
**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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Abbreviations

ARI	acute respiratory infection
CDC	Centers for Disease Control and Prevention
Ct	cycle threshold
GIP	Global Influenza Programme
GISRS	Global Influenza Surveillance and Response System
ICD	International Classification of Diseases
ILI	influenza-like illness
NIC	National Influenza Centre
NICD	National Institute for Communicable Diseases
PCR	polymerase chain reaction
PHE	Public Health England
QCMD	Quality Control for Molecular Diagnostics
RSV	respiratory syncytial virus
SARI	severe acute respiratory infection
United Kingdom	United Kingdom of Great Britain and Northern Ireland
USA	United States of America
WHO	World Health Organization

WHO regions:

AFR	African Region
AMR	Region of the Americas
EMR	Eastern Mediterranean Region
EUR	European Region
SEAR	South-East Asia Region
WPR	Western Pacific Region

1. Introduction

Respiratory syncytial virus (RSV) has long been recognized as an important respiratory pathogen that often causes 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 hospitalizations and 59 600 in-hospital deaths in children aged under 5 years. Furthermore, RSV-associated acute lower respiratory infections accounted for 1.4 million hospitalizations and 27 300 in-hospital deaths in infants aged under 6 months (1). Many countries have recognized the importance of this pathogen and have established surveillance of RSV in certain settings.

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). There are epidemiological differences between influenza and RSV disease, but also commonalities; for example, children being included in the population under surveillance, sentinel sites, specimen source, laboratory diagnostic infrastructure and personnel. Thus, 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, and its seasonality in different countries and geographical regions, as well as the health-care burden due to RSV disease. Most importantly, RSV surveillance will help to identify at-risk groups that will profit most from immunization once vaccines become available. The RSV surveillance platform will provide baseline information against which vaccine effectiveness can be evaluated following implementation of vaccination programmes. 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 3 years, appropriate and feasible processes for RSV surveillance will be established and evaluated in the RSV surveillance pilot. To achieve 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, and activities will only be conducted at selected laboratories and sentinel sites. The pilot must not affect established national surveillance systems; however, national systems may benefit from the experiences and results of the pilot.

This document presents WHO's 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 either directly or indirectly in RSV surveillance.

2. 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 in which existing surveillance criteria can be expanded 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 disease.

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 at-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 costs 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 programme;
- document the level of GISRS staff acceptance of additional procedures and reports, and of potential negative impacts on existing influenza surveillance;
- contribute to the development of a future platform for a broader respiratory virus surveillance; and
- provide a platform for future RSV studies such as:
 - global RSV surveillance;
 - burden of disease studies in different age and at-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 the possible relationship between evolution of strains and vaccine effectiveness.

The RSV surveillance pilot will **not** provide the following:

- diagnostic services;
- data on RSV disease burden in the general population;
- data that can be used directly to assess RSV vaccine effectiveness;
- data on economic burden due to RSV disease; and
- data that will give a complete and detailed clinical description of RSV disease in all age and at-risk groups.

3. 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) for 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.

The list of participating countries is given in 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, Georgia, United States of America (USA);
- the laboratory of Public Health England (PHE), London, United Kingdom of Great Britain and Northern Ireland (United Kingdom); and
- the National Institute for Communicable Diseases (NICD), Johannesburg, South Africa.

4. 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.

4.1 Countries implementing hospital-based RSV surveillance

Hospital-based RSV surveillance will use the extended definition of severe acute respiratory infection (SARI). SARI is currently defined by WHO (2) as follows:

- *severe* is defined as requiring hospitalization;
- *acute* is defined as onset within the past 10 days; and
- *respiratory infection* is defined as having:
 - history of fever or measured fever of 38 °C or more; and
 - cough (in some sites, cough or shortness of breath).

A significant fraction (often >50%) of young children and elderly patients infected with RSV present without fever. Therefore, hospital-based RSV surveillance will include patients of all ages, with or without fever (reported or measured), who 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 past 10 days; and
- *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 or sepsis (or both):

- *apnoea* is defined as temporary cessation of breathing from any cause (3); and

- sepsis in children aged 0–6 months is defined as (4):
 - fever (≥ 37.5 °C) or hypothermia (< 35.5 °C); and
 - shock (lethargy, fast breathing, cold skin, prolonged capillary refill or fast weak pulse); and
 - seriously ill with no apparent cause.

4.2 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:

- *acute* is defined as sudden onset of symptoms; and
- *respiratory infection* is defined as having at least one of the following:
 - cough;
 - sore throat;
 - shortness of breath; or
 - 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 place of the ARI case definition for community-based RSV surveillance, to also include those without fever. ILI is currently defined by WHO as follows (2):

- *acute* is defined as onset within the past 10 days; and
- *respiratory infection* is defined as having:
 - measured fever of 38 °C or more; and
 - cough.

