WHO Meeting of Mid-term Review of the RSV Surveillance Pilot based on GISRS

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RSV suveillance: WHO strategy

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Context

- RSV vaccine on the horizon and data on RSV needed ahead of global policy development

- Key national stakeholders not aware of RSV disease burden
  - MOHs need in-country data to make decisions
  - No routine health data on RSV in most countries
  - Large gaps in RSV research data global coverage
  - Almost no surveillance of RSV disease
    - potential to utilise modified GISRS for RSV

RSV surveillance based on GISRS

Advantages

- Established global system handling ~2M samples /year in large number of sites
- Existing data collection/ reporting system with links to national policy makers
- Substantial local investment in the system
- Potential to understand flu & RSV together

GISRS: what can be measured?

Hospital inpatients

- Estimates of RSV ALRI hospitalizations
  - vaccines will aim to prevent severe (hospitalised) cases
  - main policy driver for vaccine decisions
  - main focus of RSV surveillance is hospital-based
- Information on key age groups and risk groups
- Estimates of RSV ALRI hospital CFR/ deaths

Hospital outpatients / health centre

- Estimates of RSV A(L)RI out-patient attendances

- RSV seasonality

GISRS: what cannot be measured?

- NOT direct estimates of incidence of RSV ALRI / RSV severe ALRI
  - needs community based studies

- NOT estimates of sequelae due to RSV ALRI
  - secondary bacterial infection
  - subsequent wheeze episodes

- NOT estimates from all risk groups of interest
  - premature; low birth weight; chronic conditions

RSV Surveillance Pilot: primary objectives

- Establish feasibility of RSV surveillance built on the GISRS platform for future global expansion
- Identify RSV seasonality in different countries/regions
- Provide improved knowledge on RSV healthcare burden in hospitalized and community patients
- Determine age/ risk groups for severe RSV disease
- Evaluate RSV case definitions/ sampling strategies
- Assess feasibility of FluNet & FluID for data reporting
- Report surveillance statistics to raise awareness and provide evidence to inform policy decisions
- Build lab capacity for RSV testing in pilot countries
- Standardize laboratory procedures for RSV detection and quality assurance

RSV Surveillance Pilot: secondary objectives

- Gain experience from pilots to define role of RSV Reference Labs within a global RSV surveillance programme
- Assess additional costs incurred through implementation of RSV surveillance (additional clinical and laboratory costs)
- Document GISRS staff acceptance of additional procedures and reports and negative impacts on existing flu surveillance
- Provide a platform for future RSV studies such as:
  - Global RSV surveillance
  - Vaccine studies (vaccine effectiveness studies and studies evaluating age incidence changes after vaccines)
  - Cost effectiveness/ impact analyses of vaccines
  - Broader respiratory virus surveillance
- Future platform for a broader respiratory virus surveillance
- Assess the efficacy of RSV treatment strategies
- Bank samples for future studies: evolution of strains (subtype; genotype) & relationship to vaccine effectiveness

Challenges in using GISRS for RSV surveillance: case definition

Challenges

- Need for modified case definitions

- Fever is NOT found in >50% of RSV ALRI cases in young children and in the elderly
  - Case definitions that require fever to be present will under-estimate RSV ALRI

- Would be counter-productive to set up a system that gave falsely low estimates of RSV as this would not give good advice to policy makers and will not be accepted internationally

Challenges in using GISRS for RSV surveillance: gather RSV data without disrupting GISRS

Challenges

- Will need additional data collection - potential to have negative effect on vital GISRS
- Strike a balance between an ideal surveillance programme for RSV and one that makes the least changes to GISRS for flu but still gives valid data on RSV
- This RSV surveillance pilot will help to identify how this is best achieved

Present definition used for Hospitalized cases in GISRIS

- SARI:
- 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/ difficulty breathing]
- However if used for RSV hospital surveillance will miss many cases

Response to challenge: need for modified case definition

- Hospital surveillance - RSV case definition will ALSO include patients of all ages who do NOT have fever or history of fever but otherwise meet the SARI case definition:
- "Extended SARI" case definition
- 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/ difficulty breathing]

Response to challenge: need for modified case definition

- Community surveillance - RSV case definition is based on the ARI case definition
  - Acute - sudden onset of symptoms
  - Respiratory infection - at least one of cough / sore throat / shortness of breath / coryza
- If this is not possible then an extended ILI case definition: patients of all ages who do NOT have fever but otherwise meet the ILI case definition:
  - onset within the last 10 days
  - cough

Challenges in using GISRS for RSV surveillance: different age pattern

Challenges

- Different age pattern
- RSV ALRI is much more important in young infants than flu ALRI
  - ~50% of cases in 0-5 year children have already occurred by age 6 months
  - RSV ALRI cases in 0-2 months are important
- May need enhanced recruitment in this age group

