed COVID-19 cases. Next, a stratified analysis will be conducted to identify possible confounding factors and effect modifiers. Finally, the multivariate analysis will provide an estimate that is adjusted for the confounding factors and effect modifiers identified through the stratified analysis.

3.19.5. Univariate analysis

The association (OR) between the characteristics and COVID-19 vaccination status for cases and controls will be measured through Chi-square, Fisher's exact, t-, or Mann-Whitney tests (according to the type of variable and its distribution).

3.19.6. Stratified analysis

The presence of effect modifiers and confounding factors will be examined (see section 3.11) through stratified analysis. Effect modification will be evaluated by comparing the OR in the given variable's strata. If the OR in each stratum are statistically significantly different (by test of homogeneity), the variable will be considered a potential effect modifier.

When effect modification is ruled out, the presence of confounding will be evaluated by verifying whether the potential confounding factors are associated with both vaccination and the disease, by comparing the crude or adjusted OR (Mantel-Haenszel) for every factor. If the relative difference between the crude and adjusted estimates exceeds 20%, the adjusted OR will be presented.

3.19.7. Multivariate analysis

In case-control studies, the logistic regression statistical model used makes it possible to control for confounding factors and examine multiple interactions among the factors. Before conducting the multivariate analysis, the strategy for including variables in the model will be determined. Generally, the multivariate analysis model will be adjusted for the variables identified as potential confounding factors in the stratified analysis, and consider other relevant variables as interactions (age, sex, preexisting conditions, etc.). Annex 6 presents an example of a VE table adjusted for covariates.

3.20. Sensitivity analysis

Different sensitivity analyses will be conducted to estimate VE against COVID-19:

- For different intervals (number of days) between symptom onset and sample collection, symptom onset and hospitalization, and vaccination date and symptom onset.
- For different disease severity criteria and definitions
- Excluding controls (patients with SARI and a negative SARS-CoV-2 test) with prior SARS-CoV-2 infection (confirmed by RT-PCR, ELISA serology, rapid test, or clinical criteria)

3.21. Pooled analysis

Adequate sample size is needed to be able to stratify the data to obtain precise estimates of VE in important subgroups. Pooling of data from the different VE evaluations produces a larger sample size that makes it possible to both develop estimates stratified by subgroups and obtain more precise estimates. Data pooling can be done through a meta-analysis of the reported VE estimates or by pooling individual data. In all cases, data pooling presents several challenges that should be considered. Evaluations that are grouped should measure the same outcome and the same vaccine product, as well as have the same type of location for case capture (for example, hospital versus ambulatory clinic). Pooled evaluations should be sufficiently similar regarding the case definition, exclusion criteria, and definitions of vaccination status, and have comparable access to vaccination and health care for COVID-19 disease.

3.22. Dissemination of results

The preliminary results will be reviewed with the national teams for their validation and approval. Countries will prepare national reports. The regional team will prepare a regional report on behalf of the working group for the evaluation of the effectiveness of the COVID-19 vaccine. The regional report will be reviewed and approved by the national teams. The final report will be shared with health authorities and collaborating public health organizations in the Region. The regional team will support countries that want to prepare manuscripts or national reports. In this case, the national coordinator will lead the drafting of the manuscript as principal author.

In addition, feedback at the national level will be provided according to strategies defined by each country, such as workshops and debriefing meetings with the personnel who participated in the evaluation. The regional team may also present the regional results in public health scientific conferences. These presentations will be subject to authorizations from the countries, similar to those provided prior to participation in a publication.

Finally, following the countries' approval, results can be shared with relevant agencies, institutions, and committees to contribute to global evaluations.

4. LOGISTICAL ASPECTS

4.1. Coordination

A national multidisciplinary and interinstitutional team (for example, the team formed within the framework of the REVELAC-i network) will coordinate the evaluation and be responsible for the planning, implementation, and monitoring of the evaluation at the national level. This team includes technical personnel from influenza surveillance programs, immunization programs, and COVID-19 and influenza reference laboratories, as well as focal points for immunization, COVID-19, and influenza surveillance at PAHO local offices. To facilitate the organization of activities, the same multidisciplinary team can designate a primary individual responsible/coordinator. Each national team will develop a work plan and define the team members' roles and responsibilities and the human resource needs. This organizational chart can be annexed to the national protocol. The national coordinators will send letters, including the national protocol, to the authorities of the participating hospitals to promote and facilitate their participation. In every hospital or service that participates in the evaluation, an investigator will be the individual responsible for data collection and reports to the surveillance units.