A significant fraction (often >50%) of young children and elderly patients infected with RSV 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 follows, for community-based RSV surveillance in the pilot:

- *acute* is defined as onset within the past 10 days; and
- *respiratory infection* is defined as having cough.

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

Countries implementing both hospital-based and community-based RSV surveillance should consider prioritizing hospital-based RSV surveillance sites over community-based RSV surveillance, to target more severe forms of RSV disease. Also, in the pilot they should use the **extended SARI** and **extended ILI** or ARI case definition for hospital-based and community-based RSV surveillance, respectively.

5. 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.

5.1 Hospital-based RSV surveillance

The sites chosen for hospital-based RSV surveillance sites should meet the minimum sample size for the pilot. Where possible, sites should include:

- pre-admission outpatient units:
 - accident and emergency rooms;
 - hospital outpatient clinics;
- inpatient wards:
 - paediatric;
 - adult general medical;
 - adult medical specialty wards – respiratory and infectious diseases; and
- intensive care units:
 - adult intensive care; and
 - paediatric intensive care and neonatal intensive care.

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

5.2 Community-based RSV surveillance

The RSV surveillance pilot will enrol patients with ARI and **extended ILI** from outpatient sentinel sites. Surveillance should thus take place in primary and secondary health-care sentinel sites or health-care facilities.

6. Sampling strategy

RSV surveillance should primarily be hospital based. The reason for this is that once RSV vaccines become available, their use will primarily be aimed at preventing severe cases (i.e. cases that require hospital treatment).

The SARI case definition does not meet optimal criteria for RSV surveillance. SARI case definitions require that the patient has a fever of 38 °C or more when seen by a health-care worker, or a history of fever during the previous 10 days. Children and the elderly often present without fever or history of fever. Thus, 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 3 months of life. This age group is often not well covered by influenza surveillance; therefore, sampling strategies would need to be expanded to include these infants. Since this is an important aspect of the health-care burden for RSV, it is important to ensure that sufficient cases are sampled in this age group – hence the sampling quotas given below. In some GISRS settings, ensuring that surveillance

covers very young children may require new surveillance sites to be set up in paediatric hospitals. Even in settings where new surveillance sites are not required, it may be necessary to give increased priority to surveillance in this age group.

Community-based RSV surveillance should be built on the ARI case definition because 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 that 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.

6.1 Sample size by age distribution for RSV surveillance

Countries should aim to collect at least 20 samples per week, giving a total of about 1000 samples per year. These samples should cover all age groups. To ensure that these quotas are being met, laboratories should report back to the sentinel sites so they can adjust patient recruitment as necessary. Sampling strategies should also include individuals belonging to special at-risk groups.

Minimum sample size requirements for hospital surveillance and RSV testing:

- 250 samples per year from children aged under 6 months (including samples across the whole of this age group, not just samples from infants aged 4–6 months);
- 250 samples per year from children aged 6 months to under 5 years;
- 250 samples per year from individuals aged 5–64 years; and
- 250 samples per year from the elderly (≥65 years).

A sample size of 250 would allow an RSV prevalence of 5–10% to be detected with an absolute precision of about 2.5% with 95% confidence in each of the age groups.¹

6.2 Selection of patients for collecting specimens

6.2.1 Age groups 6 months and above

- 1) Check whether the case meets the 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; or
 - 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, 5–64 years and ≥65 years).

6.2.2 Age group under 6 months

- 1) Check whether 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; or

¹ For information on how these calculations have been done, see <http://sampsize.sourceforge.net/iface/>.

- c) meets neither SARI nor “SARI with no fever” nor apnoea nor sepsis case definition – **not** eligible for testing stop.
- 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 the quota for the group aged under 6 months.

A true random sampling scheme is most representative but may not be practical in surveillance settings. The scheme that is most likely to be representative of the population eligible for sampling is a systematic random sampling scheme that does not involve health-care providers in selecting the patients to test (other than to determine eligibility for testing), and that covers different times of the day and different days of the week (2). Sentinel surveillance sites can adopt whichever sampling approach they find to be most appropriate locally to conduct the RSV surveillance so that sampling quotas are reached. The approach may vary from site to site; however, a few general comments are relevant to all sites:

- ensure that, across all age groups, at least 20 samples are taken and tested for RSV **each week throughout the entire year**, so that RSV seasonality can be assessed;
- 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 the sampling strategy accordingly; and
- 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 the submission of samples weekly to ensure that the minimal sample sizes by age group are met, as outlined above. Also, 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, the laboratory should maintain an *average* testing of 20 samples per week unless there are additional resources available to test the additional samples (generally, resources for undertaking more than 1000 tests annually are limited). Where sample submission does not meet the quota of 20 samples per week, additional samples collected for influenza surveillance should be tested for the relevant age groups during periods of increased respiratory activity.

