Meeting report

WHO Informal Consultation on Surveillance of RSV on the Global Influenza Surveillance and Response System (GISRS) Platform

25–27 March 2015

Starling Hotel & Conference Centre,

Geneva, Switzerland

 WHO/HSE/PED/GIP/RSV/2015.01

Contents

Executive summary

Respiratory syncytial virus (RSV) is the leading viral cause of acute lower respiratory tract infections in infants and young children in whom this virus is the cause of the primary infection. Several novel vaccines have shown promising results in clinical trials; therefore, it is 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. The WHO-coordinated Global Influenza Surveillance and Response System (GISRS) continuously monitors the global epidemiology of influenza viruses, as well as the antigenic and genetic characteristics of circulating and novel influenza viruses. A number of GISRS laboratories have already included RSV and other respiratory pathogens in their surveillance programme.

To design strategies for coordinated, systematic and global RSV surveillance, the WHO Global Influenza Programme convened an informal consultation with representatives from academia and public health from 25 to 27 March 2015, in Geneva, Switzerland. The meeting included presentations from experts on the clinical presentation of the infection, the epidemiology of RSV, the burden of disease, vaccines under development and in clinical trials, and the RSV surveillance that has been established in several countries. Working groups discussed possible case definitions, sampling strategies, technical aspects of laboratory testing, reporting and analysis of surveillance data.

One primary objective of RSV surveillance is to provide information on the seasonality of RSV epidemics in different parts of the world and shed light on the burden of disease RSV infections cause in different geographical areas and population groups. RSV is one of the most common severe acute respiratory illnesses (ARIs) during the first year of life, and up to one third of serious RSV infections are seen during the first 6 weeks of life. The young age at which many serious infections occur limits the potential use of many sentinel influenza surveillance systems because very young children are underrepresented in these systems. Influenza disease generally occurs later in life.

Since about half of RSV-infected children present without fever, the influenza-like illness case definition – which includes fever and is often used for influenza surveillance – may miss many RSV infections. Thus, a case definition that does not require fever would capture more RSV-infected infants.

Clinical samples commonly collected for the detection of influenza viruses are suitable also for the detection of RSV. Nasopharyngeal aspirates and nasal washes may be the preferred specimens from young children. Many GISRS laboratories use real-time polymerase chain reaction (PCR) techniques for the detection of influenza viruses, and such assay protocols are also available for RSV. When testing samples from young children, detection of RSV by immunofluorescent techniques also provides satisfactory sensitivity. However, for older children, adolescents and adults, this technique is clearly inferior to PCR.

The well-established, internet-based FluNet reporting system for influenza data maintained by the WHO Global Influenza Programme can easily be adapted to integrate RSV data.

The meeting concluded that it is possible to build standardized RSV surveillance systems, and that the existing influenza surveillance system is the most practical platform. The surveillance would provide useful information about the seasonality of RSV epidemics in different geographical regions and associated virological information. To understand fully the burden of disease caused by RSV, special studies beyond routine surveillance are required. Standardized sampling and testing protocols will be evaluated and made available to laboratories and institutions able to participate in RSV surveillance. Institutions with profound experience in RSV diagnostics and surveillance could serve as reference laboratories for RSV. Ideally, one or more of these institutions should have the capacity to provide testing protocols, and eventually reagents or test kits, to laboratories participating in RSV surveillance. The WHO Global Influenza Programme will establish a group of experts that will provide advice on various aspects of RSV surveillance and burden of disease estimates.

1 Introduction

Respiratory syncytial virus (RSV) is an important respiratory pathogen that often causes severe and even fatal infections, particularly in children aged under 6 months. In low- and middle-income countries in particular, RSV infection in those aged under 6 months may be fatal. Several studies have shown that other population groups may be vulnerable to severe RSV infections; for example, pregnant women, immunocompromised individuals and patients with chronic medical conditions. The clinical presentation usually does not differ from that caused by other respiratory pathogens, and RSV often co-circulates with other respiratory viruses including influenza.

Several RSV vaccines are currently being tested, and some of those may be used widely in the foreseeable future. A commercially available neutralizing monoclonal antibody can prevent severe RSV infections in prematurely born infants when given regularly throughout the entire RSV period. Similar products and anti-RSV drugs may soon become available for clinical use.

More precise knowledge about the epidemiology of RSV and its seasonality in different geographical regions, and a better understanding of the burden of disease caused by RSV are needed, to help identify individuals who might profit most from vaccines or antiviral treatment. To acquire this information, a coordinated, global surveillance of RSV needs to be established. The WHO Global Influenza Surveillance and Response System (GISRS) provides a well-established platform on which RSV surveillance could be built.

A WHO informal consultation was held in Geneva, Switzerland, from 25 to 27 March 2015. At the meeting, RSV experts from academia and from public health, as well as representatives from GISRS entities, discussed the needs for global RSV surveillance and deliberated on the requirements of an RSV surveillance system. In the planning phase of this meeting, several teleconferences were held with RSV experts, to identify session topics and discussion items for group work. The expected outcomes of this informal consultation were to:

- develop strategies for RSV surveillance;
- design an operational plan towards implementation of RSV surveillance;
- agree on standardized laboratory protocols for RSV detection;
- find agreement on surveillance protocols and reporting systems; and
- outline functions of a WHO expert group on RSV surveillance.