The PAHO regional team will provide technical assistance during project implementation in countries. The regional project coordinator will update the generic protocol based on the national teams' revisions and prepare the tools needed for data collection with support from the information system team. The coordinator will also facilitate aggregation of the participating countries' data and conduct a preliminary regional analysis when sufficient sample size is reached. The final analysis will be conducted once all data has been submitted at the close of the evaluation period. The regional team can coordinate feedback meetings with the national teams (for the national, regional, or local level that participated in the evaluation, including hospital, EPI, and laboratory personnel), as defined by each country.

4.2. Training

Since this evaluation is based on the SARI sentinel surveillance strategy, the project will encourage national teams to organize trainings for SARI surveillance and EPI personnel, emphasizing the importance of data quality and completeness, including the vaccination history. The national teams can request support or materials from the regional team as needed during any phase of the evaluation.

5. ETHICAL CONSIDERATIONS

5.1. Fulfillment of ethical requirements

This evaluation is observational and based on data collected as part of the surveillance activities for the monitoring and evaluation of the COVID-19 vaccination program. Each country's authorities and ethics committees will define the necessary approvals prior to the implementation of the evaluation. Participation in the evaluation is considered as part of the evaluation of the routine surveillance and will not interfere with the regular course of vaccine delivery to the target populations or routine clinical management of patients with SARI.

If requested, participating countries will present the national protocols to the pertinent ethics committees, following local standards, and will meet the corresponding committees' requirements. The national ethics committees will specify whether consent from the participants is required.

The evaluation will be implemented in accordance with each country's applicable ethical requirements, including privacy-related and confidentiality requirements, and the guiding principles of the Declaration of Helsinki [23].

5.2. Data confidentiality

Only surveillance personnel will have access to patients' personal identifiers (identification number, name, medical record number, contact details). All of each patient's sociodemographic, clinical, epidemiological, and laboratory data and collected specimens will be registered in the evaluation database without personal identifiers and using unique project-specific codes.

5.3. Indirect benefits for evaluation participants

The evaluation of COVID-19 vaccine effectiveness will help to strengthen SARI surveillance and the quality and completeness of COVID-19 and influenza surveillance data, as well as contribute to strengthening awareness of the benefits of vaccination. The evidence generated could also contribute indirectly to the health of the populations involved.

6. PARTICIPATION REQUIREMENTS

The countries that request to participate in the evaluation of the effectiveness of a COVID-19 vaccine should meet a series of requirements:

6.1. Entry requirements

a) Implementation and quality of SARI surveillance

- Has complete SARI surveillance data for the variables defined as critical for evaluating influenza and COVID-19 vaccines: age, sex, symptom onset date, sample collection date, influenza vaccination status for the current season, vaccination date, number of influenza vaccine doses in children receiving their first vaccination (and date of last dose), preexisting conditions, antiviral treatment and treatment administration date, RT-PCR result.
- Has sufficient potential sample size for the evaluation: number of SARI cases in the target groups, with respiratory specimen collected and RT-PCR results, according to a review of surveillance data for the last 2 years.
- In hospitals whose participation is being considered:
    - Must fulfill standardized surveillance performance indicators according to Annex 7 of the Operational Guidelines for Sentinel Severe Acute Respiratory Infection (SARI) Surveillance. Pan American Health Organization. September 2014 [5].

- Must adequately apply the SARI case definition (to avoid hospitals where clinical criteria intervene in a patient's report or sample collection), according to the surveillance team's appraisal or based on evidence, as applicable.
- Must have systematic specimen collection in SARI patients, without prioritization by age or risk groups.

b) Laboratory capacity

- Has technologies available to conduct RT-PCR techniques to detect SARS-CoV-2 and influenza virus.
- Has reports of the influenza virus type/subtype and the SARS-CoV-2 genetic variant.
- Has information available on circulating strains: Sequencing at the national level or shipment to the CDC.

c) Availability of quality information about vaccination status

- Has a national nominal registry with unique individual identifiers.
- When there is no electronic nominal registry, has individual documentation of vaccination for the vaccination target groups: vaccination cards, paper-based nominal registry, etc.
- Ideally, has evidence of validation of information sources (e.g., evaluation of the "unvaccinated" status).

