Multicenter Evaluation of the Effectiveness of Seasonal Influenza Vaccine

Generic Protocol—Updated April 2018

TABLE OF CONTENTS

TABLE OF CONTENTS 2

EXECUTIVE SUMMARY 5

Participants 10

1. BACKGROUND AND RATIONALE 16

2. OBJECTIVES 27

3. METHODS 27

3.1. Evaluation Design 27

3.2. Population to be Evaluated 27

3.3. Evaluation Period 29

3.4. Resulting Variable (Outcome) 30

3.5. Definitions 30

3.5.1. Patient with a severe acute respiratory infection (SARI) 30

3.5.2. Inclusion criteria 31

3.5.3. Exclusion criteria 31

3.5.4. Influenza cases 32

3.5.5. Preexisting conditions 32

3.6. Sentinel Surveillance of SARIs 33

3.7. Case-finding 34

3.8. Controls 34

3.9. Exposure (Vaccination against Influenza) 35

3.10. Possible Confounding Factors and Effect Modifiers 38

3.11. Possible Errors in the Classification of Cases and Controls 39

3.12. Information to be Collected 40

3.13. Considerations Regarding Sample Size 43

3.14. Data Collection and Integration 44

3.15. Monitoring Data Quality 47

3.16. Data Analysis 47

3.17. Dissemination of the Results 51

4. LOGISTIC ASPECTS 51

4.1. Coordination 51

4.2. Training 52

5. ETHICAL CONSIDERATIONS 52

5.1. Fulfillment of Ethical Requirements 52

5.2. Confidentiality of the Data 53

5.3. Indirect Benefits for Participants in the Evaluation 53

6. TIMETABLE OF PROJECT ACTIVITIES 53

7. BUDGET AND FINANCING 55

8. REFERENCES 55

ANNEXES 58

ANNEX 1. Indicators of Surveillance System Performance 58

ANNEX 2. Verification of Eligibility Form 60

Inclusion Criteria 60

Exclusion Criteria 60

..... 60

ANNEX 3. Variables Collected for the Evaluation, Definitions, and Codes 62

ANNEX 4. REVELAC-i Data Management Flow Charts 70

ANNEX 6. Selection of SARI Patients for Sampling in the Participating Countries 82

ANNEX 7. Example of Procedure for Capturing Influenza and Pneumococcal Vaccination Information, Multicenter Evaluation of Influenza Vaccine, Paraguay, 2013 86

ANNEX 8. Algorithm of the Surveillance Laboratory for Influenza and Other Respiratory Viruses, Ecuador, 2017 87

ANNEX 9. Algorithm of the Surveillance Laboratory for Influenza and Other Respiratory Viruses, Peru, 2017 88

ANNEX 10. Algorithm of the Surveillance Laboratory for Influenza and Other Respiratory Viruses, Colombia, 2017 89

ANNEX 11. Algorithm of the Surveillance Laboratory for Influenza and Other Respiratory Viruses, Argentina, 2017 90

ANNEX 12. Algorithm of the Surveillance Laboratory for Influenza and Other Respiratory Viruses, Brazil, 2017 91

ANNEX 13. Algorithm of the Regional Surveillance Laboratory for Influenza and Other Respiratory Viruses, PAHO/WHO, 2017 92

ANNEX 14. Suggested Format for National Reports on Findings from the REVELAC-i Evaluation of Vaccine Effectiveness 94

ANNEX 15. Suggested Analysis P 98

This document is intended to serve as a generic protocol to guide countries in the preparation of their national protocols. While every effort has been made to reflect the many aspects involved in evaluating the effectiveness of the influenza vaccine, allowance should be made for the possibility of more recent updates in government policies and strategies on vaccination and the surveillance of respiratory viruses. It is important to ensure that national protocols are kept up to date. In this document, the 2017 evaluation year is used for purposes of illustration. However, the protocol should be updated every year to take into account the characteristics of the season in progress, the vaccines used, and the type of vaccination campaigns.

EXECUTIVE SUMMARY

Background. Influenza is responsible for a sizable burden of disease in the countries of Latin America and the Caribbean, particularly in the risk groups targeted for vaccination. Major progress has been made in introducing the influenza vaccine and achieving adequate vaccination coverage in most of the countries in the Region. So far, however, very few evaluations of its effectiveness have been published. Effectiveness of the vaccine depends on several factors, including age and health of the person receiving it, the type of vaccine used, and the match between vaccine strains and circulating strains, which vary from one influenza season to the next. It is therefore necessary to know how well the vaccine is performing each year to assess the impact of vaccination, guide complementary prevention and control measures during seasons when the vaccine's effectiveness is low, and gain an idea of the vaccination program's impact over the medium term while still allowing for variations from one year to the next.

Objective. The objective of this evaluation is to estimate the effectiveness of the seasonal trivalent inactivated influenza vaccine in preventing disease due to severe laboratory-confirmed influenza in target vaccination groups in Mexico, selected countries of Central America (Costa Rica, El Salvador, Honduras, and Panama), selected countries of South America (Argentina, Brazil, Chile, Colombia, Ecuador, Paraguay, Peru, and Uruguay), and Cuba during the 2017 influenza season. The secondary objectives are to estimate vaccine effectiveness by influenza virus type/subtype and geographic sub region.

Design. Using a test-negative study design, cases and controls will be observed and evaluated in the regional network of sentinel hospitals engaged in the surveillance of severe acute respiratory infections (SARIs). Patients included in the study will be drawn from the vaccination target groups defined by the countries (Table 1) and will be receiving treatment for SARI in the participating hospitals. An influenza case will be a patient with SARI (according to the definition adopted by the country consistent with protocols developed by PAHO or the U.S. Centers for

Disease Control and Prevention) whose infection was confirmed to be influenza based on laboratory testing by reverse-transcription polymerase reaction (RT-PCR) of respiratory samples. Only patients with samples collected within 10 days of symptom onset will be included. The controls will be SARI patients who meet the same selection criteria but whose RT-PCR test is negative for influenza viruses (only). To show 50% vaccine effectiveness in children, it will be necessary to identify at least 99 influenza cases and 297 controls with complete data; to show 40% effectiveness in older adults, it will be necessary to have 176 cases and 582 controls, assuming 50% vaccination coverage (controls) for both groups and a power of 80% for the evaluation. Assuming 15% positivity for influenza viruses in patients with SARIs during the entire season, it will be necessary to identify at least to 660 children and 1,173 older adults with SARIs in the pool of participating hospitals during the evaluation period. The sample size obtained in each country will depend on national vaccination coverage of the included groups, the number and performance of participating sentinel hospitals, and the closeness of the match between the influenza viruses in circulation and those in the vaccine.

Population. The study population will include children and older adults receiving care at the participating sentinel hospitals in all the countries and persons with chronic diseases in selected countries, depending on the definitions of the target groups (Table 1) eligible to receive the free vaccine provided by the Expanded Program on Immunization (EPI).

Evaluation period. The study will last from two weeks after the start of the influenza vaccination campaign and continue until the influenza viruses cease to circulate in the country. This period usually lasts at least from May through September in countries where the circulation of influenza viruses follows its typical pattern in the Southern Hemisphere and from October through February in countries where the virus circulation follows its usual pattern in the Northern Hemisphere.

Collection of the data. The data set will include all the information collected within the framework of SARI surveillance. The following information will be obtained from the country's

SARI case report records or equivalent information systems: demographics (age, sex), clinical information (date of symptom onset, hospitalization in intensive care (yes/no), hospital admission and discharge dates, condition at discharge (deceased/living), preexisting conditions, antiviral treatment, date of administration of antiviral treatment, vaccination history (influenza vaccine for current season, number of doses in children under 9 years old, date of vaccination, influenza vaccination in the previous season (where feasible), pneumococcal vaccination, source of information (nominal registry, vaccination card, other EPI document or registry, clinical file), laboratory data (date sample was taken, RT-PCR influenza virus findings, influenza A subtype, influenza B lineage, and positivity for other viruses). The information on vaccination histories will be taken from EPI electronic or paper nominal registries, vaccination cards, or clinical files. Only documented vaccination records will be considered, not verbal reports. A patient will be considered vaccinated if he/she received at least one dose of vaccine more than two weeks prior to symptom onset. In children under 9 years old, a distinction will be made between *full vaccination*, i.e., when he or she has received two doses the first time vaccinated or one dose plus a previous vaccination, and *partial vaccination*, i.e., when he or she has received only a single dose and was previously unvaccinated. The data will be entered in an online data management system that has an interface for keying in information from paper records and also the capability of downloading data from existing digital information systems (the country will indicate the most appropriate method). In addition, data will be collected at the country level on the vaccine formulation used, type of vaccine, and brand name(s)/product(s) used.

Analysis. In the evaluation of vaccine effectiveness, patients with less than two weeks between vaccination and symptom onset will be excluded from the analysis and those who received the vaccine after symptom onset will be considered unvaccinated. The characteristics and the proportion of patients vaccinated for influenza will be compared between the cases and controls and the presence of effect modifiers and confounding factors will be examined. Vaccine effectiveness (VE) will be calculated as 1 minus the vaccination odds ratio of cases versus controls with an estimated confidence interval of 95% (CI 95%). Each target group will be

analyzed separately. VE will be adjusted for month of symptom onset and for any confounding factors identified using a logistic regression model. The data will be aggregated using a meta-analysis of random effects models. Quantitative and qualitative heterogeneity between countries will be examined.

Coordination and implementation. Multidisciplinary and interinstitutional teams drawn from within the Network for the Evaluation of Influenza Vaccine Effectiveness in Latin America and the Caribbean (REVELAC–i) will coordinate planning and implementation of the evaluation at the national level. These teams will include technical personnel from influenza surveillance units, immunization programs, national influenza reference laboratories, and statistics units, as well as the focal points for immunization and epidemiological surveillance in the PAHO/WHO Representative Offices. The regional PAHO-CDC team will provide technical assistance during the course of project implementation in the countries and will add regional data for analysis half way through and at the end of the evaluation period (31 July and 31 December for countries in the Southern Hemisphere and 31 December and 31 March for those in the Northern Hemisphere). The national teams will refine and validate their data prior to final submission.

Dissemination of results. The preliminary results will be reviewed with the REVELAC-i national teams for their validation and approval. The final results will then be disseminated in the form of a publication and as a regional report submitted to the public health authorities and organizations in the Region. In addition, feedback will be provided at the national level depending on the strategies that each country has defined. The regional team will be available to work with countries that wish to prepare manuscripts or national reports based on the findings from the evaluation of vaccine effectiveness.

Ethical considerations. This study of vaccine effectiveness is observational, based on data collected within the context of sentinel influenza surveillance. Therefore, the Ethics Committee of the Centers for Disease Control and Prevention has deemed it a program evaluation and not

a research project. However, the authorities and ethics committees in the respective countries will indicate the approvals required prior to the start of this evaluation.

Collaborating agencies. The evaluation will be conducted in coordination of the health authorities in the participating countries and with technical support from the PAHO/WHO Regional Office in Washington, D.C. and the Influenza Division of the CDC. The PAHO/WHO Representative Offices will support implementation of the field activities, in some cases receiving funds for this purpose from the U.S. Department of Health and Human Services (HHS), CDC, and/or the George Washington University Center for Global Health (CGH) under cooperative agreements between PAHO/WHO and these agencies.

Table 1. Definition of influenza vaccine target groups considered for the multicenter evaluation of vaccine effectiveness in 2017

Country	Influenza vaccination target groups in the evaluation of vaccine effectiveness		
	Children	**Older adults**	**Persons with chronic illnesses**
Argentina	6-24 months	≥65 years	
Brazil	6-23 months	≥60 years	
Chile	6-59 months	≥65 years	2–64 years
Colombia	6-23 months	≥60 years	
Costa Rica	6 months to 11 years with diseases chronic	≥60 years	
Cuba	6-23 months	≥65 years	
Ecuador	6-59 months	≥50 years	5–49 years
El Salvador	6-59 months	≥60 years	
Honduras	6-35 months	≥60 years	
Mexico	6-59 months; 3-9 years with chronic diseases	≥60 years	20–59 years
Nicaragua	6-35 months	≥50 years with chronic diseases	
Panama	6-59 months	≥60 years	
Paraguay	6-35 months	≥60 years	5–59 years
Peru	7-23 months	≥65 years	2–64 years

Participants

Regional Team

- Nathalie El Omeiri, Comprehensive Family Immunization Project (FGL/IM), PAHO/WHO, Washington D.C.
- Alba María Ropero, Comprehensive Family Immunization Project (FGL/IM), PAHO/WHO, Washington D.C.
- Rakhee Palekar, Influenza Surveillance, PAHO/WHO, Washington, D.C.
- Paula Couto, Influenza Surveillance, PAHO/WHO, Washington, D.C.
- Eduardo Azziz-Baumgartner, Influenza Division, CDC, Atlanta, Georgia, USA
- Sofía Arriola, Influenza Division, CDC, Atlanta, Georgia, USA
- Cuauhtémoc Ruiz, Comprehensive Family Immunization Project (FGL/IM), Washington, D.C.
- Joseph Bresee, Influenza Division, CDC, Atlanta.

National Teams

Argentina

- Raúl Forlenza, Epidemiology Directorate, Ministry of Health
- Julián Antman, Epidemiology Directorate, Ministry of Health
- Carlos Giovacchini, Epidemiology Directorate, Ministry of Health
- Teresa Varela, Epidemiology Directorate, Ministry of Health
- Paula Couto, Epidemiology Directorate, Ministry of Health
- Carla Vizzotti, National Directorate of Vaccine-preventable Diseases (DiNaCEI)
- Nathalia Katz, National Directorate of Vaccine-preventable Diseases (DiNaCEI)
- Elsa Baumeister, Respiratory Viral Disease Service, Department of Virology, National Reference Laboratory, National Institute of Infectious Diseases, Carlos G. Malbrán Administration of Health Laboratories and Institutes (INEI-ANLIS)

Brazil

- Carla Magda Allan S. Domingues, National Immunization Program, Ministry of Health
- Ricardo Pio Marins, Ministry of Health
- Walquiria Aparecida de Ferreira de Almeida, Ministry of Health
- Marilda Siquiera, FIOCRUZ, Director, Respiratory Virus Laboatory and National Influenza Center, Rio de Janeiro
- Dayana Araujo, Ministry of Health
- Ana Carolina Lacerda, Ministry of Health
- Ernesto Isaac Montenegro Renoiner, Ministry of Health
- Ana Freitas Ribeiro, Project Coordinator and Principal Investigator, São Paulo State Secretariat of Health
- Leticia Garay Martins, Project Coordinator and Principal Investigator, Rio Grande do Sul State Secretariat of Health

- Eduardo Marques Macário, Project Coordinator and Principal Investigator, Santa Catarina State Secretariat of Health
- Deise Aparecida dos Santos, Superintendent of Health and Project Coordinator and Principal Investigator, Minas Gerais State Secretariat of Health
- Laurinda Setsuko Tanabe, Project Coordinator and Principal Investigator, Paraná State Secretariat of Health
- Janaina Fonseca Almeida, Minas Gerais State Secretariat of Health
- Samia Abdul Samad, PAHO/WHO Representative Office in Brazil

Chile

- Bernardo Martorell, Directorate of Health Planning, Ministry of Health
- Sergio Loayza, Department of Epidemiology, Ministry of Health
- Viviana Sotomayor Proschle, Coordinator, Sentinel Surveillance of Influenza, Department of Epidemiology, Ministry of Health
- Natalia Vergara, Department of Epidemiology and Department of Statistics and Health information, Ministry of the Health,
- Fernando Muñoz-Porras, National Immunization Program, Ministry of Health
- Cecilia González, National Immunization Program, Ministry of Health
- Rodrigo Fasce, Reference Laboratory, Institute of Public Health
- Roberto Del Águila, PAHO/WHO Representative Office in Chile

Colombia

- Jacqueline Palacios G., Vaccine-preventable Diseases, Ministry of Health and Social Protection
- Marta Lucia Ospina, Director-General, National Institute of Health
- Claudia Cuéllar, Ministry of Health
- Consuelo Pinzón, Ministry of Health
- Franklyn Edwin Prieto, National Institute of Health
- Oscar Eduardo Pacheco, National Institute of Health
- Paola Andrea Pulido, National Institute of Health
- Juliana Barbosa, Virology Department, National Institute of Health
- Diana Carolina Malo, National Institute of Health
- Erika Espitia, National Institute of Health
- Wilmer Marquiño, PAHO/WHO Representative Office in Colombia
- Viviana Calderón, PAHO/WHO Representative Office in Colombia

Costa Rica

- Jenny Lara, National Influenza Center, Costa Rican Institute for Research and Education on Nutrition and Health (INCIENSA)
- Vicenta Machado, Costa Rican Social Security Fund (CCSS)
- Xiomara Badilla, Costa Rican Social Security Fund (CCSS)
- Mariel López, Costa Rican Institute for Research and Education on Nutrition and Health (INCIENSA)

- Hilda Salazar, Preventable Disease Surveillance, Ministry of Health
- Roberto Arroba, Director, Expanded Program on Immunization, Ministry of Health

Cuba

- Antonio Marrero, Responsible Officer, Program on Acute Respiratory Infections, Ministry of Public Health
- Marlén Valcárcel, Head, Expanded Program on Immunization, Ministry of Health, Ministry of Public Health
- Mabel González, Head, National Pediatric Infectious Diseases Group; Adviser, National Maternal Health Program (PAMI)
- Ismell Alonso, Specialist, National Directorate of Statistics (DNE), Ministry of Public Health
- Libia López, National Directorate of Statistics (DNE), Ministry of Public Health
- Miguel Angel Galindo, Adviser, Expanded Program on Immunization, Ministry of Public Health
- Lourdes Suárez, National Bureau of Epidemiology, Ministry of Public Health
- María Guadalupe Guzmán, Head, Virology Department, Pedro Kouri Institute (IPK)
- Belsy Acosta, Responsible Officer, National Influenza Laboratory
- Belkis Galindo, Epidemiologist, Pedro Kouri Institute (IPK)
- Susana Borroto Gutiérrez, Epidemiologist, Pedro Kouri Institute (IPK)
- Sandra Rodríguez, Responsible Officer, Program on Acute Respiratory Infections, Provincial Center for Hygiene, Epidemiology, and Microbiology (CPHEM)/Havana
- Marta Morales Leslie, Head, Provincial Microbiology Group
- Carlos Dotres, Respiratory Services, Juan Manuel Márquez Hospital
- Ángel Manuel Álvarez, PAHO/WHO Representative Office in Cuba

Ecuador

- Jenny Ojeda, Responsible Officer, Sentinel Surveillance
- Jackeline Pinos, National Directorate of Surveillance
- Maria Eugenia Mejía, Laboratory, National Directorate of Surveillance
- Marco Cando, Expanded Program on Immunization
- Maria del Carmen Grijalva, Expanded Program on Immunization
- Patricia Marines, Expanded Program on Immunization
- Jacobo Moreta, Expanded Program on Immunization
- Patricio Montenegro, Expanded Program on Immunization
- Ana Burbano, Expanded Program on Immunization
- María Angélica Becerra, National Influenza Center
- Gladys Ghisays, PAHO/WHO Representative Office in Ecuador

El Salvador

- Eduardo Suarez-Castañeda, Expanded Program on Immunization, Ministry of Health
- Héctor Ramos, Directorate of Surveillance, Ministry of Health
- Miguel Elas, Expanded Program on Immunization, Ministry of Health
- Wilfrido Clará, CDC Representative in El Salvador

- Celina de Lozano, National Influenza Center
- Elizabeth De Cuellar, Santa Ana Hospital
- José Eduardo Oliva, PAHO/WHO Representative Office in El Salvador

Mexico

- Alberto Díaz, Deputy Director-General, Epidemiological Diagnosis and Reference Institute (InDRE)
- Arturo Revuelta, Director of Epidemiological Information, Directorate General of Epidemiology (DGE)
- Verónica Carrión Falcón, Director, Child and Adolescent Health Services, Secretariat of Health
- Irma López Martínez, Head, Virology Department, Epidemiological Diagnosis and Reference Institute (InDRE)
- Gabriela Nucamendi, Head, Information Department, General Directorate of Epidemiology (DGE)
- Tamara Mancero, PAHO/WHO Representative Office in Mexico

Honduras

- Homer Mejía Santos, Coordinator, Influenza Surveillance, Secretariat of Health
- Ida Berenice Molina, Director, Expanded Program on Immunization
- Diana Nuñez, Secretariat of Health
- Odalys García, General Coordinator, Surveillance of Vaccine-preventable Diseases
- Dulcelina Urbina, Expanded Program on Immunization
- Engels Banegas, National Reference Laboratory, Secretariat of Health
- Rudvelinda Rivera, National Reference Laboratory, Secretariat of Health
- Dilberth Cordero, PAHO/WHO Representative Office in Honduras

