UK/PHE approach to RSV surveillance pilot and reference laboratory activities – what can countries expect as learning points and support?

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RSV surveillance in England

Key RSV related surveillance objectives:

- To detect onset and period of RSV circulation
- To determine which groups affected (by age)
- To describe the burden in primary and secondary care

- Performed as part of established influenza surveillance systems: ILI and ARI are measured
- Respiratory virus testing strengthened since 2009 influenza pandemic, especially SARI. ICU networks established
- RSV laboratory detections in symptomatic cases from the community and hospital settings are recorded
- Reporting on laboratory confirmed RSV infections is voluntary
Current RSV surveillance in England

1. **Sentinel (community)**
   - Sentinel GP swabbing – combined clinical and virological surveillance through participating physicians: system is designed for influenza surveillance - based on ILI
   - RSV uses same surveillance system
     - influenza and RSV co-circulate in England during most of the winter season
     - have some similar clinical symptoms
   - System not targeted specifically at detecting RSV but could be utilised more specifically for this purpose

2. **Non-sentinel (secondary care)**
   - Second generation surveillance system (SGSS) – routine lab reports positive for respiratory pathogens by PHE, NHS and private microbiology laboratories in England and Wales (mainly based on ARI)
   - Weekly respiratory Datamart – virological surveillance in secondary care in England (mainly based on ARI). Positive and negative results are recorded by 14 diagnostic PHE/NHS laboratories
   - Both sentinel and non-sentinel RSV data currently reported weekly nationally and in Europe
   - Only sentinel data has information on RSV A and RSV B by subtype
Kits prepared

Contents

Nose and throat swabs collected

Kits sent to GPs

~100 practices

Sentinel Physician Surveillance Sampling Pathway

Kits sent to GPs

~100 practices

Samples received processed and tested by real-time PCR for detection of several respiratory viruses including RSV

Samples posted to PHE Colindale
How effective will this year’s flu vaccine be?
Virological testing of sentinel samples

Combined nose & throat swabs from community scheme

Two real-time multiplex PCRs for detection of several respiratory viruses:

- Influenza A(H3), A(H1)pdm09, B/Yamagata, B/Victoria,
- RSVA, RSVB, hMPVA, hMPVB

Comments about sampling

- RSV highly cell associated: must have cells in sample
- Ideal sample for adults different than children (NPA vs Swab)
- Decrease in viral load with age (pay attention to LoD in adults)
RCGP sentinel sample PCR workflow

Sample reception

Sample processing

Nucleic acid extraction

Reverse transcription

Suite of Multiplex PCRs

Sample archiving

Data handling and reporting
Putting it all together: Surveillance outputs

• Early warning; winter pressures
• Antiviral prescribing in the community
• Public health programmes; Vaccine Uptake & Effectiveness

Rapid communications

Detection of influenza A(H3N2) virus in children with suspected mumps during winter 2014/15 in England
PHE Weekly National Influenza Report
Summary of UK surveillance of influenza and other seasonal respiratory illnesses
14 December 2017 – Week 50 report (up to week 49 data)

This report is published weekly on the PHE website. For further information on the surveillance schemes mentioned in this report, please see the PHE website and the related links at the end of this document.

Summary

Figure 11: DataMart samples positive for influenza, England

Figure 12: DataMart % positive for RSV by age, England

Figure 13: DataMart % positive for other respiratory viruses, England
PHE RSV sentinel surveillance
Long time series

Temporal distribution RSV A vs RSV B

Age distribution RSV A vs RSV B
RSV A & B Whole genome sequencing

- **Kumaria et al. 2011**
  - 15 overlapping amplification areas ~1.3kb, covering 15k+ RSV A genome
  - 9 primer pairs out of 15 had to be modified/redesigned
  - In addition designed: 6 internal sequencing primers per each fragment: $\sum 90$

- Design amplification primers and internal sequencing primers for RSV B following the same principle as above described
RSV Whole genome sequencing (Sanger) 2008-2014

RSVA - Total 42 samples sequenced
RSVB - Total 73 samples sequenced
Trees constructed with MEGA6 program, bootstrap value 1000
Trees constructed with MEGA6 program, bootstrap value 1000
Average depth coverage for N2: 22962 reads

Average depth coverage for 9320: 18316 reads
Issues for RSV surveillance in UK

Epidemiology

- Enhance sampling <5 years
- Use broad case definition
- Unfunded
- Relies on goodwill
- Some data linkage & release issues

Laboratory

- Increase sample numbers <5
- Sequencing unfunded at present
- Data release & linkage arrangements
Summary

- Molecular detection methods are PCR based, as for influenza, optimal sample types and viral load patterns may be different.
- As for influenza, there is a need to be vigilant concerning genetic drift in diagnostics.
- Need to share sequences and build a global database, in order to check diagnostics and understand virus evolution.
- The utility of differentiation into RSV A and B is not clear.
RSV R&D projects

- Sequential samples from COPD and Immunocompromised adult patients (PhD student)
- Metagenomics/agnostic approaches for severe respiratory infections
- Use of MinIon sequencing for respiratory sample sequencing
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RSV has long been recognized as a major cause of respiratory tract infection worldwide, particularly in very young children, but also in other ages and at-risk groups.

Many countries have recognized the importance of RSV and have already established surveillance in certain settings.

Important to get a better understanding of RSV epidemiology and the burden of disease it causes, particularly in low- and middle-income countries where the greatest RSV-associated mortality is observed.

Several candidate vaccines have shown promising results in clinical trials.
WHO recently focused on planning towards implementation of RSV surveillance

WHO RSV surveillance pilot started in 2016, and aims to test the feasibility of utilising the Global Influenza Surveillance and Response System platform for RSV surveillance without adversely affecting the well-established ILI and SARI surveillance of influenza (http://www.who.int/influenza/rsv/en/)

Two or three countries to participate in the pilot in each of six WHO regions where RSV surveillance is already being performed

Three RSV reference laboratories to provide support

Objectives include testing for optimal case definitions for RSV infection for different high-risk age groups and to standardise laboratory procedures for RSV detection and quality assurance.