Each country should select its sampling strategy according to the resources available. However, whichever sampling strategy is selected, it should be a strategy that minimizes bias, and it must be well documented and reported (**Error! Reference source not found.**).

6.3 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 one geographical region to another within a country. To better characterize RSV seasonality, RSV surveillance should continue throughout the entire year. Even if the RSV peak season is known in a country or region, surveillance should be continued after the peak period throughout the year.

To determine RSV seasonality and to meet the objectives, the pilot will require at least 20 samples to be tested for RSV each week throughout the year. A 10% threshold of RSV-positive specimens during 2 consecutive weeks may indicate the onset of the season (5). 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.

7. Laboratory testing

The information given here is based on the WHO *Manual for the laboratory diagnosis and virological surveillance of influenza* (6, 7).

7.1 Collection of clinical specimens

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

- *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 (8, 9) (Appendix D);
 - as an alternative, nasopharyngeal aspirates may be collected, particularly from young children;
- *older children, adolescents and adults:*
 - both nasal and throat swabs should be collected in the same tube, which should contain viral transport medium;
 - specimens must be collected using flocked nylon swabs (not cotton-tipped or calcium alginate swabs); and
- *older adults and the elderly* – collection of sputum samples may be an option (9) in certain cases.

The optimal type of sample also depends on the severity of the illness. In severe hospitalized cases, lower respiratory specimens may also be collected where indicated; these include tracheal aspirate and bronchoalveolar lavage.

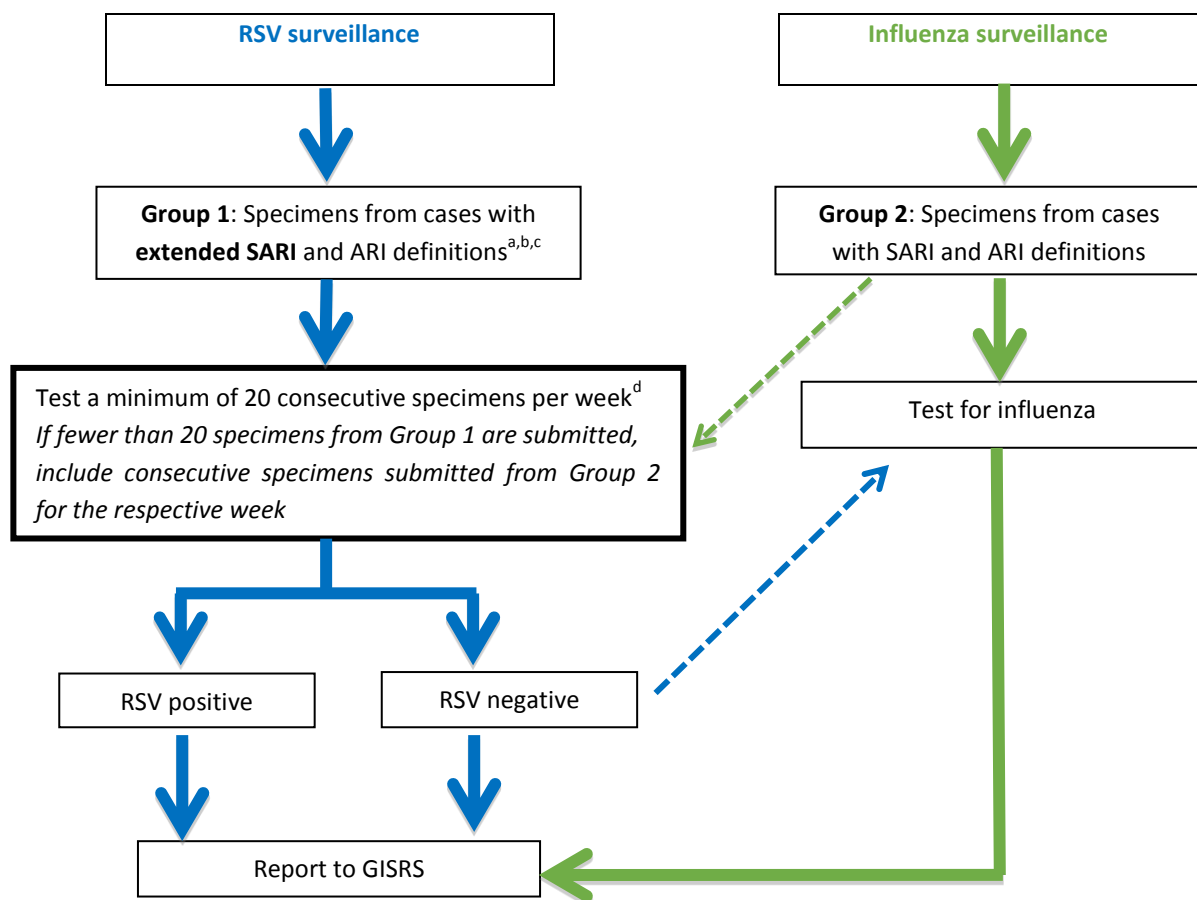
For each specimen collected, a corresponding RSV data collection form must be duly completed. The forms must be placed in a separate pouch (envelope) and sent to the laboratory along with the specimen.