Challenge: need for more focus on 0-6m group

- Case definitions not showing substantial recruitment of 0-6m cases:
  - will greatly under-estimate RSV ALRI
  - wont guide maternal/ infant vaccine policy
  - will not be accepted internationally

Challenge: need for more focus on 0-6m group

- Need to ensure adequate numbers recruited across this age group
  - may need consideration of additional new recruitment sites in some settings

- Need to recognise that RSV disease presents with different signs in young infants and so will need a different case definition

Response to challenge: need for focus on 0-6m group

- Suspected RSV disease in 0-6 month old infants
- Because RSV disease commonly presents also with other signs in young infants, RSV surveillance will ALSO include infants 0-6 months of age with:
  - Apnea and/or Sepsis

- Sepsis in infants is defined by WHO as:
  - Fever (37.5 C or above) or hypothermia (less than 35.5 C)
  - Shock (lethargy, fast breathing, cold skin, prolonged capillary refill, fast weak pulse)
  - Seriously ill with no apparent cause

Challenges in using GISRS for RSV surveillance: often different seasonality

Challenges

- Different seasonality
- RSV seasonal is typically NOT the same as the flu season
  - Flu season surveillance needs to be extended or many / most / all RSV cases will be missed

- RSV season not well known and can vary from year to year so it is safer to do year round surveillance until clear seasonal pattern is established (over a few years)

Challenge: account for different seasonality to flu

- Need to extend flu season surveillance or many / most / all RSV cases will be missed
- Estimates based on flu season samples only wont be well accepted internationally

Response to challenge: different seasonality to flu

RSV surveillance to be conducted throughout the year (even when peak period is known)

- Data generated during the Pilot will better indicate the seasonality of RSV in participating countries.

To determine RSV seasonality: a minimum of 20 samples are to be collected / tested for RSV each week throughout the year.

- 10% threshold of RSV-positive specimens during two consecutive weeks indicates season onset
- RSV positivity rate falling <10 % indicates season offset
- Enhance sampling and testing during the season

Challenge: need sufficient surveillance data on key age groups

Challenges

- Need surveillance data on specific groups for policy / programme purposes
  - Young children
  - Elderly

- Important to gather a minimum quota of samples in 4 distinct groups to ensure we can get precise estimates
  - Young infants 0-5m
  - Young children 6-59m
  - Older children / adults 6-64y
  - Older adults 65y+

Response to challenge: need minimum data in key age groups

Challenge: need for data from all key age groups

- Gather a minimum quota of samples in 4 distinct groups to ensure we can get precise estimates
- Sample size
  - 500 children 0-5 years
    - 250 from 0-5 months;
    - 250 from 6-59 months
  - 250 from elderly (65 years or over)
  - 250 from 6 years to 64 years

WHO Strategy to pilot global RSV surveillance based on GISRIS

Laboratory Testing

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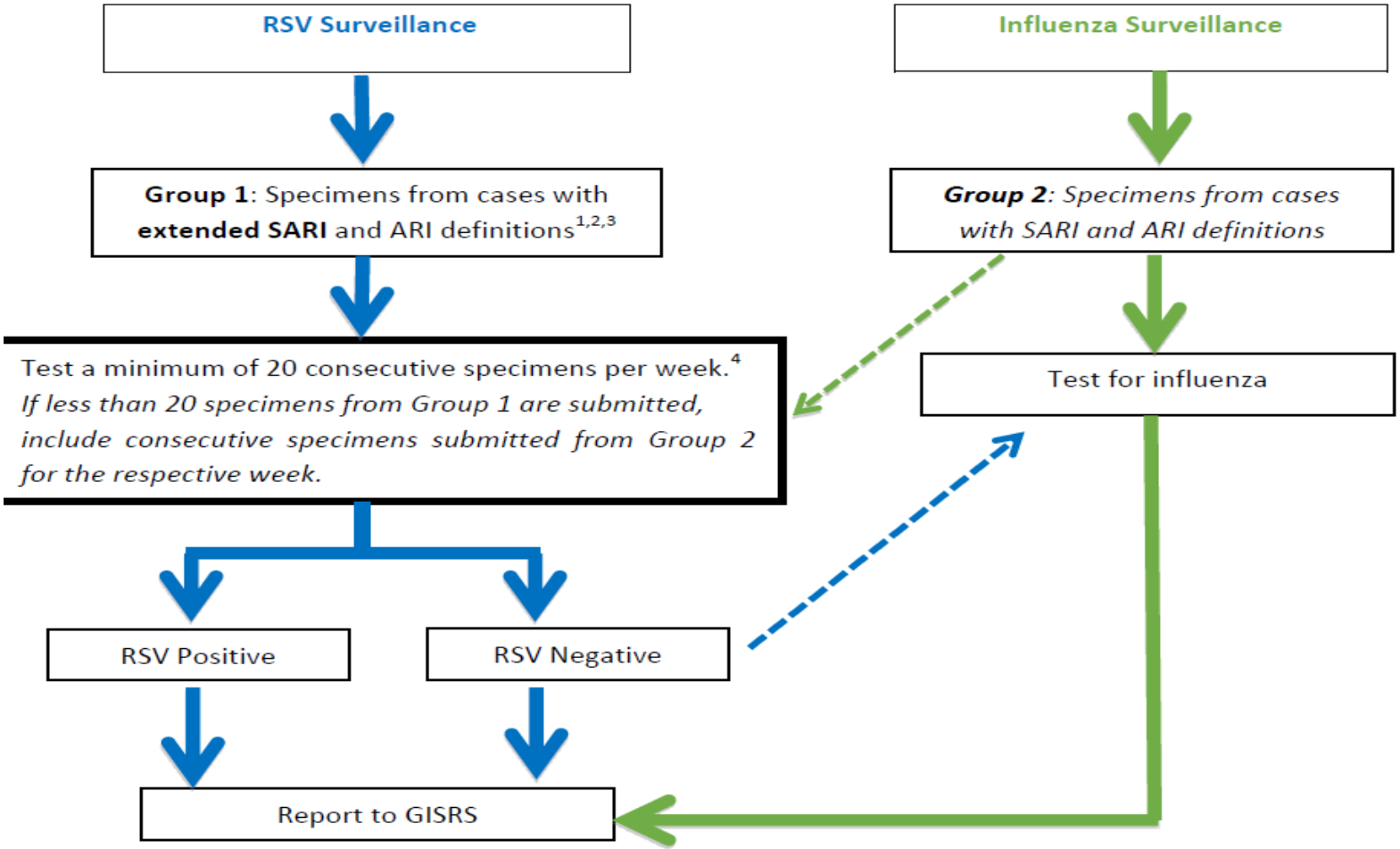
sampling strategy