d) Information on vaccination coverage in target groups

e) Sustainability of the evaluation of effectiveness

- Has own resources (including human resources) to ensure the systematic evaluation of vaccine effectiveness.
- If the evaluation requires specific support, has a cost estimate to complete the necessary data.

f) Monitoring of ethical requirements for the effectiveness evaluation in the country

6.2. Operational requirements

a) Designation of an official focal point for the project and formation of a national multidisciplinary team (EPI, influenza surveillance, National Influenza Center (NIC), individuals or institutions responsible for the corresponding information systems)

b) Adaptation of the generic protocol and adjustments to forms/registries to ensure the collection of the variables that are critical for analyzing effectiveness

c) Availability of the focal point to monitor progress and provide feedback to the national and regional coordination teams (PAHO-CDC)

d) Timeliness when submitting data to the REVELAC-i data manager (or through the dedicated platform for that purpose)

e) Availability of units of analysis

f) Participation from the national team in the validation and interpretation of the effectiveness evaluation results

g) Feedback for the sentinel hospital teams through meetings, visits, or calls, as well as epidemiological surveillance bulletins.

6.3. Continuity requirements

a) Analysis of the national data from the hospital case-control for validation, effectiveness estimate, interpretation, and dissemination

b) Collection of additional information needed for the interpretation of results (e.g., strategy and chronogram of the vaccine introduction, flow chart of SARI cases captured through surveillance versus subjects enrolled in the evaluation, etc.)

c) Achievement of "reportable" effectiveness estimates (e.g., confidence intervals for effectiveness that do not exceed 100%) or contribution of at least 8-10% of the regional sample size

d) Implementation of vaccination data quality validation/supervision activities to guarantee the internal validity of the effectiveness estimates

e) Existence of established mechanisms for information dissemination:

- Feedback to the national teams
- Information aimed at technical personnel and specific audiences

7. TIMELINE OF PROJECT ACTIVITIES

The project activities will be carried out according to the work plan established in each country. The following stages are proposed for implementation of the evaluation:

Period	Activities
March-April 2021	• Review and development of the national protocol • Formation of the national team • Provision of resources and training
May-December 2021	• Implementation and data collection • Monitoring and verification of data quality • Periodic analyses of the data reported
January-February 2022	• Finalization of the estimates with the national teams • Preparation of reports and feedback • Presentation and dissemination of results

8. BUDGET AND FINANCING

This project is based on participating countries' existing resources, with occasional financial support from the PAHO Immunization Unit or through cooperative agreements with the CDC Influenza Division. This support can include materials for sentinel surveillance, laboratory materials, technical assistance or training of teams, costs of field work to verify the evaluation subjects' vaccination status, and human resources for integration of the surveillance and immunization data and for data analysis.

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ANNEX 1. Eligibility Verification Form

Inclusion criteria

1.	The patient meets the SARI case definition	YES □	NO □
2.	The patient has been hospitalized for at least 24 hours in a participating hospital	YES □	NO □
3.	The patient is eligible for COVID-19 vaccination	YES □	NO □
4.	Vaccination has started in the group or sub-group to which the patient belongs	YES □	NO □
5.	The patient has provided a respiratory specimen within the framework of SARI surveillance	YES □	NO □
6.	A respiratory specimen has been collected within 10 days of symptom onset	YES □	NO □

Exclusion criteria

1.	The patient has a contraindication to the COVID-19 vaccine	YES □	NO □
2.	The patient has a contraindication to or difficulty with collection of the respiratory sample	YES □	NO □
3.	The patient has had a hospitalization during the 14 days prior to admission for SARI	YES □	NO □
4.	The patient's symptoms began after being hospitalized	YES □	NO □
5.	The patient's vaccination status cannot be determined	YES □	NO □

For the patient to be eligible for the evaluation, all inclusion criteria should have a "YES" response and all exclusion criteria should have a "NO" response.

