WHO Expert Working Group Meeting on
RSV Surveillance based on the GISRS Platform
2–3 February, 2016

Starling Hotel & Conference Center, Geneva, Switzerland
Executive summary

As a follow up to the WHO efforts in 2015 on establishing RSV surveillance based on GISRS, this expert group meeting aimed to define optimal case definitions that will cover not only influenza patients but also individuals infected with RSV, identify possible strategies for case selection, and agree on the best laboratory methods for RSV testing.

This RSV pilot covers 14 countries and is planned to last 3 years. The pilot should make it possible to determine whether RSV surveillance can be built on the influenza surveillance platform; that is, whether useful baseline data on RSV epidemiology can be obtained without negatively affecting the quality of influenza surveillance.

In each of the six WHO regions, the regional office identified two or three countries in which RSV surveillance has already been taken on by the national influenza centre. In addition, three laboratories with longstanding experience on RSV diagnostics, surveillance and research agreed to take on support activities for the participating laboratories in the 14 pilot countries.

Many RSV-infected individuals do not meet the criteria for the case definitions for influenza-like illness (ILI) or severe acute respiratory infection (SARI). In RSV patients, fever is often absent, and the infection can be particularly severe in very young infants. Thus, for RSV surveillance, it is necessary to include these patients in addition to those that match the ILI and SARI case definitions. Also, national surveillance networks need to recruit additional sentinel sites in order to obtain meaningful information about RSV epidemiology. The RSV pilot will provide opportunities to test the value of different case definitions and sampling strategies.

Participants acknowledged that real-time polymerase chain reaction (rt-PCR) is the most sensitive and specific laboratory test for the detection of RSV in clinical specimens. Laboratories participating in this RSV pilot should use rt-PCR, and should perform RSV surveillance throughout the year in order to obtain a clear picture of RSV seasonality. RSV surveillance will require the collection and reporting of detailed clinical, demographic and epidemiological data. Platforms for integrating such data for detailed analyses are already established for influenza surveillance, and RSV pilot countries have experience in using these platforms.

The group agreed that detailed guidelines need to be produced in collaboration with experts and the pilot countries so that the project can be successfully rolled out in the latter half of 2016.
Meeting report

1 Background

The WHO Global Influenza Programme (GIP) is in the process of establishing global surveillance of respiratory syncytial virus (RSV) infections, using the well-established WHO Global Influenza Surveillance and Response System (GISRS) as a platform. When working towards building RSV surveillance, RSV activities must be carefully planned so that they do not undermine influenza surveillance. WHO-coordinated RSV surveillance has several objectives; it will:

- provide baseline data on the epidemiology and seasonality of RSV in different parts of the world;
- reveal information about disease severity and about different population groups at risk for severe infection;
- reveal data on the burden of disease caused by this virus; and
- advocate the use of RSV vaccines once they become available.

Ultimately, RSV surveillance may help to reduce the impact of RSV on the population.

In March 2015, the WHO GIP held a meeting bringing together experts from the fields of influenza and RSV. The goal of that meeting was to summarize current scientific knowledge of RSV, its epidemiology, the clinical pictures it causes, the current status of vaccine development and antiviral treatment, and ongoing clinical studies and surveillance activities. Preliminary plans for setting up an RSV surveillance pilot were discussed, and the need for subsequent discussion of technical details for the surveillance pilot was recognized. The March 2015 meeting was followed by a series of WHO internal discussions, teleconferences and correspondence with international experts. This led to the WHO Expert Working Group Meeting on RSV Surveillance based on the GISRS platform being convened on 2–3 February, 2016.

Dr. Siri Hauge from the Norwegian Institute of Public Health was chair of the meeting.

2 General aspects of RSV surveillance

A global RSV surveillance system is expected to provide virological and epidemiological data in a timely manner; it must also be representative of the population under surveillance and the disease impact. With a characteristic clinical presentation, syndromic surveillance may be possible; however, laboratory confirmation of identified cases yields more precise information. To build RSV surveillance on the GISRS platform, a sentinel surveillance system relying on laboratory-confirmed cases is the recommended platform for RSV surveillance.