7.2 Transport and storage of clinical samples

Storage of clinical specimens at the site of collection and their transport to the laboratory should follow guidelines that are similar to those used for influenza specimens. After collection, and before 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, the specimen should be aliquoted immediately (in three or four vials of about 0.5 mL) and then stored at –70 °C.

7.3 Algorithm for surveillance and testing

Fig. 1. RSV surveillance algorithm



ARI, acute respiratory infection; GISRS, Global Influenza Surveillance and Response System; RSV, respiratory syncytial virus; SARI, severe acute respiratory infection

^a Minimum sample size requirements for hospital surveillance and RSV testing:

- 250 samples per year from children aged <6 months;
- 250 samples per year from children aged 6 months to <5 years;
- 250 samples per year from individuals aged 5–64 years; and
- 250 samples per year from the elderly (≥65 years).

^b SARI and ARI with and without fever, including infants aged 0–6 months with apnoea and sepsis.

^c All specimens submitted from suspected RSV cases must be accompanied by a fully completed RSV specimen submission form (**Appendix E**).

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

7.4 Laboratory techniques for the detection of RSV

Several countries and laboratories detect RSV and other respiratory viruses using immunofluorescent staining of exfoliated respiratory epithelial cells. Although this technique produces reliable results on

specimens collected from young children, its sensitivity 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 Atlanta PCR assay, they may opt to either continue with their existing RSV protocols or use the protocol supplied by the CDC Atlanta. Three RSV reference laboratories have been selected for the pilot: the CDC Atlanta, PHE London and NICD Johannesburg.

All reference laboratories 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 each. All three laboratories achieved maximum scores and correctly identified all panel samples. WHO then analysed and compared the QCMD RSV proficiency test results, including cycle threshold (Ct) values. Results from the three reference laboratories were comparable. All three laboratories will provide technical support to pilot countries, but the CDC will provide pilot countries with the real-time PCR protocol for RSV, proficiency test panels, and RSV primers and probes.

Testing strategies are either real-time or batch testing:

- in real-time testing, laboratories test incoming specimens for influenza viruses and for RSV when the specimens arrive at the laboratory; and
- in batch testing:
 - laboratories test specimens for RSV in batches (e.g. once a week); and
 - testing strategies must be chosen by the laboratories according to available resources.

A 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.

7.5 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 should return their results within a specified period. Where laboratories achieve suboptimal scores with their own, in-house RSV tests, they will be encouraged to use the testing protocol provided by CDC Atlanta. During the RSV surveillance pilot period of 3 years, the CDC will distribute similar quality assurance panels annually.

- Internal quality assurance – laboratories must maintain and document rigorous internal quality control.
- External quality assurance – Appendix C provides the terms of reference for RSV reference laboratories.

8. Data collection

The RSV specimen 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.

9. Reporting of case-based data

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

Meeting the objectives of this RSV surveillance pilot requires case-based reporting of epidemiological, clinical information and laboratory results to WHO headquarters. Case-based data, as outlined in the RSV specimen submission form, will be submitted together 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 spreadsheet or, as directed by 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 analysed separately to evaluate the most suitable case definition for RSV surveillance.

Countries should take responsibility for assuring the confidentiality of case-based data and the 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.

10. Outputs from the pilot

10.1 Surveillance outputs

The RSV surveillance will report the proportion of cases meeting the standard RSV case definitions that are RSV positive in different age groups. This section discusses outputs of the RSV surveillance that give some information about the hospital burden of RSV.

The primary outputs of RSV surveillance are:

- percentage of cases identified using **extended SARI** case definition that are RSV positive by age group (used to identify the most important age groups at risk); and
- number and percentage of cases identified using **extended SARI** case definition that are RSV positive by calendar week (used 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 case** definition (by age group and month). These secondary outputs are:

- estimated number of cases identified using **extended SARI** case 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 disease¹ compared to those for influenza and other locally defined priority conditions (by the specified age groups); and
- proportion of RSV-positive cases identified using **extended SARI** case definition that would have been identified with the original SARI case definition (by age group).

