WHO Global RSV Surveillance

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This presentation will describe the:

- justification and current status of RSV surveillance
  - Establishment of Global RSV surveillance based on GISRS
- aim and objectives
- Challenges
- overall strategy
- strategy to address challenges
- progress of the WHO Global RSV Pilot
- next steps
RSV

- Long recognized as a leading cause for ALRI morbidity and hospitalization in young children (Nair 2010) and elderly

**RSV surveillance – WHY NOW?**

- At least five vaccine candidates at phase II or III clinical trial stage (Neuzil 2016)
- Need to develop a global evidence-base on RSV to inform immunization policy and vaccine introduction
Current status of RSV surveillance

- **Good news**
  - Some countries have already set up RSV surveillance recently

- **Not so good news**
  - Lack of surveillance standards for RSV
    - Case definitions vary
  - Likely to be biased
  - Poor understanding of seasonality, disease burden in high risk groups, especially in low and middle income countries
Global RSV surveillance based on GISRS

- Highly functioning network since 1952 – 65th anniversary
  - 151 institutions
  - 13 countries
  - National labs for influenza, MERS, SARS-CoV ...
  - Extensive sub-national sentinel networks → GISRS
  - >2 million respiratory specimens tested per year
    - highly efficient as required for influenza epidemics and pandemic
The aim of global WHO RSV Pilot is, through **continuous** monitoring and surveillance, to

- Understand epidemiologic and virological features of RSV circulation globally

- Provide evidence for introduction of RSV vaccines including seasonality, risk groups and burden of disease
Objectives

The primary objectives:

- To describe the epidemiologic and virological features of RSV circulation globally
- To generate evidence for the introduction of RSV vaccines (including; seasonality, risk groups and burden of disease)
Objectives

The secondary objectives are to:

- Test the feasibility of RSV surveillance based on GISRS;
  - Staff acceptance, potential negative impact
- Assess the performance of case definitions for detecting RSV infection;
- Develop global standards for RSV surveillance;
- Assess incremental costs and
- Provide a global platform for
  - a broader respiratory virus surveillance
  - RSV disease and RSV vaccine studies.
The RSV Pilot will not provide

- Population based estimates of disease burden
- Economic burden of RSV
- Clinical characterization of RSV
- Risk factor data
Challenges

- **Scope different**
  - Virus monitoring v/s epidemiological monitoring

- **Objectives different**
  - Early detection of new virus v/s seasonality, burden etc.

- **Case definitions different**

- **Sampling strategy different**

- **Laboratory protocols different**

- **Reporting strategy different**
  - During season v/s year-round

Challenges

- **Age groups at risk different**
  - Infants and young children not well-covered by ILI / SARI surveillance

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**Figure 2.** Age-specific incidence rates using all-cause hospitalization for respiratory syncytial virus (RSV) and influenza-associated hospitalization rates in north India (2009–2012). The age groups are on the x-axis and incidence rate of RSV–associated hospitalization per 1000 children denoted on the y-axis. Green and orange colored bars denote incidence rates of RSV and influenza associated hospitalizations respectively with error bars for 95% confidence intervals.

Overall strategy

- To build on the capacities of the GISRS platform to test for RSV
  - but without interfering with the established influenza surveillance

14 countries

AMR: Argentina, Brazil, Canada, Chile
AFR: Côte d’Ivoire, Mozambiqûe, South Africa
EUR: Russian Federation, UK
EMR: Egypt
SEAR: India, Thailand
WPR: Australia, Mongolia

RSV surveillance

Participating countries (May 2017)
Implementation strategy

Integrate epidemiological and laboratory surveillance globally based on GISRS:

- RSV surveillance ≠ RSV results from influenza surveillance

--- Surveillance components to consider

- Case definitions, sentinel sites, sample size, lab testing algorithms
- Lab testing protocols, reagents and quality assessment
- Reporting
- Coordination and reference labs
**Case definition**