Integrating RSV and influenza surveillance gives several advantages:

- Clinical infrastructure, a network of experts, laboratory expertise and resources are already in place for influenza. Thus, with the resources already available, outbreaks of both RSV and influenza can be detected in a timely manner and risk groups identified.
There are thoroughly validated detection methods for both RSV and influenza in influenza laboratories. Combining RSV surveillance with influenza surveillance is cost-saving. Although the main target group for RSV surveillance is children aged under 5 years; an age group that is less well covered by influenza surveillance.

In temperate climate zones, the two diseases show overlapping seasonality. However, in many parts of the world, seasonal circulation of the viruses causing these diseases may differ. In some cases, RSV outbreaks may be observed at different times of the year within the same country. It is important to establish the seasonality of RSV, in particular, this information will be critical to assist in effective timing of vaccination programmes. The molecular evolution of RSV is considerably slower than that of influenza viruses; hence, detailed characterization of RSV detected in clinical specimens beyond identification of the RSV subtypes is not a primary aim of the early phase of building RSV surveillance. In a later stage, particularly once vaccines become available, determination of genotypes and sequence analyses of relevant genes and phenotypic characterization shall be integrated in RSV surveillance.

3 Recommended organizational strategy of the RSV surveillance pilot

The RSV pilot covers 14 countries and is planned to last 3 years. Two or three countries from each of the six WHO regions which already test specimens collected for influenza, for RSV, have been selected to participate in the RSV surveillance pilot, as follows:

- African Region – Côte d’Ivoire, Mozambique and South Africa;
- American Region (PAHO) – Argentina, Brazil and Chile;
- Eastern Mediterranean Region – Iran and Oman;
- European Region – Germany and Romania;
- South East Asia Region – India and Sri Lanka; and
- Western Pacific Region – Cambodia and Mongolia.

Many of these countries collect clinical specimens through sentinel networks; for example, through hospitals for surveillance of influenza-like illness (ILI) or severe acute respiratory infection (SARI), or both. The number of surveillance sites varies considerably from country to country. Each of these countries hosts a national influenza centre (NIC) and has in place successful infrastructures for the surveillance of influenza.

Three reference laboratories with long-standing experience in RSV surveillance have been identified: the Centers for Disease Control and Prevention (CDC) Atlanta, GA, United States of America (USA); the Public Health England (PHE) laboratory, London, United Kingdom; and the National Institute for Communicable Diseases (NICD), Johannesburg, South Africa. These three laboratories use thoroughly validated polymerase chain reaction (PCR) tests for the detection of RSV in clinical samples. They have agreed to share testing protocols with laboratories participating in the RSV surveillance pilot; also, to some extent they are able to provide technical and reagent support to participating countries. The reference laboratories have the capacity to subtype and conduct genetic characterization of RSV. It is desirable that they also perform subtyping on selected specimens sent from the participating laboratories.
Funds for shipping viruses to reference laboratories are available. Virus sharing problems might arise from the Nagoya Protocol.

4 Case definitions for RSV

WHO has established case definitions for ILI and SARI surveillance, but has not yet developed case definitions for RSV surveillance. ILI and SARI case definitions are commonly used when recruiting patients for influenza surveillance. Since RSV surveillance will be built on the influenza surveillance platform, a significant fraction of RSV patients might go undetected when strictly adhering to these case definitions designed for influenza surveillance. Many possible undetected RSV cases include children aged under 5 years – the population group bearing a major burden of RSV disease. Studies have found that up to about half of young children infected with RSV present without fever. Standardized criteria for inclusion of RSV patients for surveillance need to be established, particularly when RSV surveillance is targeted at yielding information about burden of disease. Possible interim case definitions could be “Acute respiratory disease caused by RSV infection” and “Acute respiratory infection (ARI)”.