Panama

- Itzel Hewitt, Director, Expanded Program on Immunization, Ministry of Health
- Lourdes Moreno Castillo, Ministry of Health
- Yadira De Molto, Responsible Officer, Influenza Surveillance, Ministry of Health
- Dilsa Lara, PAHO/WHO Representative Office in Panama

Paraguay

- Sonia Arza, Director, National Directorate of Vaccine-preventable Diseases and Expanded Program on Immunization, Ministry of Health
- Zully Suarez, Department of Vaccine-preventable Disease Surveillance, Ministry of Health
- Miryam Medina, Head, Department of Vaccine-preventable Disease Surveillance, Ministry of Health
- Martha Von Horoch, Coordinator, Influenza Surveillance, Ministry of Health
- Silvia Battaglia, Influenza Surveillance, General Directorate of Health Surveillance, Ministry of Health
- Jose Sánchez, Information Systems Unit, Ministry of Health

Peru

- Victor Fiestas Solórzano, National Institute of Health
- Maribel Huaringa Núñez, National Institute of Health
- José Medina Osis, National Center for Epidemiology and Disease Prevention and Control
- María Ticona Zegarra, National Directorate of Immunization
- Hugo Antonio Mezarina Esquivel, Pediatric Emergency Hospital
- Luis Marocho Chahuayo, National Institute of Children's Health
- Mery Ale Arratea, Archbishop Loayza National Hospital

Uruguay

- Teresa Picón, Coordinator, Expanded Program on Immunization, Ministry of Public Health
- Carlos Zunino, Immunization Program, Ministry of Public Health
- Lucia Alonso, Immunization Program, Ministry of Public Health
- Adriana Varela, Immunization Program, Ministry of Public Health
- Noelia Speranza, Immunization Program, Ministry of Public Health
- Fernando Arrieta, Immunization Program, Ministry of Public Health
- Laura Sola, Ministry of Public Health
- Henry Albornoz, Ministry of Public Health
- Rosario San Martin, Ministry of Public Health
- Fabio Grill Diaz, Ministry of Public Health
- Monica Castro, Ministry of Public Health
- Adriana Alfonso, Ministry of Public Health
- Lali Gonzalez Lamé, Ministry of Public Health
- Adriana Varela, Ministry of Public Health
- Héctor Chiparelli, Department of Public Health Laboratories, Ministry of Public Health

Partners

Regional Partners

- Bremen de Mucio, PAHO/WHO Latin American Center of Perinatology, Women and Reproductive Health (CLAP/SMR), Montevideo, Uruguay
- Gerardo Martinez, PAHO/WHO Latin American Center of Perinatology, Women and Reproductive Health (CLAP/SMR), Montevideo, Uruguay
- Susan Kaydos-Daniels, Central American Regional Office, Centers for Disease Control and Prevention (CDC-CAR), Guatemala City, Guatemala

International Partners

- Mark Thompson, Influenza Division, Centers for Disease Control and Prevention, Atlanta, GA, USA

- Sheena Sullivan, WHO Collaborating Center for Influenza, Melbourne, Australia
- Marta Valenciano, Influenza - Monitoring Vaccine Effectiveness Network, (I-MOVE), Epiconcept, Madrid, Spain
- Alain Moren, Director, Epidemiology Unit, EpiConcept, Paris, France
- Esther Kissling, EpiConcept, United Kingdom
- Marc Rondy, Epiconcept, Paris, France
- Amparo Larrauri, Coordinator, National Influenza Surveillance Network, Carlos III Institute of Health, Madrid, Spain
- Jesús Castilla, Coordinator, Cohort Studies for the Evaluation of Influenza Vaccine Efficacy, Navarra Health Institute, Pamplona, Spain

Affiliated Projects/Agencies

- SARInet
- CLAP
- IMOVE
- InHOVE [TN: no link]

1. BACKGROUND AND RATIONALE

Influenza infections and their complications impose a significant morbidity and mortality burden on the Region of the Americas. It is estimated that influenza causes between 48,880 and 160,270 deaths annually in the Americas, or an average of 79,057 deaths a year. According to data from 35 countries, 81% of these patients were adults 65 years of age or older [1]. Available findings for Latin America suggest that the disease has a more severe effect on children under 5 years and adults 60 and older with preexisting conditions [1-5].

Vaccination against influenza is one of the most effective measures for preventing severe influenza and its complications [6]. The vaccine currently in use contains antigens against three strains of the seasonal influenza virus (A/H1N1, A/H3N2, and B (Yamagata or Victoria lineage). Given the virus's tendency toward frequent genetic drift, the components of the vaccine need to be updated annually, taking into account the differences between the epidemics in the Southern Hemisphere and those in the Northern Hemisphere. The World Health Organization (WHO) Global Influenza Program, which is responsible for deciding on the composition of the vaccine collects and analyzes data on virological and epidemiological influenza surveillance from around the world and identifies the strains that are most likely to circulate in the upcoming season [7]. The vaccine's effectiveness depends not only on the age and health status of the vaccine, but also on how closely the vaccine strains match the strains in circulation [8]. Because of the heterogeneity of the influenza viruses, genetic drift can even occur during the course of a single season, also reducing the efficacy of the vaccine. For these reasons, it is essential to know how the vaccine is performing every year and to have evidence for appropriate decision-making in the interest of public health. Learning that the vaccine's effectiveness is low at the start of an epidemic can be useful in guiding the implementation of other complementary measures for prevention and control of the disease.

The countries in the Region of the Americas have made great progress in introducing the seasonal influenza vaccine in the public sector over the last decade. Two of the main references on the use of this vaccine consulted by the countries are the recommendations of the Technical WHO Advisory Group on Vaccine-preventable Diseases and the results of cost-effectiveness studies conducted in Colombia or Costa Rica, among others [9-13] (Table 2). Since 2004, of the

45 countries or territories of the Americas, the number that have instituted influenza vaccination policies has increased from 13 to 40 (Table 2).

Table 2. Trend in implementation of influenza vaccination policies in countries and territories of the Americas, 2004 2014

Countries with policies on:	2004	2008	2015
Vaccination against influenza	13	35	40
Vaccination of children*	6	22	30
Vaccination of older adults	12	33	38
Vaccination of persons with chronic diseases	9	24	35
Vaccination of health workers	3	32	38
Vaccination of pregnant women	3	7	31

*Does not include countries that only vaccinate children with chronic diseases.
Data were not collected on French Guiana, Guadeloupe, or Martinique.
Source: PAHO/WHO, Washington, D.C.

In 2012, WHO revised its stated position on vaccination against seasonal influenza, recommending that countries using or considering use of the vaccine should emphasize the following five priority groups:

- Pregnant women, to be given the highest priority,

and four other groups, not necessarily in order of priority:

- Children under 5 (particularly those aged 6 to 23 months)
- Health workers
- Older adults
- Persons with preexisting conditions

These recommendations have been reflected in vaccination programs as they have progressively expanded (Table 3).

Although great progress has been made in introducing the influenza vaccine in most of the countries, so far only a few evaluations of their effectiveness have been published in Latin America [14-17]. A 2001 cohort study of older adults in the State of São Paulo, Brazil, found a lower incidence of *influenza-like illness* in adults vaccinated against seasonal influenza

compared with unvaccinated adults [14]. However, because the sample size was small, the results were not considered significant and the data on the incidence of influenza-related hospitalizations were not conclusive. In 2001, a clinical trial in a population of healthy working adults in Medellín, Colombia, showed a 14% reduction in the incidence of acute upper respiratory infections (AURIs) in a comparison of vaccinated and unvaccinated adults, with values between 7% and 20%, and a 31% reduction of AURIs in patients unable to work compared with the placebo group, with values between 0% and 52% [16]. These estimates increased to 62% and 89%, respectively, during the period when the influenza virus was in circulation. In Argentina, a study conducted after the influenza A (H1N1) pandemic reported 50% effectiveness (40%-59%) of the pandemic vaccine as measured by hospitalizations due to influenza in all age groups [17].

In 2013, an ecological study explored the impact of vaccination on adults 65 and older in the Brazilian Northeast and South in terms of mortality associated with pneumonias and influenza [15]. The results differed significantly between the two regions. In the South, marked reductions were seen in mortality from *pneumonias and influenza* among older adults following introduction of the vaccine, as well as reductions in the average number and duration of annual influenza outbreaks. In the Northeast, however, there were increases in all the indicators during the vaccination period, suggesting poor correlation between the vaccination campaign and the epidemic period and between the vaccine strains and the circulating viruses [15].

To generate systematic evidence on vaccine effectiveness for the purpose of guiding interventions and evaluating the impact of existing vaccination programs, in 2012 the Pan American Health Organization (PAHO) and the Influenza Division of the U.S. Centers for Disease Control and Prevention (CDC) explored the possibility of evaluating the effectiveness of the influenza vaccine based on the existing influenza surveillance platform through a regional multicenter project involving several countries of the Region.

As a first step, a pilot study was conducted in 2012 in four countries of Central America with support from the local PAHO/WHO Representative Offices and the Central American Office of the Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET), which helped to conduct the field activities. In March 2013, the experiences and lessons

learned from the pilot study were shared with a team from the ministries of health of eight additional countries of the Region, leading to the proposal and official creation of the REVELAC-i Network. The implementation phase of the evaluation of vaccine effectiveness was launched during the 2013 influenza season and included the participation of Argentina, Brazil, Chile, Colombia, Costa Rica, El Salvador, Honduras, Panama, and Paraguay.

So far, 14 countries have joined in the REVELAC-i Network, which has established the following objectives:

- Develop mechanisms for sharing experiences between countries and research centers on the effectiveness of the influenza vaccine, including lessons learned and common methods, and study the impact of vaccination on morbidity and mortality due to influenza; and
- Continue to integrate data from epidemiological and virological surveillance, as well as immunization programs, to generate evidence for the prevention and control of influenza.

It is hoped that the data from the evaluation of vaccine effectiveness will provide users of the surveillance system with fuller information for sentinel surveillance and also support evidence-based decision-making. Furthermore, it is recommended that this evaluation be integrated as a component of the SARI surveillance system itself, or at least that it be recognized as a source of secondary surveillance data. The results of this analysis of vaccine effectiveness can contribute to supplementary analyses of benefit to vaccination programs, such as measurement of their impact and of costs avoided.

Table 3. Seasonal influenza vaccine in Mexico, Central America, South America, and Cuba: year of introduction, target group, vaccination campaigns, and costs of the influenza vaccination program

Country	Year vaccine was introduced[#]	Target population	Vaccination coverage	Vaccination campaign	Vaccine formulation used	Introduction of pneumococcal vaccine and groups vaccinated
Argentina	1993: Provision of the vaccine to risk groups 2010: Vaccination campaign against pandemic influenza 2011: Introduction into the national vaccination schedule	2008: Children 6-23 months old with chronic diseases, adults >65 years, health workers, pregnant women, population 2-64 years old with chronic diseases, essential services personnel, security forces 2010: The vaccination campaign against pandemic influenza was expanded to cover children 6-59 months, pregnant women in all trimesters, and puerperae with children under 6 months who were not vaccinated against AIDS during their pregnancy 2011: Inclusion of the same groups that were vaccinated during the pandemic, except children, in the national vaccination schedule.	Overall coverage: ▪ 2010: 94% ▪ 2011: 88% ▪ 2012: 87% 2010 Health Workers: 99% Pregnant women: 98% Puerperae: 91% Children 6 to 59 months: 86% (1st dose) Patients 5-65 years old with risk factors (cardiopathies, respiratory diseases, immune system deficiencies, obesity, etc.: 99% 2011 Population 2-64 years with chronic diseases: 98%, Health workers: 98% Pregnant women: 88% Puerperae: 74% Children <2 years: 73% Children 6 months to 2 years: 36% for the second dose 2012 Pregnant women: 98%	From March until the end of influenza circulation	Southern Hemisphere	In 2011 the Ministry of Health universally incorporated the 13-valent conjugate vaccine in the national schedule for children under 2 and continued to vaccinate older adults and persons at risk with the 23-valent polysaccharide vaccine. To further strengthen this strategy, the pneumococcal 13-valent conjugate vaccine has been added for vulnerable groups over 2 years old and adults over 65 using a sequential scheme under a in

		Based on findings from a study of mortality in confirmed cases of pandemic influenza and from influenza surveillance in the pediatric population, it was decided to only include children 6-24 months old in the national vaccination schedule.	Population 2-64 years with chronic diseases: 94% Health workers: 86% workers Puerperae: 77% Children 6 months - 2 years: 75%			2017-2018 biennial program
Brazil	1999	1999: Introduction of the vaccine in adults >65 years. 2000-2009: Adults >60 years. 2010–2012: Children 6-23 months, pregnant women, health workers, indigenous populations, older adults, and persons with chronic diseases. 2013: Puerperae	Older adults: 2006: 86%; 2011: 84%; 2012: 82% Children 6-23 months: 2011: 90%; 2012: 96% Health workers: 2011 and 2012: 99% Pregnant women: 2011 and 2012: 80%	From the end of April to mid-May	Southern Hemisphere	2010
Chile	1975	2008: Children 6-23 months, adults ≥65, health workers, persons with chronic diseases, pregnant women, agricultural workers	Older adults: 2007: 88.6%; 2008: 89.1%; 2012: 76% Children: 2006: 81%; 2007: 90%; 2012: 98%	From the end of March (18 March in 2013)	Southern Hemisphere	

		2016: Children 6-59 months old				
Colombia	2005	Children 6-23 months old; adults ≥60, health workers, persons with chronic diseases 2013: optional: pregnant women, the chronically ill, and health workers		From the beginning of April	Northern Hemisphere in 2005; Southern Hemisphere since 2007	2011
Costa Rica	2004	2004-2009: Children 6 months to 8 years with chronic diseases, adults ≥65 years, and health workers 2010: Pregnant women 2011: Persons with chronic diseases (all ages) and children with chronic diseases up to 10 years 2015: Adults >60		March-April in 2004–2009; January-February in 2010-2011; February-March in 2012-2013	Northern Hemisphere	The pneumococcal vaccine was introduced for at-risk groups in 2007, with the PCV7 vaccine in general use by 2009. This vaccine was replaced by the 13-valent vaccine (PCV13) in 2011.
Cuba	1998	Children <24 months with diabetes/asthma, adults ≥65, health workers, agricultural workers, persons with chronic diseases 2011: Population 6 months - 24 years with asthma or diabetes, and pregnant women	Older adults: 2006 and 2007: 100%		Northern Hemisphere	It has not been introduced.
Ecuador	2006	2008: Children 6-23 months, adults ≥65, health workers.	2013 Children 6-11 months: 68% Children 12-23 months: 60% Children 2-3 years: 53%	November-December	Northern Hemisphere	2010

		2014: Children 6-59 months, adults ≥50, health workers, pregnant women, and persons with chronic diseases	Children 3-4 years: 49% Adults ≥65 years: 41% Persons with chronic diseases: 88% Pregnant women: 31% Health workers: 88%			
El Salvador	2004	2008: Children 6-23 months, adults ≥60, health workers, and persons with chronic diseases 2011: Children <59 months	2010 Children 6-23 month: 64% Older adults: 89%	Starting at the end of April for 6 weeks (26 April to 30 June 2013)	Northern Hemisphere; Southern Hemisphere since May 2011	Introduced in 2010. 2012: Children <2 years (13-valent) and adults >60 (23-valent) 2013: Children <2 years
Guatemala	2007	2008: Institutionalized adults ≥60 years, health workers 2012: Pregnant women, children 6-35 months, personnel in senior residences, persons with chronic diseases	2007 Adults ≥60 years: 100%		Northern Hemisphere; Southern Hemisphere since 2012	2011

Honduras	2003	Prior to 2006: Adults ≥65 and health workers 2006: Chronically ill patients 6 months to 64 years 2007: Poultry farm workers 2007 and 2008: Children with chronic diseases 2008: Adults ≥60 2009: Children 6-35 months with chronic diseases	Adults ≥65 and health workers: 2003-2005: 100%; 2006-2011: 99%, 97%, 83%, 109%, 71%, and 76%, respectively; 2006-2007: 90% and 84%; 2008–2011: 86%, 84%, 97%, and 72%, respectively Adults ≥59 with chronic diseases and children with chronic diseases: 2006: 261%; 2007-2008: 43% and 82% respectively; 2009–2011: 84%, 93%, and 71%. Poultry farm workers: 2008: 41%; 2010: 132%; 2011: 97% Other at-risk groups: 2005-2011: >95% with the exception of 2009	Annual national campaign runs from 15 November to the end of December, except in 2007, when it was conducted in the second half of October. Since 2015 the campaigns have started in April-May.	Northern Hemisphere (The 2015 campaign started out with a vaccine based on the Southern Hemisphere composition.)	Since 2011 the pneumococcal conjugate vaccine has been given to infants under 1 year in a 3-dose series at 2, 4, and 6 months. In 2011-2013 the country received a donation of pneumococcal polysaccharide, which has been given to the chronically ill population aged 2-59 years and adults ≥60. This vaccine is not part of the series.
Mexico	2004	2004: Children 6-24 months, adults >65, and individuals with risk factors in other age groups 2006: Children <36 months and health workers 2009: Pregnant women 2011: Children ≥59 months, population 20-59 years with chronic diseases	2006 Older adults: 93% 2007 Older adults: 85%		Northern Hemisphere	2006

		The National Vaccination Board (CONAVA) is responsible for decision-making. 2013-2014: 25 million people were targeted for vaccination. The campaign started in mid-October 2013 and ended in March 2014.				
Panama	2005	Prior to 2008: Children 6-23 months, adults ≥60 years, health workers 2008: Poultry farm workers 2012: Children 6-59 months	2006 Adults ≥60: 86.2% Children 6-23 months with a chronic disease: 66% 2007 Adults ≥60: 79% Children 6-23 months with a chronic disease: 85%	From mid-April or May, for 6 weeks.	Southern Hemisphere	Children?
Paraguay	2005	Prior to 2012: Children 6-23 months, adults ≥60, health workers, persons with chronic diseases, and agricultural workers 2012: Children 6-35 months, pregnant women	2006 Older adults: 52% 2007 Older adults: 73% Children: 65%	From mid-April until September	Southern Hemisphere	2010: 23-valent vaccine given to older adults and at-risk individuals. 2012: 10-valent vaccine
Peru	2008	Children 7-23 months, population 2-59 years at risk with chronic medical conditions, adults ≥60, pregnant women (starting at 20 weeks), puerperae, and health workers;	2014 Pregnant women: 30% Children: 37% Older adults: 89% Health workers: 97% 2015 Pregnant women: 36%	From the end of April, with Vaccination Week in the Americas, until the end of the season	Southern Hemisphere	2009: PCV7 introduced. 2011: PCV7 replaced with PCV10. 2015: PCV13 given to children <2 years and children

		members of the armed forces; national police, Red Cross, Fire Department, and civil defense personnel; persons deprived of liberty; indigenous communities; and workers in rehabilitation centers, rest homes, and shelters	Children: 67% Older adults: 89% Health workers: 76%			2-4 years with comorbidity who had not received the vaccine previously
Uruguay	1996	2008: children 6-23 months, adults ≥65, health workers, persons with chronic diseases, and agricultural workers 2015: Children of 6-48 months 2016: Children 6-59 months	2016 Older adults: 30%, Children:29% Health workers: 69% Pregnant women: 36%	In 2016, from 2 May until 31 August, with the majority vaccinated within 1-2 months ~570,000 doses in 2016	Southern Hemisphere	

Introduction to any at-risk group.

*Countries vaccinate children from 2 months to 2 years of age against pneumococcal pneumonia according to the following schedule: depending on age at the first dose, age, children should receive 2 or 3 doses (2 months between doses) and an additional dose at 12-15 months. It is recommended that they receive the first dose before they reach 6 months.

Sources: Ropero-Álvarez, 2009, and communications from the health authorities.

2. OBJECTIVES

Main objective

- Estimate the effectiveness of the seasonal trivalent inactivated influenza vaccine in preventing **SARIs due to influenza** in the vaccination target groups being treated at sentinel hospitals in **Mexico,** Central America (**Costa Rica, El Salvador, Honduras, and Panama**), South America (**Argentina, Brazil, Chile, Colombia, Ecuador, Paraguay, Peru, and Uruguay**), and **Cuba** during the 2017 influenza season.

Secondary objective:

- Estimate the effectiveness of the vaccine by **type** of influenza virus, influenza A **subtype**, influenza B **lineage** (when possible), **sub region** (Central or South America), and **country** (large countries or countries with a sufficient patient samples).