- RSV surveillance should primarily be hospital-based
- To assess seasonality at least 20 cases / week should be tested throughout the year
  - If not enough cases from (hospital) surveillance, then include community samples or other samples from flu surveillance)
  - aim to increase recruitment, where possible, in the RSV season
    - 2/20 samples positive for 2 consecutive weeks (onset of season)

Sampling strategy

- Recruit sufficient cases to meet the age group quotas
  - 250 0-5m;
  - 250 6-59m
  - 250 6-64 years
  - 250 65 years and over
- Document the sampling strategy used
- All specimens submitted from suspected RSV cases must be accompanied by a fully completed RSV specimen submission form
- If more than 20 specimens per week are 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


RSV Surveillance
Influenza Surveillance
Group 1: Specimens from cases with extended SARI and ARI definitions[1,2,3]
Group 2: Specimens from cases with SARI and ARI definitions
Test a minimum of 20 consecutive specimens per week.[4]
If less than 20 specimens from Group 1 are submitted, include consecutive specimens submitted from Group 2 for the respective week.
Test for influenza
RSV Positive
RSV Negative
Report to GISRS

TYPE OF CLINICAL SPECIMENS

- The optimal type of clinical specimens for the detection of RSV and influenza viruses depends on the age of the patient
- For infants and young children : nasopharyngeal swab or nasal swab taken from the mid-turbinate of the nose yields high recovery of respiratory viruses

  OR
- Nasopharyngeal aspirates may also be collected particularly from young children
- From older children, adolescents and adults: both nasal and throat swabs should be collected in the same tube containing viral transport medium
- Specimen should be collected using flocked nylon swabs and not cotton-tipped or calcium alginate swabs
- In severe hospitalized cases, lower respiratory specimens may also be collected where indicated e.g. tracheal aspirate and broncho-alveolar lavage
- In older adults and elderly, collection of sputum samples may be an option in certain cases
- 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

TRANSPORT AND STORAGE OF SPECIMENS

- Similar guidelines should be followed as 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 to be strictly adhered
- 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.

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 ☐ Male ☐ Female

Date of birth (dd/mm/yyyy) ____/_____/_____

Age Years_____ Months _____

Clinical Information

Date of symptom onset (dd/mm/yyyy) _____/_____/_____

Signs & Symptoms:

Requires hospitalisation	☐ Yes	☐ No
Symptom onset within last 10 days (acute)	☐ Yes	☐ No
Cough	☐ Yes	☐ No
Shortness of breath	☐ Yes	☐ No
Measured fever ≥38°C	☐ Yes	☐ No
History of fever	☐ Yes	☐ No
Wheezing	☐ Yes	☐ No
Sore throat	☐ Yes	☐ No
Coryza	☐ Yes	☐ No
Chest-indrawing	☐ Yes	☐ No
Infant (0-6 months) presents with: Apnea	☐ Yes	☐ No
Infant (0-6 months) presents with: Sepsis	☐ Yes	☐ No

