WHO STRATEGY TO PILOT GLOBAL RESPIRATORY SYNCYTIAL VIRUS SURVEILLANCE BASED ON THE GLOBAL INFLUENZA SURVEILLANCE AND RESPONSE SYSTEM (GISRS)

GENEVA, SWITZERLAND
2017
WHO strategy to pilot global respiratory syncytial virus surveillance based on the Global Influenza Surveillance and Response System (GISRS)

ISBN 978-92-4-151320-3

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# 1. Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ARI</td>
<td>Acute respiratory infection</td>
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<tr>
<td>BAL</td>
<td>Broncho-alveolar lavage</td>
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<tr>
<td>CHD</td>
<td>Congenital Heart Disease</td>
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<tr>
<td>ED</td>
<td>Emergency department</td>
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<tr>
<td>GISRS</td>
<td>Global Influenza Surveillance and Response System</td>
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<tr>
<td>HIC</td>
<td>High-income countries</td>
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<tr>
<td>ILI</td>
<td>Influenza-like illness</td>
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<tr>
<td>IT</td>
<td>Information technology</td>
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<td>LMICs</td>
<td>Low and middle-income countries</td>
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<tr>
<td>MTA</td>
<td>Material Transfer Agreement</td>
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<tr>
<td>NIC</td>
<td>National Influenza Centre</td>
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<tr>
<td>NP</td>
<td>Nasopharynx</td>
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<tr>
<td>NPA</td>
<td>Nasopharyngeal aspirate</td>
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<tr>
<td>OPD</td>
<td>Out-patient department</td>
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<tr>
<td>RSV</td>
<td>Respiratory Syncytial Virus</td>
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<tr>
<td>SARI</td>
<td>Severe Acute Respiratory Infection</td>
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<tr>
<td>WHO CC</td>
<td>World Health Organization Collaborating Center</td>
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**WHO Regions:**

<table>
<thead>
<tr>
<th>Region</th>
<th>Description</th>
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<tbody>
<tr>
<td>AFR</td>
<td>African Region</td>
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<tr>
<td>AMR</td>
<td>Region of the Americas</td>
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<tr>
<td>EMR</td>
<td>Eastern Mediterranean Region</td>
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<tr>
<td>EUR</td>
<td>European Region</td>
</tr>
<tr>
<td>SEAR</td>
<td>South-East Asian Region</td>
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<td>WPR</td>
<td>Western Pacific Region</td>
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2. INTRODUCTION

Respiratory Syncytial Virus (RSV) has long been recognized as an important respiratory pathogen often causing severe disease and mortality, particularly in very young children but also in other age and at-risk groups. The global burden of RSV-associated acute lower respiratory infection is estimated at 33 million annually resulting in more than 3 million hospitalization and 59,600 in-hospital deaths in children under 5-years age. Furthermore, RSV-associated acute lower respiratory infection accounted for 1.4 million hospitalizations, and 27,300 in-hospital deaths in infants less than 6 months age \(^1\). Many countries have recognized the importance of this pathogen and have established surveillance of RSV in certain settings.

The World Health Organization (WHO) has conducted global surveillance of influenza for more than 60 years through a network of laboratories known as the Global Influenza Surveillance and Response System (GISRS). Despite epidemiological differences in influenza and RSV disease, commonalities such in the population including children under surveillance, sentinel sites, specimen source, laboratory diagnostic infrastructure, and personnel, the long-established, well-functioning GISRS platform offers a cost-effective opportunity to leverage existing capacity to test for RSV without disturbing ongoing influenza surveillance.

WHO is committed to building surveillance of RSV using the GISRS platform. In the long term, global RSV surveillance will provide a better understanding of this virus, the diseases it causes, its seasonality in different countries and geographic regions and the healthcare burden due to RSV disease. Most importantly, RSV surveillance will help identify risk groups that will profit most from immunization once vaccines become available. The RSV surveillance platform will provide baseline information based on which vaccine effectiveness can be evaluated following implementation of vaccination programs. Data from RSV surveillance will alert health officials and decision-makers to the importance of RSV infections and related complications as a significant public health concern.

Over a period of three years, appropriate and feasible processes for RSV surveillance will be established and evaluated in the RSV Surveillance Pilot. To this goal, WHO regional offices have identified two or three countries to participate in the Pilot in each of the six regions where RSV Surveillance is already being performed. Each country is expected to assign national RSV focal points for laboratory and epidemiological aspects of this Pilot. Activities of the Pilot will only be conducted at selected laboratories and sentinel sites. The Pilot must not affect established national surveillance systems. National systems, however, may benefit from experiences and results of the Pilot.

This document presents the WHO strategy for leveraging the existing capacities of the GISRS network for RSV surveillance without compromising influenza surveillance. It is intended for use by the GISRS network, national influenza surveillance systems that are participating in the WHO Global RSV surveillance pilot and international entities interested directly and indirectly in RSV surveillance.

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\(^1\) Shi et al (2017), [http://dx.doi.org/10.1016/S0140-6736(17)30938-8](http://dx.doi.org/10.1016/S0140-6736(17)30938-8)
3. **OBJECTIVES OF THE RSV SURVEILLANCE PILOT**

RSV surveillance is to be built on the GISRS platform. However, the GISRS platform may not cover certain important aspects of the epidemiology and clinical presentation of RSV. In addressing these aspects, an important objective of the RSV Surveillance Pilot is to assess the suitability of the GISRS platform for RSV surveillance. In addition, the Pilot will identify ways for expansion of existing surveillance criteria to meet the needs for RSV surveillance without negatively affecting influenza surveillance. The Pilot will provide information on how well case definitions currently used for influenza capture RSV diseases.