3. METHODS

3.1. Evaluation Design

In a **test-negative** design, an observational evaluation of **cases and controls** will be undertaken in the regional network of SARI sentinel surveillance hospitals. This design was selected mainly because of the low incidence of severe acute respiratory infections confirmed by RT-PCR to be due to the influenza virus and by the ease of recruitment of controls. Test-negative controls have frequently been used to study the effectiveness of the influenza vaccine, especially in evaluations based on surveillance [18].

3.2. Population to be Evaluated

The study population will include children and older adults (in all the countries) and persons with chronic diseases (in selected countries) being treated in the participating sentinel hospitals, depending the definitions of target groups eligible for the free vaccine provided by the Expanded Program on Immunization (EPI) (Table 4).

Table 4. Influenza vaccination target groups included in the evaluation and number of proposed sentinel hospitals in each country

Country	Vaccination target groups			Number of participating hospitals (n=80)
	Children	Older adults	Persons with preexisting conditions	
Argentina	6-24 months	≥65 years		4
Brazil	6-23 months	≥60 years		29
Chile	6-23 months	≥65 years	Any age with risk factors	6
Colombia	6-23 months	≥60 years		7
Costa Rica	6 months to 10 years with chronic diseases	≥65 years		7
Cuba	6-23 months	≥65 years		To be determined
Ecuador	6-59 months	≥50 years	Any age with risk factors	4
El Salvador	6-59 months	≥60 years		4
Honduras	6-35 months with chronic diseases	≥60 years		3
Mexico	6-59 months; 3-9 years with chronic diseases	≥60 years	20-59 years with a preexisting condition	To be determined
Panama	6-59 months	≥60 years		10
Paraguay	6-35 months	≥60 years		2
Peru	7-23 months	≥65 years	2-64 years	4
Uruguay	6-59 months	≥65 years		7

Depending on the country, either all the sentinel hospitals or a selection thereof will participate in the study, taking into account the following criteria:

- Hospitals that treat the **target groups**
- The **relative representation** of certain populations and the influenza season in the country
- The **volume of SARI patients** reported in the previous influenza season
- The number of SARI patients who have provided respiratory samples that have been submitted for **RT-PCR** analysis
- The **performance of surveillance** according to the indicators established in the PAHO-CDC regional protocol (**Error! Not a valid bookmark self-reference.**) and **the q uality** of the laboratory data
- The availability of **information on vaccination** in the hospital
- The quality of the **vaccination/EPI records** associated with the hospital at the local level

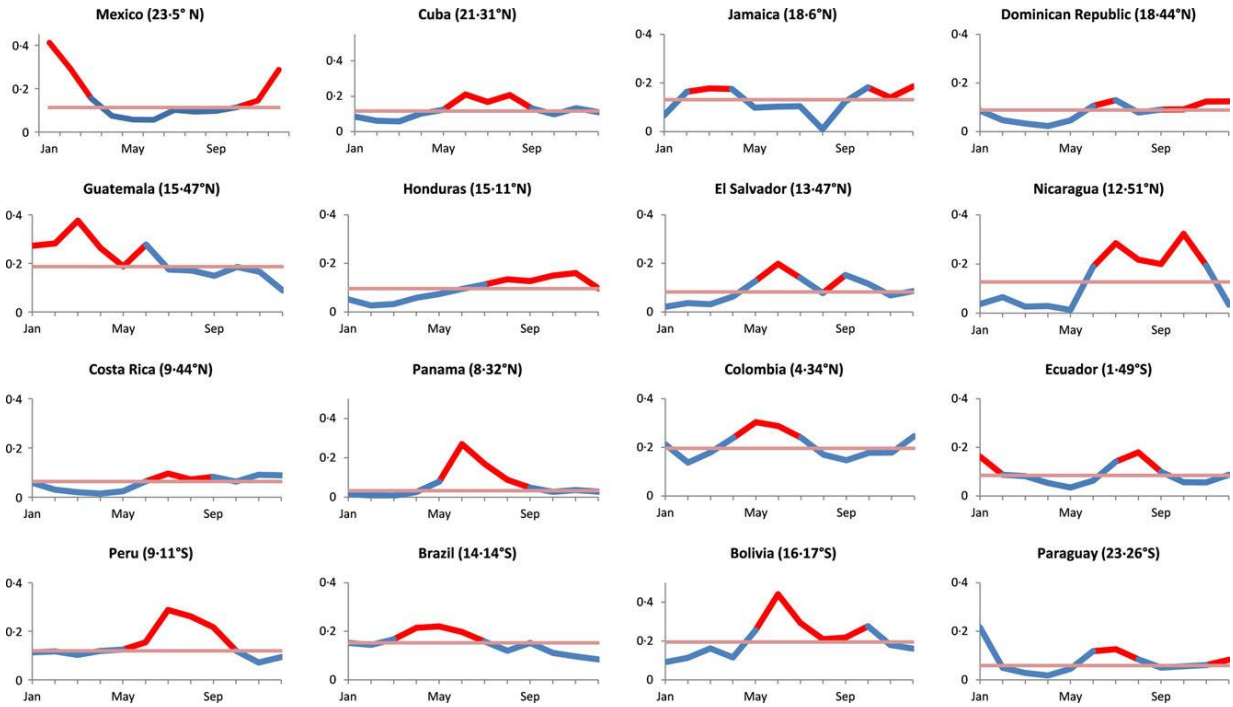
- **Logistic aspects** (e.g., conditions for transportation of samples) and **security**
- The hospital team's commitment to surveillance and their interest in participating

3.3. Evaluation Period

The evaluation will start two weeks after initiation of the vaccination campaign in the country (usually May) and continue until at least September or ideally until the virus ceases to circulate in the country. Each country will define its exact period based on when the first and last RT-PCR-confirmed case of influenza occurs in the study population. The span from May through September, which typically includes the year's peak circulation, is considered the usual period for the majority of LAC countries (see examples in Figures 1 and 2).

In Mexico and other countries that have a virus circulation pattern typical of the Northern Hemisphere, the influenza season corresponding to 2016-2017 in the Northern Hemisphere, as defined by the country, will be used.

Figure 1. Annual activity of seasonal influenza in the American tropics (binomial model)

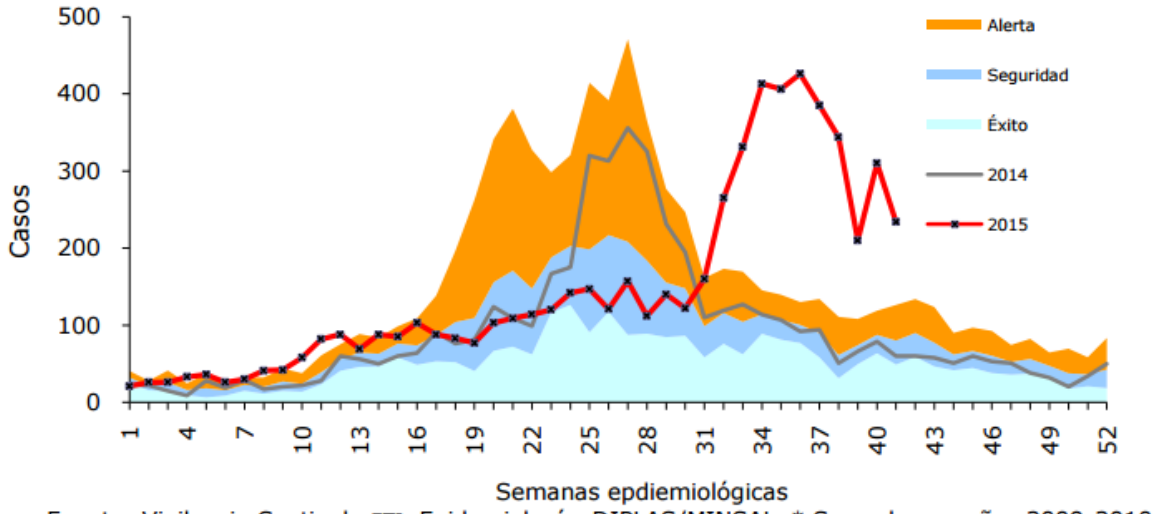


Y axis: Projected proportion of positive respiratory samples to be tested for influenza virus. Red: Time corresponding to the epidemic period. Data years to be used: Bolivia, Cuba, Dominican Republic, Ecuador, and Jamaica: 2011-2014; Mexico (tropical region): 2011–2014; Brazil and Costa Rica: 2003-2008 and 2011-2014; Colombia: 2002-2007 and 2011-2014; Guatemala: 2002, 2006-2008, and 2011-2014; El Salvador:

2005-2008 and 2011-2014; Honduras, Nicaragua, and Panama: 2008 and 2011-2014; Paraguay 2003-2005 and 2011-2014; and Peru: 2004-2008 and 2011-2014.

Source: Durand LO et al. Timing of influenza epidemics and vaccines in the American tropics, 2002-2008, 2011-2014. Influenza Other Respir Viruses. 2016 May;10(3):170-5.

Figure 2. Endemic channel of Influenza-like Illness, by epidemiological week (EW), 2008-2014, Chile, 2015 (EW 1-41)



Fuente: Vigilancia Centinela ETI. Epidemiología, DIPLAS/MINSAL. * Se excluyen años 2009-2010 por corresponder a años epidémicios. Información provisoria

[Countries may contribute figures or data for this section if they wish.]

3.4. Outcome

The outcome is SARI confirmed by RT-PCR for the presence of any seasonal influenza virus.

3.5. Definitions

3.5.1. Patient with a severe acute respiratory infection (SARI)

A patient with SARI shall be defined as a person who meets the following criteria:

- History of fever or a measured fever of ≥38°C
- Cough
- Onset within the last 10 days
- Need for hospitalization [per Operational Guidelines for Sentinel Severe Acute Respiratory Infection (SARI) Surveillance. PAHO; September 2014].

If the definition of a case is different in any of the countries, the national team will adapt its case definition and make a note accordingly in the national protocol in order to ensure appropriate interpretation of the regional results. It is recommended that each country indicate its current definition of *hospitalization*—e.g., *at least 24 hours of hospital admission*.

3.5.2. Inclusion criteria

A patient with SARI is eligible for the evaluation if he/she:

- Meets the definition of a SARI case (see previous paragraph):
  - Provides a respiratory sample within the context of SARI surveillance;
  - Provides the sample no more than 10 days after the onset of symptoms (≥10 days).
- Is a child within the following age range for his/her country at the time of the vaccination campaign:
  - **6-23 months** in Argentina, Brazil, Colombia, or Chile;
  - **6-59 months** in Ecuador, El Salvador, Mexico, Panama, or Uruguay;
  - **6-23 months** with chronic diseases (asthma or diabetes) in Cuba;
  - **7-23 months** in Peru;
  - **6-35 months and has chronic diseases** in Honduras;
  - **6-35 months** in Paraguay;
  - **3-9 years and has chronic diseases** in Mexico;
  - **6-59 months years or ≥5 years and has chronic diseases** in Costa Rica;

Or:

- Is an adult within the following age range for his/her country at the time of the vaccination campaign:
  - **≥50 years** in Ecuador;
  - **≥60 years** in Brazil, Colombia, Costa Rica, El Salvador, Honduras, Mexico, Panama, or Paraguay;
  - **≥ 65 years** in Argentina, Chile, Cuba, Peru, or Uruguay.

3.5.3. Exclusion criteria

A patient with SARI will be excluded if he/she:

- Has a **contraindication for the vaccine**—e.g., a severe reaction allergic to a previous dose of influenza vaccine, or a severe allergy to a component of the vaccine such as allergy to egg.
- Provided a respiratory sample:

- Specifically because of the case's **atypical presentation** or severity and not as part of routine surveillance;

– Had a previous **positive** laboratory test **for influenza** during the same season;
– Develops **symptoms after hospitalization**.

The reasons for excluding these SARI patients will be documented.

3.5.4. Influenza cases

– A case of influenza will be defined as a SARI case eligible for the evaluation with a respiratory sample positive for any seasonal influenza virus.
– The case shall be confirmed using reverse-transcription polymerase chain reaction (RT-PCR). All the participating national laboratories currently use standard RT-PCR procedures in testing for seasonal influenza [19].

It is recommended that each country detail the processes and procedures it follows to confirm an infection due to influenza or any other virus (if it collects such information) in its national protocol.

3.5.5. Preexisting conditions

In some countries of Central and South America, chronic diseases or preexisting conditions are a criterion for defining a target vaccination group. In such cases, it will be important for each country to indicate the diseases covered in the definitions.

The effectiveness analysis will consider anyone who suffers from at least one of the conditions reported in the SARI surveillance records to be a person with a preexisting condition. The lists of preexisting conditions is likely to vary from country to country, which means it will be important to include them in the national protocols. The preexisting condition status will be based on the information available on record and no further confirmation will be sought in clinical files or other sources.

To aggregate the data at the regional level, the following list will be used to reclassify the preexisting conditions reported by the countries. This list corresponds to the standard list for reporting vaccination coverage in the Americas (PAHO/UNICEF Joint Reporting Form) [20].

Table 5. List of preexisting conditions considered in the analysis of vaccine effectiveness, 2017	
1.	**Respiratory disease**
	a. Asthma
	b. Chronic bronchitis or emphysema
2.	**Heart disease**
	a. Atherosclerosis
	b. Cardiomyopathy/heart failure
3.	**Neurological developmental disorders**
	a. Cerebral palsy
	b. Muscular dystrophy
	c. Cognitive disorders
4.	**Metabolic disorders**
	a. Diabetes
5.	**Immune system disorders**
	a. HIV/AIDS
	b. Chemotherapy
	c. Organ transplant or immunosuppressive therapy
	d. Chronic use of corticosteroids
6.	**Chronic kidney disease with dialysis**
7.	**Chronic liver disease, especially with cirrhosis**
8.	**Morbid obesity**
9.	**Hematological disorders**
	a. Sickle-cell disease
	b. Thalassemia major
10.	**Children on long-term daily aspirin therapy (at risk for Reye's syndrome)**

3.6. Sentinel Surveillance of SARIs

Within the framework of sentinel surveillance, participating hospitals report SARI cases to the health authorities on a weekly basis. The reports include, at the very at least, the total number of SARI cases, regardless of whether a respiratory sample was taken, disaggregated by age groups and risk groups. The frequency of sampling depends on each country's guidelines and available laboratory resources. It may be as high as 100% of the SARI cases or 100% of the weekly SARI subgroups of (e.g., at-risk groups, patients in the intensive care unit, etc.) or a simple quota (e.g., five samples a week). In the case of a weekly quota, the methodology used to select patients for sampling may differ from country to country. It will be very important to document them in the national protocols (see **Annex 6, Selection of SARI Patients for Sampling in the Participating Countries**).

The samples are usually sent to the national reference laboratory (the national influenza center) for analysis. The evaluation protocol does not call for modifying any sampling procedure. It will be left to each country to decide whether to step up the frequency of their sampling of SARI patients or adapt their procedures if they consider that the change will be beneficial for national surveillance. The laboratory procedures for the diagnostic tests and for the collection, transportation, and storage of samples in the surveillance routine are adapted from the generic protocol for influenza surveillance PAHO-CDC [21; PAHO-CDC, 2009; PAHO 2014].

3.7. Case-finding

The SARI cases will be identified from among the patients who have presented at the participating hospitals during the evaluation period. Ideally, the surveillance personnel will conduct **active case-finding** to find eligible patients for the evaluation from among the patients admitted with respiratory symptoms in the various hospital units and hospitalization services (see **Error! Not a valid bookmark self-reference.**). Personnel will r eview the hospital admission records and consult with the clinical staff. They will also review laboratory records to identify patients with respiratory samples sent to the reference laboratory. In hospitals where active case-finding is not guaranteed on weekends, surveillance personnel will collect the information retrospectively every Monday from admission and discharge records. In the event of multiple SARI admissions, the first positive admission for influenza virus will be considered, or if all were all negative, the first admission for a SARI.

3.8. Controls

A control will be a SARI patient eligible for the evaluation whose RT-PCR test was **negative for influenza** with. *Note: A control may have had a sample that was positive for other respiratory viruses.*

In countries where it is not feasible to include all the patients who meet the definition of a case because of the field work involved, **three controls** will be selected at random from among the patients whose RT-PCR test was negative for influenza. They

should be from the same target group (e.g., adults 60 or over, or children aged 6 months to 5 years) and, ideally, they should also come from the same hospital. *They do not have to be the same age.*

If countries wish to include an additional **control group**, such as hospital controls admitted for non-respiratory causes, the process of selecting such controls should be documented in the national protocol. Having an additional control group can be valuable for validating the test-negative design and confirming the cases and controls within the hospital area.

3.9. Exposure (Vaccination against Influenza)

Definition of Vaccination Status

Full vaccination: An individual will be considered **vaccinated** against influenza if he/she received **one dose** of the **trivalent inactivated** vaccine, or, **in the case of previously unvaccinated children under 9 years old, two doses,** at least 14 days prior to the onset of symptoms [18, 19]. *This operational definition means that countries need to know the exact dates of vaccination and symptom onset.*

Partial vaccination: When a child received the vaccine *for the first time* more than 14 days prior to symptom onset but did not receive the second recommended dose for the season, he/she will be considered *partially vaccinated. If it is not possible to identify the children under 9 years old who were already vaccinated once, the entire group of children under 9 years old may potentially be regarded as receiving their first vaccination (i.e., no previous vaccine, or "vaccine-naïve").*

In 2017, all the participating countries have used the trivalent inactivated vaccination recommended by WHO. If countries include other vaccine types in subsequent seasons, a distinction will be made in the in protocol.

Verification of Vaccination Status

Most SARI surveillance records include fields for data on the individual's influenza vaccination history, including whether the person has been vaccinated (yes/no) and the date of the latest dose received. The current updates to the PAHO guidelines for SARI

surveillance recommend including the number of doses given to children when they were first vaccinated—information that had not been previously collected as part of SARI surveillance.

Since the vaccination history of individuals has tended to be incomplete on the surveillance records [REVELAC-i, 2012-2013], it is recommended to emphasize the importance of checking patients' vaccination cards when they are hospitalized, especially in countries that do not have a nationwide electronic nominal registry. If this information cannot be checked at the time of admission to the hospital, the surveillance epidemiologist can review the patient's clinical file or consult staff with the Expanded Program on Immunization (EPI) to see if he/she is on record with the program using his/her name, date of birth, and/or address. While national electronic nominal registries can be checked in some countries (e.g., Chile, Colombia, and Costa Rica), others may have paper registries such as a daily record, vaccination books maintained by health promoters, vaccination card files, etc.

Occasionally, EPI personnel may look for a person in the community if his/her registry data do not confirm any exposure or vaccination dates, but only if the country's health authority has defined such an action as part of surveillance or the EPI process. Vaccination cards will be reviewed during these visits.

Subjects will be considered **vaccinated** against influenza if:

— They show the surveillance personnel a vaccination card with evidence of vaccination for influenza;

Or:

— Their SARI surveillance file states that they have been vaccinated (based on a vaccination card, not merely a verbal report);

Or:

— They have been recorded as vaccinated in the national EPI vaccination registry.

Patients will be considered **not vaccinated** for influenza if they states that they did not receive the influenza vaccine and:

— Their SARI surveillance report states that they have not been vaccinated (based on their vaccination card);

Or:

— Their name is not on record as being vaccinated in the national (EPI) vaccination registries;

Or:

— Their vaccination card does not show vaccination for influenza and the card contains information on other vaccines or a record of past vaccination for influenza.

Patient's vaccination status will be considered uncertain ("no information") if:

— Their SARI surveillance report does not state whether they were vaccinated;

Or:

— They do not have a record in the national vaccination registries;

Or:

— They do not have a vaccination card.

In addition to following the definitions indicated above, it is important for **each country to document how an unvaccinated patient is classified**. In principle, unvaccinated patients have no proof that they were not vaccinated and should be classified as "no information." If a country regards the absence of a vaccination record as "unvaccinated", they will have to report this information when submitting their data so that it is taken into account in interpreting their results.

An example of the procedure for capturing a patient's vaccination history can be seen in **Annex 7**, which describes the capture of information on influenza and pneumococcal vaccination in a multicenter evaluation of influenza vaccine conducted in Paraguay in 2013.

To verify the quality of information with regard to exposure, it is recommended to select a random sample of 10% of the patients enrolled in the evaluation and confirm their vaccination history using the various information sources available to compare their vaccination status (including the number of doses in children under 9 years old) and dates of vaccination against the most reliable source (e.g., nominal vaccination registry or vaccination card). If countries that have conducted studies on the quality of previously

used information sources could share their findings with the regional team, it would be very useful for understanding and interpreting the data on vaccine effectiveness.