Respiratory rate (breaths per minute) _____

Diagnosis

Hospital admission diagnosis _____

SARI	☐ Yes	☐ No
SARI without fever	☐ Yes	☐ No
ARI	☐ Yes	☐ No
ILI	☐ Yes	☐ No
ILI without fever	☐ Yes	☐ No

Pre-existing medical conditions: ADULTS

Chronic cardiac disease	☐		
Chronic respiratory disease (specify)	☐ _____		
Diabetes	☐		
Immunocompromised	☐		
Other chronic medical condition (specify)	☐ Yes, specify _____	☐ No	☐ Not known
Pre-existing medical condition unknown	☐		
Pregnant	☐		

Pre-existing medical conditions: CHILDREN

Premature	☐		
Chronic respiratory disease (specify)	☐ _____		
Malnutrition	☐		
Immunocomprimised	☐		
Other chronic medical condition (specify)	☐ Yes, specify _____	☐ No	☐ Not known

Laboratory Information

Specimen details

Type of specimen ☐ Nasal/throat swab ☐ Nasopharyngeal aspirate ☐ Tracheal aspirate ☐ Sputum ☐ BAL

Date sample received at laboratory (dd/mm/yyyy) ____/_____/_____

Date sample tested (dd/mm/yyyy) ____/_____/_____

Results

RSV results ☐ RSV positive ☐ RSV negative ☐ Inadequate sample ☐ Sample not tested ☐ Sample rejected

RSV CT value (if RSV positive)

If subtype known, report ☐ RSV A ☐ RSV B

RNP ☐ Positive ☐ Negative

RNP CT value _____

LABORATORY TECHNIQUES FOR THE DETECTION OF RSV

Immunofluorescent staining of exfoliated cells (low sensitivity in older children and adults)

- Detection of viral RNA
  - Regular PCR
  - Real-time polymerase chain reaction (standard test for pilot labs)
    - CDC assay
    - In-house assay validate with CDC assay

Testing strategies:

Real time strategy

Laboratories test incoming specimens for influenza viruses and for RSV when the specimens arrive at the laboratory

Batch testing

Laboratories test specimens for RSV in batches, for example, once a week

- 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

Quality assurance

- At the beginning of the Pilot, CDC Atlanta will distribute a panel of specimens containing RSV at different concentrations (already carried out)
- Laboratories to return their results within a specified period
- If 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

Reporting

- RSV pilot not intended for diagnostic purposes
- Sentinel sites will, receive laboratory results in keeping with surveillance guidance as established in the participating country
- Case-based reporting of epidemiological, clinical information and laboratory results to WHO headquarters to 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
- upload data on a weekly basis
- confidentiality of case-based data to be maintained using locally-accepted procedures

RSV reference laboratories

Laboratories which can provide technical guidance on virological component

- Technical resource to WHO and RSV Pilot Laboratories
- Monitor RSV Pilot Laboratories in Quality Assessments of their assays
- Prepare and distribute RSV diagnostic reagents as agreed with WHO
- Analyse performance of RSV Pilot Laboratories on 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
- Maintain and strengthen active communication and collaboration with RSV Pilot Laboratories and WHO to ensure that up-to-date information is exchanged

RSV reference laboratories

CDC Atlanta

Teresa P. C. Peret

Gastroenteritis and Respiratory Viruses Laboratory Branch

PHE London

Joanna Ellis

Respiratory Virus Unit (RVU), Virus Reference Department

National Infection Service, Public Health England

NICD Johannesburg

Florette Treurnicht

National Institute for Communicable Diseases (NICD)

Centre for Respiratory Diseases and Meningitis (Virology)

Monitoring at the national laboratory

- Staff training
- Availability of appropriate equipment and reagents
- Performance in internal and external quality assurance
- Adherence to standard operational procedures in storage and laboratory facilities
- Biosafety and biosecurity measures
- Data entry and reporting to the GISRS platform and reporting back to the sentinel sites
- Interaction between sentinel site, national focal point, and WHO headquarters
- Documentation of Pilot-related activities,
- Internal and external quality control

LABORATORY OUTPUTS

Primary

- 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

Typing and molecular characterization of representative RSV samples

Summary :RSV surveillance

RSV surveillance should primarily be hospital-based

Sites should be chosen to ensure that minimum sample sizes are achieved:

- Hospital in-patient wards (adult and paediatric) including specialists like respiratory ID
- intensive care units (adult and paediatric and neonatal)
- Modified SARI and ARI definition to be used
- All age group
- All year around

Summary –Laboratory testing

- Uniform strategies for sample collection and testing : 20 samples /week
- Uniform assays in all pilot laboratories
- Quality control
  - Internal and External
- Training
- Case based reporting
- Seasonality