Primary objectives of the RSV Surveillance Pilot are to:

- standardize laboratory procedures for RSV detection and quality assurance
- establish the feasibility of RSV surveillance built on the GISRS platform for future global expansion
- identify clinical signs and symptoms associated with RSV infections in order to propose case definitions for RSV in different age groups
- assess the performance of proposed sampling strategies for RSV diagnosis
- identify RSV seasonality in different countries and geographical regions
- determine age and risk groups for severe RSV disease
- assess the feasibility of FluNet and FluID for reporting RSV data
- report surveillance statistics to raise awareness and provide evidence to inform global and national policy decisions, and
- assess additional cost incurred through the implementation of RSV surveillance (including additional clinical, epidemiological, and laboratory costs)

Secondary objectives of the RSV Surveillance Pilot are to:

- provide improved knowledge on RSV burden in hospitalized and community patients
- gain experience from the Pilot to define the role of RSV Reference Laboratories within a future global RSV surveillance program
- document the level of GISRS staff acceptance of additional procedures and reports, and of potential negative impacts on existing influenza surveillance
- contribute to development of a future platform for a broader respiratory virus surveillance
- provide a platform for future RSV studies such as:
  - global RSV surveillance
  - burden of disease studies in different age and risk groups
  - vaccine studies (including vaccine effectiveness studies and studies evaluating any changes in age incidence after introduction of vaccines)
  - cost effectiveness and impact analyses of vaccines and other interventions, and
  - studies of the evolution over time of RSV strains by subtype and genotype and its possible relationship to vaccine effectiveness

The RSV Surveillance Pilot will **not** provide the following:

- diagnostic services
- data on general population-based RSV disease burden
- data which can be used directly to assess RSV vaccine effectiveness
- data on economic burden due to RSV disease, and
- data which will give a complete and detailed clinical description of RSV disease in all age and at-risk groups
4. COUNTRIES PARTICIPATING IN THE PILOT

The WHO Global Influenza Programme (GIP) and the six WHO regional offices jointly invited two to three countries in each WHO region to participate in the RSV Surveillance Pilot. The Pilot countries have a functioning Sentinel Influenza Surveillance System and National Influenza Centre (NIC) of GISRS. The countries perform influenza surveillance based on a well-structured sentinel surveillance network, regularly provide influenza data to WHO, and have included various RSV detection protocols in their routine activities.

For the list of participating countries, refer to appendix B. In addition, three reference laboratories with extensive experience in RSV diagnostics and research have agreed to assume a reference function and to provide support to the Pilot laboratories. These three laboratories are:

- The Centers for Disease Control and Prevention (CDC), Atlanta GA, USA
- The laboratory of Public Health England (PHE), London, UK, and
- The National Institute for Communicable Diseases (NICD), Johannesburg, South Africa

5. CASE DEFINITIONS FOR THE PILOT

The following case definitions provide a background for the Pilot and may help to identify patients that could be included in the Pilot.

Countries implementing hospital-based RSV surveillance

Hospital-based RSV surveillance will be based on the extended definition of Severe Acute Respiratory Infection (SARI).

SARI is currently defined by WHO [1] as follows:

- **severe** is defined as requiring hospitalization
- **acute** is defined as onset within the last 10 days
- **respiratory infection** is defined as having
  - history of fever or measured fever of ≥38 °C, and
  - cough [in some sites cough or shortness of breath]

A significant fraction (often >50%) of RSV-infected young children and elderly patients present without fever. Therefore, hospital-based RSV surveillance will include patients of all ages with or without fever (reported or measured) that otherwise meet the SARI case definition.

Countries implementing SARI surveillance should use the **extended SARI** case definition for hospital-based RSV surveillance as follows:

- **severe** is defined as requiring hospitalization
- **acute** is defined as onset within the last 10 days
- **respiratory infection** is defined as having
  - cough [in some sites cough or shortness of breath]

RSV disease commonly presents with other signs in the 0-6 months age group. Therefore, hospital-based RSV surveillance in children aged 0-6 months must additionally include those who present with apnoea and / or sepsis.
• Apnoea is defined as temporary cessation of breathing from any cause\(^2\)
• Sepsis, in children 0-6 months of age is defined as [2]:
  o fever (37.5 °C or above) or hypothermia (less than 35.5 °C), and
  o shock (lethargy, fast breathing, cold skin, prolonged capillary refill, fast weak pulse), and
  o seriously ill with no apparent cause

**Countries implementing community-based RSV surveillance**

RSV surveillance in the community should be based on the Acute Respiratory Infection (ARI) definition.

ARI is defined as follows\(^3\).

- **acute** is defined as sudden onset of symptoms.
- **respiratory infection** is defined as having at least one of the following:
  - cough
  - sore throat
  - shortness of breath
  - coryza

**Countries implementing ARI surveillance should continue to use the ARI case definition for community-based RSV surveillance in the Pilot.**

However, in countries implementing influenza-like illness (ILI) surveillance, an extended ILI case definition may be used in its place to also include those without fever.

**ILI is currently defined by WHO as [1] follows:**

- **acute** is defined as onset within the last 10 days
- **respiratory infection** is defined as having:
  - measured fever of ≥38 °C, and
  - cough

A significant fraction (often >50%) of RSV-infected young children and elderly patients present without fever. Therefore, community-based RSV surveillance will also include patients of all ages who do not have fever or a history of fever, but otherwise meet the ILI case definition.

**Countries implementing ILI surveillance should use the extended ILI case definition as above for community-based RSV surveillance in the Pilot.**

- **acute** is defined as onset within the last 10 days
- **respiratory infection** is defined as having:
  - cough

**Countries implementing both hospital- and community-based RSV surveillance**

Countries implementing both hospital and community based surveillance should consider prioritizing hospital-based surveillance sites over community-based surveillance to target more severe forms of

\(^3\) European Centre for Disease Prevention and Control. Influenza case definitions.