10.1.1 Estimating the burden of RSV-associated hospitalization

Data on the total number of hospitalizations associated with RSV disease at each surveillance site is useful to:

- indicate the hospital burden of disease at that surveillance site; and
- estimate the proportional contribution of RSV-associated disease episodes to all-cause hospitalization, and 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. Not all cases meeting the case definition will have been recruited and tested; hence, to estimate the total number of RSV-positive cases, this under-detection of RSV-associated disease episodes must be corrected for, as shown in the following example.

Example

A hospital-based RSV surveillance site admits 500 cases meeting the **extended SARI** case definition over a 1-year period. It 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 estimated to be about 200 (100 / 0.5) in this age group over the 1-year period.

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

$$\frac{\text{No. of cases identified using } \mathbf{extended\ SARI} \text{ definition that are RSV positive}}{\text{Proportion of cases identified using } \mathbf{extended\ SARI} \text{ definition that were tested for RSV}}$$

This equation is based on two assumptions: 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. Because these assumptions are often not fully met, this estimation of the true number of RSV-positive cases can only be an approximation.

¹ RSV disease defined by cases identified using **extended SARI** case definition that are RSV-positive.

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 (i.e. <5 years, 5–64 years, and ≥65 years).

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

If it is not possible to obtain data on the total number of cases meeting the **extended SARI** case definition, then in some settings it may be possible to obtain an approximation of the true number of cases identified using the **extended SARI** case definition by reviewing 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 publication, *A manual for estimating disease burden associated with seasonal influenza (10)*. These include:

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

Coding practices can vary from country to country. Therefore, it would be helpful if, in interpreting these data, countries made an audit of how these ICD codes relate to the **extended SARI** case definition. An estimate could 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 RSV 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 SARI (also include admissions for sepsis in those aged 0–5 months).

10.1.2 Population-based burden of RSV disease

Surveillance data on RSV cases do not provide population-based burden of disease estimates, because the denominator (or catchment) populations of the surveillance sites are not generally known. However, in settings in which population-based denominators are available, it may be possible to obtain these estimates using the methods described in the WHO publication, *A manual for estimating disease burden associated with seasonal influenza (11)*.

10.2 Laboratory outputs

Primary outputs from pilot laboratories will be as follows:

- build and improve capacity for RSV testing by real-time PCR;

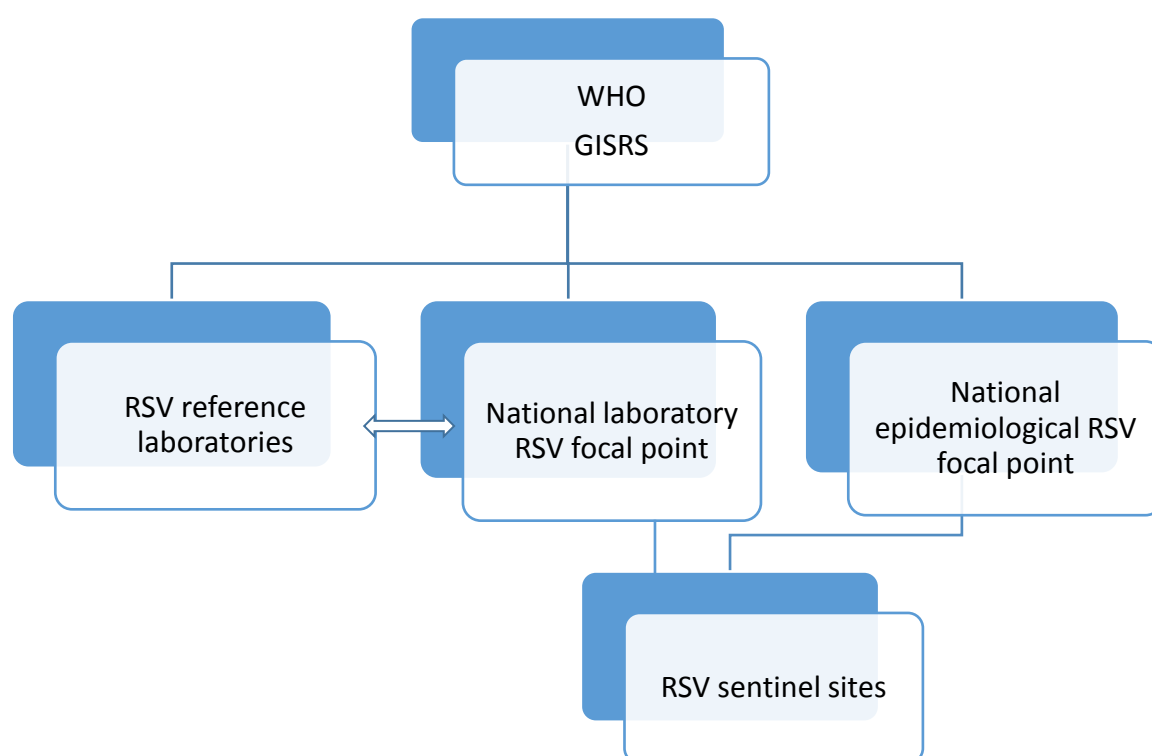
- evaluate, analyse and standardize non-CDC RSV PCR protocols;
- implement annual RSV proficiency testing;
- report RSV results in a standardized format; and
- report on seasonality of RSV in pilot countries.