ANNEX 2. ICD-10 Codes for Respiratory Tract Diseases

ICD-10 CODE	DESCRIPTION
ICD-10, Acute upper respiratory infections	
J00	Acute nasopharyngitis [common cold]
J01	Acute sinusitis
J02	Acute pharyngitis
J03	Acute tonsillitis
J04	Acute laryngitis and tracheitis
J05	Acute obstructive laryngitis [croup] and epiglottitis
J06	Upper respiratory infections, of multiple or unspecified sites
ICD-10, Influenza, pneumonia, and other acute lower respiratory infections	
J09	Influenza, avian influenza virus identified
J10	Influenza, other influenza virus identified
J10.0	Influenza with pneumonia, other influenza virus identified
J10.1	Influenza with other respiratory manifestations, other influenza virus identified
J10.8	Influenza with other manifestations, other influenza virus identified
J11	Influenza, virus not identified
J11.0	Influenza with pneumonia, virus not identified
J11.1	Influenza with other respiratory manifestations, virus not identified
J11.8	Influenza with other manifestations, virus not identified
J12	Viral pneumonia, not elsewhere classified
J12.0	Adenoviral pneumonia
J12.1	Respiratory syncytial virus pneumonia
J12.2	Parainfluenza virus pneumonia
J12.8	Other viral pneumonia
J12.9	Viral pneumonia, unspecified
J13	Pneumonia due to *Streptococcus pneumoniae*
J14	Pneumonia due to *Haemophilus influenzae*
J15	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious microorganisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere (see specific diseases in the ICD-10)
J18	Pneumonia, organism unspecified
J20	Acute bronchitis (see specific diseases in the ICD-10)
J21	Acute bronchiolitis
J21.0	Acute bronchiolitis due to respiratory syncytial virus
J21.8	Acute bronchiolitis due to others specified microorganisms
J21.9	Acute bronchiolitis, unspecified
J22	Unspecified acute lower respiratory tract infection

Source: World Health Organization. International Statistical Classification of Diseases Health Problems. 10th Revision. https://icd.who.int/browse10/2008/en

ANNEX 3. Flowchart REVELAC-COVID-19

SARI case definition

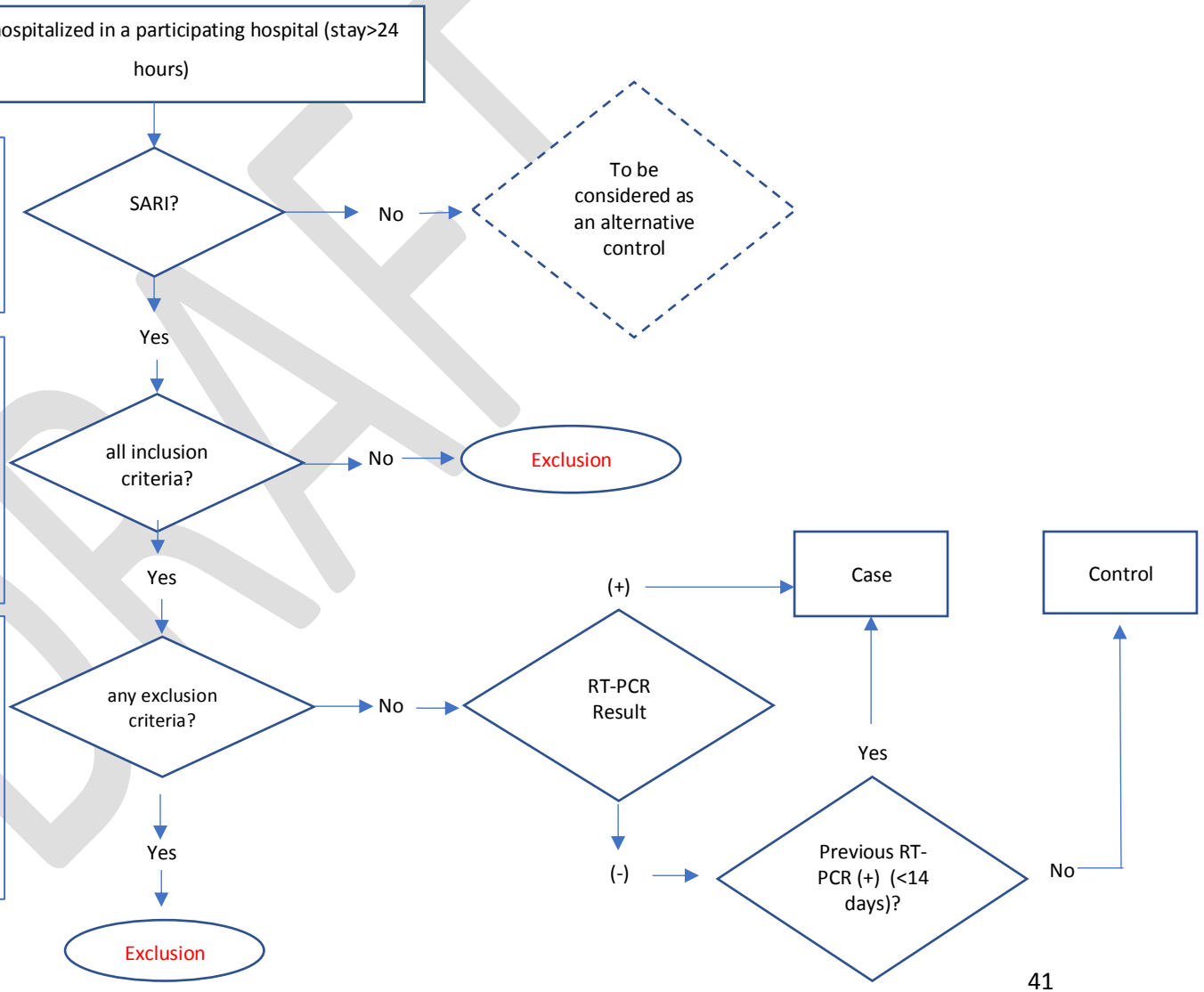
- History of fever or a measured fever of ≥38 °C,
- And cough,
- And symptom onset within the last 10 days,
- And who requires hospitalization