- **Challenge**
  - SARI and ILI case definition does not capture up to 50% of RSV infection in infants and young children (Saha 2015)

<table>
<thead>
<tr>
<th>Population under surveillance</th>
<th>Under–2 years (N = 3956)</th>
<th>Under–5 years (N = 9740)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. met case definition</td>
<td>No. of RSV positive cases (%)</td>
</tr>
<tr>
<td>All Medical</td>
<td>386</td>
<td>67 (17)</td>
</tr>
<tr>
<td>ARI (WHO)</td>
<td>239</td>
<td>60 (25)</td>
</tr>
<tr>
<td>SARI (WHO)</td>
<td>90</td>
<td>34 (38)</td>
</tr>
<tr>
<td>SARI (Old)</td>
<td>35</td>
<td>10 (29)</td>
</tr>
<tr>
<td>ILI (WHO)</td>
<td>37</td>
<td>10 (27)</td>
</tr>
<tr>
<td>ILI (Old)</td>
<td>106</td>
<td>26 (25)</td>
</tr>
</tbody>
</table>

- **Community-based surveillance**
  - Existing ARI definition (with or without fever)
    - Acute onset cough or sore throat or shortness of breath or coryza
SARI

- **SARI is currently defined by WHO 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 $\geq 38$ °C, and
    - cough [in some sites cough or shortness of breath]

- **Extended SARI is defined as:**
  - *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]
0 to 6 months

- 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

- Sepsis, in children 0-6 months of age is defined as:
  - fever (37.5 °C or above) or hypothermia (less than 35.5 °C), and
  - shock (lethargy, fast breathing, cold skin, prolonged capillary refill, fast weak pulse), and
  - seriously ill with no apparent cause

Countries implementing community-based RSV surveillance

- ARI is defined as follows:
  - 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.

Extended ILI case definition

- ILI is currently defined by WHO as follows:
  - *acute* is defined as onset within the last 10 days
  - *respiratory infection* is defined as having:
    - measured fever of $\geq 38 \, ^\circ C$, and
    - cough

- Extended ILI case definition may be used in its place to also include those without fever.
Age groups at risk

- **Challenge**
  - Infants and young children not well-covered by ILI / SARI surveillance

- **Minimal** sample size
  - 1000 samples per year
    - 500 samples per year from children 0 – <5 years of age
      - 250 from children between 0 – 5 months
      - 250 from children 6 months – < 5 years
    - 250 samples per year from individuals 5 – 64 years of age
    - 250 samples per year from elderly (≥65 years of age)
Algorithm for RSV Surveillance and Testing

RSV Surveillance

Group 1: Specimens from cases with extended SARI and ARI definitions\(^1,2,3\)

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.

RSV Positive
RSV Negative

Report to GISRS

Influenza Surveillance

Group 2: Specimens from cases with SARI and ARI definitions

Test for influenza

World Health Organization
Data collection and reporting

- Case-based data collection
  - Symptoms, signs, pre-existing illness
  - Laboratory data
  - Denominator data (by age group, calendar month)
    - No. of all-cause hospitalizations
    - No. of hospitalization due to pneumonia or severe ALRI (J09-J11 codes), sepsis (P36, R65, A40-41 codes)
    - No. of hospitalizations that meet RSV case definition
    - No. of hospitalization that meet RSV case definition that were tested for RSV
  - All year-round

- FluMart
  - Weekly upload
Outputs

- **Surveillance outputs**
  - Weekly, stratified by age group
    - No. and % RSV+ by age group
    - No. and % RSV+ by calendar week
    - % total hospitalizations that are RSV+ by age group, calendar month
    - No. of RSV+ relative to influenza+
    - Prop. RSV+ cases that would be missed by SARI / ILI case definition
  - Biweekly surveillance report

- **Hospitalization burden**
  - Total no. of RSV+ hospitalizations
  - Prop. contribution of RSV to all-cause hospitalization
  - Prop. contribution of RSV to respiratory-cause hospitalization

- **Sensitivity analysis to assess performance of case definitions**
RSV Reference Laboratories & Reagent Support

- **RSV Reference Laboratories**
  - Gastroenteritis and Respiratory Viruses Laboratory Branch at the CDC, Atlanta
  - National Institute for Communicable Diseases, Johannesburg, South Africa.