3.10. Possible Confounding Factors and Effect Modifiers

Measurement of a vaccine's effectiveness can be affected by confounding factors or effect modifiers. There could be a distortion in the effect observed versus the real effect due to unequal distribution of a confounding variable in the groups studied (confounding effect). It is also possible to acquire an unexpected effect—one that is real nevertheless—as a product of the simultaneous interrelationship of two or more factors associated with the effect being studied (effect modification or interaction).

In the case of confounding, the effect of the exposure is mixed with the effect of this other variable, creating a bias. Thus, the confounding factor is related to the exposure (in this case vaccination for influenza) but not the result thereof. At the same time, it is related to the disease (in this case, SARI due to influenza). A common example in the evaluation of the vaccines is "confounding by indication." When effectiveness is being measured in observational studies, it is possible that the people who received the vaccine by indication may not be the same as those who would have received it without medical indication. Although the comparison group includes people with the same disease who did not receive the vaccine, there may be differences between the two groups in terms of severity of the disease or risk factors.

An effect modifier is a factor that it is related to the disease but, unlike a confounding factor, it causes a real change in the correlation. It has to do with effects that are truly different according to the groups defined by this variable—for example, the difference in effectiveness between children and older adults. To cite another example, different effects have been documented for many vaccines a because of the characteristics of the subjects' immune systems.

In addition to age and sex, the following factors reported in the scientific literature will be evaluated as potential confounding factors or effect modifiers in estimating the effectiveness of the influenza vaccine [18]:

a. <u>Preexisting conditions</u>

The absence or presence of preexisting conditions will be considered. Information on specific diseases will be collected for grouping or adding them to the list in exploring the effect of these conditions in greater detail. Countries should specify the sources of their information on preexisting conditions and how this information was collected—whether during surveillance, from a review of the clinical file, or based on the patient's report during a medical consultation in answer to the question "Do you have any chronic disease?"

b. Previous vaccinations

Data will be collected on vaccination for seasonal influenza in the previous season. Available studies at the international level differ in their interpretation of the effect of previous vaccinations on vaccine effectiveness. It is hoped that the present evaluation will contribute evidence for improving our understanding of its possible effect. Also, previous pneumococcal vaccination will be documented as a proxy for the level of access to routine vaccination programs. This information will be obtained using the same process that was enlisted for capturing the history of vaccination for influenza. Additional efforts to collect this variable will not be recommended.

3.11. Possible Errors in the Classification of Cases and Controls

The use of an antiviral prior to respiratory sampling can affect the laboratory result, resulting in the classification of an influenza case as a control. To avoid this misclassification, data on medication will be collected and patients who received an antiviral will be excluded from the analysis prior to sampling.

Misclassification of patients with unknown vaccination status as "unvaccinated" can affect the assessment of vaccine effectiveness if this systematic error is also associated with infection due to influenza. In other words, if the probability of testing influenza(+) is greater for patients classified as "unvaccinated," there would appear to be an increase in vaccine effectiveness.

For children being vaccinated for the first time, two doses are recommended to achieve adequate protection. However, it can be a challenge to document the number of doses administered to a child within the surveillance framework. If children who received

only one dose are classified as “vaccinated,” vaccine effectiveness can be underestimated when partially immunized children develop a case of influenza.

3.12. Information to be Collected

Data will be collected on the patients’ sociodemographic characteristics, clinical and laboratory findings, and vaccination history based on the variables in the national SARI surveillance records. *Note that if a country opts for a more complete survey that involves research, this should be specified in the national protocol.*

At the regional level, the following **general information** will be collected:

- Country
- Type of SARI surveillance (sentinel or universal)
- Region
- Hospital
- Vaccine type and formulation used
- Vaccine brand(s) used

In addition, the following information will be extracted from the SARI surveillance records or the country’s corresponding databases:

- **Demographic**
  - Age
  - Sex
- **Clinical**
  - Date of symptom onset
  - Hospital admission and discharge dates
  - Hospitalization in intensive care (yes/no)
  - Condition upon discharge (living/deceased)
  - Preexisting condition (has at least one preexisting condition (yes/no); specific preexisting conditions based on the country’s SARI surveillance list

- Antiviral treatment administered to date (*specify in the national protocol whether the variable on record refers only to antiviral treatment prior to sampling*)
- Type of antiviral administered (optional)

- **Vaccination history**
  - Influenza vaccination during the current season (2017) and date of vaccination
  - Number of doses in the case of children <9 years
  - Influenza vaccination during the previous season (2016) *(use only an evidence-based source for the information, either the patient's vaccination card or the nominal immunization registry)*
  - Pneumococcal vaccination (whether or not it is up to date according to the national schedule)
  - Information source used in determining the vaccination status (surveillance record, clinical file, nominal registry, vaccination card, or other EPI documents or registries)
- **Laboratory data**
  - Sampling date
  - Result of RT-PCR test for influenza
  - Virus type
  - Influenza A subtype
  - Influenza B lineage
  - Positivity finding for other respiratory viruses

See **Annex 3** on the variables collected in the evaluation, together with their definitions and codes. *Note: All dates should be recorded in dd/mm/yyyy format.*

Since the feasibility of collecting all the variables varies from country to country, some of them have been defined as critical for estimating vaccine effectiveness. Patients with data missing for one or more of these variables shall be excluded from the analysis.

- Age

- Date of symptom onset
- Sampling date (in dd/mm/yyyy format)
- RT-PCR result for influenza (positive or negative)
- Presence of at least one preexisting condition
- Vaccination for current seasonal influenza (2017)
- Date of vaccination for current influenza
- Number of vaccine doses in the case of children <9 years old

The following additional variables are considered important but have not been classified as critical because they are difficult to collect in the field and could therefore significantly reduce the size of the sample:

- Type of preexisting conditions. This information would make it possible to explore the differences between cases and controls in greater detail and establish a score representing an approximation of the severity of the preexisting conditions.
- Administration of an antiviral prior to sampling (antiviral treatment and date administered)
- Influenza type or subtype (e.g., A(H3N2)). If there is a predominant type/subtype during the season and sufficient data are available, this information would make it possible to explore the vaccine's effectiveness by type or subtype.

Countries that include **pregnant women** as a target group for the evaluation should collect the following additional information:

- Pregnant (yes/no)
- Week of pregnancy
- Trimester when vaccinated

For countries that choose to undertake <u>research</u>, it is suggested that they explore the following additional variables:

- **Demographic characteristics**
  - Ethnic group, based on the definition used in the country
  - Level of education

- Total number of children living in the household

- **Clinical information**
  - Smoking history
  - Barthel Index in the case of older adults (measure of functional independence)
  - Total hospitalizations for chronic disease in the last year
- **Vaccination history**
  - Vaccination for influenza in the last two years

3.13. Sample Size considerations

A sufficient number of samples should be obtained to ensure that there are enough cases and controls in the analysis strata to obtain precise estimates. The following calculation of the sample size is based on a ratio of 1:3—in other words, three controls for every case. At the regional level, it is anticipated that at least **99 cases** of influenza in **children** and **297 child controls**, all with complete data, will need to be identified in order to show 50% effectiveness, or **176 cases** and **582 controls** in **older adults** in order to show 40% effectiveness (based on 2013 results), assuming **50%** vaccination coverage in the source population for both groups and a power of 80% for the evaluation.

If the seasonal influenza positivity rate is assumed to be **15%** in patients with SARI (based on previous surveillance data), the countries as a group will need to identify **at least to 660 children and 1,173 older adults with SARI, all with complete data,** from the participating hospitals during the evaluation period. The target sample size for each country will depend on national vaccination coverage of the population in the included groups, total number of participating sentinel hospitals (number of hospitals, patient volume, frequency of sampling, and hospital performance, as well as circulation of the virus at the local level).

If the country wants to have a national estimate, it will need to identify **660 children and 1,173 older adults with SARI** exclusively in its hospitals. Table 5 summarizes the number of cases and controls needed for each target group vis-à-vis vaccination coverage and anticipated effectiveness. It is important to keep in mind that administrative coverage

methods usually generate higher percentage estimates than the figures that would be obtained in a hospital population based on a review of vaccination documents [REVELAC-i 2012-2014].

Precision may be affected if the size of the sample is smaller, if vaccination coverage is lower, if real vaccine effectiveness is less than what has been assumed, or if there is an important effect modifier for the age group. Any of these circumstances can limit the conclusions to merely a hypothesis or to an interpretation based on point estimates of vaccine effectiveness.

Table 5. Variations in size of sample for the evaluation relative to anticipated vaccination coverage and vaccine effectiveness assuming 3 controls per case, a power of 80%, and a type I error of 0.05

	Efectividad esperada de la vacuna contra influenza											
	20%		30%		40%		50%		60%		70%	
Cobertura vacunal en la poblacion	**casos**	controles	**casos**	controles	**casos**	controles	**casos**	controles	**casos**	controles	**casos**	controles
20%	**1469**	4407	**616**	1848	**326**	978	**195**	585	**126**	378	**86**	258
30%	**1091**	3273	**450**	1350	**235**	705	**138**	414	**87**	261	**58**	174
40%	**929**	2787	**378**	1134	**193**	579	**112**	336	**70**	210	**46**	138
50%	**869**	2607	**348**	1044	**176**	582	**99**	297	**60**	180	**38**	114
60%	**881**	2643	**348**	1044	**171**	513	**96**	288	**57**	171	**34**	102
70%	**980**	2940	**381**	1143	**184**	552	**100**	300	**57**	171	**33**	99
80%	**1252**	3756	**478**	1434	**227**	681	**120**	360	**67**	201	**38**	114

*3 controles, potencia de 80%, 5% error alpha, prueba de Fisher exact.

3.14. Data Collection and Integration

The primary source of information for the evaluation will be SARI surveillance data. The data may be on paper (SARI surveillance records), in electronic format (surveillance databases at the local or national level), or in Web-based electronic format (national online system). If necessary, the vaccination history will be completed by consulting EPI registries or other documents (see **0**, Verification of Vaccination Status). If the laboratory data have not been recorded on a regular basis, they will be recovered from the corresponding databases.

The data will be entered using an online data management system that has an interface for keying in data from paper records or uploading data stored in existing digital database systems. The country will decide on the most appropriate method and the regional team will be available to provide technical assistance in adapting the database

manager to the existing systems. Diagram 1 summarizes the flow of data collection and aggregation.

Flow Chart 1. Flow of data for aggregation and regional analysis [REVELAC-i 2013]

Database Manager

The REVELAC-i database manager uses Web-based technologies, a Linux-Apache-MySQL-PHP (LAMP) platform and Model-View-Controller (MVC) architecture. It is designed to facilitate the following operations:

- Collection and validation of data on the variables needed for the evaluation, whether classified as critical or optional;
- Integration of data from the countries participating in the evaluation to create a single repository; and
- Export of the integrated data in Microsoft Excel format for import into STATA or other programs for analysis.

The software has four features for meeting these objectives:

- **Data entry**. This feature makes it possible to key in data on the evaluation variables by country and **evaluation year**.[1] It also includes an automated influenza

[1] **Evaluation year** is defined as the year that includes the evaluation period established for the season.

surveillance information system for participating countries that do not have one. In addition, it has field control options that help to minimize data entry errors.

- **Data upload**. This feature makes it possible to import data from a file in comma-separated values (CSV) format.[2] It was incorporated into the system to avoid duplicated entries from countries that have an automated surveillance information system that contains the variables requested for the evaluation. The feature is used when a system offers the possibility of extracting the variables from the database, turning them into the required values, and generating a file in CSV format.
- **Data export**. This option makes it possible to export data in Microsoft Excel format with the values and formats needed for the analysis. The data can be exported by country, year of evaluation, or all countries and year of evaluation.
- **Maintenance**. This feature makes it possible to configure the starting and ending dates of the vaccination period in each country for every year of the evaluation, thus ensuring that the vaccination dates entered or uploaded fall within the corresponding vaccination period.

The software has a security system based on user roles which is administered through the **CAUS** console.[3]

The data manager allows users who have been granted the privilege to review the input data for missing information, errors, and inconsistencies. In the case of data entry, these users can modify the information previously entered directly into the system. In case of data uploads from a surveillance database, the review/modification is done in the source file itself and the changes are captured in the next upload. The feature also allows national coordinators to export their national data for analysis at any time.

---

[2] A standard format for transferring files between database managers.

[3] System Users Administration Console (Consola de Administración de Usuarios del Sistema). Standardized software developed by the information technology Group of the FLU-IT Project under a cooperation agreement between TEPHINET and CDC for the management of users of Web- and LAMP-based technology. This software makes it possible to assign access to different application features and functions based on the definition of roles.

Annex 4 illustrates the flow of data entry and data upload to the REVELAC-i database management system.

3.15. Monitoring Data Quality

During the data collection process, the national team will be responsible for monitoring the coverage and quality of the data. The national teams will organize the required activities for strengthening surveillance. The strategies will depend on each country and may include any of the following:

- Promote active SARI case-finding, with emphasis on daily review of new registry inputs, shipments of samples to the reference laboratory, and visits to hospital services to identify new SARI cases with the support of medical personnel (screening);
- Raise awareness among surveillance personnel about the importance of completeness and quality of the critical variables in the surveillance records through training, supervisory visits, periodic monitoring, and feedback;
- Make certain that input files are reviewed by surveillance personnel on a daily basis to identify any errors or missing information and obtain the latter from patient hospital records;
- Make certain that patients' vaccination cards are reviewed when they are in the hospital to obtain precise and up-to-date information on their vaccination status, especially in countries that do not have national nominal registries;
- Establish clear and timely mechanisms for coordination with surveillance personnel and the EPI to obtain the vaccination history of patients; and
- Document any other strategies in the national protocols.

3.16. Data Analysis

Data cleaning

The national team will review the data for possible errors or missing information. The national coordinator will coordinate retrieval of the data and arrange for any needed corrections prior to the transmission to the regional team. If necessary, the national team

will send additional information to help the regional team interpret the data (field observations may be included).

The regional team will use frequency tables and graphs to detect erroneous or illogical values or missing data. They will also review the data for inconsistencies (e.g., sampling dates earlier than onset of symptoms), if necessary consulting the national teams for clarification to validate the data or pointing out any need for corrections. All changes in the data will be documented and stored separately from the raw data in the original database. Any changes in the classification codes (e.g., a person classified as "vaccinated" who received the vaccine two weeks after symptom onset, then reclassified as "unvaccinated") will also be documented.

Selection of Patients for Analysis

The regional team will confirm whether the enrolled patients meet the inclusion criteria and will exclude those that meet the exclusion criteria (see 0). Controls with symptom onset prior to the first confirmed case of influenza or two weeks after the last confirmed case of influenza in each country will be excluded. For estimating vaccine effectiveness, patients with less than two weeks between vaccination and onset of symptoms (and therefore with a protection status that is difficult to classify) will also be excluded, and those who received the vaccine after the onset of symptoms will be considered unvaccinated.

The initial analysis will be conducted by target group based on regional data. If the sample size is sufficient, further analyses will be limited to:

- Patients with respiratory samples collected 4-7 days after symptom onset;
- Phases of the epidemic, dividing the season into two phases based on the distribution influenza cases;
- Strata of time since vaccination (at least two strata of approximately three to four months between vaccination and symptom onset);
- Subregions (Central versus South America);
- Influenza A(H1N1), A(H3N2), or B as an outcome variable;
- Influenza B Victoria or Yamagata lineage as an outcome variable;

- Another control group in the countries that have included an additional group.

Descriptive and Univariate Analysis

The cases and controls will be described in terms of their sociodemographic characteristics, clinical findings, and vaccination history. The characteristics will be compared using the chi-squared test, Fisher's exact test, t-test, or Mann-Whitney U test, depending on the type of variable and its distribution. The correlation between each person's characteristics and their 2017 influenza vaccination status will be measured for both cases and controls.

Measurement of the Effect (Vaccine Effectiveness)

Vaccine effectiveness (VE) will be calculated as 1 minus the vaccination odds ratio in cases versus controls with an estimated confidence interval of 95% [CI 95%]. VE will be calculated based on full vaccination and, in the case of children, on both full and partial vaccination ("has received at least one dose of vaccine in the current year").

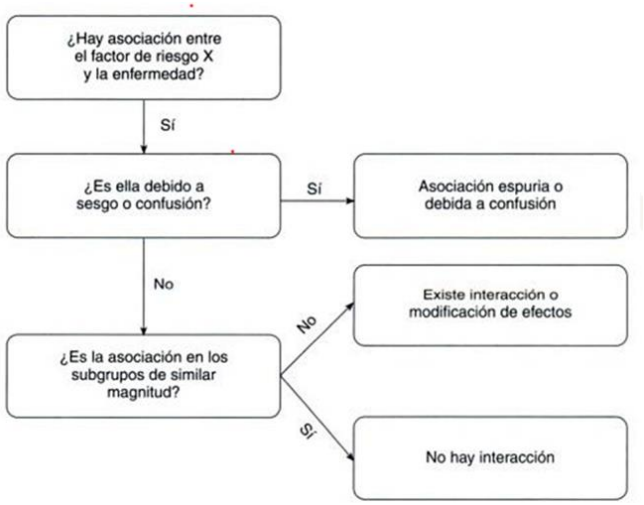
Stratified Analysis

The presence of effect modifiers and confounding factors will be examined (see 0 above).

Effect modification (e.g., due to the presence of preexisting disease) will be evaluated by comparing the odds ratio (OR) in the variable strata (e.g., stratum "does not suffer from any preexisting condition and stratum "suffers from at least one preexisting condition). If the difference in the odds ratios (ORs) between the two strata is statistically significant (according to the homogeneity test), the variable will be regarded as a potential effect modifier.

Once any effect modification is ruled out, we will evaluate the presence of confounding by determining whether the potential confounding factors are associated with both vaccination and the disease and comparing the raw or adjusted odds ratio (Mantel-Haenszel) for each factor. If the relative difference between the crude and adjusted estimates exceeds 20%, we will use the adjusted odds ratio (see Flow Chart 2).

Flow Chart 2. Conceptual framework for the definition of interaction (effect modification) based on the homogeneity concept



Source: Textbook. Rothman 2008.

Multivariate Analysis

In case and control studies, a statistical logistic regression model makes it possible to control for confounding factors and examine multiple interactions between factors. This model will be used to calculate the odds ratio standard error and look for multicolinearity between the variables. Interactions between variables will be tested using the likelihood ratio test (*which makes it possible to test the hypothesis of independence of the effect of the vaccine factors*), or else the Wald test, and they will be included in the model with a significance level of 5%. In addition to statistical significance, other criteria for the inclusion of interactions or factors in the model will be studied, such as the magnitude of the odds ratio. Based on previous analyses and variables collected, we propose to examine the following model:

$$\text{Case } (0/1)_{2017} = \beta_0 + \beta 1 \text{ And} + \beta 2 \text{ CP} + \beta 3 \text{ MIS} + \beta 4 \text{ Vi}_{2017} + \beta 5 \text{ Vn} + \beta 6 \text{ Vipr} + \beta 7 \text{ P}$$

where*:*

- E = age group (within a target group)
- CP = presence of a preexisting condition (0/1)
- MIS = month of SARI symptom onset
- Vi_{2017} = 2017 influenza vaccine
- Vn = up to date on pneumococcal vaccine

- Vipr = influenza vaccine received the previous year
- P = country, always to be included in the analysis
- β = vaccine exposure coefficient

The model will be adjusted to reflect the month of symptom onset and any confounding or pertinent factors identified using logistic regression. To obtain a regional estimate, a random effects meta-analysis will combine all the county estimates. If an effect modifier is identified, adjusted estimates for each stratum of this variable (stratum models) will be presented.

3.17. Dissemination of the Results

The preliminary results will be reviewed with the national REVELAC-i teams for their validation and approval. The regional team will prepare a draft regional manuscript on behalf of REVELAC-i, which will be reviewed by the national teams. The final manuscript will be shared with the health authorities and, once it is published, with the collaborating public health organizations in the Region. The regional team will work with the countries that wish to prepare national manuscripts or reports. In such cases, the national coordinator will be in charge of drafting the manuscript as its principal author.

In addition, feedback will be provided at the national level in the format to be defined by each country, such as debriefings with the personnel who participated in the evaluation. The regional team may decide to present the regional results in scientific meetings or conferences on public health. Any presentation will be subject to prior authorization by the countries, as would any publication. Finally, once the countries have given their approval, the results will be shared confidentially with the Global Influenza Vaccine Effectiveness (GIVE) group, which compiles information on the selection of vaccines strains for WHO meetings.