RSV disease, and should use the extended SARI and extended ILI or ARI case definition for hospital-based and community-based RSV surveillance respectively, in the Pilot.

6. SELECTION OF SENTINEL SITES

Countries participating in the Pilot need to develop instructions for the identified surveillance sites, according to the WHO Strategy for the Global RSV Surveillance Pilot.

Hospital-based RSV surveillance

Hospital-based surveillance sites should be chosen to ensure that the minimum sample size for the Pilot is achieved. This should include where available:

- Pre-admission out-patient units:
  - Accident and emergency rooms
  - Hospital out-patient clinics
- In-patient wards:
  - Pediatric
  - Adult general medical
  - Adult medical specialty wards – respiratory, infectious diseases
- Intensive care units:
  - Adult intensive care
  - Pediatric intensive care and neonatal intensive care

Sample collection should, where possible, take place prior to a patient’s admission to a hospital ward, (at the site where the decision to admit the patient is made).

Community-based RSV surveillance

The RSV Surveillance Pilot will enroll patients with ARI and extended ILI from outpatient sentinel sites. Surveillance should thus take place in primary and secondary health care sentinel sites/health care facilities.

7. SAMPLING STRATEGY

RSV surveillance should primarily be hospital-based. The reason for this is that once RSV vaccines become available, they will primarily aim at preventing severe cases, that is cases that require hospital treatment.

The SARI case definition does not meet optimal criteria for RSV surveillance. SARI definitions require that the patient has a fever of ≥ 38 °C when seen by a health care worker or a history of fever during the previous 10 days. RSV-infected children and elderly often present without fever or history of fever. This means that the sampling strategy eventually needs to be expanded beyond patients meeting SARI case definitions to also include cases that do not have fever or a history of fever.

RSV causes severe infections in very young children, particularly in infants during their first three months of life. This age group is often not well covered by influenza surveillance, which means that sampling strategies would need to be expanded to cover for these infants. Since this is an important aspect of the health care burden for RSV, it is important to ensure that there are a sufficient number of cases sampled in this age group; hence the sampling quotas given below. In some GISRS settings, this
may require new surveillance sites to be set up in pediatric hospitals. In other settings, this may not be required but increased priority may need to be given to surveillance in this age group.

Community-based RSV surveillance should be based on the ARI case definition as this does not require fever or history of fever as one of the inclusion criteria. If ILI surveillance is being used, then countries should adopt an extended ILI definition which does not require the presence of fever. However, these case definitions are likely to miss very young infants who often present with apnoea and signs of sepsis.

**Sample size by age distribution for RSV surveillance:**

Countries should aim to collect a minimum of 20 samples per week totaling approximately 1000 samples per year. These samples should cover all age groups. In order to ensure that these quotas are being met, laboratories should report back to the sentinel sites so they can adjust patient recruitment as required. Sampling strategies should also include individuals belonging to special risk groups.

- 250 samples per year from children between 0 to <6 months. This should include samples across all of this age group and not just samples from older infants 4-6 months of age
- 250 samples per year from children 6 months to <5 years
- 250 samples per year from individuals 5 to 64 years
- 250 samples per year from elderly (≥65 years)

A sample size of 250 would allow a RSV prevalence of 5 to 10% to be detected with an absolute precision of about 2.5% with 95% confidence in each of the age group. For information on how these calculations have been done, please refer to: [http://sampsize.sourceforge.net/iface/](http://sampsize.sourceforge.net/iface/)

**Selection of patients for collecting specimens**

**Age groups 6 months and above**

1) Check if case meets SARI or “SARI with no fever” case definition
2) Check eligibility for testing:
   a) Meets “SARI with no fever” case definition – eligible for RSV testing only
   b) Meets SARI case definition – eligible for both influenza and RSV testing
   c) Meets neither SARI nor “SARI with no fever” case definitions – not eligible for testing
3) Select a sample of cases to take a respiratory specimen and test for RSV (among eligible cases in categories 2a and 2b above) to make up quotas for each age group (6 months to <5 years; 5 to 64 years; ≥65 years)

**Age group less than 6 months**

1) Check if case meets SARI or “SARI with no fever” or “apnoea” or “sepsis” case definition
2) Check eligibility for testing:
   a) Meets “SARI with no fever” or apnoea or sepsis case definitions – eligible for RSV testing only
   b) Meets SARI case definition – eligible for both influenza and RSV testing
   c) Meets neither SARI nor “SARI with no fever” nor apnea nor sepsis case definition – not eligible for testing
3) Select a sample of cases to take a respiratory specimen and test for RSV (among eligible cases in categories 2a and 2b above) to make up quota for the <6 months age group

A true random sampling scheme is most representative but may not be practical in surveillance settings. A systematic random sampling scheme that does not leave the selection of patients to test up
to health care providers (other than to determine eligibility for testing) and that covers different times of the day and different days of the week, is most likely to be representative of the population eligible for sampling. Sentinel surveillance sites can adopt a sampling approach they find to be most appropriate locally to conduct the RSV surveillance so that sampling quotas are reached. It is understood that the approach may vary from site to site. However, a few general comments are relevant to all sites.

- Ensure that across all age groups a minimum of 20 samples are taken and tested for RSV each week throughout the entire year so that RSV seasonality can be assessed
- In order to meet age group quotas by the end of the year, obtain regular feedback from the Pilot coordinator (or Pilot study laboratory) on progress towards meeting these targets and adjust your sampling strategy accordingly
- Ensure that the cases selected for RSV testing include a reasonably representative selection of all eligible cases (in 2a and 2b). This may mean that there will be a similar number of cases tested in the SARI and in the “SARI with no fever” groups

The laboratory should monitor the recruitment of patients and submission of samples weekly to ensure that the minimal sample sizes by age group are met as outlined above. The laboratory should provide regular feedback to sentinel sites regarding age group distribution to ensure that the minimum quotas for respective groups are met.

