WHO Meeting of Final Review of the RSV Surveillance Pilot Based on the Global Influenza Surveillance and Response System

Bangkok, Thailand

23 to 25 October 2018

World Health Organization

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Background

Respiratory Syncytial Virus (RSV) is a leading viral cause of acute lower respiratory tract infections in infants and young children. The RSV vaccine development landscape is evolving rapidly with several vaccine candidates and monoclonal antibodies in various stages of clinical development. RSV surveillance has the potential to provide an evidence-base on seasonality, healthcare burden (such as hospitalisations) and risk groups to guide immunization practices once the RSV vaccine becomes available. Current evidence gaps also include RSV associated mortality both in the community and healthcare setting, long term impact of RSV infection on future wheeze and lung function, the economic burden of RSV, cost-effectiveness modelling of prevention strategies, RSV disease burden in pregnancy. The RSV surveillance may provide a platform for special studies to address some of these research questions.

A three-year pilot project on RSV surveillance based on the Global Influenza Surveillance and Response System (GISRS) was initiated globally in 14 countries across all six WHO regions in 2016. The overall aim was to assess the suitability of the influenza surveillance platform for RSV surveillance and identify ways for expansion of existing surveillance criteria to meet the needs for RSV surveillance without negatively affecting influenza surveillance. At the end of the pilot project, a meeting was organised in Bangkok to bring together about 65 international experts from the influenza and RSV communities, participating countries, and other stakeholders, to review and share the final outcomes of the pilot and discuss post-pilot issues and actions including sustainability of the RSV surveillance.

It was noted that when an effective RSV vaccine becomes available there will be a sudden increase in interest in RSV data among policy makers and so data-driven guidance to them will be very valuable. The pilot represents an opportunity to establish a mechanism to generate RSV data for policy purposes at the RSV surveillance pilot sites at low incremental cost. It was agreed that this was a timely opportunity to shape RSV surveillance and establish global guidelines and best practice. It was considered that virologic surveillance would be important to monitor any genetic or antigenic drift, to identify escape mutants, and to understand if genetic changes result in antigenic change and impact on virulence or monoclonal efficacy. The possible impact of any changes on the effectiveness of interventions could then be analysed at the molecular level.

At a time when the RSV research community is mainly focused on product development and research, this RSV surveillance pilot would complement by adding new public health dimensions to the global effort to enrich prevention strategies. Participants supported the approach of building RSV surveillance with available resources to be later scaled up once a vaccine becomes available.

The Pilot Phase (phase 1)

The pilot has made very good progress in terms of the primary objective of the pilot. It has confirmed the feasibility of adding RSV surveillance to GISRS with limited additional support. The RSV surveillance platform can produce useful RSV disease morbidity estimates such as proportion of hospitalizations associated with RSV, evaluate the performance of an RSV surveillance case definition, better understand the local RSV seasonality and global circulation of RSV. Extension of surveillance to additional (paediatric) sites has also been a benefit for influenza surveillance. No important adverse impacts, to date, were noted by countries. There was enthusiasm among participating countries for continuing RSV surveillance with similar

level of financial and technical support along with careful monitoring of any potential negative impact on GISRS. Several aspects of the RSV surveillance strategy were discussed including a focus on children less than 2 years with the highest disease burden, the need to define severe clinical outcomes and a clinical severity score to allow a comparison across sites. Monitoring of the implementation of surveillance, referral patterns, contribution of nosocomial RSV infection, to improve data quality and reduce missingness so as to better interpret the findings, was emphasized.

Case definition

Despite initial concerns about possible adverse effects on GISRS of adoption of an extended SARI / ILI case definition, as the pilot progressed, all countries reported acceptance of these case definitions without any significant negative impact on influenza surveillance. It was clarified that the SARI case definition for influenza surveillance remained unchanged. Early challenges for physicians to use the extended SARI case definition were resolved through training. More than 21,000 patients were recruited and tested for RSV, of whom 73% were hospital admissions. Overall, 60% of patients tested were less than 5 years (20% less than 6 months, 30% between 6 months to 2 years and 10% between 2 and 5 years age). There was limited recruitment in older age groups. Use of SARI / ILI case definitions would have missed 29% of cases in infants less than 6 months (compared to when using the extended SARI definition).