4. LOGISTIC ASPECTS

4.1. Coordination

The multidisciplinary and interinstitutional teams created within the REVELAC-i network will coordinate planning and implementation of the evaluation at the national level. These teams include technical personnel from the influenza surveillance system,

immunization programs, influenza reference laboratories, and statistics offices, as well as the focal points for influenza immunization and surveillance in the local PAHO/WHO Representative Offices. To facilitate organization of the activities, multidisciplinary teams may designate a principal or responsible coordinator. Each national team will develop a plan of work and define the roles and responsibilities of the members of the team. The organization chart may be appended to the national protocol. The national coordinators will send letters to the participating hospitals inviting the establishments to participate in the exercise, along with a copy of the national protocol.

The PAHO-CDC regional team will provide technical assistance while the project is being conducted in the countries. The project coordinator will update the generic protocol to incorporate any changes made by the national teams and prepare the tools needed for data collection with support from the information system team. Regional data will be added in preparation for the initial diagnosis on 31 July and for the preliminary analysis once a sufficiently large sample is obtained.

The final analysis will be done after all the data have been delivered at the end of the evaluation period (December 2017 - January 2017). The regional team will coordinate meetings with the national teams to share feedback. Depending on the criteria defined by each country, the meetings may include personnel at the national, regional, or local level who participated in the evaluation and personnel from the hospitals, the EPI program, and the laboratories.

4.2. Training

Since this evaluation is based on influenza surveillance, the project will encourage the national teams to organize training sessions for SARI surveillance and EPI personnel, emphasizing the importance of data quality and completeness, including the patients' vaccination history. If needed, the national teams may request support or materials from the regional team.

5. ETHICAL CONSIDERATIONS

5.1. Fulfillment of Ethical Requirements

The evaluation will be conducted in compliance with applicable ethical requirements, including Good Epidemiological Practice (GEP) (*IEA Guidelines for Proper Conduct in Epidemiologic Research*; available from http://ieaweb.org/guidelines/] other applicable guidelines, privacy requirements for research subjects, and the ethical principles set forth in the Declaration of Helsinki.

This evaluation is observational, based on data collected within the framework of surveillance. Hence, each country's authorities and ethics committees will define the necessary approvals prior to preparation of the evaluation. The CDC Public Health Ethics Committee, based on its review of the protocol, has ruled that the proposed multicenter evaluation is an evaluation program and not a research project.

The evaluation will not interfere with normal vaccine delivery to target populations or with routine clinical management of the SARI patients.

5.2. Confidentiality of the Data

Only the surveillance personnel will have access to the personal information about the patients (identification number, name, medical record number, contact details). All sociodemographic, clinical, epidemiological, and laboratory data for each patient, as well as information on the samples collected, will be entered in the evaluation database using codes specifically for the project and no other personal identification.

5.3. Indirect Benefits for Participants in the Evaluation

It is possible that the evaluation may help to strengthen the quality and completeness of influenza surveillance data and that it will raise awareness among members of the evaluation's clinical team regarding the benefits of vaccination in the target groups. At the same time, the evidence generated could contribute indirectly to the health of the populations involved.

6. TIMETABLE OF PROJECT ACTIVITIES

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

Dates	Activities
April - May 2017	Review of the protocol by the national teams, training, and planning of monitoring and supervision
May - August 2017	Project implementation and first submission of data by 31 August for early estimate (including report GIVE for WHO)
September - December 2017	Ongoing data collection; data analysis; validation with countries and corrections
January 2018	End of season and submission of final data for the 2017 season by 15 January (contribution to the GIVE report for WHO)
February - March 2018	Completion of 2017 estimates with the national teams; feedback to the field team; presentation of the findings to the health authorities

7. BUDGET AND FINANCING

This project is based on existing resources in the participating countries with occasional financial support from the PAHO Immunization Unit or TEPHINET through cooperative agreements with the CDC Influenza Division. Such support may include materials and equipment for sentinel monitoring, training of the teams, field work costs for verifying the vaccination status of the evaluation subjects, and human resources for integrating the surveillance and immunization data.

8. REFERENCES

1. Cheng PY, Azziz-Baumgartner E, Iuliano D, Alencar AP, Bresee J, Oliva O et al. Widdowsona
2. Savy V, Ciapponi A, Bardach A, Glujovsky D, Aruj P, Mazzoni A, et al. Burden of influenza in Latin America and the Caribbean: a systematic review and meta-analysis. Influenza and other respiratory viruses. 2013 Nov;7(6):1017-32. PubMed PMID: 23210504.
3. Azziz-Baumgartner E, Cabrera AM, Chang L, Calli R, Kusznierz G, Baez C, et al. Mortality, severe acute respiratory infection, and influenza-like illness associated with influenza A(H1N1)pdm09 in Argentina, 2009. PloS one. 2012;7(10):e47540. PubMed PMID: 23118877. Pubmed Central PMCID: 3485247.
4. Freitas AR, Francisco PM, Donalisio MR. Mortality associated with influenza in tropics, state of sao paulo, Brasil, from 2002 to 2011: the pre-pandemic, pandemic, and post-pandemic periods. Influenza research and treatment. 2013;2013:696274. PubMed PMID: 23844285. Pubmed Central PMCID: 3694379.
5. Clara W, Armero J, Rodriguez D, de Lozano C, Bonilla L, Minaya P, et al. Estimated incidence of influenza-virus-associated severe pneumonia in children in El Salvador, 2008-2010. Bulletin of the World Health Organization. 2012 Oct 1;90(10):756-63. PubMed PMID: 23109743. Pubmed Central PMCID: 3471049.
6. Organización Mundial de la Salud 2005. http://www.who.int/immunization/wer8033influenza_August2005_position_paper.pdf
7. Organización Mundial de la Salud 2010. Virus recomendados para vacunas de influenza para uso en el 2014 en el hemisferio sur, http://www.who.int/influenza/vaccines/virus/recommendations/2014_south/en/.
8. Orenstein EW, De Serres G, Haber MJ, Shay DK, Bridges CB, Gargiullo P, et al. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. International journal of epidemiology. 2007 Jun;36(3):623-31. PubMed PMID: 17403908.
9. WHO. Prevention and control of influenza pandemics and annual epidemics. Fifty-sixth World Health Assembly, Resolution WHA56.19.28. Geneva2003. Available from: http://apps.who.int/gb/archive/pdf_files/WHA56/ea56r19.pdf.

10. Weekly Epidemiological Record (WER) for 23 November 2012, vol. 87, 47 (pp.461–476) includes: Vaccines against influenza—WHO position paper – November 2012. http://www.who.int/entity/wer/2012/wer8747.pdf
11. Ropero-Alvarez, A., H. Kurtis, et al. (2009). "Expansion of seasonal influenza vaccination in the Americas." BMC Public Health **9**(1): 361.
12. Porras-Ramirez A., Alvis-Guzmán N., Rico-Mendoza A., Alvis-Estrada L., Castañeda-Orjuela C.A., Velandia-González M.P., de la Hoz-Restrepo F. Cost effectiveness of influenza vaccination in children under 2 years old and elderly in Colombia. Rev Salud Publica (Bogota). 2009 Oct ;11(5):689-99.
13. Arguedas, Machado, Morice. Vacunación contra influenza en grupos de riesgo en Costa Rica: una decisión basada en la evidencia, Boletín Informativo PAI (OPS), Vol.XXVI, No. 3 (Junio 2004). Pan American Health Organization: Influenza Vaccination Among Risk Groups in Costa Rica: An Evidence-based Decision. EPI Newsletter 2004, XXVI(3):2-4.]. (*Vacunación contra influenza en grupos de riesgo en Costa Rica: una decisión basada en la evidencia, Boletín Informativo PAI (OPS), Vol.XXVI, No. 3 (Junio 2004)).*
14. Gutierrez EB, Li HY, Santos AC, Lopes MH. Effectiveness of influenza vaccination in elderly outpatients in Sao Paulo city, Brasil. Revista do Instituto de Medicina Tropical de Sao Paulo. 2001 Nov-Dec;43(6):317-20. PubMed PMID: 11781600.
15. De Oliveira Jde F, Boing AF, Waldman EA, Antunes JL. Ecological study on mortality from influenza and pneumonia before and after influenza vaccination in the Northeast and South of Brasil. Cadernos de saude publica. 2013 Dec;29(12):2535-45. PubMed PMID: 24356698.
16. Mesa Duque SS, Perez Moreno A, Hurtado G, Arbelaez Montoya MP. [Effectiveness of an influenza vaccine in a working population in Colombia]. Revista panamericana de salud publica = Pan American journal of public health. 2001 Oct;10(4):232-9. PubMed PMID: 11715169. Efectividad de una vacuna antigripal en una poblacion laboral colombiana.
17. Orellano PW, Reynoso JI, Carlino O, Uez O. Protection of trivalent inactivated influenza vaccine against hospitalizations among pandemic influenza A (H1N1) cases in Argentina. Vaccine. 2010 Jul 19;28(32):5288-91. PubMed PMID: 20541580.
18. Valenciano, M., E. Kissling, et al. (2010). "Study designs for timely estimation of influenza vaccine effectiveness using European sentinel practitioner networks." Vaccine 28(46): 7381-7388.
19. Berman L. CDC Real-time RT-PCR Protocol for Detection and Characterization of Influenza 2012; Virus Surveillance and Diagnosis Branch, June 8, Influenza Division.
20. Pan American Health Organization. Annual Immunization Data Collection in the Americas: PAHO EPI Tables Meet the WHO/UNICEF Joint Reporting Form. Available from: http://www.paho.org/immunization/toolkit/resources/reporting-monitoring/EPI-Newsletter-Annual-Immunization-Data-Collection-in-the-Americas.pdf?ua=1

21. PAHO-CDC Generic protocol for influenza surveillance, 2009. http://new.paho.org/col/index.php?option=com_docman&task=doc_details&gid=181&Itemid=99999999
22. Gross PA, Russo C, Dran S, Cataruozolo P, Munk G, Lancey SC. Time to earliest peak serum antibody response to influenza vaccine in the elderly. Clinical and diagnostic laboratory immunology. 1997 Jul;4(4):491-2. PubMed PMID: 9220171. Pubmed Central PMCID: 170557.
23. Vaccines against influenza WHO position paper—November 2012. Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations. 2012 Nov 23;87(47):461-76. PubMed PMID: 23210147.
24. Valenciano M, Ciancio BC, Moren A, the influenza vaccine effectiveness working group. First steps in the design of a system to monitor vaccine effectiveness during seasonal and pandemic influenza in EU/EEA Member States. Euro Surveill. 2008;13(43):pii=19015.
25. Kissling E, Moren A, Valenciano M — EpiConcept, Paris, France commissioned by the European Centre for Disease Prevention and Control. Protocol for case-control studies to measure influenza vaccine effectiveness in the European Union and European Economic Area Member States (http://ecdc.europa.eu)**.**
26. Kissling E, Valenciano M, Falcão JM, Larrauri A, Widgren K, Pitigoi D, Oroszi B, Nunes B, Savulescu C, Mazick A, Lupulescu E, Ciancio B, Moren A. "I-MOVE" towards monitoring seasonal and pandemic influenza vaccine effectiveness: lessons learnt from a pilot multi-centric case-control study in Europe, 2008-9. Euro Surveill. 2009;14(44):pii=19388. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19388
27. Valenciano M., E. Kissling, et al. (2011). "Estimates of Pandemic Influenza Vaccine Effectiveness in Europe, 2009–2010: Results of Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) Multicentre Case-Control Study." PLoS Med **8**(1): e1000388.
28. Rothman KJ, Greenland S, Las T. Modern Epidemiology. 3rd ed. Philadelphia :Lippinicott Williams & Wilkins, 2008.

The primary reference for this protocol is the generic protocol used for the European I-MOVE Network case and control study on estimating the effectiveness of the influenza vaccine, shared by its authors. https://sites.google.com/site/epiflu/

ANNEXES

ANNEX 1. Indicators of Surveillance System Performance

Steps in sentinel surveillance	Indicators related to surveillance and evaluation	Indicator	Structure or calculation	Target
Step 1 Identification of hospitalized patients who meet the definition of a SARI case	Percentage of weeks with timely reporting of denominators	Timely reporting of denominators	(Number of epidemiological weeks in which denominators were reported on a timely basis / total epidemiological weeks covered by the report) x 100	80%
	Percentage of hospitalized SARI cases captured by the surveillance system	Underreporting	(SARI cases reported during the period / cases identified during the period through active case-finding) x 100	80%
	Median interval in days between date of hospitalization and date of notification	Timely reporting of cases	Median interval (in days) between date of hospitalization and date of notification	1 day
Step 2 Form for collecting and entering the data	Percentage of cases investigated and closed	Coverage of case-finding	(Total SARI cases fully investigated and closed / total cases reported and discharged) x 100 **** Fully investigated and closed" means that all the required clinical and epidemiological data were obtained, tests were performed to establish the etiological diagnosis; and the patient was either discharged or died.***	90%
Step 3 Taking of respiratory tract samples and results of the tests	Percentage of SARI cases from which a sample was taken	Coverage of SARI cases from which a sample was obtained	(Number of SARI cases from which a sample was taken / number of SARI cases with valid criteria for sampling) x 100 **** The samples should be taken within the ten days of symptom onset.***	90%
	Percentage of good quality samples received	Quality of the samples	(Number of good quality samples received / total samples properly received) x 100 **** "Good quality" means that the samples were properly obtained, preserved, and transported up until their arrival at the laboratory.***	90%
	Percentage of processed good quality samples processed	Coverage of processing	(Number of samples processed / total of samples properly received) x 100	90%
	Median interval between date of hospitalization and date on which the sample was taken	Timely sampling	Median interval (number of days) between date of hospitalization and date on which the sample was taken	2 days
	Median interval between date sample was taken and date the sample was received in the laboratory	Timely receipt of the samples	Median interval (number of days) between date on which the sample was taken and date the sample was received in the laboratory **** If the date of receipt is unknown, use the date on which it was dispatched for this indicator.***	1 day

	Median interval between date of receipt of the sample and date on which processing started	Timely processing	Median interval between date the sample was received in the laboratory and date on which it was processed	3 days
	Median interval between date of receipt of the sample and date of delivery of the results	Timely delivery of results	Median interval between date of receipt of the sample and date of delivery of the results	3 days
	Percentage of SARI cases treated in an intensive care unit from which a sample was obtained	Coverage of SARI cases treated in intensive care units from which a sample was obtained	(Number of SARI cases treated in intensive care units from which a sample was obtained / number of SARI cases treated in intensive care units) x 100	100%
	Percentage of patients dying of SARI from whom a sample was obtained	Coverage of deaths from SARI from which a sample was obtained	(Number of patients dying of SARI from whom a sample was obtained / number of deaths from SARI) x 100	100%
Step 4 Data analysis and interpretation	Number of cases reported monthly			
	Number of samples submitted monthly			
	Percentage of samples submitted that test positive for influenza			
Step 5 Dissemination of data and results	Percentage of weeks in which are sent data to the national or regional levels	Timely reporting		80%
	Timeliness of the data presented in the weekly reports on influenza surveillance	Timely reporting	Number of weeks between the current epidemiological week and the week corresponding to the data reported	< 2 weeks

ANNEX 2. Verification of Eligibility Form

Inclusion Criteria

1. Is the patient eligible for vaccination? Si No
2. Does the patient have symptoms that began during the evaluation period in the country? Si No
3. Does the case meet the following definition of **SARI**? Si No

Fever or history of fever **and** cough **and** shortness of breath or difficulty breathing **and** hospital admission? (*Modify according to the national surveillance protocol.*) Si No

Exclusion Criteria

1. Patient has **contraindications** for the vaccine (e.g., severe allergy to eggs). Si No
2. He/she **gave** a **respiratory sample more than 10 days after onset of symptoms**. Si No
3. Was the respiratory sample taken because of an **unusual presentation** or for **a purpose other than surveillance?** Si No
4. Has the patient had a **positive** laboratory test **for influenza during the same season**? Si No
5. Did the symptoms begin **after the patient was hospitalized?** Si No

……

In order for the patient to be eligible for the evaluation, every inclusion criterion should have a YES answer and every exclusion criterion should have a NO answer.

ANNEX 3. Variables Collected for the Evaluation, Definitions, and Codes

Variable	Codes	Critical variable?	Name of variable in the REVELAC-i database manager	Source of data	Comments
General data					
Country	1= Guatemala, 2=El Salvador, 3=Honduras, 4=Nicaragua, 5=Costa Rica, 6=Panama, 12=Paraguay, 13=Brazil, 14=Colombia, 15=Chile, 16=Ecuador, 17=Argentina, 18=Cuba, 19= Jamaica, 20=México, 21=Peru, 22=Trinidad and Tobago, 23=Uruguay	Yes	country	Surveillance	
State	*Text*	Yes	state	Surveillance	For Brazil
Region	*Text*	No	region	Surveillance	For large countries or regions with circulation of potentially different influenza
Hospital	*Text*	Yes	hosp	Surveillance	Countries will provide the names in the national protocols or include them in the data submitted.
Type of surveillance	0=unusual SARI case, 1= sentinel SARI surveillance, 2=universal SARI surveillance, 8=no information	No	surv	Surveillance	Unusual SARI cases are excluded from the evaluation.

Start date of last vaccination campaign in the country	Date (dd/mm/yy)	Yes	camp	National vaccination program	Official date, defined as the start of the evaluation period (from current vaccination + 2 weeks to develop immunity)
Type of vaccine against seasonal influenza	0=trivalent inactivated without adjuvant, 1=trivalent inactivated with adjuvant, 2=live attenuated, 3=quadrivalent	No	vaccine type	National vaccination program	To be collected at the country level
Brand of vaccine used		No	brand	National vaccination program	To be collected at the country level
Age (years)	*Number*	Yes	age_yrs	Surveillance	Age in months or years (0,1,2), preferably converted to decimal fractions of the year in order not to lose the original information
Sex	male=1, female=0	Yes	sex	Surveillance	

Information on vaccination					
Did subject receive the influenza vaccine in the current season? (2017)	0=no, 1=yes, 8=no information	Yes	curr_vacc	Surveillance / vaccination registries or documents	If this is confusing, use the last 12 months.
Date of influenza vaccination in the current season (2017)[$]	dd/mm/yyyy	Yes	curr_vacc_date		This date is important for reclassifying immunization status in the course of analysis.

In children <9 years, is this their first vaccination?	1=yes, 0=no, 8=no information	No	st_vacc_child		We know it is difficult to collect this variable in surveillance, so whenever it is feasible.
Second dose of influenza vaccine in the current season (2017)*	0=no, 1=yes, 8=no information	No	curr_vacc_dose2		
Date of second dose in the current season (2017)	dd/mm/yyyy	No	curr_vacc_dose2_date		
Did subject receive the influenza vaccine in the previous season (2014)?	1=yes, 0=no, 8=no information	No	prev_flu_vacc		
Did subject receive the influenza vaccine in the 2013 season?	1=yes, 0=no, 8=no information	No	prev2_flu_vacc	Research	Pilot project in countries with nominal registries?
Did subject receive the pneumococcal vaccine with the full influenza series for his/her age?	1=yes, 0=no, 8=no information	No	pneumo_vacc	Surveillance / vaccination registries or documents	In children or older adults: PCV-7, PCV-10, PCV-13 or PPSV-23. Proxy for access to health services?
Source of information on the vaccine	0= vaccination card physically reviewed, 1=nominal registry on paper, 2=electronic nominal registry, 3=clinical record, 4=other EPI registries, 5=vaccination card read by telephone, 6=verbal report without card, 8=no information	Yes	vacc_source	Surveillance / Registries or documents of vaccination	*Cartão espelho* in Brazil is a vaccination card that is physically reviewed.

[$]Date of vaccination is the 1st dose of influenza vaccine in the current season in children receiving their first vaccination.			
** In children being vaccinated for the first time.*			
9 years: Per WHO position paper on influenza vaccine, Nov 2012			

Information from the laboratory					
Sampling date	dd/mm/yyyy	Yes	sample_date	Surveillance / laboratory	
Result of RT-PCR for influenza	1=positive, 0=negative	Yes	case	Surveillance / laboratory	Having this information is an inclusion criterion in itself, so there is no "no information" category
Influenza type A	0=no, 1=yes, 8=no information	Yes	flu_A	Surveillance / laboratory	
Influenza type B	0=no, 1=yes, 8=no information	Yes	flu_ B		
Influenza A(H1N1pdm09)	0=no, 1=yes, 8=no information	Yes	flu_H1	Surveillance / laboratory	
Influenza A(H3N2)	0=no, 1=yes, 8=no information	Yes	Flu_H3		
Influenza B lineage	1=Yamagata, 2=Victoria, 3=not applicable, 8=no information	No	lineage	Surveillance / laboratory	This information is included to measure effectiveness of the influenza B component of the vaccine (with the lineage included), as agreed in Cartagena
Is the sample positive for another respiratory virus?	0=no, 1=yes, 8=no information	No	other_virus	Surveillance / laboratory	A virus that is not influenza

Type of virus (if not influenza)	0=respiratory syncytial virus, 1=parainfluenza, 2=metaneumovirus, 3=adenovirus, 4=rinovirus, 5=bocavirus, 6=other	No	other_virus_type	Surveillance / laboratory	When possible, the information is taken from the surveillance record.