Secondary outputs from pilot laboratories will be typing and molecular characterization of representative RSV samples.

11. Monitoring and evaluation

11.1 Monitoring

Fig. 2. Organizational structure for the RSV surveillance pilot



GISRS, Global Influenza Surveillance and Response System; RSV, respiratory syncytial virus; WHO, World Health Organization

Continued evaluation, using designated indicators, will be used to ascertain the success of this pilot. Monitoring will be conducted throughout the pilot on all levels involved, including sentinel sites, national laboratories, national epidemiologists, reference laboratories and WHO headquarters (Fig. 2Error! Reference source not found.).

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, and compilation and analysis of data at WHO headquarters.

Compliance with regulations, including those on patient confidentiality, must be strictly maintained. Countries should monitor additional resources used for the pilot, such as reagents, staff training, data management and project logistics. Countries must ensure that the pilot does not have a negative effect on their existing influenza surveillance.

Monitoring at the sentinel site should include the following (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 forms;
- 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 reference; and
- adequate documentation of pilot-related activities.

Monitoring at the WHO GISRS level should include:

- availability of sufficient and qualified staff;
- quality of laboratory and case-based data submitted (accuracy, completeness, timeliness and relevance);

- reliability and function of GISRS database;
- feedback to RSV focal points;
- pilot budget use; and
- effect on influenza surveillance.

11.2 Evaluation

During and at the end of the 3-year period, the pilot must be thoroughly evaluated as to whether the aims and objectives have been achieved. The pilot will be evaluated by WHO, in collaboration with external experts and stakeholders.

Key aspects of the evaluation will 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 geographical regions;
- identification of at-risk groups for severe RSV infection; and
- effect of pilot on improved RSV awareness at the national and international level.

12. Acknowledgements

The development of this manual was funded by the Bill & Melinda Gates Foundation, Seattle, USA, through WHO grant number OPP1127419.

The WHO 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, United Kingdom), Siri Hague (Norwegian Institute of Public Health, Norway), Teresa Peret (CDC, USA), Florette Teurnicht (NICD, South Africa) and Maria Zambon (PHE, United Kingdom). 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 WHO headquarters involved in the process of developing the strategy include Terry Besselaar, Julia Fitzner, Christian Fuster, Iris Hasibra, Siddhivinayak Hirve, Sandra Jackson, Rakhee Palekar, Kaat Vandemaele, Thedi Ziegler and Wenqing Zhang.

13. References

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Appendices

Appendix A: Contact information

WHO Global Influenza Programme

Email: gisrs-whohq@who.int (attn: Wenqing Zhang, Terry Besselaar, Siddhivinayak Hirve, Sandra Jackson)

WHO regional offices

Regional Office for Africa, Brazzaville, Congo

Telephone: +47 241 39100 / +242 770 02 02

Facsimile: +47 241 39503

Email: regafro@afro.who.int

Regional Office for the Americas, Washington DC, United States of America (USA)

Telephone: +1 202 974 3000

Facsimile: +1 202 974 3663

Email: postmaster@paho.org

Regional Office for South-East Asia, New Delhi, India

Telephone: +91 11 2337 0804

Facsimile: +91 11 2337 9507

Email: perrec@searo.who.int

Regional Office for Europe, Copenhagen, Denmark

Telephone: +45 45 33 70 00

Facsimile: +45 45 33 70 01

Email: postmaster@euro.who.int

Regional Office for the Eastern Mediterranean, Cairo, Egypt

Telephone: +202 2276 50 00

Facsimile: +202 2670 24 92 / 2670 24 94

Email: postmaster@emro.who.int

Regional Office for the Western Pacific, Manila, Philippines

Telephone: +63 2 528 8001

Facsimile: +63 2 521 1036 / 526 0279

Email: postmaster@wpro.who.int

Reference laboratories

Centers for Disease Control and Prevention (CDC), Atlanta

Teresa PC Peret

Gastroenteritis and Respiratory Viruses Laboratory Branch

Division of Viral Diseases

CDC

Telephone: +1 404 432 6991

Email: tbp0@cdc.gov

Public Health England (PHE), London

Joanna Ellis

Respiratory Virus Unit, Virus Reference Department

National Infection Service

PHE

Telephone: +44 020 8327 6239

Email: Joanna.ellis@phe.gov.uk

National Institute for Communicable Diseases (NICD), Johannesburg

Florette Treurnicht

NICD

Centre for Respiratory Diseases and Meningitis (Virology)