Inclusion criteria

- The patient is eligible for COVID-19 vaccination
- Vaccination has started in the group or sub-group to which the patient belongs (e.g age group, area, professional group, etc.
- Has provided a respiratory specimen within the framework of SARI surveillance
- The specimen was taken within a maximum of 10 days after the onset of symptoms

Exclusion criteria

- Has a contraindication to the COVID-19 vaccine
- Has a contraindication to or difficulty providing the respiratory specimen
- Has been hospitalized during the 14 days prior to their admission for SARI, including hospital transfers
- The patient's symptoms began after being hospitalized
- His/her vaccination status cannot be determined



ANNEX 4. Variables to be Collected

Variable	Coding	Critical variable
General data		
Country	*1 = Argentina, 4 = Brasil, 7 = Chile, 8 = Colombia, 9 = Costa Rica, 10 = Cuba, 13 = Ecuador, 26 = El Salvador, 14 = Guatemala, 15 = Honduras, 17 = Jamaica, 19 = México, 20 = Nicaragua, 21 = Panamá, 24 = Paraguay, 22 = Perú, 27 = Trinidad y Tobago, 29 = Uruguay*	yes
State or province	*text*	no
Region	*text*	no
Hospital	*text*	yes
Hospital/service type	*0=Hospital/COVID-19 service, 1=Pulmonology, 2=Internal medicine, 3=Infectious diseases, 4=Emergency, 5=Cardiology, 6=Geriatrics, 7=ICU, 8=Others,9=no information*	no
Patient characteristics		
Age (years)	*numeric*	yes
Birthdate	*date (dd/mm/yyyy)*	no
Sex	*1=male, 2=female, 3=unknown*	yes
Smoker	*0=never, 1=ex-smoker, 2=current smoker, 9=no information*	no
Pregnant woman	*0=no, 1=yes, 9=no information*	yes
If pregnant woman (weeks)	*numeric*	yes
Health worker	*0=no, 1=yes, 9=no information*	no
Place of residence	*0=in residence, independent person, 1=in residence, dependent person, 2=in residence/ institution, 3=others, 9=no information*	no
Main occupation	*text*	no
Ethnic group or race	*text*	no
Educational level	*0=no education, 1=elementary education, 2=secondary education, 3=university education, 4=professional training, 9=no information*	no
Belongs to minority or disadvantaged groups	*0=no, 1=yes, 9=no information*	no
Risk behaviors		
Frequency of mask use	*0=never, 1=sometimes, 2=almost always, 3=always*	no
Frequency of hand washing	*0=never, 1=sometimes, 2=almost always, 3=always*	no
Frequency of social distancing	*0=never, 1=sometimes, 2=almost always, 3=always*	no
Perception of the pandemic	*0=denial, 1=partial awareness, 2=acceptance/worry, 3=no opinion, 9=no information*	no
Preexisting conditions		
Suffers from at least one chronic disease	*0=no, 1=yes, 9=no information*	yes
Asthma	*0=no, 1=yes, 9=no information*	no
Cancer	*0=no, 1=yes, 9=no information*	no
Hypertension	*0=no, 1=yes, 9=no information*	no