Seasonality

RSV peaked in colder months in temperate regions (duration 5-35 weeks) and in the rainy season in tropical regions. The peaks seemed consistent from year to year in individual countries. There was no difference in season onset across age groups. It was considered essential that further details of the surveillance sites and how they implemented the surveillance (e.g. referral patterns, ICU availability, contribution of nosocomial RSV) be presented to be able to interpret data. It was noted that large sample size and data for more seasons will be required to better understand seasonality. For countries with a large latitudinal spread, sentinel sites would need to be geographically representative of the climactic zones at the sub-national level.

Disease burden estimation

RSV surveillance is not expected to produce detailed and robust burden of disease estimates in all or most LMIC. Nonetheless, national policy makers should find useful estimates of RSV-associated hospitalizations in the absence of sophisticated special disease burden estimation studies. A tiered approach was discussed wherein a range of options of morbidity or healthcare burden estimates would be available based on a review of availability of (and effort to generate) denominator-related data along with an explicit understanding of quality, limitations and potential bias of the data. The burden estimates are grouped based on increasing levels of complexity of collecting data from a sentinel surveillance platform. Tier 1 groups burden estimates related to proportions of hospitalization associated with RSV. Tier 2 groups population-based incidence estimates of hospitalization, ICU-based burden, and mortality estimates including case-fatality ratio and proportion of hospital deaths due to RSV. The third tier refers to national extrapolation of population-based hospitalization incidence rates. Countries generally agreed to collect the most basic data (tier 1) required to estimate proportions of hospitalization associated with RSV in the second phase of the surveillance.

Countries with additional resources and capacities may opt to use more sophisticated approaches for estimation of RSV disease burden. It was agreed that future directions should make clearer that the RSV surveillance is not trying to encourage all countries towards sophisticated RSV disease burden estimates. Notwithstanding, it was agreed that it was important for some level of burden data feasible from surveillance platform, to be collected in the next phase.

Phase 2

The main aims of RSV surveillance pilot phase 1 were focused on establishment of the essential parameters for surveillance. In Phase 2 geographical representation will be increased from the current 1-2 countries per region, focusing on GAVI-eligible countries. The general aim will be to support the future introduction of vaccine into countries. An ICD codes-based methodology for RSV surveillance developed using ICD-codes data from clinics and hospitals in Germany will be tested in other country contexts. Case definitions will be kept the same and will focus on children less than 2 years in phase-2. Case-based data would be retained in Phase 2 to gather these data over several years. The case report form (CRF) will be revised in line with the comments made at this meeting and will aim to include some readily available clinical severity-related data. The feasibility of collecting some specific economic data (direct costs of surveillance) will be explored as costs are likely to vary greatly by setting. Periodic reviews of data quality will be conducted with regular feedback to pilot sites to improve quality.

RSV detection, typing and sequencing

It was considered that virologic surveillance would be important to monitor genetic or antigenic drift, to identify escape mutants, and to understand if genetic changes result in antigenic change and impact on virulence or monoclonal efficacy. The possible impact of any changes on the effectiveness of interventions could then be analysed at the molecular level. The consensus was that RSV-A/RSV-B typing results and partial or complete RSV genome data would be important. RSV typing will be conducted in all sites by the National Influenza Centres (NIC)s. RSV sequencing will be supported in a few laboratories to bridge the gap of understanding and to help inform future vaccine development. Protocols for RSV sequencing will be developed in Phase 2. This will build on influenza experience with GenBank, GISAID and software tools linking sequence and clinical data. An EQA for RSV typing and for genetic sequencing and detailed guidelines on how laboratories should maintain internal quality control procedures will be developed. WHO will engage with other stakeholders to promote and support international agreement on nomenclature. It was suggested that Phase 2 should aim to show feasibility of generating quality sequence data from the GISRS RSV surveillance platform. A more formal designation as a RSV reference laboratory together with clear terms of reference (including the level of country support envisaged) will be developed to help facilitate getting support from national authorities. It was noted that the project needed a solution for sample storage so that these can be available for future detailed genetic and antigenic characterization studies.

Way forward

In the second phase, geographical representation will be increased with a focus on GAVI-eligible countries. The overall aim will be to support the future introduction of vaccine into countries. The project will develop protocols for RSV typing and sequencing, shipment of virus

materials, data sharing and use, and will maintain the high quality of laboratory performance through EQA monitoring.

There was clear support from the Regional Offices and pilot countries for Phase 2 with similar levels of resources being made available. It was considered important to secure funding support from donor agencies to provide additional support to develop laboratory capacity and readiness. Ongoing consideration of future post-pilot sustainability was important given the context that the main financial support was external.