2 Understanding of RSV

Based on the clinical presentation, it is difficult to distinguish RSV from other respiratory viruses such as human metapneumovirus, parainfluenza and influenza viruses. RSV is the most important respiratory pathogen in children aged under 1 year. Up to 30% of all RSV cases appear in children aged under 6 weeks. Peak hospitalizations occur at about 1 month of age, and RSV-related case-fatality rate is highest in children aged under 2 months. Tachypnoea, cough and wheezing are important signs of RSV infection. Cough is one of the

leading symptoms, but almost half of RSV-infected children present without fever. If fever occurs in small children, it often is followed by lower respiratory tract infection. In young children, adjusted rates for hospitalization are highest for RSV, followed by parainfluenza virus type 3 and influenza. In children aged under 5 years, RSV causes a higher burden of disease than influenza. Risk factors for RSV-related hospitalization are premature birth, chronic lung diseases and congenital heart disease. RSV causes a significant burden of disease both in hospitalized individuals and outpatients, and RSV infection may predispose children to long-term sequelae up to the age of 13 years and even beyond, with wheezing and asthma being the most frequently observed long-term problems. More precise information on the burden of disease caused by RSV will provide a case for vaccine interventions, and enhance awareness at the national and international levels.

A better understanding of RSV epidemiology and seasonality is needed for the timing of preventive interventions. RSV epidemics do not necessarily overlap with the influenza seasons. Intensified surveillance may reveal that the RSV season is longer than currently assumed. In tropical areas, RSV often circulates during the rainy season, whereas south of the equator, RSV mainly occurs during the dry season. However, seasonality can vary even within countries, and in some countries, year-round RSV circulation is observed.

A major obstacle to RSV immunization is the fact that RSV infects early in life. Immune responses are reduced in infancy, and the safety of any vaccine is a major concern. Several different approaches to vaccine manufacturing are underway and some companies may file for marketing authorization in a few years. These vaccine approaches include F protein antigens with a stable and immunogenic structure, parainfluenza or Sendai viruses expressing the RSV F protein, virus-like particles, virosomes and live-attenuated RSV. Maternal immunization has proven feasible as a measure to prevent severe RSV infection in the newborn. High titres of maternally acquired RSV-specific neutralizing antibodies correlate with decreased disease in young infants. However, RSV infections occur in the presence of pre-existing immunity, and re-infections are frequently seen in all age groups.

With regard to interventions other than vaccines, the humanized monoclonal antibody Palivizumab has proven moderately effective in preventing RSV disease in high-risk young infants. In the United States of America, this intervention is recommended for premature infants of less than 29 weeks gestational age. However, the need for repeated application of this expensive prophylactic approach has set clear limitations on this intervention. Novel, similar products and three anti-RSV drugs are in clinical evaluation and may help to reduce the burden of RSV within the next few years.

Subtypes A and B of RSV are co-circulating, and these two subtypes can be further divided into several genotypes. These genotypes replace each other in circulation and may thus also contribute to re-infections. Even within different regions of a given country (e.g. Kenya), the two subtypes can circulate at different times. There may be peak activity of one subtype while the other subtype is almost or even completely absent.

3 National and global objectives for RSV surveillance

In many regions, RSV is co-circulating with other respiratory pathogens; also, in the absence of laboratory testing, surveillance may underestimate the burden of disease in the community. Hence, there is a need for standardized case definitions for RSV. Surveillance for influenza-like illness (ILI) and severe acute respiratory illness (SARI) as used for influenza can help to determine the seasonality of RSV and to track genetic diversity among circulating RSV strains. However, ILI case definitions require the presence of fever, or reported fever, for inclusion. Since almost 50% of children have no fever when infected with RSV, surveillance using fever as an inclusion criterion will miss many cases. The acute respiratory illness (ARI) definition does not require fever and thus covers all respiratory pathogens. Hence, ARI might be the preferable case definition for RSV surveillance. An increasing number of countries participating in GISRS are expanding their influenza surveillance to SARI cases. With frequent severe RSV infections in the very young, RSV surveillance should also include SARI patients with or without fever. Any form of RSV surveillance may underestimate RSV mortality, because in low- and middle-income countries in particular more RSV-infected children die at home than in hospitals. Currently, RSV mortality estimates are limited to only a few scientific studies.

Recruiting of RSV surveillance sites is critical. General practitioner offices, paediatricians' offices and hospitals should be represented in an RSV surveillance network, and should cover all age groups and risk groups. Children with the most severe outcome are also the ones with the least access to health-care services. Among the specific risk groups identified are malnourished and immunocompromised individuals, pregnant women, army conscripts, prison inmates, individuals who are HIV-positive or are exposed to HIV, people with Down syndrome, patients with chronic obstructive pulmonary disease or other chronic conditions, native populations, patients in long-term care and older people. These groups may benefit most from vaccination in the future and should therefore be covered by surveillance systems. Surveillance may underestimate the burden of disease in the community, but can nevertheless help to demonstrate that RSV is a health priority.

Various patterns of seasonality have been identified for RSV. Most geographical areas experience annual epidemics, whereas others may experience them only every second year; also, epidemics may vary over time. Surveillance can help to characterize the timing of epidemics from year to year.