Clinical information					
Date of symptom onset	dd/mm/yyyy	Yes	onset_date	Surveillance	
Date of admission	dd/mm/yyyy	Yes	sample_date	Surveillance	
Date of discharge	1=positive, 0=negative	Yes	case		
Fever		No			To confirm definition as a case
Cough		No			To confirm definition as a case
Admitted to ICU		No			
Deceased		No			
Did patient receive antiviral treatment?		Yes			
Date of administration of the antiviral		Yes			
Preexisting conditions					
Does subject have at least one chronic disease?	0=no, 1=yes, 8=no information	Yes	preexist_cond	Surveillance	
1. Respiratory disease	0=no, 1=yes, 8=no information	No	resp_dis	Surveillance	Up to item 10 is the standardized list from the PAHO/WHO UNICEF Joint Reporting Form (JRF), 2013, which is designed to standardize reports on vaccination coverage.
a. Asthma	0=no, 1=yes, 8=no information	No	asthma		
b. Chronic bronchitis or emphysema	0=no, 1=yes, 8=no information	No	chron_bronch		
c. Other respiratory diseases	0=no, 1=yes, 8=no information	No	other_resp		
2. Heart disease	0=no, 1=yes, 8=no information	No	cardio_dis		
a. Atherosclerosis	0=no, 1=yes, 8=no information	No	athero		

b. Cardiomyopathy /heart failure	0=no, 1=yes, 8=no information	No	cardiomyop		
3. Neurological development disorders	0=no, 1=yes, 8=no information	No	neuro_dis		
a. Cerebral palsy	0=no, 1=yes, 8=no information	No	paralysis		
b. Muscular dystrophy	0=no, 1=yes, 8=no information	No	musc_dyst		
c. Cognitive disorders	0=no, 1=yes, 8=no information	No	cogn_dis		
4. Metabolic disorders	0=no, 1=yes, 8=no information	No	metab_dis		
a. Diabetes	0=no, 1=yes, 8=no information	No	diab		
5. Immune system disorders	0=no, 1=yes, 8=no information	No	immuno		
a. HIV/AIDS	0=no, 1=yes, 8=no information	No	hiv		
b. Chemotherapy	0=no, 1=yes, 8=no information	No	chemo		
c. Organ transplant or immunosuppressive therapy	0=no, 1=yes, 8=no information	No	immunosup		
d. Chronic use of corticosteroids	0=no, 1=yes, 8=no information	No	steroid		
6. Chronic kidney disease with dialysis	0=no, 1=yes, 8=no information	No	renal_dis		
7. Chronic liver disease, especially with cirrhosis	0=no, 1=yes, 8=no information	No	liver_dis		

8. Morbid obesity	0=no, 1=yes, 8=no information	No	obese		The countries that collect data on obesity will have to specify the definition when they submit their data—e.g., obesity in general, BMI definition, or morbid obesity diagnosed by a physician.
9. Hematological disorders	0=no, 1=yes, 8=no information	No	hemato_dis		
a. Sickle-cell disease	0=no, 1=yes, 8=no information	No	anem		
b. Thalassemia major	0=no, 1=yes, 8=no information	No	thalassemia		
10. Children on long-term daily aspirin therapy (at risk for Reye's syndrome)	0=no, 1=yes, 8=no information	No	chron_aspirin		
11. Smoking	0=nonsmoker, 1=smoker currently, 3=ex smoker 8=no information	No	smok		It depends on whether the countries collect this information.
12. Down syndrome	0=no, 1=yes, 8=no information	No	down_syn		Added after the visit to Brazil.
13. Indigenous population	0=no, 1=yes, 8=no information	No	indig		For Brazil, it will be collected from the list of risk factors.

ANNEX 4. REVELAC-i Data Management Flow Charts

Below is a description of the data management flow for the following operations:

— Data flow using the Data Entry feature of the REVELAC-i Data Management System

— Data flow using the Data Retrieval feature of the REVELAC-i Data Management System

It is assumed, as a precondition for both flow charts, that data for influenza surveillance are being routinely recorded in compliance with each country's national protocol and that the criteria for the definition of cases and controls for purposes of this evaluation are being followed.

Data entry

— Required preconditions

- The person entering the data has a user profile created in CAUS consistent with the role of **Data Entry Clerk**.[4]
- The person exporting the data has a user profile created in CAUS consistent with the role of **Researcher**.[5]
- The person entering the data has configured his/her personalized password. First-time users are given a temporary password assigned by the software administrator through CAUS.

— Steps

a. The user goes to the program at the following link: http://www.revelac-i.org

b. The user enters his/her valid username and password.

[4] The role of Data Entry Clerk gives the user access to Data Entry in the REVELAC-i Data Management System, with privileges to consult, input, modify, and delete data.

[5] The role of Researcher gives the user access to Data Export in the REVELAC-i Data Management System. Depending on the way the environment is configured, the Researcher may have permission to export (download) all the data (all the countries and all the years) or national data for a given country (one country, all the years).

c. The program brings up the data consultation interface.
d. The user clicks on Add Data in the menu.
e. The program takes the user to the data input interface.
f. The user enters the data following the order of the variables listed in the menu.
g. When all the required data (marked with a red asterisk on the menu) have been entered, the user clicks on Save.
h. The program confirms that the required data have been entered and that the data appears in the proper format and corresponds to the values defined in the data dictionary being used for the study.
i. If the data meet the verification criteria, they are stored in the database and the program proceeds with the steps after *paragraph c*, sending messages to the user if any errors are found.
j. Users can correct the erroneous data and click again on Save, which returns them to the steps in *paragraphs h and i*, or they may decide not to correct the data click on Cancel, which returns them to the interface described in *paragraph c*.
k. If the user wishes to enter another record, they again follows the steps after *paragraph c*.
l. If the user wishes to export data, they click on the Export Data option in the main menu.
m. The program takes the user to the Export Data interface.
n. Depending on the privileges that have been granted to the user (Study Researcher or National Researcher), they select the country and study year to be exported, unless they want to export data from all the countries, in which case they only select the year of the study. After making the desired selection, the user then clicks on the Export button.
o. The program brings up the download interface and opens a file in Microsoft Excel format containing the data from the selected ranges.
p. Depending on the configuration of the Internet browser, users can select the location where the file will be downloaded.
q. The user imports the downloaded file using the STATA software.
r. If the user is ready to sign off from the REVELAC-i Data Management system, they click on Exit.

- Other steps that the program executes during a **user session**[6]

a. The program creates a table in the **transaction log**[7] itemizing all the transactions performed by the user.
b. The program confirms its interactions with the user, and if there is no activity for more than 30 minutes, it automatically closes the session, requiring the user to go back and sign in again (*paragraph b*).

Data retrieval

- Required preconditions
    - The person entering the data has a user profile created in CAUS consistent with the role of **Data Retrieval Clerk**.[8]
    - The person exporting the data has a user profile created in CAUS consistent with the role of **Researcher**.[9]
    - The person entering the data has configured their personalized password. First-time users are given a temporary password assigned by the software administrator through CAUS.

- Steps

a. The user goes to the program at the following link: http://www.revelac-i.org
b. The user enters a valid username and password.
c. The program brings up the data consultation interface.
d. The user clicks on Upload Record in the menu.

---

[6] The **user session** is the period of time during which the person is interacting with the program, based on having entered a username and valid password, until the user chooses the Leave option or until it detects inactivity for more than 30 minutes, at which point it ends the user's connection with the software.

[7] The **transaction log** is a database table that stores the date, time username, and action taken by the user—for example: *enters the program*, *saves data*, *modifies data*, *deletes data,* etc.

[8] The role of Data Retrieval Clerk gives the user access to the option to upload data from the REVELAC-i Database Management system.

[9] The role of Researcher gives the user access to Data Export in the REVELAC-i Data Management System. Depending on the way the environment is configured, the Researcher may have permission to export (download) all the data (all the countries and all the years) or national data for a given country (one country, all the years).

e. The program takes the user to the record retrieval interface.
f. The user clicks on the Browse button and selects CSV File Format, which contains the data to be uploaded from the REVELAC-i Database Management system in the location in which it is found.
g. The user selects the country and year of the data evaluation of interest and clicks on the button Upload.
h. The program confirms that the data in the CSV file meets all the validation criteria.
i. If all the records with meet all the validation criteria, the program uploads the records to the Database Management system. If some of the records fail to meet all the criteria, it uploads only the ones that do.
j. Regardless of the outcome of the step described in *paragraph i*, a text (.txt) file is generated with a summary of the process and, if any errors were found during validation by the program, it describes them in detail.
k. If the user wishes to upload more data, they should repeat the steps starting with *paragraph f*.
l. If the user wishes to export data, they click on Export Data in the main menu.
m. The program takes the user to the Export Data interface.
n. Depending on the privileges that have been granted to the user (Study Researcher or National Researcher), they selects the country and study year to be exported, unless they want to export data from all the countries, in which case they only selects the year of the study. After making the desired selection, the user then clicks on the Export button.
o. The program brings up the download interface and opens a file in Microsoft Excel format containing the data from the selected ranges.
p. Depending on the configuration of the Internet browser, the user can select the location where the file is downloaded.
q. The user imports the downloaded file using the STATA software.
r. If the user is ready to sign off from the REVELAC-i Data Management system, they click on Exit.

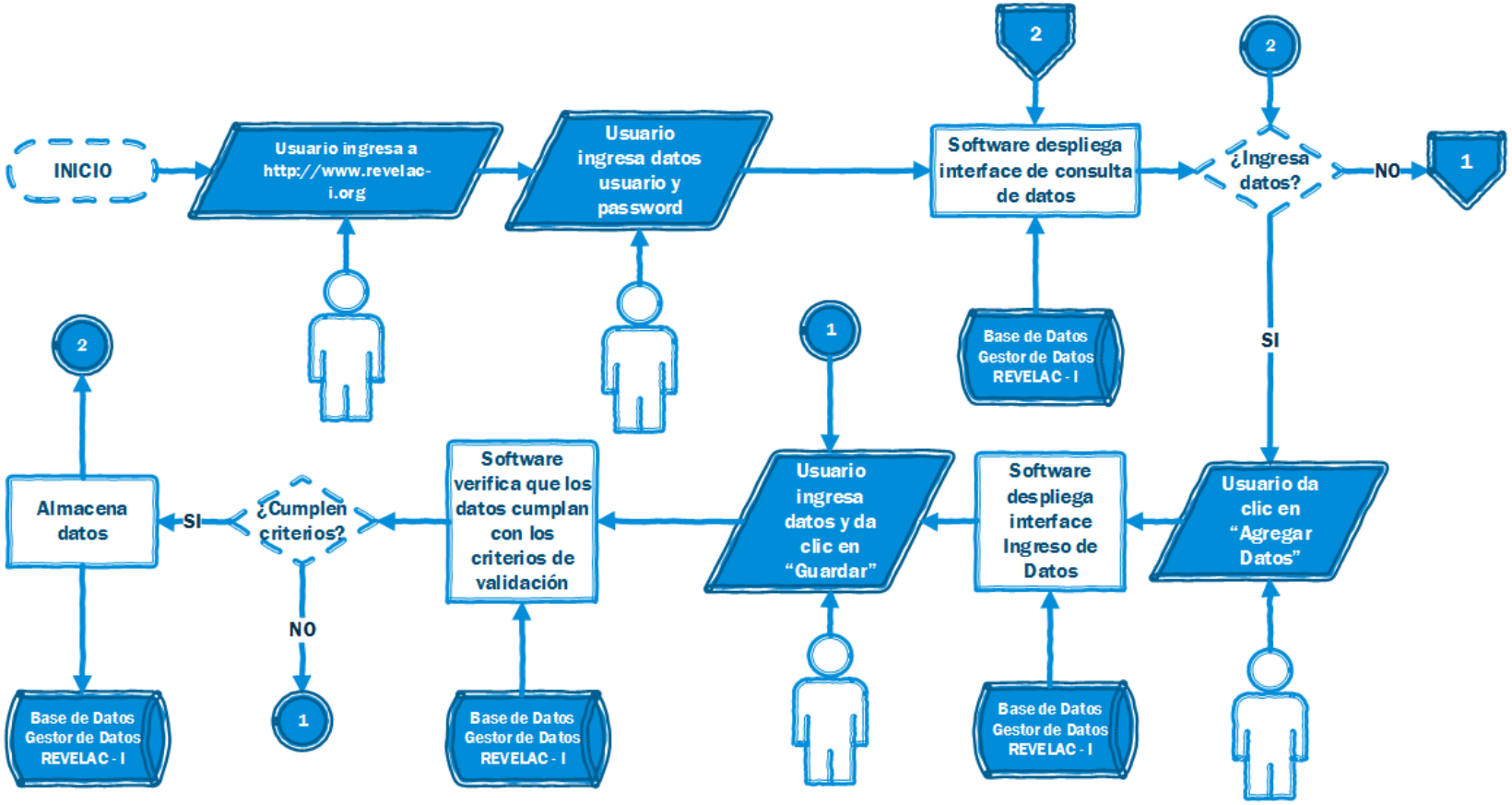
— Other steps that the program executes during a **user session**[10]

[10] The **user session** is the period of time during which the person is interacting with the program, based on having entered a username and valid password, until the user chooses the Leave option or until it detects inactivity for more than 30 minutes, at which point it ends the user's connection with the software.

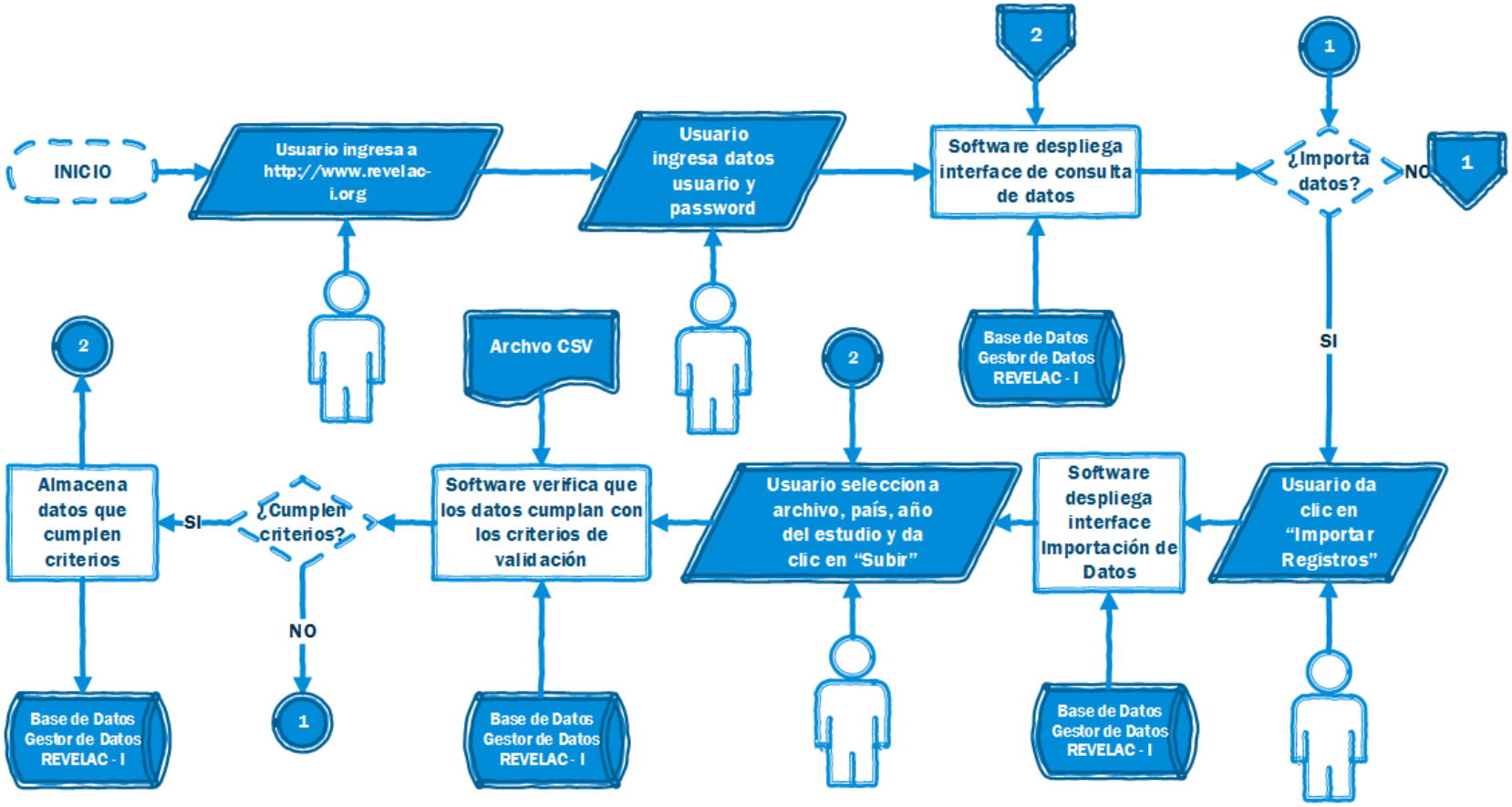
a. The program creates a table in the **transaction log**[11] itemizing all the transactions performed by the user.
b. The program confirms its interactions with the user, and if there is no activity for more than 30 minutes, it automatically closes the session, requiring the user to go back and sign in again (*paragraph b*).

[11] The **transaction log** is a database table that stores the date, time username, and action taken by the user—for example: *enters the program*, *saves data*, *modifies data*, *deletes data,* etc.