Where sample submission exceeds the quota of 20 samples per week, as resources for more than 1000 tests annually is limited, the laboratory should maintain an average testing of 20 samples per week unless there are additional resources available to test the additional samples. Where sample submission does not meet the quota of 20 samples per week, additional samples collected for influenza surveillance should be tested for respective age groups in the periods of increased respiratory activity.

Each country should select its sampling strategy according to available resources, but the sampling strategy used should be selected to minimize bias and must be well documented and reported (Figure 1).

**Duration of surveillance period**

During the Pilot, RSV surveillance will be conducted all year round. In many countries, the seasonality of RSV has not been exactly defined, and the RSV season may even differ from geographic region to region within a country. To better characterize RSV seasonality, RSV surveillance should be extended to continue throughout all of the year. Even if the RSV peak season is known in a country or region, surveillance should be continued after this peak period throughout the year.

To determine RSV seasonality and to meet the objectives, the Pilot will require a minimum of 20 samples to be tested for RSV each week throughout the year. A 10% threshold of RSV-positive specimens during two consecutive weeks may indicate the onset of the season. If the positivity rate falls below 10%, this may indicate the offset of the season. When laboratory results indicate an increased number of RSV-positive specimens, enhance sampling and testing accordingly and achievable with existing resources. Data generated during the course of the Pilot will better indicate the seasonality of RSV in participating countries.


8. LABORATORY TESTING

a) COLLECTION OF CLINICAL SPECIMENS

i. The optimal type of clinical specimens for the detection of RSV and influenza viruses to some extent depends on the age of the patient.

ii. For infants and young children, the nasopharyngeal swab or nasal swab taken from the mid-turbinate of the nose have been found to yield high recovery of respiratory viruses 7,8 (Appendix D).

iii. As an alternative, nasopharyngeal aspirates may be collected particularly from young children.

iv. From older children, adolescents and adults, both nasal and throat swabs should be collected in the same tube containing viral transport medium. Collection of specimens must be done using flocked nylon swabs and not cotton-tipped or calcium alginate swabs.

v. In severe hospitalized cases, lower respiratory specimens may also be collected where indicated. These include tracheal aspirate and broncho-alveolar lavage.

vi. In older adults and elderly, collection of sputum samples may be an option9 in certain cases.

vii. For each specimen collected, a corresponding RSV data collection form must be duly completed. The forms must be placed in a separate pouch (envelope) and sent to the laboratory along with the specimen.

b) TRANSPORT AND STORAGE OF CLINICAL SAMPLES

Storage of clinical specimens at the site of collection and their transport to the laboratory should follow similar guidelines as used for influenza specimens. After collection, prior to and during transport specimens should be kept at 4 °C for no longer than 72 hours before being processed in the laboratory. For longer storage periods, specimens must be kept at -70 °C. For storage and transport, appropriate biosafety recommendations must be strictly adhered to. When the specimen arrives at the laboratory, aliquot the specimen immediately (in 3-4 vials of approximately 0.5 ml) and freeze at -70 °C.

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6 WHO Manual for the laboratory diagnosis and virological surveillance of influenza.2011


8 Centre for Disease Control and Prevention. Influenza Specimen Collection.

c) **ALGORITHM FOR SURVEILLANCE AND TESTING**

![Algorithm Diagram]

**FIGURE 1: RSV SURVEILLANCE ALGORITHM**

1 Minimum sample size requirements for hospital surveillance and RSV testing:
   - 250 samples per year from children between 0 to <6 months
   - 250 samples per year from children 6 months to <5 years
   - 250 samples per year from individuals 5 to 64 years
   - 250 samples per year from elderly (≥65 years)

2 SARI and ARI with and without fever including infants aged 0-6 months with apnoea and sepsis

3 All specimens submitted from suspected RSV cases must be accompanied by a fully completed RSV specimen submission form

4 If more than 20 specimens per week can be collected from both groups 1 and 2 above, attempt to test 40% to 50% of specimens from patients with the **extended SARI** (SARI patients without fever) or ARI definition

**d) LABORATORY TECHNIQUES FOR THE DETECTION OF RSV**

Several countries and laboratories perform immunofluorescent staining of exfoliated respiratory epithelial cells for the detection of RSV and other respiratory viruses. While this technique produces reliable results on specimens collected from young children, the sensitivity of this technique rapidly
decreases with increasing age of the patient. Real-time polymerase chain reaction (PCR) for RSV is the gold standard test used in the Pilot. Once countries have validated their existing assays against the CDC PCR assay, they may opt to continue using their existing RSV protocols or use the protocol supplied by CDC. Three Reference RSV Laboratories have been selected for the Pilot. These include CDC Atlanta, PHE London, and NICD Johannesburg.

All Reference Laboratories have participated successfully in the 2015 RSV panel provided by Quality Control for Molecular Diagnostics (QCMD) using their own in-house testing assays. The QCMD Proficiency Test consisted of 10 RSV-positive and RSV-negative samples. All three laboratories achieved maximum scores and correctly identified all panel samples. This was followed by the analysis and comparison by WHO of the QCMD RSV Proficiency Test results including Ct values. Results were comparable between the three laboratories. Whereas all three Reference Laboratories will provide technical support to Pilot countries, CDC will provide the real-time PCR Protocol for RSV, Proficiency Test panels and RSV primers and probes to Pilot countries.

