WHO Technical Meeting on Piloting RSV Surveillance based on the Global Influenza Surveillance and Response System

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Executive summary

Respiratory syncytial virus (RSV) is an important viral respiratory pathogen, causing acute, sometimes fatal lower respiratory tract infections in infants and young children. In addition, RSV contributes substantially to severe morbidity in the elderly. With significant and rapid progress in the development of RSV vaccine, it is expected that a RSV vaccine would become available in the next few years. There is a need to develop a global surveillance platform to serve as evidence base including a better understanding of the epidemiology, seasonality, high risk groups and circulation of the RSV.

The WHO Global Influenza Programme (GIP) is in the process of implementing a pilot of RSV surveillance based on the influenza surveillance platform, the WHO Global Influenza Surveillance and Response System (GISRS). The aim of the pilot is to test the feasibility of building on the capacities of GISRS, an established, well-functioning and long-term network, where many countries already collect and test samples, for targeting RSV.

Two meetings, in March 2015 and in February 2016, brought together experts from the scientific communities of RSV and influenza. The first meeting was an informal consultation on RSV surveillance leading to a strategic plan proposal for global RSV surveillance. The second one was an expert working group meeting that focused on the agreement of structures and component details of an RSV pilot. This included discussions on case definitions, strategies for case selection, laboratory protocols for RSV detection, and data collection and reporting procedures.

A third meeting was held in June 2016 in Geneva wherein 14 selected countries agreed on the strategies and operational elements to roll-out the RSV pilot surveillance by the end of 2016. Countries presented their existing surveillance methodologies and agreed upon changes that were needed in case definitions and selection, need to test at least 1000 respiratory specimens per year, targeted sampling of infants and under-five age group, year-round sampling, laboratory testing, data management and case-based reporting required to roll-out the RSV pilot. The pilot is planned for 3 years in 2 or 3 countries in each WHO region. Two documents, the WHO surveillance guidance for the RSV pilot, and Instructions for use of the CDC real-time RT-PCR assay for RSV were finalized at this meeting. The potential role of reference laboratories was defined, testing protocols validated, and algorithms for selection cases for specimen collection was developed. The minimum dataset for collection was defined, the need for case-based data, reporting periodicity and platforms was agreed upon. It was agreed that each country develops a detailed manual that could be referred to by the participating sentinel site to ensure that all sites use a consistent methodology. Each country would ensure training of all the participating sentinel sites at the start of the pilot that would focus on the selection and testing of cases, completing the forms, laboratory protocols and timely reporting.

As participating countries enlist and train sentinel sites, train laboratory staff in testing protocols, participate in proficiency tests, concurrent efforts have been initiated to expand the FluMart platform to include case-based RSV surveillance information.

Meeting Report

Background

Respiratory syncytial virus (RSV) is an important viral respiratory pathogen, causing acute, sometimes fatal acute lower respiratory tract infections in infants and young children. Re-infections are common and occur in all age groups. In children below the age of 5, the RSV burden of disease exceeds the burden of disease from influenza and other respiratory viral agents. RSV disease is known to occur in the elderly and in adults with chronic medical conditions (such as COPD) but the global disease burden is not well known. At present there are several RSV vaccine trials underway, of which one is in phase 3. With the expectation that RSV vaccines may become available in a few years time, there is a need for RSV surveillance data. RSV surveillance data will provide baseline data on the epidemiology and seasonality of RSV in different parts of the world. It will help define to what extent severe RSV disease in certain age and risk groups is a health priority.

The WHO Global Influenza Programme (GIP) is in the process of developing a pilot study of RSV surveillance based on the influenza surveillance platform, the WHO Global Influenza Surveillance and Response System (GISRS). The advantage of using the GISRS is that one can build from an established, well-functioning network, where many countries already collect and test samples for RSV. There are links to national policy makers and there is the potential to understand influenza and RSV together. The GISRS is considered to be the most efficient and effective platform to pilot test RSV surveillance.