Telephone: +27 011 386 6390

Cell: +27 73 287 5708

Facsimile: +27 011 386 6455

Email: florettet@nicd.ac.za

Website: www.nicd.ac.za

Appendix B: List of participating pilot countries

- WHO African Region: Côte d'Ivoire, Mozambique, South Africa
- WHO Region of the Americas: Argentina, Brazil, Canada, Chile
- WHO Eastern Mediterranean Region: Egypt
- WHO European Region: Russian Federation, United Kingdom of Great Britain and Northern Ireland
- WHO South-East Asia Region: India, Thailand
- WHO Western Pacific Region: Australia, Mongolia

Appendix C: Respiratory syncytial virus reference laboratories – terms of reference for pilot

Background

Respiratory syncytial virus (RSV) is an important viral respiratory pathogen, causing acute and 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 should include the documentation of RSV epidemiology, seasonality and virology, and identification of high-risk groups.

Two WHO consultations were held with both RSV and influenza scientists and public health experts in March 2015 and February 2016. After these consultations, 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 should be launched as a pilot in representative countries from all six 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, referred to as “respiratory syncytial virus reference laboratories” or “RSV RLs”, 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 global RSV surveillance expands.

General conditions

Respiratory syncytial virus reference laboratories:

- work under the coordination of the WHO Global Influenza Programme (GIP);
- fulfil the terms of reference using financial support provided only by governmental or other non-commercial sources;
- 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
- appropriately acknowledge, in presentations and publications, the contributions of collaborators, including RSV laboratories and countries participating in the WHO global RSV surveillance pilot.

General activities

RSV reference laboratories:

- serve as a technical resource to WHO and RSV pilot laboratories as time and resources permit;
- monitor RSV pilot laboratories in quality assessments of their assays;
- prepare and distribute RSV diagnostic reagents as agreed with WHO, and as time and resources permit;
- analyse the performance of RSV pilot laboratories on external quality assurance (EQA) panels and submit timely feedback and reports to RSV pilot laboratories and WHO;
- provide training and laboratory support to RSV pilot laboratories on laboratory techniques, as time and resources permit; and

- 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		Nasopharyngeal/Nasal Aspirate	Nasopharyngeal/Nasal Wash	Deep Nasal Swab	Combined Nasal & Throat Swab
Materials	<ul style="list-style-type: none">Sterile Dacron/nylon swabViral transport media tube (should contain 1-3 ML of sterile viral transport medium)	<ul style="list-style-type: none">Sterile suction catheter/suction apparatusViral transport media tube (should contain 1-3 ML of sterile viral transport medium)	<ul style="list-style-type: none">Sterile suction catheter/suction apparatusSterile normal saline	<ul style="list-style-type: none">Sterile polyester swab (aluminum or plastic shaft preferred)Viral transport media tube (should contain 1-3 ML of sterile viral transport medium)	<ul style="list-style-type: none">2 dry sterile polyester swabs (aluminum or plastic shafts preferred)Viral transport media tube (should contain 1-3 ML of sterile viral transport medium)
Procedure	<ol style="list-style-type: none">Tilt patient's head back 70 degrees.Insert swab into nostril. (Swab should reach depth equal to distance from nostrils to outer opening of the ear.) Leave swab in place for several seconds to absorb secretions.Slowly remove swab while rotating it. (Swab both nostrils with same swab.)Place tip of swab into sterile viral transport media tube and snap/cut off the applicator stick.	<ol style="list-style-type: none">Attach catheter to suction apparatus.Tilt patient's head back 70 degrees.Insert catheter into nostril. (Catheter should reach depth equal to distance from nostrils to outer opening of ear.)Begin gentle suction. Remove catheter while rotating it gently.Place specimen in sterile viral transport media tube. <p><i>Note: NP aspirate may not be possible to conduct in infants</i></p>	<ol style="list-style-type: none">Attach catheter to suction apparatus.Tilt patient's head back 70 degrees.Insert several drops of sterile normal saline into each nostril.Insert catheter into nostril. (Catheter should reach depth equal to distance from nostrils to outer opening of ear.)Begin gentle suction. Remove catheter while rotating it gently.Place specimen in sterile viral transport media tube. <p><i>Note: NP aspirate may not be possible to conduct in infants</i></p>	<ol style="list-style-type: none">Tilt patient's head back 70 degrees.While gently rotating the swab, insert swab less than one inch into nostril (until resistance is met at turbinates).Rotate the swab several times against nasal wall and repeat in other nostril using the same swab.Place tip of the swab into sterile viral transport media tube and cut off the applicator stick.	<ol style="list-style-type: none">Tilt patient's head back 70 degrees.While gently rotating the swab, insert swab less than one inch into nostril (until resistance is met at turbinates).Rotate the swab several times against nasal wall and repeat in other nostril using the same swab.Place tip of the swab into sterile viral transport media tube and cut off the applicator stick.For throat swab, take a second dry polyester swab, insert into mouth, and swab the posterior pharynx and tonsillar areas. (Avoid the tongue.)Place tip of swab into the same tube and cut off the applicator tip.