Testing strategies:

i. Real-time
   1. Laboratories test incoming specimens for influenza viruses and for RSV when the specimens arrive at the laboratory

ii. Batch testing
   1. Laboratories test specimens for RSV in batches, for example, once a week
   2. Testing strategies must be chosen by the laboratories according to available resources

Positive control must be included in each test run. If the Ct value of the positive control falls below range, the positive control should be changed.

e) QUALITY ASSURANCE

Laboratories participating in the RSV Surveillance Pilot should use highly sensitive and specific PCR methods. At the beginning of the Pilot, CDC Atlanta will distribute a panel of specimens containing RSV at different concentrations. Laboratories are requested to return their results within a specified period. Should laboratories achieve suboptimal scores with their own, in-house RSV tests, they are encouraged to use the testing protocol provided by CDC. During the RSV Surveillance Pilot period of three years, CDC will distribute similar quality assurance panels annually.

- Internal quality assurance: laboratories must maintain and document rigorous internal quality control
- External quality assurance: refer to appendix C for the Terms of Reference for RSV Reference Laboratories

9. DATA COLLECTION

The RSV Submission Form (appendix E) to be used for the Pilot includes the optimal case-based, clinical, epidemiological and laboratory data that should be collected from sentinel sites and laboratories. The case-based clinical data will be assessed to determine the performance of the case definition for RSV infection in different age groups. The epidemiological and laboratory data will be monitored for seasonality trends and disease burden.
10. Reporting of Case-based Data

Laboratory testing of surveillance specimens is not intended for diagnostic purposes. It is not the intention of the Pilot, therefore, to provide a diagnostic service to submitting health care workers. Sentinel sites will, however, receive laboratory results in keeping with surveillance guidance as established in the participating country.

In order to meet the objectives of this RSV Surveillance Pilot, case-based reporting of epidemiological, clinical information and laboratory results to WHO headquarters is required. Case-based data, as outlined in the RSV specimen submission form, will be submitted along with the specimen to the designated national laboratory (NIC) for testing for RSV. Countries are encouraged to adapt their specimen submission form without compromising the minimum information that is required for the Pilot.

Anonymized case-based data, along with the laboratory results, will be uploaded by the designated person at the GIP website as an Excel sheet, or as directed by the WHO, to the GISRS on the FluMart platform. Countries are requested to upload data on a weekly basis. Queries in uploading and mapping the data should be communicated to the GISRS support team.

The FluMart platform will be used to aggregate data to generate real-time outputs for age-stratified trends in RSV activity and seasonality. Additionally, the case-based data will be analyzed separately to evaluate the most suitable case definition for RSV surveillance.

Countries should take responsibility to assure confidentiality of case-based data and for quality control of data collection, management, storage and reporting (including electronic transfer) using locally-accepted procedures. Data access will be restricted to participating countries and WHO.

11. Outputs from the Pilot

a) Surveillance Outputs

The RSV surveillance will report the proportion of cases meeting the standard RSV case definitions which are RSV-positive in different age groups. Outputs of the RSV surveillance that give some information about the hospital burden of RSV therefore include:

Primary outputs:

- Percentage of cases identified using extended SARI definition that are RSV-positive by age group [to identify most important age groups at risk]

- Number and percentage of cases identified using extended SARI definition that are RSV positive by calendar week [to define seasonality]

A number of additional, secondary, epidemiological outputs can be reported if an estimate is made of the total number of cases identified using extended SARI definition [by age group and month].
Secondary outputs:

- Estimated number of cases identified using extended SARI definition that are RSV-positive [by age group and month]
- Percentage of total hospital admissions that are due to RSV positive disease [by the specified age group and by month]
- Relative number of cases of RSV-positive disease compared to those for influenza and other locally defined priority conditions [by the specified age groups]
- Proportion of RSV-positive cases identified using extended SARI definition that would have been identified with the original SARI case definition [by age group]

Estimating the burden of RSV-associated hospitalization

Data on the total number of hospitalization associated with RSV disease at each surveillance site is useful to indicate the hospital burden of disease at that surveillance site and to estimate the proportional contribution of RSV-associated disease episodes to all-cause hospitalization and to compare that with hospitalizations due to other diseases.

If the surveillance screens and tests all cases meeting the extended SARI case definition, then these should be reported by age group and by month. However, in many surveillance sites, the Pilot will not aim to recruit and test all cases but only the recommended target number of cases so that the 1000 case quota for each country is achieved. Since not all cases meeting the case definition will have been recruited and tested, in order to estimate the total number of RSV positive cases, there needs to be correction for this under-detection of RSV-associated disease episodes.

- Thus, in the example of a hospital-based RSV surveillance site that admits 500 cases meeting the extended SARI case definition over a one-year period, and tests 250 of these and finds that 100 of those tested are positive for RSV. The sampling proportion is therefore 250 / 500 or 0.5. The total number of RSV positive cases can then be approximately estimated to be 200 (100 / 0.5) in this age group over the one-year period

The total number of RSV-positive cases in a specific age group in a hospital-based RSV surveillance site is thus:

\[
\text{No. of cases identified using extended SARI definition that are RSV positive} \\
\text{Prop. of cases identified using extended SARI definition that were tested for RSV}
\]

(Note: This assumes that the percentage of RSV-positive cases is similar in those who were tested and those who were not tested (during a particular time period) and that there is no significant bias in the selection of patients for RSV testing. Since these assumptions are often not fully met, this estimation of the true number of RSV-positive cases can only be an approximation.)

To carry out this calculation, the total number of cases meeting the extended SARI case definition in each group needs to be counted through a chart audit. This should be done:

- separately for each surveillance site, and
- separately for the main age groups: 0-4 years, 5-64 years, and 65 years and above

Ideally, this should be done by calendar month and then aggregated to give an annual estimate. But if this is not possible, then this can be done based on annual aggregate data.