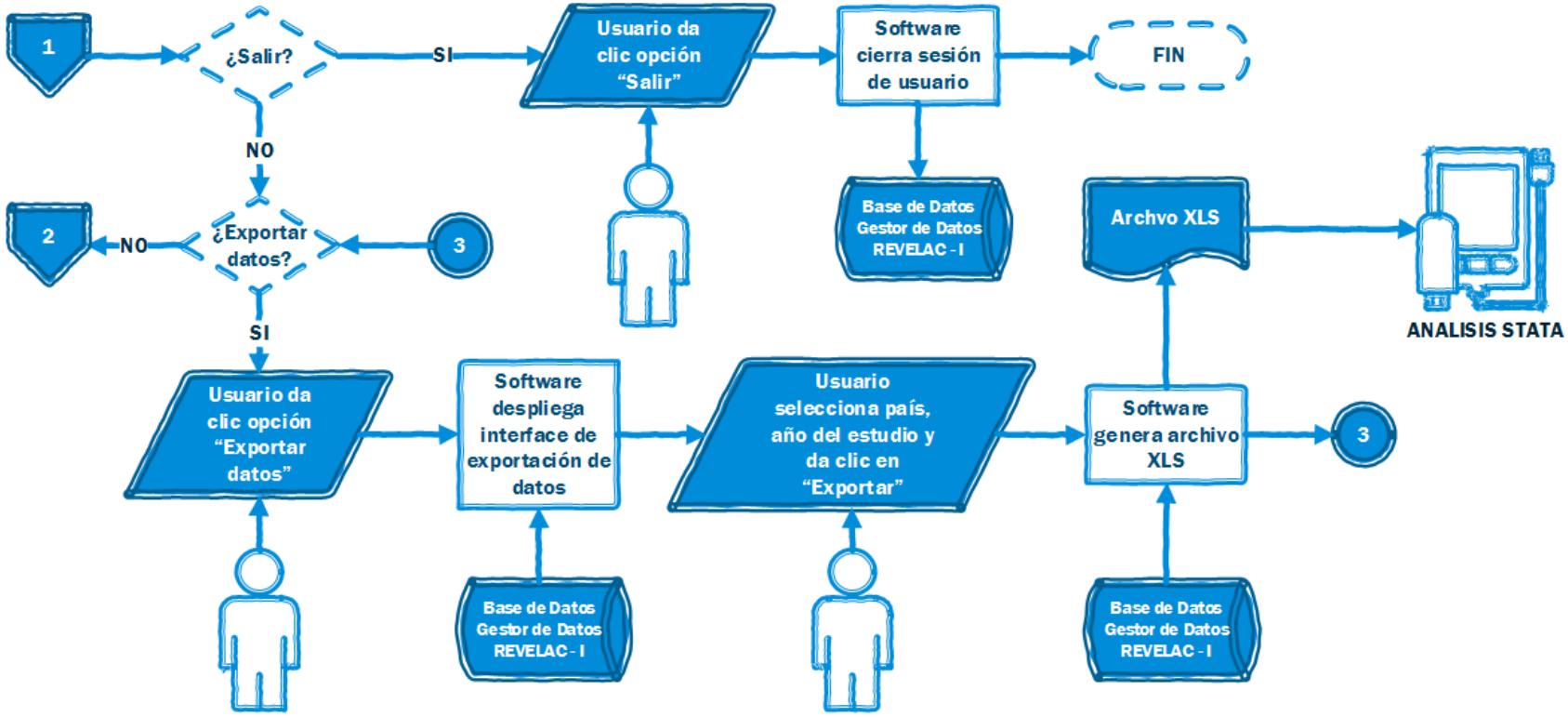
Data Entry


INICIO
Usuario ingresa a http://www.revelac-i.org
Usuario ingresa datos usuario y password
Software despliega interface de consulta de datos
¿Ingresa datos?
NO
1
2
2
SI
Base de Datos Gestor de Datos REVELAC - I
1
Usuario da clic en "Agregar Datos"
Software despliega interface Ingreso de Datos
Usuario ingresa datos y da clic en "Guardar"
Software verifica que los datos cumplan con los criterios de validación
¿Cumplen criterios?
SI
NO
Almacena datos
2
1
Base de Datos Gestor de Datos REVELAC - I
Base de Datos Gestor de Datos REVELAC - I
Base de Datos Gestor de Datos REVELAC - I

Data Upload


INICIO
Usuario ingresa a http://www.revelac-i.org
Usuario ingresa datos usuario y password
Software despliega interface de consulta de datos
¿Importa datos?
NO
1
2
SI
Base de Datos Gestor de Datos REVELAC - I
Usuario da clic en "Importar Registros"
Software despliega interface Importación de Datos
Usuario selecciona archivo, país, año del estudio y da clic en "Subir"
Archvo CSV
Software verifica que los datos cumplan con los criterios de validación
¿Cumplen criterios?
SI
NO
Almacena datos que cumplen criterios
Base de Datos Gestor de Datos REVELAC - I

Data Export


1
¿Salir?
SI
Usuario da clic opción "Salir"
Software cierra sesión de usuario
FIN
NO
2
NO
¿Exportar datos?
3
Base de Datos Gestor de Datos REVELAC - I
Archvo XLS
ANALISIS STATA
SI
Usuario da clic opción "Exportar datos"
Software despliega interface de exportación de datos
Usuario selecciona país, año del estudio y da clic en "Exportar"
Software genera archivo XLS
3
Base de Datos Gestor de Datos REVELAC - I
Base de Datos Gestor de Datos REVELAC - I

ANNEX 5. Description of Hospitals Participating in the Evaluation

(*This section should be filled out by each participating country.*)

Costa Rica:

1) Tony Fació Hospital
2) Max Peralta Hospital
3) San Carlos Hospital, Monsignor Sanabria Hospital
4) Escalante Pradilla Hospital
5) San Rafael Hospital
6) Liberian Hospital
7) National Children's Hospital

Argentina

1) Dr. Humberto J. Notti Pediatric Hospital, Mendoza
2) Schestakow Regional Provincial Hospital, San Rafael, Mendoza
3) Buenos Aires Italian Hospital, City of Buenos Aires
4) Victorio Tetamanti Interzonal Specialized Maternal and Children's Hospital, Mar del Plata, Province of Buenos Aires
5) Prof. Posadas National Hospital (HGA)
6) Avellaneda Hospital, Tucumán
7) Dr. Alassia Pediatric Hospital, Santa Fe

Brazil

Rio Grande do Sul

1) Our Lady of Conception Hospital CNES:2237571
2) General Hospital, Caxias do Sul CNES:2223538
3) Santa Cruz do Sul Hospital CNES:2254964

Paraná

4) Clinics Hospital
5) Evangelical Hospital
6) Little Prince Children's Hospital

Santa Catarina

7) Dr. Homero Miranda Gomes Hospital Regional, São José dos Campos, CNES: 2555646
8) Nereu Ramos Hospital, CNES: 2664879
9) Joana de Gusmão Children's Hospital, CNES: 2691868

Minas Gerais

10) 20 hospitals, 9 of which are sentinel hospitals

Chile

1) San Juan de Dios Hospital, Metropolitan Region / Western Metropolitan Region Health Services (public)
2) Military Hospital, Metropolitan Region
3) Iquique Hospital, Tarapacá Region / Iquique Health Services (public)
4) Puerto Montt Hospital, Los Lagos Region / Reloncaví Health Services (public)
5) Gustavo Fricke Hospital, Valparaiso Region / Viña del Mar–Quillota Health Services (public)
6) Guillermo Gran Benavente Hospital, Biobío Region / Concepción Health Services (public)

Colombia

1) Fundación Cardioinfantil Hospital, Bogotá (private)
2) Santa Clara Hospital, Bogotá
3) San Rafael de Itaguí Hospital, Antioquia
4) San Vicente de Paúl University Hospital, Antioquia.

5) Northern General Clinic, Barranquilla
6) Valle del Lili Foundation Hospital, Cali
7) Ladera de Siloe Health Network, Cali

El Salvador

1) Benjamín Bloom Children's Hospital
2) Hospital San Juan de Dios, Santa Ana
3) Hospital San Juan de Dios, San Miguel
4) Our Lady of Fatima Hospital, Cojutepeque

	Santa Ana	Benjamin Bloom	Cojutepeque	San Miguel
Number of hospital beds	469	285	90	422
Number of ICU beds	30	34	0	22

Honduras

1) THORAX Cardiopulmonary Institute, Tegucigalpa
2) Catarino Rivas Hospital, San Pedro Sula
3) Honduran of Social Security Institute, San Pedro Sula

Panama

1) Children's Hospital
2) Pediatric Specialty Hospital
3) José Domingo de Obaldía Maternal and Children's Hospital, Chiriquí
4) José Luis "Chicho" Fábrega Hospital Center, Veraguas
5) Rafael Hernández Hospital, Chiriquí
6) Rafael Estévez Hospital
7) Joaquín Pablo Franco Hospital

8) Chepo Regional Hospital
9) San Miguel Archangel Hospital
10) Nicolás Asolano Hospital

Paraguay

1) Children of Acosta Ñú General Pediatric Hospital, Reducto San Lorenzo
2) Social Welfare Institute Central Hospital, Asunción
3) National Hospital, Itauguá

Peru

1) Pediatric Emergency Hospital (HEP)
2) National Institute of Children's Health (INSN)
3) Archbishop Loayza National Hospital (HAL)

Uruguay

The six hospitals of the SARI sentinel network:

1) Pereira Rossell Pediatric Hospital Center (CHPR), Montevideo
2) British Hospital, Montevideo
3) Las Piedras Hospital, Montevideo
4) SEMM Mautone Sanatorium, Maldonado
5) Police Hospital, Montevideo
6) Mercedes CAMS Sanatorium, Soriano

ANNEX 6. Selection of SARI Patients for Sampling in the Participating Countries

(*This section should be filled out by each participating country.*)

Country	**Sampling strategy in SARI groups / subgroups with 100%** respiratory sampling	**Method of selecting** patients for sampling (if not all)	**Type of sample taken**	**Personnel who take the respiratory sample**	**Maximum days between symptom onset and sampling** (specify differences, if any: e.g., ≤5 days but ≤7 days with chronic diseases)	Sample analysis **flow** for influenza virus (up to RT-PCR)	**Strategy for RT-PCR** testing on **IFI-negative samples** (if applicable)
Example	*100% of hospitalized SARI patients are in ICU; 5 weekly samples taken in other groups.*	*Patients are selected systematically every Monday and Wednesday until reaching the quota of 7 samples a week.*	*Nasal/pharyngeal swab preferred except in children <5 years (nasal aspirate).*	*Surveillance personnel in all except ICU (physician in attendance).*	*5 days; 7 days for patients in ICU.*	*IFI (+) samples sent to national laboratory for RT-PCR.*	*10% of IFI(-) samples sent to NIC for RT-PCR.*
Argentina Tetamanti HIEMI, Mar del Plata	100 % in hospitalized SARI patients; children 6 to 23 months.	Not applicable	Nasopharyngeal aspirate	Surveillance personnel (kinesiologists) in all cases	Up to7 days in all cases		100% of IFI(-) samples sent to NIC for RT-PCR.
Chile	100% of SARI patients	100%—Not applicable	Nasopharyngeal aspirate in most cases (nasopharyngeal swab at La Reina Military Hospital, Santiago, Chile); tracheal aspirate or bronchoalveolar lavage in patients in ICU patients.	Nurse (most often), respiratory therapist, physician	Preferably within 72 hours from fever onset and maximum 5 days. Up to 10 days for patients admitted to ICU	IFI performed in hospital. IFI(+) for influenza sent to regional laboratory for PCR. IFI(+) for RSV, adenovirus, parainfluenza, or other viruses:	Samples IFI(-) for respiratory virus panel are sent to regional laboratory for PCR. If PCR(+), they are sent to Public Health Institute

						only the result is reported. The positive cases for influenza are sent to the Public Health Institute.	
Colombia	100% of SARI patients	100%—Not applicable	Nasal aspirate, nasal /pharyngeal swab	Surveillance personnel, respiratory therapist, physician	7 days	Samples sent to public health laboratories in departments that have them and to National Health Institute for RT-PCR (if the hospital does only IFI), or for quality control if the sample was already analyzed by RT-PCR.	
Costa Rica	100% of hospitalized SARI patients (<5 days from date of symptom onset); 100% of SARI patients in ICU; 90% of deceased patients.	100% SARI – Not applicable	Nasopharyngeal aspirate preferred	Hospitals: respiratory therapy personnel, nurses, or surveillance personnel	<5 days: all SARI patients in sentinel hospitals (except for the cases mentioned below). >5 days: case hospitalized for unusual SARI, ICU, death, pregnant woman, or neonate	Samples sent to the national laboratory for IFI and RT-PCR. Only 2 laboratories in the entire CCSS sentinel network do IFI. All samples sent to INCIENSA for RT-PCR	*1*0% of IFI(-) samples sent to NIC for RT-PCR.
El Salvador	5 weekly samples in any patient or age group with SARI	By quotas until obtaining the five weekly samples (sampling for desirability, not random).	Combination of nasal and pharyngeal swab	Residents and laboratory personnel previously trained to take the samples	Up to 3 days for SARI patients; Up to 5 days for SARI patients in ICU	IFI(+) samples are sent to the central laboratory for RT-PCR.	10% of IFI(-) samples sent for RT-PCR.

Honduras	100% of SARI patients	100%—Not applicable	Combination of nasal and pharyngeal swabs in all the groups	Laboratory staff in 2 hospitals; surveillance personnel in 1 hospital	Up to 10 days, but preferably during the first 72 hours	IFI (+) samples sent to national laboratory national for RT-PCR.	IFI and RT-PCR performed on 100% of cases, including IFIS-negative.
Panama	5 weekly samples in SARI patients. For SARI patients in the ICU the recommendation is 100%, although it can vary in practice	Systematic sampling until reaching the weekly quota	Nasopharyngeal swab	Epidemiological surveillance personnel and physicians in the different services	5 days; 7 days for patients admitted to ICU	IFI (+) samples sent to national laboratory for RT-PCR. Hospitals in Panama City send samples directly to Gorgas Laboratory for RT-PCR.	10% of negative samples are sent randomly to the national reference laboratory for further testing and quality control.
Paraguay	100% of SARI patients	100%—Not applicable	Combination of nasal and pharyngeal swabs in adults and children ≥5 years; nasopharyngeal aspirate in children <5 years or in children or adults with serious cases that pose limitations in performing a swab	Surveillance personnel in all cases and staff physicians especially in the ICU	Preferably within **72 hours** and maximum of**10** days regardless of symptom onset interval, SARI case admitted to **ICU**, death, or SARI related to a case cluster		In hospitals that perform IFI, all samples IFIS-negative for influenza are sent to the NIC for RT-PCR. Positive samples are not tested for other viruses. The other hospitals send all the samples for RT-PCR for influenza to the NIC.

Peru	100% of SARI patients in sentinel hospitals	Not applicable	Nasal and pharyngeal swab	Laboratory staff in the sentinel hospitals	Within the first 7 days of disease	Samples processed for real-time RT-PCR (90% of samples) are sent to NIC and two other laboratories (Cusco and Iquitos)	The regional laboratories send 100% of IFI(-) samples to the NIC.

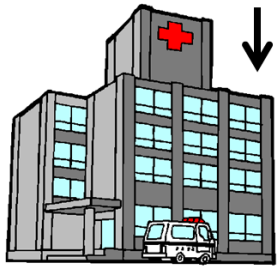
ANNEX 7. Example of Procedure for Capturing Influenza and Pneumococcal Vaccination Information, Multicenter Evaluation of Influenza Vaccine, Paraguay, 2013

Organización de la recuperación de antecedentes de vacunación en REVELAC-i, 2013 Paraguay.

2. Revisión de los casos de IRAG en niños y adultos mayores : identificación de pacientes con estado de vacunación pendiente.

Vigilancia de influenza

1. Revisión del carnet de vacunación en los servicios durante hospitalización.



Reporte semanal de casos de IRAG

- Hospital del Instituto de Previsión Social (IPS)
- Hospital Pediátrico

5. Para pacientes de otras regiones, el PAI nacional contacta a los PAI distritales para revisión de registros nominales .

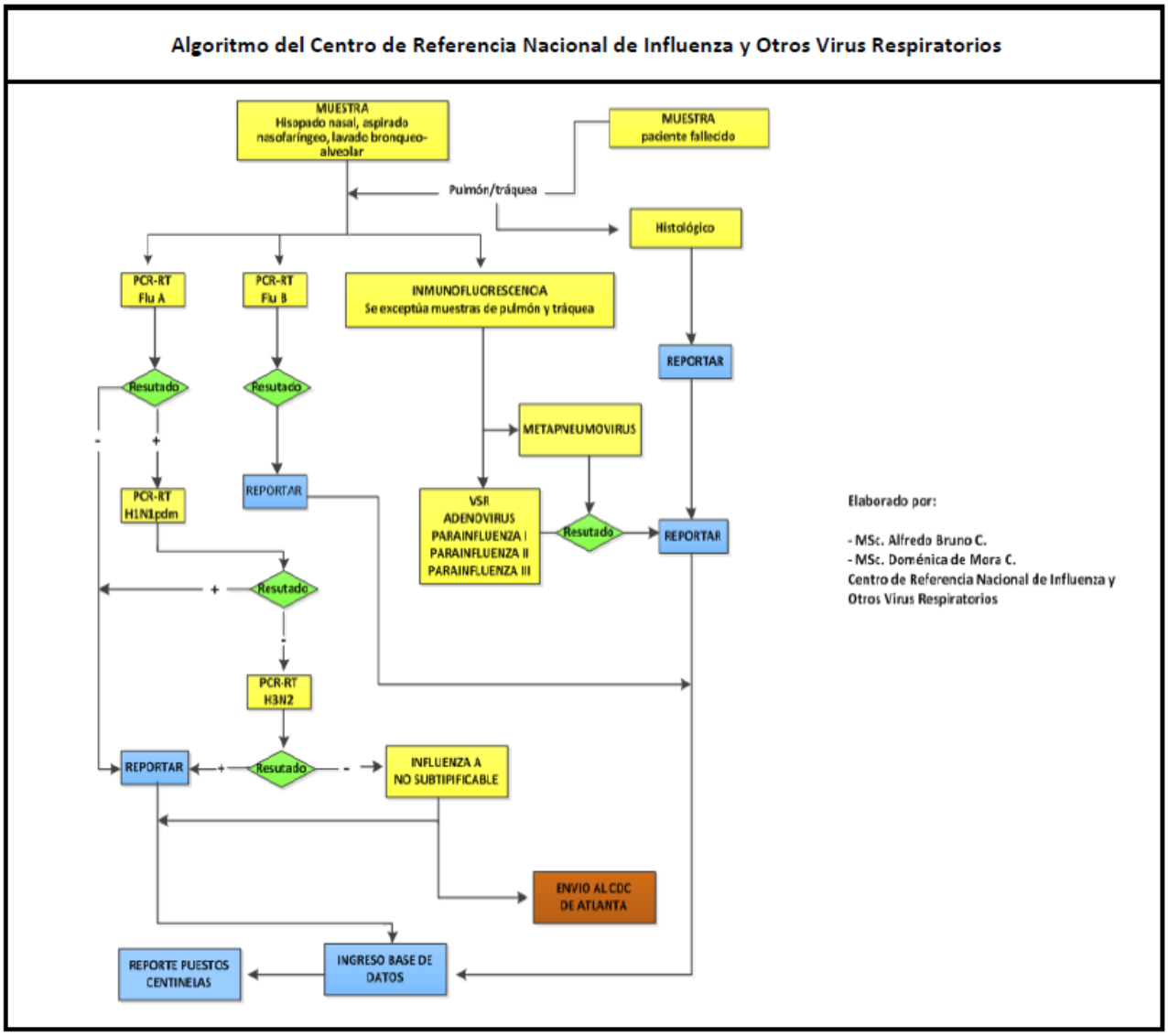
PAI Central

3. Envió de lista de "pendientes" según procedencia de los pacientes.

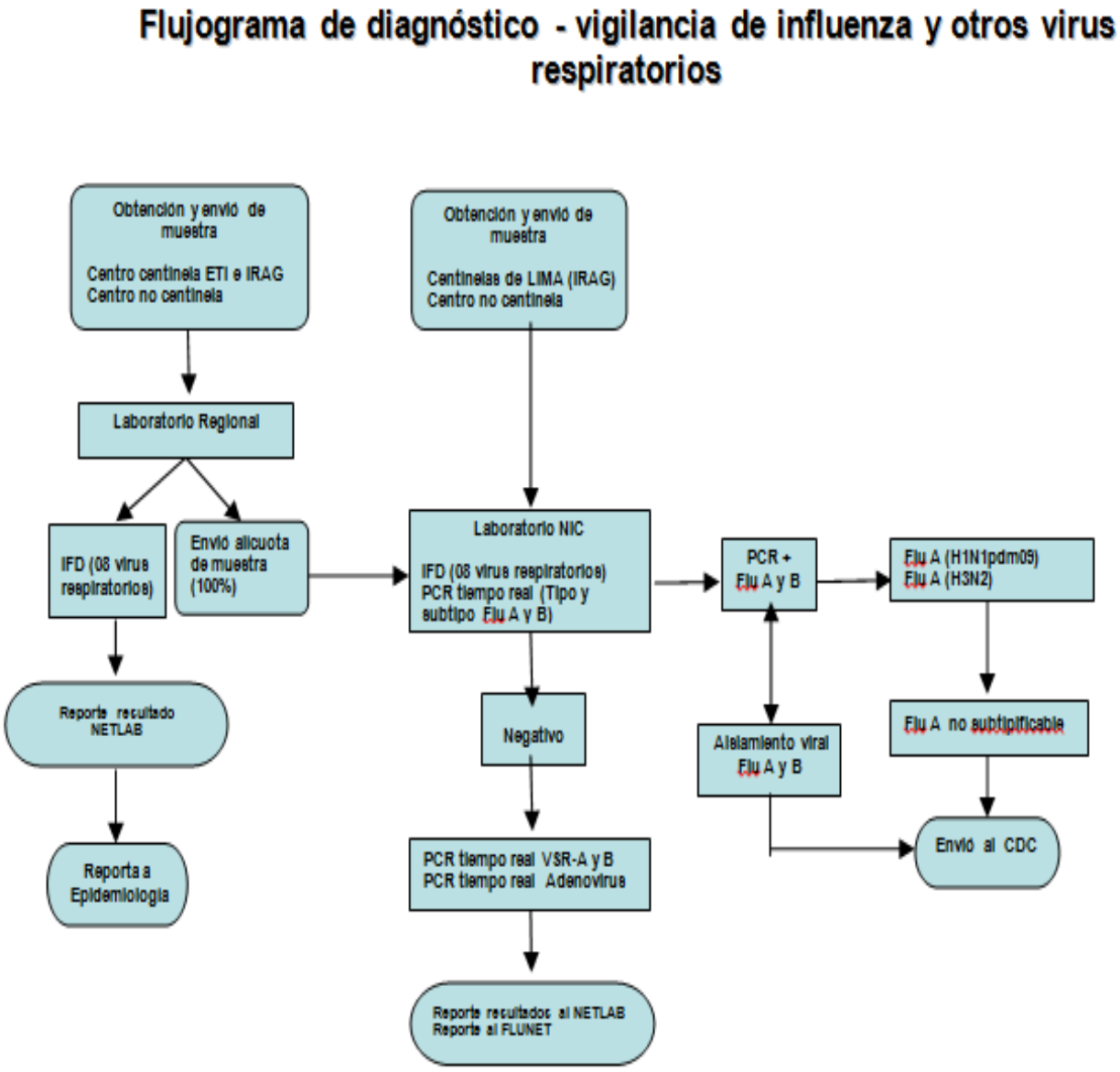
PAI Regional (Asunción/Central)

4. El equipo del PAI contacta a sus PAI distritales para revisión de registros nominales (mayoría en papel, excepto digitalizado en IPS).