Two previous RSV meetings, in March 2015 and in February 2016, were held to bring together experts from the fields of RSV and influenza. The first meeting was an informal consultation on RSV surveillance leading to a strategic plan proposal for global RSV surveillance. The second one was an expert working group meeting and focused on the agreement of structures for an RSV pilot. This included the discussion of suitable case definitions, identification of strategies for case selection, agreement on the optimal laboratory methods for RSV detection, and identification of the best data collection and reporting procedures.

The next step is to launch the pilot of RSV surveillance. The meeting objective of this 3rd meeting, held in June 2016, was therefore to reach a common understanding to facilitate implementation of RSV pilot surveillance after the meeting and get countries ready for implementation. Since the meeting in February, two documents were further developed: 1) the WHO surveillance guidance for the RSV pilot, and 2) Instructions for use of the CDC real-time RT-PCR assay for RSV. At the meeting the group aimed to reach consensus on the strategies and operational elements for piloting RSV surveillance in the selected countries.

The roll-out of the pilot is planned for 3 years in 2 or 3 countries in each WHO region. Selected countries are: AFR: Côte d'Ivoire (CI), Mozambique (MOZ), South Africa (SA) AMR (PAHO): Argentina (ARG), Brazil (BRA), Chile (CHI) EMR: Iran (IRA), Oman (OMA), Egypt (EGY) EUR: Germany (GER), Russia (RUS) SEAR: India (IND), Sri Lanka (SrL) WPR: Cambodia (CAM), Mongolia (MON)

In addition, three laboratories with extensive experience in RSV diagnostics and research have agreed to provide support to the pilot laboratories. These three laboratories are: - The Centers for Disease Control and Prevention (CDC), Atlanta GA, USA;

- The laboratory of Public Health England (PHE), London, UK;

- The National Institute for Communicable Diseases (NICD), Johannesburg, South Africa.

Objectives pilot RSV surveillance

The primary objectives of the RSV pilot are to:

- Assess the suitability and feasibility of RSV surveillance based on the GISRS platform
- Identify RSV seasonality in different countries and regions
- Determine the age and/or risk groups for severe RSV disease
- Evaluate RSV case definitions and sampling strategies
- Provide improved knowledge on RSV healthcare burden
- Assess feasibility of using the FluNet and FluID for data reporting
- Build laboratory capacity for RSV testing in pilot countries
- Standardize laboratory procedures for RSV detection and quality assurance
- Document possible negative impact on existing influenza surveillance
- Report surveillance data to raise awareness and provide evidence to inform policy decisions

Secondary objectives have also been defined and include:

- the assessment of the additional costs incurred through implementation of RSV surveillance
- provide a platform for future RSV studies (such as vaccine effectiveness studies, cost effectiveness studies; assess efficacy of RSV treatment strategies, and bank samples i.e. evolution of strains over time and relation to vaccine strains).

The RSV pilot will not provide the following: data on population-based RSV disease burden, data which can be used to assess RSV vaccine effectiveness, data on economic burden of RSV, and data which will give a complete and detailed clinical description of RSV disease in all age and at-risk groups.

Epidemiological aspects of RSV surveillance

The guidance document for RSV surveillance contains important information to perform RSV surveillance in pilot countries. Information on the case definitions to be used for different age groups is included, as well as minimum criteria for the number of samples to be collected per year and pilot country, and the sampling strategy. Another aspect is year-round data collection in order to define the seasonality. The RSV surveillance should be primarily hospital-based. The reason for this is that when RSV vaccines become available they will primarily aim at preventing severe cases, i.e. case that require hospital treatment. The pilot includes all age groups since although RSV burden is mainly associated with young children there is also a significant disease burden that is not well understood nor recognised in older age groups.

There are several challenges in using the GISRS platform for RSV surveillance. There is the need for modified case definitions, enhanced recruitment in the very young age group (first few months of life) and year round testing. In order to collect surveillance data on specific groups for policy and programme purposes (young children and elderly), it is important to collect a minimum quota of samples in 4 distinct age groups (0-<6m; 6-59m; 5-64 years; ≥65 years). Finally, there is a need to collect additional data which may be challenging as this potentially may have a negative effect on the current GISRS. A balance must be found between making the least changes to flu surveillance, but at the same time still providing valid RSV data. The pilot will help to identify how this is best achieved.