---

10 RSV disease defined by cases identified using extended SARI definition that are RSV-positive
If it is not possible to obtain data on the total number of cases meeting extended SARI case definitions, then in some settings it may be possible to obtain an approximation of the true number of cases identified using extended SARI definition by a review of hospital discharge codes where these are available and of high quality. A review should be made of International Classification of Diseases (ICD) coding (in any of the first three diagnostic code positions for an episode) of admissions. The relevant ICD9 and ICD10 codes are given in the WHO Manual for Estimating Disease Burden Associated With Seasonal Influenza [3]. These include:

- ICD9 codes 487, 488.01, 488.11 [for SARI] and 771.81, 995.91, 995.92 [for sepsis] or
- ICD10 J09.01, J09.11, J10.0, J11.0 [for SARI] and P36.0-36.9, R65.2, A40, A41 [for sepsis]

It would be helpful in interpreting these data if countries made an audit of how these ICD codes relate to the extended SARI case definition as coding practices can vary from country to country. An estimate can then be made of what proportion of those admitted with these ICD codes were recruited and tested for RSV in each surveillance site.

To be able to estimate the secondary outputs, countries should also collect the following monthly aggregated denominator data for each hospital-based surveillance site aggregated by the specified age groups and by month:

- total number of all-cause hospital admissions, and
- total number of hospital admissions for pneumonia or other severe acute respiratory illness (also include admissions for sepsis in those 0-5 months of age)

**Population-based burden of RSV disease**

Surveillance data on RSV cases do not provide population-based burden of disease estimates since the denominator (or catchment) populations of the surveillance sites are not generally known. However, in settings in which population-based denominators are available then it may be possible to obtain these estimates using the methods described in the WHO Manual for Estimating Disease Burden Associated With Seasonal Influenza [3].

**b) LABORATORY OUTPUTS**

- Pilot laboratories will build and improve capacity for RSV testing by real-time PCR
- Evaluation, analysis and standardization of non-CDC RSV PCR protocols
- Implementation of annual RSV proficiency testing
- Reporting of RSV results in a standardized format
- Seasonality of RSV in Pilot countries

**Secondary outputs:**

- Typing and molecular characterization of representative RSV samples.
a) Monitoring

Continued evaluation, using designated indicators would be developed to ascertain success of this Pilot. Monitoring will be conducted throughout the duration of the Pilot and on all levels involved which include: sentinel sites, national laboratories, national epidemiologists, reference laboratories and WHO headquarters (Figure 2).

The following parameters will be monitored:

- patient selection at the sentinel site
- quality of collected specimens including storage
- completeness, accuracy and reliability of specimen submission forms, and
- turnaround time of specimen transport to the laboratory, laboratory analysis, timely reporting of laboratory and case-based data to the GISRS platform, support provided by reference laboratories, compilation and analysis of data at headquarters

Compliance with regulations including patient confidentiality must be strictly maintained. Countries should monitor additional resources used for the Pilot (reagents, staff training, data management, and project logistics. Countries must ensure that their existing influenza surveillance is not impacted negatively by the Pilot.
Monitoring at the sentinel site should include (to be performed by the national focal points assigned for virological and epidemiological aspects of the Pilot):

- staff training
- appropriate recruitment of patients according to Pilot criteria
- availability of appropriate specimen collection supplies
- completeness and accuracy of specimen submission forms
- storage and transport of specimens and submission form
- interaction between sentinel site, laboratory and national focal point, and
- adequate documentation of Pilot-related activities

Monitoring at the national laboratory should include:

- staff training
- availability of appropriate equipment and reagents
- performance in internal and external quality assurance
- adherence to standard operational procedures
- storage and laboratory facilities
- biosafety and biosecurity measures
- data entry and reporting to the GISRS platform
- reporting back to the sentinel sites
- interaction between sentinel site, national focal point, and WHO headquarters
- adequate documentation of Pilot-related activities, and
- internal and external quality control

Monitoring at the RSV reference laboratories should include:

- performance in internal and external quality assurance
- communication with Pilot countries and WHO headquarters
- adherence to terms of references, and
- adequate documentation of Pilot-related activities

Monitoring at WHO GISRS level should include:

- availability of sufficient and qualified staff
- quality of laboratory and case-based data submitted:
  - Accuracy
  - Completeness
  - Timeliness
  - Relevance
- reliability and function of GISRS database
- feedback to RSV focal points
- Pilot budget utilization, and
- impact on influenza surveillance

b) **EVALUATION**

During and at the end of the three-year period, the Pilot must be thoroughly evaluated as to whether the aims and objectives have been achieved. Evaluation will be done by the WHO in collaboration with external experts and stakeholders.
Key aspects include:
- establishment of baseline epidemiological data for RSV
- establishment of the feasibility of RSV surveillance built on the GISRS platform
- validity of case definitions for RSV
- defined seasonality of RSV in different geographic regions
- identification of risk groups for severe RSV infection, and
- impact of Pilot on improved RSV awareness at the national and international level

13. ACKNOWLEDGEMENTS

The development of this manual was funded through a WHO grant no. OPP1127419 from the Bill & Melinda Gates Foundation, Seattle.

The WHO Global Influenza Programme (GIP) wishes to acknowledge the contributions of the experts who participated in the development and peer review of this manual – Shobha Broor (New Delhi, India), Harry Campbell (University of Edinburgh, UK), Siri Hague (Norwegian Institute of Public Health, Norway), Teresa Peret (CDC, USA), Florette Teurnicht (NICD, South Africa) and Maria Zambon (PHE, UK). Thanks are also due to all the national epidemiology and virology experts who provided their inputs at the WHO RSV meetings held in February and June 2016.