ANNEX 8. Algorithm of the Surveillance Laboratory for Influenza and Other Respiratory Viruses, Ecuador, 2017

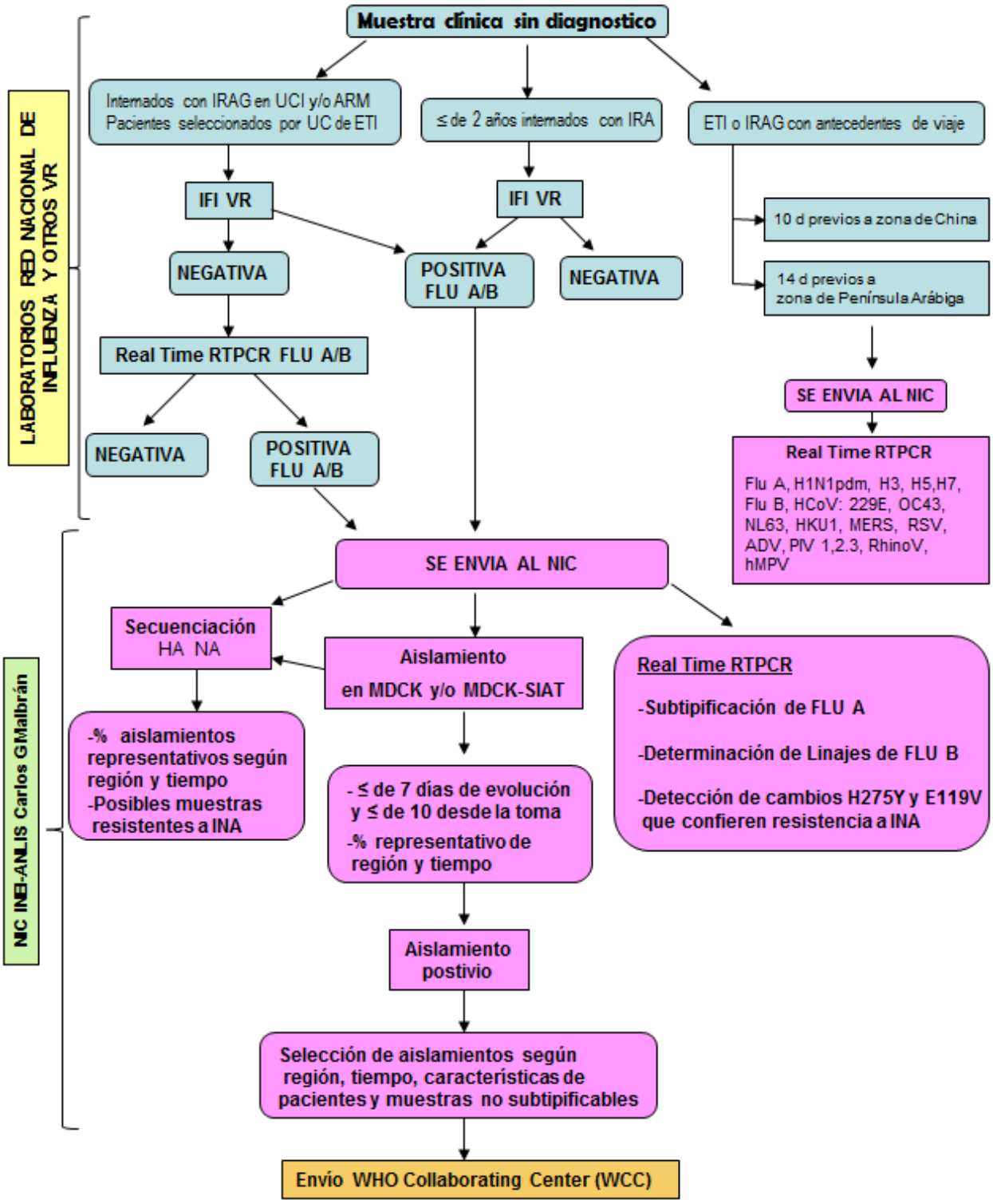


ANNEX 9. Algorithm of the Surveillance Laboratory for Influenza and Other Respiratory Viruses, Peru, 2017

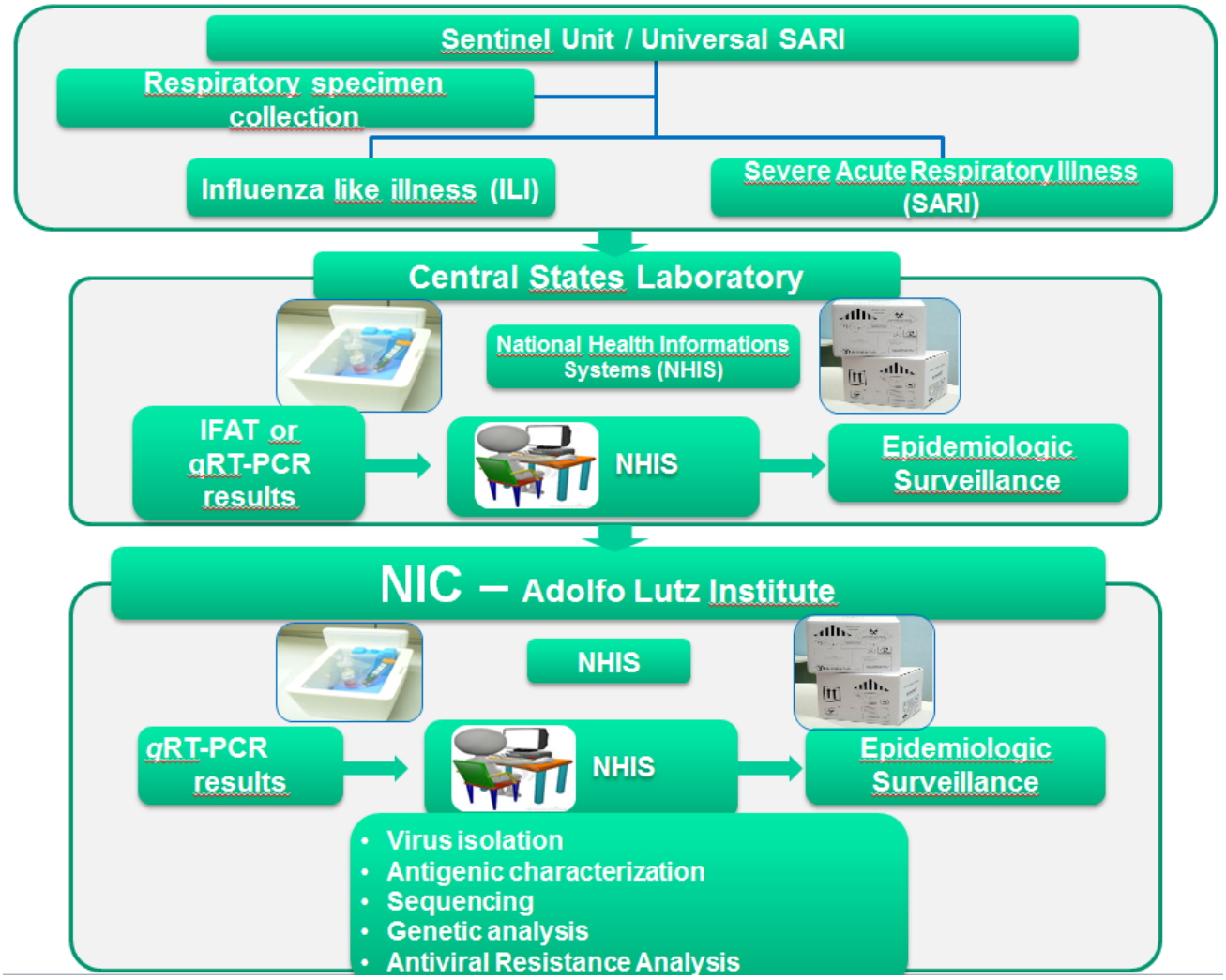


ANNEX 10. Algorithm of the Surveillance Laboratory for Influenza and Other Respiratory Viruses, Colombia, 2017

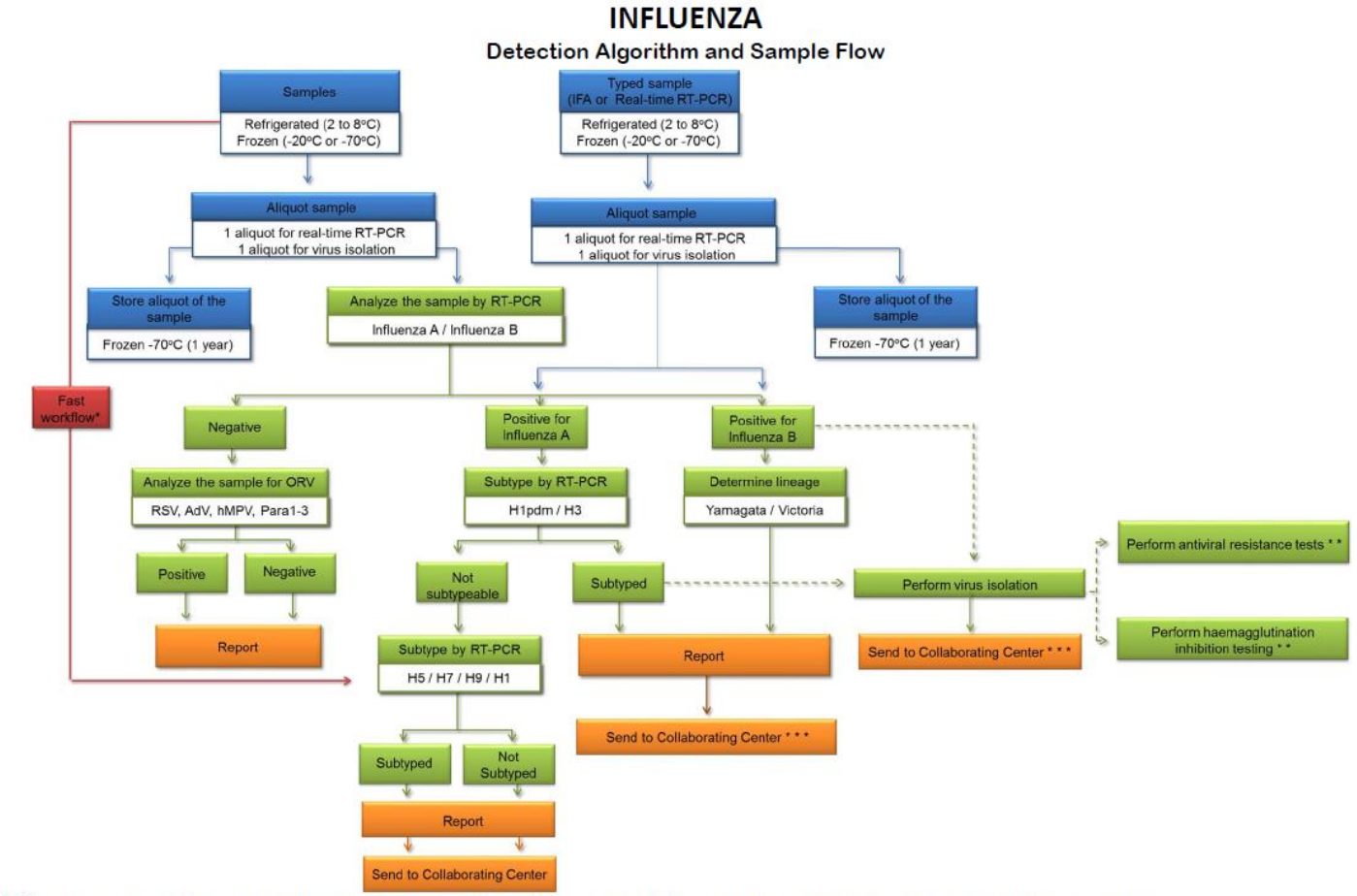
ANNEX 11. Algorithm of the Surveillance Laboratory for Influenza and Other Respiratory Viruses, Argentina, 2017



ANNEX 12. Algorithm of the Surveillance Laboratory for Influenza and Other Respiratory Viruses, Brazil, 2017



ANNEX 13. Algorithm of the Regional Surveillance Laboratory for Influenza and Other Respiratory Viruses, PAHO/WHO, 2017


INFLUENZA
Detection Algorithm and Sample Flow
Samples
Refrigerated (2 to 8°C)
Frozen (-20°C or -70°C)
Typed sample
(IFA or Real-time RT-PCR)
Refrigerated (2 to 8°C)
Frozen (-20°C or -70°C)
Aliquot sample
1 aliquot for real-time RT-PCR
1 aliquot for virus isolation
Aliquot sample
1 aliquot for real-time RT-PCR
1 aliquot for virus isolation
Store aliquot of the sample
Frozen -70°C (1 year)
Analyze the sample by RT-PCR
Influenza A / Influenza B
Store aliquot of the sample
Frozen -70°C (1 year)
Fast workflow*
Negative
Positive for Influenza A
Positive for Influenza B
Analyze the sample for ORV
RSV, AdV, hMPV, Para1-3
Subtype by RT-PCR
H1pdm / H3
Determine lineage
Yamagata / Victoria
Positive
Negative
Not subtypeable
Subtyped
Perform virus isolation
Perform antiviral resistance tests * *
Perform haemagglutination inhibition testing * *
Report
Subtype by RT-PCR
H5 / H7 / H9 / H1
Report
Send to Collaborating Center * * *
Send to Collaborating Center * * *
Subtyped
Not Subtyped
Report
Send to Collaborating Center
* Fast workflow of the sample to the NIC must be considered in unusual cases situations (eg. avian influenza cases)
** Viral isolation and antivirals resistance or HI tests are performed according to the laboratory capacity
*** Selection of samples for shipping to WHOCC according to criteria in the document

ANNEX 14. Suggested Format for National Reports on Findings from the REVELAC-i Evaluation of Vaccine Effectiveness

Estimate of the Effectiveness of the Influenza Vaccine against Acute Disease in Target Groups in Latin America and the Caribbean

Background

- Burden of disease associated with influenza in the country and vaccination policy (year of introduction, target populations, and strategies)
- Available evidence on the vaccine in the country (e.g., previous studies of efficacy/effectiveness)
- Justification for effectiveness studies in general
- Country's interest in evidence on vaccine effectiveness (VE)
- Participation in the REVELAC-i multicenter vaccine evaluation
- Use to be made of the findings

Objectives of the Evaluation

- Objective at the national level
- Contribution to the multicenter evaluation to estimate regional and subregional VE
- *See protocol, section on Objectives.*

Methods

- *See protocol—section on Methods.*
- Design of the evaluation (case-control, type of controls)
- Evaluation population
    - Target groups, populations from participating hospitals
- Evaluation period (definition of the season and justification for data collection period)
- Resulting variable (SARI, confirmation by RT-PCR, references)
- Description of SARI surveillance in the country
- SARI case-finding
- Hospitals selected for participation in the evaluation (description and justification)
- Definitions
    - Cases
    - Controls

- Criteria for inclusion/exclusion
- Exposure
    - Vaccines used
    - Campaigns, coverage, strategies
    - Definition of risk factors for recommendation of the vaccine, if applicable
    - Definition of "immunized" (*see protocol*)
    - Verification of vaccination history (information sources, definition of vaccinated or unvaccinated)
- Definition of risk factors: preexisting conditions, variables recorded in the SARI files, defined by whom?
- Other factors (potential effect modifiers or confounding factors)
- Sample size
- Data collection
    - Sources, flow, responsible personnel, integration of the data
    - Variables used from the SARI record and variables from the vaccination history
- Validation of data, quality control
- Analysis (*see protocol or analysis plan*)
- Measurement of crude/adjusted VE
    - Univariate, stratified, multivariate analyses
- Ethical considerations
    - Secondary analysis of surveillance data, project not considered "research"
- Logistic aspects

Results

- Preparation for the evaluation? (Communication, training, materials?)
- The influenza season according to surveillance data for the year
    - Duration, peaks, predominant viruses, genetic changes, vaccine match with circulating viruses
- Patients included in the analysis (application of exclusion criteria)
    - Flow chart available to be filled out
    - Figure showing the distribution of SARI cases included in the analysis by week of symptom onset
    - Type/subtype?
- Univariate analysis
    - Comparison of characteristics of the cases and controls: sociodemographic, clinical, and vaccination status
    - Crude estimate of VE (1 minus vaccination odds ratio between cases and controls)

- Stratified analysis
    - Identification of possible effect modifiers or confounding factors
- Multivariate analysis
    - Selection of final logistic regression models for the adjusted VE
    - Exploration of heterogeneity between countries/regions
- Sensitivity analysis (according to sample size)
    - VE by subgroups
        - *Example:* children under 2 years old
        - Chronically ill persons
        - According to days between symptom onset and sampling
    - By different exposure
        - Children with full vaccination only
        - Vaccinated both years, current year only, or previous year only
    - By other outcomes
        - VE by type/subtype
        - ICU/death
    - Using other controls (positive for other respiratory viruses)

Discussion

- Main observations/findings:
    - Are the results congruent? Conclusive?
    - Are there factors affecting the crude vs. adjusted VE?
- Comparison with the literature
- Internal validity (exposure, illness…), quality control
- Possible sources of bias:
    - Classification of the disease and degree of exposure
    - Definition of a SARI case applied in the field
    - Selection of patients for sampling
    - Time elapsed between symptoms and sampling
    - Do controls have the same probability of being vaccinated?
- Limitations
    - Sample size?
    - Coverage reported at the national level versus proportion of the population vaccinated in the course of the evaluation
    - Integration of the data?
- Elements to take into account in the interpretation: characteristics of the season, population studied, matchup between the vaccine and the circulating strains, comparison with data from the region level, surveillance, other studies

- Next steps: Other seasons, system improvements, complementary studies, dissemination and use of the results

Conclusions

- Do the results suggest that the vaccine is effective? If so, for which groups?
- Has this method been able to provide precise estimates?
  - Have confounding factors been considered?
  - Has it provided estimates for prompt action?
  - Are they sustainable?

Recommendations

  - Practices, methodologies, organization of the work
  - Variables or definitions to be used
  - Laboratory techniques

References

Acknowledgments

- Include the members of the REVELAC-i team in the country.

ANNEX 15. Suggested Analysis Plan for the REVELAC-i Evaluation of Vaccine Effectiveness

1. **Description** of the characteristics of the "study site"(in this case, the country):
    a. Target populations for vaccination
    b. Organization of the campaign (dates, strategy)
    c. Populations included in the evaluation of vaccine effectiveness (VE)
    d. Organization of surveillance
    e. Characteristics of the participating hospitals
    f. Influenza season (including type/subtype)
    g. Contribution to the regional sample size; number of SARI cases reported by each hospital (cases/controls)

2. **Validation** of the data
    a. Verification of consistency/quality of the data
    b. Duplicates (same episode)
    c. Description of data coverage
    d. Correction of the information

3. **Recoding**, establishment of variables, creation of labels
    a. Variables without missing data (no information, does not know, etc.)
    – Other new variables: For example, cases of influenza A/B, A(H3N2), A(H1N1), influenza B Yamagata or Victoria lineage; vaccinated; days between symptom onset and sampling; presence of at least one chronic disease; days between vaccination and symptom onset; full vaccination (children)

4. **Selection of patients** for the analysis
    a. Confirm criteria for inclusion/exclusion

5. **Univariate analysis**
    a. Comparison of cases and controls

6. Measurement of **crude VE**
    a. 1 minus odds ratio (OR)

7. **Stratified analysis**
    a. Effect modification: Different OR between strata
    b. Confounding: OR (adjusted vs. crude)/crude >=10%?
    c. Correlation between outcome variable and exposure

8. **Multivariate analysis**
    a. Factors identified in the literature or recommended
    b. Factors identified in the univariate analysis
    c. Selection of final models

9. **Sensitivity analysis**
    a. By subgroups
        - For example: children under 2 years old
        - Chronically ill persons
        - According to days between symptom onset and sampling
    b. By time since vaccination: 2 weeks up to 3 (or 4) months; after 3 (or 4) months
    c. By different exposures
        - Only fully vaccination children
        - Vaccination both years, only current year, only previous year
    d. By other outcomes
        - VE by type/subtype
        - ICU/death
    e. Using other controls
        - Positive for other respiratory viruses