Summary

The meeting summarized the outcomes and the lessons learnt from the pilot phase. Key takeaway messages included the feasibility of leveraging the influenza surveillance platform for RSV surveillance without any significant adverse impact; the application of the extended SARI case definition for RSV surveillance; the focus on young children with the highest RSV disease burden; the need to ascertain seasonality patterns and measure simple RSV disease burden estimates such as proportions of hospitalizations due to RSV that would inform policy decisions on vaccine investment and introduction.

Going forward, the meeting concluded to revise the WHO RSV Surveillance strategy for the next phase of surveillance to further focus on children less than 2 years with the highest burden; adopt a tiered approach to disease burden estimation with emphasis on basic estimates of hospital burden of RSV; ascertain RSV circulation by virus type A or B; develop laboratory protocols for RSV typing and schema for sequencing; and expand to countries that are geographically more representative as well as are eligible to receive investment from the Gavi Alliance for RSV vaccine introduction when it becomes available.

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The report was prepared by Harry Campbell and reviewed internally by Siddhivinayak Hirve, Sandra Jackson, Ann Moen and Wenqing Zhang and externally by Harish Nair, Chair of the meeting.

Annexes

Annex 1: Agenda

WHO Meeting of Final Review of the RSV Surveillance Pilot based on the Global Influenza Surveillance and Response System (GISRS)

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PROVISIONAL AGENDA

Chair: H. Nair
Rapporteur: H. Campbell

Tuesday, 23 October 2018		
08:30 – 09:00	Registration	
09:00 – 09:20	Opening and welcome	Kertesz D, WHO Representative, Thailand Moen A, Chief, IPR, WHO Karnkawinpong O, Dir General, Dept. of Medical Sciences, Ministry of Public Health, Thailand
09:20 – 09:30	Introduction of work Disclosure of interest Housekeeping announcement	Zhang W, Head, GIP, WHO
Session I: RSV - Setting the context		**Session co-chair: Chittaganpitch M**
09:30 - 09:45	RSV vaccine development - strategic priorities	Higgins D
09:45 - 10:00	RSV epidemiology - knowledge gaps	Nair H
10:00 - 10:15	WHO RSV surveillance strategy – recap	Broor S
10:15 - 10:30	RSV surveillance - progress so far	Hirve S
10:30 - 11:00	***Coffee Break***	
11:00 - 11:30	Focused plenary discussion	Moderator: Gerber S
11:30 - 11:45	Variability in RSV F protein - implications for global surveillance	Williams T (Webex)
Session II: RSV surveillance - Pilot Outcomes		**Session co-chair: Mott J**
11:45 - 11:55	Outcome # 1: WHO RSV surveillance strategy	Campbell H
11:55 - 12:15	Plenary feedback	Moderator - Ziegler T
12:15 - 13:15	***Lunch break***	
13:15 - 13:25	Outcome # 2: External Quality Assurance	Baumeister E
13:25 - 13:45	Plenary feedback	Moderator - Ziegler T
13:45 - 14:00	Outcome # 3: Case definition	Crawford N

14:00 - 14:15	Outcome # 4: RSV seasonality	Chadha M
14:15 - 14:30	Outcome # 5: RSV disease burden	Moyes J
14:30 - 15:00	***Coffee break***	
15:00 - 17:30	WG - case definition	Moderator: Broberg E
	WG - seasonality	Moderator: Ziegler T
	WG – burden	Moderator: Pebody R
19.00 – 21.00	***Cocktail Reception***	

Wednesday, 24 October 2018		
09:00 – 09:10	Recap of Day 1	Nair H / Campbell H
09:10 - 10:00	Feed-forward -	
	WG (case definition)	Broberg E
	WG (seasonality)	Ziegler T
	WG (burden)	Pebody R
10:00 - 10:15	Outcome # 6: Using ICD-10 based data for RSV surveillance	Cai W
10:15 - 10:30	Outcome # 7: Risk factors for severe RSV disease based on ICD codes	Cai W
10:30 - 11:00	***Coffee break***	
11:00 - 11:15	Plenary discussion: Limitations and challenges in use of ICD codes for RSV surveillance	Moderator – Buda S
11:15 - 11:45	Panel discussion: RSV surveillance outcomes - caveats and their implications on the outcomes	Moderator: Gerber S *Panelist:* *Baumeister E;* *Bont L;* *Pebody R;* *Nair H*
11:45 - 12:15	Plenary discussion - what could have been done differently?	Moderator – Fasce R