Diabetes	*0=no, 1=yes, 9=no information*	no
Heart disease (excluding hypertension)	*0=no, 1=yes, 9=no information*	no
Immunocompromised (e.g., HIV/AIDS, organ transplantation, etc.)	*0=no, 1=yes, 9=no information*	no
Pulmonary disease (excluding asthma)	*0=no, 1=yes, 9=no information*	no
Obesity	*0=no, 1=yes, 9=no information*	no
Height (cm)	*numeric*	no
Weight (kg)	*numeric*	no
BMI (if height and weight are unavailable)	*numeric*	no
Number of medical visits for condition in last year	*numeric*	no
Number of hospitalizations for condition in last year	*numeric*	no
Other preexisting conditions		
Anemia	*0=no, 1=yes, 9=no information*	no
Asplenia	*0=no, 1=yes, 9=no information*	no
Cognitive disorders	*0=no, 1=yes, 9=no information*	no
Liver disease	*0=no, 1=yes, 9=no information*	no
Neuromuscular disease	*0=no, 1=yes, 9=no information*	no
Renal disease	*0=no, 1=yes, 9=no information*	no
Rheumatic disease	*0=no, 1=yes, 9=no information*	no
Stroke	*0=no, 1=yes, 9=no information*	no
Tuberculosis	*0=no, 1=yes, 9=no information*	no
Medication prior to symptoms		
Statins	*0=no, 1=yes, 9=no information*	no
ACE inhibitor	*0=no, 1=yes, 9=no information*	no
ARA-II	*0=no, 1=yes, 9=no information*	no
NSAID	*0=no, 1=yes, 9=no information*	no
Metformin	*0=no, 1=yes, 9=no information*	no
Corticosteroids	*0=no, 1=yes, 9=no information*	no
Monoclonal antibodies (e.g., rituximab, tocilizumab, etc.)	*0=no, 1=yes, 9=no information*	no
Chemotherapy	*0=no, 1=yes, 9=no information*	no
Psychotropics (e.g., benzodiazepines, barbiturates)	*0=no, 1=yes, 9=no information*	no
Antiviral drugs	*0=no, 1=yes, 9=no information*	no
Type of antiviral	*1=oseltamivir, 2= other, 9=no information*	no
Chloroquine or hydroxychloroquine	*0=no, 1=yes, 9=no information*	no
Other medication prior to symptoms	*text*	no
Clinical information		
Symptom onset date	*date (dd/mm/yyyy)*	yes

Admission date	*date (dd/mm/yyyy)*	yes
Discharge date (discharge or death)	*date (dd/mm/yyyy)*	yes
ICU admission	*date (dd/mm/yyyy)*	no
Fever	*0=no, 1=yes, 9=no information*	no
Headache	*0=no, 1=yes, 9=no information*	no
Sore throat	*0=no, 1=yes, 9=no information*	no
Cough	*0=no, 1=yes, 9=no information*	no
Shortness of breath	*0=no, 1=yes, 9=no information*	no
Difficulty breathing	*0=no, 1=yes, 9=no information*	no
Malaise	*0=no, 1=yes, 9=no information*	no
General deterioration (asthenia, weight loss, or anorexia)	*0=no, 1=yes, 9=no information*	no
Muscle pain	*0=no, 1=yes, 9=no information*	no
Anosmia (loss of smell)	*0=no, 1=yes, 9=no information*	no
Ageusia (loss of taste)	*0=no, 1=yes, 9=no information*	no
Dysgeusia (altered taste)	*0=no, 1=yes, 9=no information*	no
Chills or tremors	*0=no, 1=yes, 9=no information*	no
Tachypnea (>30 breaths/minute)	*0=no, 1=yes, 9=no information*	no
Hypoxemia (oxygen saturation ≤90% without oxygen therapy)	*0=no, 1=yes, 9=no information*	no
Acute respiratory distress syndrome	*0=no, 1=yes, 9=no information*	no
Sepsis	*0=no, 1=yes, 9=no information*	no
Septic shock	*0=no, 1=yes, 9=no information*	no
Rhinitis	*0=no, 1=yes, 9=no information*	no
Confusion	*0=no, 1=yes, 9=no information*	no
Dizziness	*0=no, 1=yes, 9=no information*	no
Chest pain	*0=no, 1=yes, 9=no information*	no
Palpitations	*0=no, 1=yes, 9=no information*	no
Diarrhea	*0=no, 1=yes, 9=no information*	no
Nausea	*0=no, 1=yes, 9=no information*	no
Vomiting	*0=no, 1=yes, 9=no information*	no
Abdominal pain	*0=no, 1=yes, 9=no information*	no
Dermatological manifestations	*0=no, 1=yes, 9=no information*	no
Other symptoms	*text*	no
Antiviral drugs for symptoms	*0=no, 1=yes, 9=no information*	no
Type of antiviral	*1=oseltamivir, 2= other, 9=no information*	no
Antiviral treatment start date	*Date (dd/mm/yyyy)*	no