Staff in WHO regional offices and HQ involved in the process of development of the strategy include: Terry Besselaar, Julia Fitzner, Christian Fuster, Iris Hasibra, Siddhivinayak Hirve, Sandra Jackson, Rakhee Palekar, Kaat Vandemaele, Thedi Ziegler and Wenqing Zhang.
14. REFERENCES


15. **APPENDICES**

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E-mail: florettet@nicd.ac.za | www.nicd.ac.za
b) **LIST OF PARTICIPATING PILOT COUNTRIES**

- AFR: Côte d’Ivoire, Mozambique, South Africa
- AMR (PAHO): Argentina, Brazil, Chile, Canada
- EMR: Egypt
- EUR: Russia, UK
- SEAR: India, Thailand
- WPR: Cambodia, Mongolia
Background

Respiratory syncytial virus (RSV) is an important viral respiratory pathogen, causing acute, sometimes fatal lower respiratory tract infections in infants, young children and the elderly. With rapid progress in the development of RSV vaccines, it is expected that a vaccine will be available in the near future. In light of the significant public health impact of this virus, there is a critical need to develop and standardize RSV surveillance and to provide evidence based support for vaccination policies at the national, regional and global levels. Such evidence shall include the documentation of RSV epidemiology, seasonality, virology, and identification of high risk groups.

After two WHO Consultations with both RSV and influenza scientists and public health experts in March 2015 and February 2016, a consensus was reached to establish global RSV surveillance based on the existing influenza surveillance platform, the WHO Global Influenza Surveillance and Response System (GISRS). It was agreed that an integrated virological and epidemiological RSV surveillance system be launched as a Pilot in representative countries from all 6 WHO regions. Laboratories in these countries are referred to as RSV Pilot Laboratories. It was also agreed that selected laboratories with technical expertise, capacity and experience on RSV be designated to provide technical guidance on the virological component of RSV surveillance. These specialized laboratories, henceforth referred to as “Respiratory Syncytial Virus Reference Laboratory” or “RSV RL”, will function in the WHO Global RSV Surveillance Pilot according to WHO Terms of Reference for RSV Reference Laboratories. Additional Reference Laboratories may be designated as needs develop with the expansion of Global RSV Surveillance.

General conditions:

Respiratory Syncytial Virus Reference Laboratories;

1. work under the coordination of the WHO Global Influenza Programme (GIP);
2. fulfil the terms of reference using financial support provided only by governmental and/or other non-commercial sources;
3. assume full responsibility for complying with their respective national biosecurity and biosafety regulations on the understanding that such regulations and rules shall, at a minimum, meet the relevant and current WHO standards; and
4. appropriately acknowledge in presentations and publications, the contributions of collaborators, including RSV Laboratories and countries participating in the WHO RSV Surveillance Pilot.

General activities:

Respiratory Syncytial Virus Reference Laboratories:

1. serve as a technical resource to WHO and RSV Pilot Laboratories as time and resources permit;
2. monitor RSV Pilot Laboratories in Quality Assessments of their assays;
3. prepare and distribute RSV diagnostic reagents as agreed with WHO and as time and resources permit;
4. analyse performance of RSV Pilot Laboratories on EQA panels and submit timely feedback and reports to RSV Pilot Laboratories and WHO;
5. provide training and laboratory support to RSV Pilot Laboratories on laboratory techniques as time and resources permit; and
6. maintain and strengthen active communication and collaboration with RSV Pilot Laboratories and WHO to ensure that up-to-date information is exchanged.
Influenza Specimen Collection

Nasopharyngeal Swab

Materials:
- Sterile dacron/nylon swab
- Viral transport media tube (should contain 1-2 mL of sterile viral transport medium)

Procedure:
1. Hold patient’s head back 70 degrees.
2. Insert swab into nostril (Swab should reach depth equal to distance from nostril to outer opening of eustachian tube.)
3. Leave swab in place for several seconds to allow secretions to accumulate.
4. Slowly remove swab while rotating it. (Swab both nostrils with same swab)
5. Place tip of swab into sterile viral transport media tube and snap off the applicator tip.

Nasopharyngeal/Nasal Aspirate

Materials:
- Sterile suction catheter/suction apparatus
- Viral transport media tube (should contain 1-2 mL of sterile viral transport medium)

Procedure:
1. Attach catheter to suction apparatus.
2. Tilt patient’s head back 70 degrees.
3. Insert suction catheter into nostril (Catheter should reach depth equal to distance from nostril to outer opening of ear.)
4. Begin gentle suction. Remove catheter while rotating it gently.
5. Place specimen in sterile viral transport media tube.

Note: Nasal aspirate may not be possible to conduct in infants.

Nasopharyngeal/Nasal Wash

Materials:
- Sterile suction catheter/suction apparatus
- Sterile normal saline

Procedure:
1. Attach catheter to suction apparatus.
2. Tilt patient’s head back 70 degrees.
3. Insert several drops of sterile normal saline into each nostril.
4. Insert catheter into nostril. (Catheter should reach depth equal to distance from nostril to outer opening of ear.)
5. Begin gentle suction. Remove catheter while rotating it gently.
6. Place specimen in sterile viral transport media tube.

Note: Nasal aspirate may not be possible to conduct in infants.

Deep Nasal Swab

Materials:
- Sterile polyester swab (aluminum or plastic shaft preferred)
- Viral transport media tube (should contain 1-2 mL of sterile viral transport medium)

Procedure:
1. Tilt patient’s head back 70 degrees.
2. While gently rotating the swab, insert swab less than one inch into nostril until resistance is met (at the turbinates).
3. Rotate the swab several times against nasal wall and repeat in other nostril using the same swab.
4. Place tip of the swab into sterile viral transport media tube and cut off the applicator stick.

