WHO Meeting of Mid-term Review of the RSV Surveillance Pilot Based on the Global Influenza Surveillance and Response System

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The report was prepared by Sandra Jackson and reviewed internally by Siddhivinayak Hirve and Wenqing Zhang from WHO and externally by Harish Nair and Shobha Broor, co-chairs for the meeting.

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Executive summary

A standardized and robust global Respiratory Syncytial Virus (RSV) surveillance system is important to better understand the seasonality of RSV infections and support the programmatic need for future introduction of RSV vaccines. Following a series of consultations with RSV experts organized by the WHO Global Influenza Program (GIP), a draft WHO global strategy for RSV surveillance was developed in June 2016. The WHO Global RSV Surveillance Strategy (World Health Organization 2017) was developed with standards specific to RSV surveillance using the functioning mechanisms and infrastructure of the WHO Global Influenza Surveillance and Response System (GISRS)[1] . The GISRS network comprises 153 institutions in 114 countries, of which, National Influenza Centers (NICs) form the backbone. With a strategy identified to build on GISRS as the most cost-effective approach for global RSV surveillance, a two-year Global RSV Surveillance Pilot (2017-18) was rolled out in 2016 in 14 countries representative of the six WHO regions. The Pilot is an integrated epidemiological and laboratory surveillance coordinated by WHO in sentinel sites engaged in ARI, SARI and ILI surveillance. Each Pilot country selected several sentinel sites which would collect and send specimens to the National Influenza Centre (NIC) to test for RSV. In addition, WHO identified three reference laboratories for RSV. After one-year of implementation, a meeting was held in December 2017 to review the progress and early outcomes of the Pilot. This meeting brought together 61 participants from six WHO regions, including the laboratory and surveillance focal points, international RSV experts, MOH officials, global and regional partners and other entities. The objectives of the three-day meeting were to review the progress, early outcomes, review the strategy for any mid-course corrections, discuss challenges, develop plans for estimating incremental costs, and discuss strategies for sustainability.

Progress and accomplishments of the Pilot included the functioning of three RSV Reference Laboratories under the Terms of Reference for WHO RSV Reference Laboratories[2], the establishment of an External Advisory Group, the expansion of sentinel sites to include young children and elderly, standardization of RSV molecular testing, the adaption of the WHO FluMart data platform for reporting of case-based RSV surveillance data, and the development of a RSV website under the WHO Global Influenza Program website. Preliminary results from surveillance of over 13,000 respiratory specimens from across all age groups using extended SARI and ARI case definition (including apnea and sepsis in young infants) which has been shown to be more sensitive for RSV, were analyzed. Results showed the highest burden of RSV (93%) in children under-five years especially infants less than 6 months and those less than 2 years of age. Percent positivity for RSV infection was highest (29% and 16%) at 0 - <6m and 6m - <5y ages respectively. Increased RSV activity preceded and / or overlapped with that of influenza and coincided with the rainy season in the tropics and colder months in the temperate zone. The inclusion of either history of fever or measured fever significantly reduced the odds ratio and the sensitivity to detect RSV hospitalization infection across all age groups. Apnea and sepsis were found to be highly specific for detection of RSV in infants less than 6 months of age. The implementation of RSV surveillance using the GISRS system did not adversely impact influenza surveillance. Key challenges reported by countries included the use of the extended SARI case definition by physicians in the early phase of the pilot, recruitment of the required sample size in the different age groups, incompleteness of some clinical data and difficulties and delays in reporting. The need to consider RSV sub-typing for a better

[1] http://www.who.int/influenza/gisrs_laboratory/en/

[2] http://www.who.int/influenza/rsv/RSV_TOR_Lab_20170504.pdf?ua=1

understanding of the circulating RSV types and disease severity, and the role of sequencing to generate baseline evidence to monitor escape mutations following vaccine introduction were discussed.

Follow up actions proposed included 1) to publish key outcomes as scientific manuscripts in peer-reviewed journals, 2) to improve data completeness and data quality, 3) to collect denominator-related data from countries to allow estimation of RSV associated hospitalization burden, 4) to develop an estimate of incremental costs of adding RSV surveillance to routine influenza surveillance, and 5) to use the outcomes of the pilot to refine the WHO RSV surveillance strategy as necessary. The mid-term review meeting concluded that RSV Pilot had progressed well and had generated valuable experience for long term RSV surveillance.

Introduction

Respiratory Syncytial Virus (RSV) is one of the leading causes of acute lower respiratory infection with an estimated 59,600 in-hospital deaths per year in children younger than 5 years (Shi et al. 2017). The WHO Global RSV Surveillance based on the established infrastructure of the Global Influenza Surveillance and Response System (GISRS) was launched as a Pilot in 2016 in 14 countries representing all six WHO regions. The goal of global RSV surveillance is to generate evidence through standardized surveillance described in the WHO Global RSV Surveillance Strategy (World Health Organization 2017). Each participating country was required to test up to 1000 respiratory specimens annually using an extended SARI or an ARI case definition that did not require fever as a criterion, for hospital and community-based surveillance respectively. The WHO data platform for influenza was adapted to receive case-based epidemiological, clinical and virology data. In December 2017 the WHO Meeting of Mid-term Review of the RSV Surveillance Pilot was held at PAHO to assess the progress, discuss implementation challenges, review early outcomes, and determine the need to adjust the RSV surveillance strategy. The meeting brought together 61 national and international experts from all six WHO regions.

The RSV landscape

Significant knowledge has been gained from over 60 years of research on RSV pathogenesis, risk factors, and vaccine development (Simões et al. 2015). RSV infection in healthy pre-term infants is associated with recurrent wheeze and an increased risk for asthma in early childhood. Infants with chronic lung disease and congenital heart disease are particularly susceptible to developing severe RSV disease necessitating re-hospitalization and medical therapy, including supplemental oxygen and mechanical ventilation, following discharge from Neonatal Intensive Care Units (Pérez-Yarza et al. 2015). The REGAL (RSV evidence—a geographical archive of the literature) series provides a comprehensive review of the published evidence in the field of respiratory syncytial virus (RSV) in Western countries over the last 20 years. Risk factors for RSV-associated hospitalization include age less than 10 weeks at the onset of RSV season, presence of school-age siblings, day care attendance and smoking during pregnancy. The importance of neutralizing antibodies to Prefusion F (pre-F) protein in protection is well documented. Although pre-F is the major viral target for monoclonal antibody to RSV, the G protein is also important. Maternally derived RSV-specific antibodies play a role in protection against RSV infection in early life. Antibodies directed to pre-F, followed by antibodies directed to G, can modulate RSV disease severity in young infants. Palivizumab remains the only product licensed for RSV prophylaxis, and only available for high-risk infants. For the general population, there are several promising vaccines and monoclonal