Previous SARS-CoV-2 infection (prior to the start of symptoms for this hospitalization due to SARI)	*0=no prior infection, 1=yes, confirmed by RT-PCR, 2=yes, confirmed by ELISA serology, 3=yes, confirmed by rapid test (antigen or antibody),4=yes, through clinical suspicion (without laboratory result), 9=no information*	no
Date of prior SARS-CoV-2 infection	*Date (dd/mm/yyyy)*	
Natural history of disease		
Needs oxygen therapy (without intubation)		no
Needs assisted ventilation (with intubation)		no
Natural history of disease	*1=death, 2=discharge, 4=in treatment, 9=no information*	no
Leading cause of death	*1=COVID-19, 2=other causes, 9=no information*	no
Laboratory information		
Date of specimen collection	*Date (dd/mm/yyyy)*	yes
Type of specimen collected	*1=nasopharyngeal swab, 2=nasal swab, 3=oropharyngeal or throat swab, 4= combined nasopharyngeal and oropharyngeal swab, 5=nasopharyngeal aspirate, 6=nasal lavage, 7=traqueal aspirate, 8=bronchoalveolar lavage, 9=pulmonary biopsy, 10=Serum, 12=Other, 13=bronchoalveolar lavage o sputum, 14=Nasopharyngeal swab Antigen COVID-19*	yes
Has SARS-CoV-2 RT-PCR test	*0=no, 1=yes, 9=no information*	no
Result of SARS-CoV-2 RT-PCR test	*0=negative, 1=positive, 9=no information*	yes
Has other test for SARS-CoV-2	*1=ELISA serology, 2=rapid antigen test, 3=rapid serology test, 4=others, 9=no information*	no
Result of other test for SARS-CoV-2	*0=negative, 1=positive, 9=no information*	no
Has genomic sequencing of the positive SARS-CoV-2 specimen	*0=no, 1=yes, 9=no information*	no
Identification of genomic sequencing	*text*	no
Result of the genomic sequencing (lineage, clade)	*text*	no
Influenza virus test result	*0=negative, 1=positive, 2=not done, 9=no information*	yes
Influenza type A	*0=no, 1=yes, 9=no information*	no
Influenza type B	*0=no, 1=yes, 9=no information*	no
Influenza A (H1N1) pdm09	*0=no, 1=yes, 9=no information*	no
Influenza A (H3N2)	*0=no, 1=yes, 9=no information*	no
Influenza B (lineage)	*1=not performed, 2=Yamagata, 3=Victoria, 4=Victoria Δ 162/163, 5=Victoria Δ 162/163/164, 9=no information*	no
Result of test for other respiratory viruses	*0=negative, 1=positive, 2=not done, 9=no information*	no
Type of virus (not influenza)	*0= respiratory syncytial virus, 1=parainfluenza, 2=metapneumovirus, 3=adenovirus, 4=rhinovirus, 5=bocavirus, 6=others 3=Parainfluenza I, 4=Parainfluenza II, 5=Parainfluenza III, 6=RSV, 7=Adenovirus, 8=Metapneumovirus, 9=Other, 10=Rhinovirus, 11= seasonal coronavirus (excluded SARS-CoV-2), 12=Bocavirus, 13=Parainfluenza*	no
Information on COVID-19 vaccination		
Received the COVID-19 vaccine	*0=no, 1=yes, 9=no information*	yes
Number of doses received	*0=none, 1=one dose, 2=two doses, 3=three doses, 9=no information*	yes
Date of first vaccine dose	*Date (dd/mm/yyyy)*	yes