The RSV hospital surveillance case definition is based on SARI as defined in existing GISRS influenza surveillance However, the RSV "extended SARI" 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. In addition to

this extended case definition additional criteria have been included for infants 0-6 months of age: apnea and/or sepsis. This is because RSV disease may present with other symptoms in young infants.

The defined sampling strategy is that at least 20 cases/week should be recruited and tested so that all pilot sites can describe the RSV seasonal pattern. These cases should also be recruited in order to meet age groups quotas. More details on the specific requirements can be found in the surveillance guidance document.

For the pilot project the sampling strategy should be well documented and sites should be chosen to ensure that the minimum sample sizes are achieved. This should include, where possible, both in-patient wards (adult general medical and specialist medical; respiratory/infectious disease; and pediatric) and intensive care units (ICU) (both adult, pediatric and neonatal care).

At the meeting each pilot country presented their implementation plan for RSV surveillance and identified challenges and actions to be taken in the application of the proposed RSV case definition, ensuring an adequate number of samples in particular from the youngest age group, and ensuring all-year round surveillance.

External advisors highlighted that there is a need to track whether local or national ALRI case definitions change over time in order to interpret results and that the collection of clinical data is an opportunity to assess case definitions. Furthermore, for the 5-64 age group, there was a plea to reconsider increasing the (low) priority given to data on RSV in pregnant women as this may be relevant for the maternal vaccination. This target group could be included in surveillance by giving priority to recruitment in female wards. However, it was recognised that to study this issue properly special studies may also be required. Regarding the interpretation of seasonality data, special care is needed when data are coming from widely dispersed sites with a wide latitude range (since seasonality may vary across these sites and this information may be lost when pooling data).

Following the country presentations, the participants were divided into 3 working groups and discussed the challenges in the epidemiological data collection, changes required in existing reporting systems and actions that need to be taken.

From the group work the following points were made:

Site selection and quotas:

- It is important to record descriptive information about the recruitment site settings in the pilot as case characteristics may vary by type of facility;
- There is a need for information on the surveillance site setting (urban/rural, socio-economic status, pollution levels, climate/seasons; type of wards included in surveillance);
- It was proposed to introduce the extended case definition in a limited number of sites to assure high quality of data collected;
- The defined quotas for the age groups pose a challenge. It is difficult to recruit older adults, as many SARI cases in this age group are not admitted to hospital. For the very young it will be a challenge to recruit the most sick /or youngest (0-2 month) age group as clinicians may be resistant.
- It was highlighted that the predefined quotas are per country. This is a minimum and countries can opt to increase this, especially during the RSV season

Year round surveillance, sampling strategy and data reporting:

- The working groups acknowledged the need to do year-round surveillance. Some countries were concerned about recruitment and sampling cases outside the RSV season. However, it is important to perform this in the pilot phase in order to identify the seasonality and possible year-to-year variation.
- The focus on hospital surveillance with extended SARI case definition was generally accepted.

The strength of this pilot is that all participating countries will use a common approach. This means that countries will <u>not</u> just test influenza negative samples for RSV, as this will create unacceptable bias; and will <u>not</u> just test SARI cases, as this will miss many or even most RSV cases. Adoption of the extended SARI case definition will increase recruitment and help achieve sample quotas.

• Case-based data will be collected from <u>all</u> cases (all tested cases; either negative or positive) that meet the extended case definition.

There was general recognition of the importance of training of staff in application of the extended case definitions, sampling procedures and completion of the new/adapted forms. There is also a need to assess the number of cases meeting the SARI and extended SARI case definitions and look at the performance of different case definitions in sites.

For the future of the project, we will need to understand what evidence is required for policy making groups to make decisions and align with this. Ongoing RSV surveillance may not be needed at the same scale and intensity as influenza as several years of hospital data will be available for policy makers, and the RSV virology is less dynamic than influenza.

While the countries generally expect to be able to meet the required criteria, a few countries indicated that additional staff and/or funding is required and training needs to be provided. WHO HQ requested for each country to provide details of essentials costs to be covered by the project.