Packing:

- 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/tfp/professionals/diagnosis/index.htm.
- ## Storing:
- Specimens should be placed into sterile viral transport media and immediately placed on refrigerant gel packs or at 4 degrees Celsius (refrigerator) for transport to the state public health laboratory.
 - Keep specimens refrigerated (2-8 degrees Celsius, 28-46 degrees Fahrenheit) prior to shipping.

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 specimen to be collected. Alternatively, a combined nasal and throat swab specimen or aspirate specimens 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 empiric 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/2007IP/2007ip_part4.html#4.



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Appendix E: RSV specimen submission form

RSV SUBMISSION FORM			
Country code			
Site code (geographic location)			
Patient's unique identification no.			
Type of surveillance site (e.g. hospital, medical centre)			
Name of healthcare worker			
Date of sample collection and completion of form (dd/mm/yyyy)			
Patient Identification			
Family name			
Given name			
Gender	<input type="checkbox"/> Male	<input type="checkbox"/> Female	
Date of birth (dd/mm/yyyy)			
Age	Years	Months	
Clinical Information			
Date of symptom onset (dd/mm/yyyy)			
Signs & Symptoms:			
Requires hospitalisation	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Symptom onset within last 10 days (acute)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Cough	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Shortness of breath	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Measured fever $\geq 38^{\circ}\text{C}$	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
History of fever	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Wheezing	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Sore throat	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Coryza	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Chest-indrawing	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Infant (0-6 months) presents with: Apnea	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Infant (0-6 months) presents with: Sepsis	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Respiratory rate (breaths per minute)			
Diagnosis			
Hospital admission diagnosis			
SARI	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
SARI without fever	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
ARI	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
ILI	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
ILI without fever	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Pre-existing medical conditions: ADULTS			
Chronic cardiac disease	<input type="checkbox"/>		
Chronic respiratory disease (specify)			
Diabetes	<input type="checkbox"/>		
Immunocompromised	<input type="checkbox"/>		
Other chronic medical condition (specify)	<input type="checkbox"/> Yes, specify	<input type="checkbox"/> No	<input type="checkbox"/> Not known
Pre-existing medical condition unknown	<input type="checkbox"/>		
Pregnant	<input type="checkbox"/>		
Pre-existing medical conditions: CHILDREN			
Premature	<input type="checkbox"/>		
Chronic respiratory disease (specify)			
Malnutrition	<input type="checkbox"/>		
Immunocompromised	<input type="checkbox"/>		
Other chronic medical condition (specify)	<input type="checkbox"/> Yes, specify	<input type="checkbox"/> No	<input type="checkbox"/> Not known
Laboratory Information			
Specimen details			
Type of specimen	<input type="checkbox"/> Nasal/throat swab	<input type="checkbox"/> Nasopharyngeal aspirate	<input type="checkbox"/> Tracheal aspirate
	<input type="checkbox"/> Sputum	<input type="checkbox"/> BAL	
Date sample received at laboratory (dd/mm/yyyy)			
Date sample tested (dd/mm/yyyy)			
Results			
RSV results	<input type="checkbox"/> RSV positive	<input type="checkbox"/> RSV negative	<input type="checkbox"/> Inadequate sample
	<input type="checkbox"/> Sample not tested	<input type="checkbox"/> Sample rejected	
RSV CT value (if RSV positive)			
If subtype known, report	<input type="checkbox"/> RSV A	<input type="checkbox"/> RSV B	
RNP	<input type="checkbox"/> Positive	<input type="checkbox"/> Negative	
RNP CT value			

ARI, acute respiratory infection; BAL, bronchoalveolar lavage; CT, cycle threshold; ILI, influenza-like illness; RNP, ribonucleoprotein; RSV, respiratory syncytial virus; SARI, severe acute respiratory infection

Appendix 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.
http://www.who.int/influenza/resources/publications/report_rsv_meeting/en/
- 2) WHO Expert Working Group Meeting on RSV Surveillance Based on the GISRS Platform 2–3 February, 2016.
<http://apps.who.int/iris/bitstream/10665/252625/1/WHO-OHE-PED-GIP-2016.7-eng.pdf>
- 3) WHO Technical Meeting on Piloting RSV Surveillance Based on the Global Influenza Surveillance and Response System, 28–30 June 2016.
<http://apps.who.int/iris/bitstream/10665/252617/1/WHO-OHE-PED-GIP-2016.6-eng.pdf>