Vaccine brand for first dose	*Coded values*	yes
Date of second vaccine dose	*Date (dd/mm/yyyy)*	yes
Vaccine brand for second dose	*Coded values*	yes
Date of third d vaccine dose	*Date (dd/mm/yyyy)*	yes
Vaccine brand for third dose	*Coded values*	yes
Information source on vaccination for COVID-19	*9=vaccination card reviewed in person, 10=nominal paper-based registry, 11=national nominal electronic registry, 12=medical record, 13=other immunization registries, 14= vaccination card read by telephone, 15=verbal report without card, 16=no information*	yes
Information on other vaccinations (not against COVID-19)		
Vaccination against influenza virus during the current season	*0=no, 1=yes, 9=no information*	yes
Date of influenza vaccine during current season	*Date (dd/mm/yyyy)*	yes
Second dose of influenza vaccine during current season	*0=no, 1=yes, 9=no information* *does not apply if information on the first dose is not entered*	yes
Date of second influenza dose during the current season	*Date (dd/mm/yyyy)* *does not apply if information on the first dose is not entered*	yes
Information source on vaccination for influenza	*9=vaccination card reviewed in person, 10=nominal paper-based registry, 11=national nominal electronic registry, 12=medical record, 13=other immunization registries, 14= vaccination card read by telephone, 15=verbal report without card, 16=no information*	yes
Vaccination against pneumococcus	*0=unvaccinated, 1=yes, polysaccharide vaccine (PPV23), 2=yes, conjugate vaccine (PCV7/10/13), 9=no information*	no
Date of last pneumococcal vaccine	*Date (dd/mm/yyyy)*	no
Information source about the pneumococcal vaccine	*9=vaccination card reviewed in person, 10=nominal paper-based registry, 11=national nominal electronic registry, 12=medical record, 13=other immunization registries, 14= vaccination card read by telephone, 15=verbal report without card, 16=no information*	no

ANNEX 5. Sample Descriptive Table for Cases and Controls

Variable	Total cases n (%)	Total controls n (%)	p-value	Total vaccinated n (%)	Total unvaccinated n (%)	p-value
Median age (IQR, interquartile range)						
Age group						
18-29	n (%)	n (%)		n (%)	n (%)	
30-44	n (%)	n (%)		n (%)	n (%)	
45-64	n (%)	n (%)		n (%)	n (%)	
≥ 65	n (%)	n (%)		n (%)	n (%)	
Health worker	n (%)	n (%)		n (%)	n (%)	
Days between symptom onset and specimen collection						
0 to 2	n (%)	n (%)		n (%)	n (%)	
3 to 5	n (%)	n (%)		n (%)	n (%)	
6 to 10	n (%)	n (%)		n (%)	n (%)	
≥ 1 pre-existing condition	n (%)	n (%)		n (%)	n (%)	
asthma	n (%)	n (%)		n (%)	n (%)	
diabetes	n (%)	n (%)		n (%)	n (%)	
heart disease	n (%)	n (%)		n (%)	n (%)	
hypertension	n (%)	n (%)		n (%)	n (%)	
pulmonary disease	n (%)	n (%)		n (%)	n (%)	
obesity	n (%)	n (%)		n (%)	n (%)	
Smoking	n (%)	n (%)		n (%)	n (%)	
COVID-19 vaccination	n (%)	n (%)				
unvaccinated	n (%)	n (%)		-	-	
one dose	n (%)	n (%)		-	-	
two doses	n (%)	n (%)		-	-	
Influenza vaccination	n (%)	n (%)		n (%)	n (%)	

ANNEX 6. Sample Table for VE of a COVID-19 Vaccine, Adjusted for Covariates

	Cases		Controls		Crude VE (95%CI)	Adjusted VE (95%CI)[&]
	vaccinated (%)	unvaccinated (%)	vaccinated (%)	unvaccinated (%)		
COVID-19 Vaccine 1						
Unvaccinated					Reference	Reference
1 doses	n (%)	n (%)	n (%)	n (%)		
2 doses	n (%)	n (%)	n (%)	n (%)		
COVID-19 Vaccine 2			n (%)	n (%)		
Unvaccinated					Reference	Reference
1 doses	n (%)	n (%)	n (%)	n (%)		
2 doses	n (%)	n (%)	n (%)	n (%)		
COVID-19 Vaccine 3						
Unvaccinated					Reference	Reference
1 doses	n (%)	n (%)	n (%)	n (%)		
2 doses	n (%)	n (%)	n (%)	n (%)		

[&] adjusted for covariates (for example: age, sex, preexisting conditions, etc.)