5 Case selection and sampling strategy

There was general agreement that testing for RSV in clinical samples collected for influenza surveillance does not provide all the information required for RSV surveillance. Countries need to carefully review their sampling strategy and eventually widen their surveillance activities so that they include RSV-infected individuals who do not meet the definitions for ARI, ILI or SARI. Medical centres providing specimens for influenza or RSV surveillance, or both, should be selected such that the country's population is well represented. Additional centres need to be considered that can provide samples from patients likely to be infected with RSV, e.g., paediatric wards, emergency rooms that provide services to all age groups, maternity clinics and other sites. It was suggested that certain countries participating in the RSV surveillance pilot could adapt different case definitions and include additional sentinel sites in order to include RSV-infected patients of all age groups, and particularly children aged under 5 years. Generally, a sentinel surveillance system should cover at least 1–2% of a country's population.

Although information on the seasonality of RSV is available in some countries, analysis of such data has shown that RSV seasonality varies from one geographic region to another, between neighbouring countries and even within countries. Some countries observe RSV activity during every month of the year. To obtain a precise understanding of RSV seasonality, countries participating in the RSV surveillance pilot are requested to conduct RSV surveillance throughout the year.

Countries should decide their sampling strategy based on WHO guidance in accordance with the resources available to them. Governments in WHO Member States support influenza surveillance. Addition of RSV surveillance will require additional resources. Each participating country will need to consider for the resources they will need for RSV

1 https://www.cbd.int/abs/text/
surveillance. Laboratories in participating countries will test suspect RSV samples according to a testing algorithm to be developed by WHO.

6 Laboratory testing

The optimal type of clinical specimens for the detection of RSV and influenza viruses to some extent depends on the age of the patient. For infants and young children, the nasopharyngeal aspirate (NPA) and mid-turbinate swabs have been found to yield high sensitivity. For older children, adolescents and adults, combined nasopharyngeal and throat swabs collected into a suitable transport medium are widely used. Various kinds of swabs are available. Excellent results have been obtained with flocked nylon swabs, which can also be used on small children.

In storing clinical specimens at the site of collection, similar guidelines to those used for influenza specimens should be followed. Generally, samples should be stored refrigerated for short periods and deep-frozen (at –40 °C or lower) for extended periods. For the transport of specimens to the laboratory, similar procedures to those used for influenza specimens can be applied.

Laboratories in several countries perform immunofluorescent staining of exfoliated respiratory epithelial cells for the detection of RSV and other respiratory viruses. This technique produces reliable results on specimens collected from young children, but its sensitivity rapidly drops with increasing age of the patient. Participants in the meeting strongly agreed that PCR should be the method of choice used in laboratories of countries participating in the RSV surveillance pilot. Many laboratories already have RSV PCR assays in place. The three reference laboratories (CDC Atlanta, PHE London and NICD Johannesburg) will make their assay protocols available to all participating laboratories. Each pilot laboratory will need to decide its testing algorithm based on the WHO RSV pilot algorithm that is under development and in the context of its ongoing testing in influenza surveillance. The RSV algorithm will be designed to ensure that it does not interfere with the existing influenza surveillance system.

Participants considered quality assurance (QA) to be very important. CDC Atlanta already provides QA panels for RSV and other respiratory pathogens to laboratories in the Pan American Health Organization (PAHO) region. Efforts are under way to make such RSV QA panels available to all laboratories participating in the RSV surveillance pilot. These panels are intended for use with real time (rt)-PCR techniques which shall be the RSV detection method in the pilot. It is proposed that QA panels be distributed at least once a year in the pilot to monitor the performance of participating laboratories.

7 Clinical data collection

It was suggested that the specimen test request form used for influenza surveillance be adjusted in order to provide specific additional information that is important for RSV surveillance. It was recommended that the division of age groups be adjusted for RSV surveillance (the exact age should be recorded, particularly for children). It is essential to record presence or absence of fever, and the use of antipyretic before clinical investigation of the patient. Additional data to be collected include information about
underlying illnesses and predisposing risk factors, disease severity, possible hospitalization, duration of hospitalization and outcome (including mortality).

8 Epidemiological data collection and reporting

FluNet, a database maintained by the WHO GIP, has been in use since 1997; more than 130 countries are regularly reporting influenza surveillance data to this platform. FluNet is currently being upgraded to contain reporting fields for other viruses, including RSV. National focal points for epidemiological influenza surveillance report data to the FluID database. This system is able to accept aggregated and case-based data, which can be entered or uploaded directly by the national laboratory or the epidemiological focal point, or indirectly through a regional database. Linking laboratory data with epidemiological data needs to be streamlined. The frequency of reporting needs to be determined for the RSV surveillance pilot, and a decision must be taken as to whether and how RSV data from the RSV surveillance pilot will be published. Verification of ethical clearance for RSV surveillance might be required in some countries.

9 Objectives of RSV surveillance pilot identified during the meeting

RSV surveillance will yield increased knowledge of RSV, including the burden of disease caused by this virus. The surveillance pilot will provide data on baseline activity and, to some extent, on the diversity of circulating RSV strains. The pilot will also make it possible to determine whether RSV surveillance built on the existing influenza surveillance is feasible. It will test the use of different case definitions and facilitate the identification of the most suitable RSV case definitions. Optimal sampling strategies and the number of samples needed to obtain useful data will be defined. Outcomes of the RSV surveillance pilot must also reveal possible negative impacts on influenza surveillance. Because the RSV surveillance pilot is expected to start during 2016, WHO GIP and WHO regional offices will need to intensify communication with participating countries. A clear strategy for the use of data needs to be built, in view of the global RSV surveillance that should be developed if the surveillance pilot is successful.

A meeting with representatives from laboratories and epidemiologists from participating countries is scheduled for late June 2016. During that meeting, technical details will be provided to the countries. It is expected that the surveillance pilot will be launched shortly after that meeting.

Building RSV surveillance means rolling out a public health programme that will have a long-term global impact.
WHO Expert Working Group Meeting on
RSV Surveillance based on the GISRS Platform
2 - 3 February, 2016
Starling Hotel & Conference Center, Geneva, Switzerland
Provisional Agenda

Day 1

Chair: Siri Helena Hauge

Tuesday, 2 February 2016

8:30- 9:00 Registration

09:00 – 09:15 Opening and welcome	Wenqing Zhang
Background and introduction
Disclosure of Interests as declared by the Experts
Selection of Chair and appointment of Rapporteur

09:15 – 09:20 Objectives and expected outcomes	Terry Besselaar

09:20 – 09:35 Report from the WHO Informal Consultation on Surveillance of RSV based on the GISRS Platform in March 2015

Thedi Ziegler

Session 1: Pilot of RSV surveillance – objectives and sampling strategy

9:35 – 9:50 Objectives and expected outcomes from RSV surveillance based on the influenza platform

Siri Helene Hauge

9:50 – 10:50 Discussion
Facilitator: Susan Gerber

10:50 – 11:20 Coffee break and group photo

11:20 – 11:50 Comparison of RSV case definitions

Cheryl Cohen
Shobha Broor

11:50 – 12:00 Introduction of Working Groups – sampling strategy
Facilitators:
Shobha Broor
Tomimasa Sunagawa

12:00 – 13:00 Working Group discussion

13:00 – 14:00 Lunch

14:00 – 14:20 Working Group report back (10 minutes each)

14:20 – 15:00 Discussion

Session 2: Pilot of RSV surveillance – readiness in countries

15:00 – 15:15 AFRO (Cote d’Ivoire, Mozambique and South Africa)

Cheryl Cohen
15:15 – 15:30  EMRO (Iran and Oman)  Talat Mokhtari-Azad

15:30 – 15:50  Coffee break

15:50 – 16:05  EURO (German and Romania)  Eeva Broberg
16:05 – 16:20  PAHO (Argentina, Brazil and Chile)  Elsa Baumeister
16:20 – 16:35  SEARO (India and Sri Lanka)  Shobha Broor
16:35 – 16:50  WPRO (Cambodia and Mongolia)  Iris Hasibra
16:50 – 17:00  Introduction of Working Groups – readiness and needs in the pilot  Facilitators: Richard Pebody Susan Gerber
17:00 – 17:40  Working Group discussion
17:40 – 17:45  Closure of day 1

Day 2

Wednesday, 3 February 2016

09:00 – 09:05  Words from Chair
09:05 – 09:25  Reporting back from Working Groups
09:25 – 09:45  Discussion

Session 3: Pilot of RSV surveillance – laboratory function

09:45 – 10:05  RSV Laboratory surveillance  Maria Zambon
10:05 – 10:15  Introduction of Working Groups  Facilitators: Maria Zambon Iris Hasibra

10:15 – 10:35  Coffee break

10:35 – 11:30  Working Group discussion
11:30 – 11:50  Reporting back from Working Groups
11:50 – 12:40  Discussion

12:40 – 13:40  Lunch

Session 4: Pilot of RSV surveillance – reporting

13:40 – 14:00  RSV surveillance reporting  Julia Fitzner
14:00 – 14:30  Discussion  Facilitator: Richard Pebody

Session 5: Pilot of RSV surveillance – guidance to the operation

14:30 – 14:40  Review of existing RSV surveillance framework  Iris Hasibra
- gaps

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<td>14:40 – 14:45</td>
<td>Introduction of Working Groups (2 different groups)</td>
<td>Iris Hasibra</td>
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<td>14:45 – 15:25</td>
<td>Working Group discussion</td>
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<td>15:25 – 15:45</td>
<td>Coffee break</td>
<td>Harry Campbell</td>
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<td>Sandra Jackson</td>
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<td>15:45 – 16:15</td>
<td>Working Group report back and discussion</td>
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<td>Roll-out of pilot of RSV surveillance</td>
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<td>16:35 – 16:55</td>
<td>Next steps for global RSV surveillance</td>
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<td>Summary</td>
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<td>Closure of the meeting</td>
<td>Wenqing Zhang</td>
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List of Participants

Elsa Baumeister, Jefa Servicio Virosis Respiratorias, Departamento Virología-Centro Nacional de Influenza de OPS/OMS, Buenos Aires, Argentina
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Harry Campbell, Centre for Population Health Sciences, The University of Edinburg, Edinburgh, UK
Cheryl Cohen, National Institute for Communicable Diseases, Johannesburg, South Africa
Kitty Fung, United Christian Hospital, Hong Kong SAR
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Siri Helene Hauge, Norwegian Institute of Public Health, Oslo, Norway
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Declaration of interests

The WHO Expert Working Group Meeting on RSV Surveillance based on the GISRS Platform, 2-3 February 2016, was organized by the Global Influenza Programme of WHO, with participation from the WHO Collaborating Centers on influenza, National Influenza Centres and experts on RSV.

In accordance with WHO policy, all participants were required to complete the WHO form for Declaration of Interests for WHO Experts. Maria Zambon declared having received honoraria for public speaking at ICAAC conference in 2012 and ISIRV in 2013-14 and being advisor to the Scientific Pandemic Influenza Group, ECDC on anti-viral resistance and pandemic planning, and ISIRV without influence on decisions on vaccine purchase. No other participant declared any personal current or recent (within the last 4 years) financial or other interests relevant to the subject of the meeting.

All declarations made were evaluated by the WHO Secretariat prior to the meeting. It was concluded that the interests declared did not conflict with the objectives of the meeting and that the above individuals could participate in full. At the start of the meeting the interests that had been declared were disclosed to all participants.