Finally, a few countries indicated that they have only recently been invited to participate in the pilot of RSV surveillance and discussions need to be continued at their institutes.

Laboratory aspects of RSV surveillance

For the RSV pilot it is important to standardize the laboratory procedures for RSV detection and assure the quality of the methods used. In addition, this work will help to improve laboratory capacity, define the role of RSV reference laboratories and provides a platform for future RSV studies.

The guidance document contains information on the type of specimens to be used, procedures on the transport and storage and testing algorithm. The agreed method to use is real-time RT-PCR, this can be an in-house method or the CDC assay. Samples can be tested real-time –simultaneously RSV and influenza testing upon arrival in the laboratory, or in batches, e.g. once a week. The testing strategy can be defined by the countries according to available resources. For internal quality assurance laboratories need to maintain and document rigorous internal quality control measures. For external control a proficiency panel will be distributed at the start of the pilot.

The CDC RSV real-time RT-PCR assay was introduced, as well as the proficiency panel and Material Transfer Agreement (MTA). Instructions for use of the CDC RSV assay are available in a separate document and were disseminated to all participants. The CDC will also provide a panel for proficiency testing as part of the external quality control assessment (EQA). All laboratories will need to complete the MTA form and send it back to CDC. As soon as the paperwork is completed, the materials (CDC assay(s), positive control, and RSV EQA) are shipped. The expected timeline for this is August 2016. The laboratory will need to test the proficiency panel with their in-house method and the CDC assay and send back the results to CDC. If the performance of the in-house methods is good, they can continue to use this method during the pilot. If the performance is not sufficient, the countries should use the CDC assay. WHO HQ will arrange the logistics of the shipping from and to the reference laboratories, and CDC can make enzymes and extraction kits available for 1000

samples per country though IRR. If a country is not yet registered with IRR this should be done immediately.

On day 2 of the meeting, the laboratory side of the pilot RSV surveillance was discussed. Following the presentations on laboratory aspects and role of RSV reference laboratories, 3 working groups discussed the implementation of the RSV testing algorithm.

Most countries are ready to make adjustments for RSV testing. Generally, countries expect to do batch testing weekly; with a few stating that fortnightly is more realistic. Few countries indicated to plan to test their negative samples for RSV, but they were highly encouraged to test all samples collected for RSV irrespective of the influenza test result.

Additional group comments related to the laboratory aspects were:

- Some countries expressed concern about the storage of samples; there may be limited space in freezers. It was not decided how long the specimens should be stored. In case of limited space, the storage could be limited to positive samples;
- Subtyping and sequencing of positive samples will need further discussion with the reference laboratories. Subtyping is not planned for the 1st pilot year, but may be done later on;
- Need for guidance on what level of positivity (% positive) countries may expect with the extended case definitions;
- Regarding the reporting back of results to the sentinel sites, it was advised to use the same procedures are used in influenza surveillance;
- The need for training needs to be assessed after results are available after the proficiency testing.
- If a country performs routine testing with methods additional to real-time PCR this will be an opportunity to identify sensitivity problems (an example was IFAT testing done parallel with PCR, and they found mismatches of primers and probes with loss of sensitivity with some of the circulating strains in the multiplex PCR).
- Information on timing of receipt of specimen in the laboratory and the conditions (e.g. whether the sample was received at the correct temperature) could be part of the internal quality control of the laboratory.

All comments were taken into consideration and the surveillance guidance has been updated accordingly. The first steps in the pilot will be the distribution of the profieciency panel and primer kits in August 2016.

In addition to the CDC in Atlanta, there are two specialized laboratories that can serve as an RSV reference laboratory: Respiratory Virus Unit - Public Health England (HPE) in London, and the National Institute for Communicable Disease (NICD) in Johannesburg. They presented the various activities being carried out in the reference laboratories. The PHE laboratory can provide a PCR protocol for RSV detection and provide support as necessary to participating laboratories. The collaborating centre from Melbourne may also have potential to function as an RSV reference laboratory in the future, but their focus so far has been on influenza surveillance and a research

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