- **Activities**
  - Preparation and distribution of CDC RSV EQA to Pilot countries annually
  - Analysis and comparison of PT results: Sensitivity/Specificity
  - Technical support to Pilot laboratories
  - Molecular analysis of representative RSV viruses

- IRR – support for RSV reagents to Pilot countries
Standardizing RSV Testing

- RSV Reference Laboratory participation in QCMD EQA

- CDC real-time RT-PCR (rRT-PCR)

- CDC-IRR biological reagent repository

- Pilot country participation in RSV EQA (CDC)
  - CDC EQA Panel
  - contemporary clades and past lineages

Examples of assays in use in Pilot countries:

- AmpliSens ARVI-screen
- CDC Protocol
- Fast Track Diagnostics (FTD) Respiratory pathogens 21
- Inhouse -RSV A & B subtype - (Nucliocapsid)
- Mag MAX (Thermo Scientific)
- Seegene-multiplex
Extraction systems

- Extraction systems used successfully with the CDC assay:
  - QIAamp® MinElute Virus
  - Viral RNA Mini Spin Kits (QIAGEN);
  - NucliSENS® EasyMag® and miniMag® (bioMérieux);
  - MagMAX™ Express and Total Nucleic Acid Isolation Kit (Life Technologies);
  - MagNA Pure Compact System and Nucleic Acid Isolation Kit 1 (Roche Applied Science)
Real-time PCR instruments

- Real-time PCR instruments used with CDC assay,
  - 7500 Fast Dx Real-Time PCR & ViiA 7 Real-Time PCR Systems (Applied Biosystems);
  - Mx3000P and Mx3005P QPCR System (Agilent Technologies);
  - iCycler IQ5 and CFX96 (Bio-Rad Laboratories)
WHO RSV Pilot Progress

- **2014 - 15**
  - Consensus reached amongst global experts to leverage GISRS for RSV testing
  - Buy-in from the WHO regional offices and countries
  - Situational mapping
  - Informal consultation on RSV surveillance (Feb 2015) in Geneva

- **2016**
  - Strategic Plan implementation developed (Feb 2016) and finalized (June 2016)
  - Preparatory activities started by countries
  - RSV Reference Laboratories participation in external RSV EQA
WHO RSV Pilot Progress

2017

- Strategic Plan implementation developed (Feb 2016) and finalized (June 2016)
- RSV Strategy published on the WHO website
- Reference laboratories established
- External Advisory Group established
- Database structure finalized / Surveillance reporting platform established
- Monitoring and evaluation strategies – in progress
  - Surveys, TCs, Meetings
WHO RSV Pilot Progress

- 2017
  - RSV Surveillance website launched

Respiratory Syncytial Virus (RSV) is a leading cause of hospitalization due to acute lower respiratory infection especially in infants and young children. Currently available options (Palivizumab) for preventing and treating RSV are limited to select populations in high-resource settings. Fortunately, several vaccine candidates are now in the human testing phase targeting young children, older adults and pregnant women, and an effective safe vaccine is likely to be available in the near future.

Several countries test for RSV as part of influenza and other respiratory virus surveillance. One of the challenges has been the use of a standardized surveillance case definition that would allow capture of RSV infection especially in infants and young children.
Next steps

- Laboratory standardization ongoing
- Reporting to GISRS by Pilot countries commenced – February 2017
- Mid-/long-term strategy
  - Network structure review
  - Country buy-in: sustainability
- Progress review and adjustment
Acknowledgement

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