Combined Nasal & Throat Swab

Materials:
- 2 dry sterile polyester swabs (aluminum or plastic shafts preferred)
- Viral transport media tube (should contain 1-2 mL of sterile viral transport medium)

Procedure:
1. Tilt patient’s head back 70 degrees.
2. While gently rotating the swab, insert swab less than one inch into nostril until resistance is met (at the turbinates).
3. Rotate the swab several times against nasal wall and repeat in other nostril using the same swab.
4. Place tip of the swab into sterile viral transport media tube and cut off the applicator stick.
5. For throat swab, take a second dry polyester swab, insert into mouth, and swab the posterior pharynx and tonsillar areas. (Avoid the tongue.)
6. Place tip of swab into the same tube and cut off the applicator tip.

Packaging:
- Label the specimen on viral transport media tube and ensure cap on tube is tightly sealed.
- (Do not use a pencil or pen for labeling, as they can rub off or smear. Instead, use a bar code or permanent marker).
- Fill out paperwork in accordance with state health department guidelines.
- Include a frozen cold pack with the specimen(s).
- Pack specimens in accordance with U.S. Department of Transportation regulations regarding shipment of biological substances, see www.cdc.gov/flu/professional/kit/guides/index.htm.

Shipping:
- Ship specimens for testing as soon as possible.
- If delivery will be delayed for more than 3-4 days, specimen should be frozen at -70 degrees Celsius (-94 degrees Fahrenheit).
- Ensure specimen will be received by the public health laboratory during normal business hours.

Considerations:
- A nasopharyngeal (NP) swab is the optimal upper respiratory tract specimen collection method for influenza testing. However, such specimens cannot be collected from infants and many older patients may not allow an NP swab to be collected. Alternatively, a combined nasal and throat swab specimen or aspirate specimen can provide good influenza virus yield.
- Some influenza tests are approved only for use with certain kinds of respiratory tract specimens, so follow guidelines provided by test. Also, some tests (e.g., rapid influenza diagnostic tests) are only approved for certain kinds of respiratory tract specimens.
- For best results (i.e., highest influenza virus yield), collect respiratory tract specimens within four days of illness onset.
- Most sensitive and accurate tests for influenza virus detection are molecular or nucleic acid amplification tests (RT-PCR).
- Negative test results obtained from rapid influenza diagnostic tests (RIDTs) that detect influenza viral antigens do not exclude influenza virus infection in patients with signs and symptoms of influenza. A negative test result could be a false negative and should not preclude further diagnostic testing such as RT-PCR and starting empirical antiviral treatment.
- A surgical mask and gloves are recommended at a minimum for all procedures. For some patients and procedures, additional precautions may be indicated, see Standard Precautions at www.cdc.gov/hicpac/2001pdf/2001/4pt.pdf. www.cdc.gov
### RSV SUBMISSION FORM

<table>
<thead>
<tr>
<th>Country code</th>
<th>Site code (geographic location)</th>
<th>Patient’s unique identification no.</th>
<th>Type of surveillance site (e.g. hospital, medical centre)</th>
<th>Name of healthcare worker</th>
<th>Date of sample collection and completion of form (dd/mm/yyyy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

#### Patient Identification

<table>
<thead>
<tr>
<th>Family name</th>
<th>Given name</th>
<th>Gender</th>
<th>Date of birth (dd/mm/yyyy)</th>
<th>Age</th>
<th>Year</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

#### Clinical Information

<table>
<thead>
<tr>
<th>Date of symptom onset (dd/mm/yyyy)</th>
<th>_<em><strong><strong><strong><strong>/</strong></strong></strong></strong></em></th>
</tr>
</thead>
</table>

#### Signs & Symptoms:

<table>
<thead>
<tr>
<th>Requires hospitalisation</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom onset within last 10 days (acute)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cough</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Measured fever ≥38°C</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>History of fever</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Wheezing</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sore throat</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Coryza</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Coughing</td>
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<td>No</td>
</tr>
<tr>
<td>Shortness of breath</td>
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<td>No</td>
</tr>
<tr>
<td>Surinfection</td>
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#### Respiratory rate (breaths per minute)

#### Diagnosis

<table>
<thead>
<tr>
<th>Hospital admission diagnosis</th>
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</thead>
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#### Pre-existing medical conditions: ADULTS

<table>
<thead>
<tr>
<th>Chronic cardiac disease</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic respiratory disease (specify)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Other chronic medical condition (specify)</td>
<td>Yes</td>
<td>Not known</td>
</tr>
</tbody>
</table>

#### Pre-existing medical condition unknown

#### Pregnant

#### Pre-existing medical conditions: CHILDREN

<table>
<thead>
<tr>
<th>Premature</th>
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<th>No</th>
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</thead>
<tbody>
<tr>
<td>Chronic respiratory disease (specify)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Other chronic medical condition (specify)</td>
<td>Yes</td>
<td>Not known</td>
</tr>
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#### Laboratory Information

<table>
<thead>
<tr>
<th>Type of specimen</th>
<th>Nasal/throat swab</th>
<th>Nasopharyngeal aspirate</th>
<th>Tracheal aspirate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date sample received at laboratory (dd/mm/yyyy)</td>
<td>_<em><strong><strong><strong><strong>/</strong></strong></strong></strong></em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date sample tested (dd/mm/yyyy)</td>
<td>_<em><strong><strong><strong><strong>/</strong></strong></strong></strong></em></td>
<td></td>
<td></td>
</tr>
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</table>

#### Results

<table>
<thead>
<tr>
<th>RSV results</th>
<th>RSV positive</th>
<th>RSV negative</th>
<th>Sample not tested</th>
<th>Sample rejected</th>
<th>Inadequate sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV CT value (if RSV positive)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If subtype known, report</td>
<td>RSV A</td>
<td>RSV B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNP</td>
<td>Positive</td>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
f) REPORTS OF WHO MEETINGS

1) WHO Informal Consultation on Surveillance of RSV on the Global Influenza Surveillance and Response System (GISRS) Platform, 25–27 March 2015:

