Human respiratory syncytial virus and influenza seasonality patterns—Early findings from the WHO global respiratory syncytial virus surveillance

Mandeep Chadha1 | Siddhivinayak Hirve2 | Christina Bancej3 | Ian Barr4 | Elsa Baumeister5 | Braulia Caetano6 | Malinee Chittaganpitch7 | Badarch Darmaa8 | Joanna Ellis9 | Rodrigo Fasce10 | Herve Kadjo11 | Sandra Jackson2 | Vivian Leung4 | Maria Pisareva12 | Jocelyn Moyes13 | Amel Naguib14 | Almiro Tivane15 | Wenqing Zhang2 | On behalf of the WHO RSV Surveillance Group

Abstract

Background: Human respiratory syncytial virus (RSV) causes illnesses among all age groups and presents a burden to healthcare services. To better understand the epidemiology and seasonality of RSV in different geographical areas, the World Health Organization (WHO) coordinated a pilot initiative to access the feasibility of establishing RSV surveillance using the existing Global Influenza Surveillance and Response System (GISRS) platform.

Objectives: To describe and compare RSV and influenza seasonality in countries in the northern and southern temperate, and tropics during the period January 2017 to April 2019.

Methods: Fourteen countries in six WHO regions participating in the GISRS were invited for the pilot. Hospitalized patients presenting with severe acute respiratory illness (SARI), SARI without fever and outpatients presenting with acute respiratory illness (ARI) were enrolled from January 2017 to April 2019. The expected minimum sample size was 20 samples per week, year-round, per country. Real-time RT-PCR was used to detect RSV and influenza viruses. Results were uploaded to the WHO FluMart platform.

Results: Annual seasonality of RSV was observed in all countries, which overlapped to a large extent with the influenza activity. In countries, in temperate regions RSV peaked in the autumn/winter months. In Egypt, a subtropical country, RSV activity peaked in the cooler season. In the tropical regions, RSV peaked during the rainy seasons.

1National Institute of Virology, Indian Council of Medical Research, Pune, India
2Global Influenza Programme, World Health Organization, Geneva, Switzerland
3Centre for Immunization and Respiratory Infections, Public Health Agency of Canada, Ottawa, Canada
4Victorian Infectious Diseases Reference Laboratory, Peter Doherty Institute for Infection and Immunity, Melbourne, Australia
5Departamento Virologia, INEI-ANLIS “Carlos G Malbrán”, Buenos Aires, Argentina
6Institute Oswaldo Cruz/FIOCRUZ, Rio de Janeiro, Brazil
7Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand
8Virology Laboratory, National Center for Communicable Diseases, Ulan baatar, Mongolia
9Virus Reference Department, Public Health England, London, United Kingdom
10Sub-department of Viral Diseases, Instituto de Salud Pública de Chile, Santiago, Chile
11Department of Epidemic Viruses, Institut Pasteur de Côte d’Ivoire, Abidjan, Côte d’Ivoire
12Laboratory of Molecular Virology, Smorodintsev Research Institute of
Influenza, St. Petersburg, Russian Federation
13 Center for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, Johannesburg, South Africa
14 Central Public Health Laboratory, Ministry of Health, Cairo, Egypt
15 Laboratório de Isolamento Viral, Instituto Nacional de Saúde, Maputo, Mozambique

Correspondence
Hirve Siddhivinayak, Global Influenza Programme, World Health Organization, Geneva, Switzerland.
Email: hirves@who.int

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1 INTRODUCTION

Globally, human respiratory syncytial virus (RSV) is recognized as the most common cause of acute lower respiratory infection (ALRI) in the pediatric population.1 ALRIs (bronchiolitis and pneumonia) due to RSV in children are among the most frequent causes of hospital admission. It was estimated that, globally, in 2015, there were 3.2 million (uncertainty range [UR] 2.7-3.8 million) RSV-associated hospital admissions and nearly 59,600 (UR 48,000-74,500) in-hospital deaths from RSV in young children. The total estimated number of deaths due to RSV among young children in developing countries in 2015 was 118,200 (UR 94,600-149,400). During the neonatal period, 6.5% (95% CI 5.8-7.6) RSV infection can present as apnea or sepsis.2,3 RSV disease among young children may be associated with long-term sequelae, including recurrent wheezing and asthma, though whether these associations are causal or due to shared susceptibility is unclear. RSV not only affects children but also causes annual outbreaks of respiratory illnesses among all age groups4,5 particularly affecting the elderly and adults with comorbidities such as diabetes, heart and lung disease.6,7

Given the high RSV disease burden, the development of effective preventive and therapeutic strategies are of high priority. Currently, 19 RSV vaccine candidates and monoclonal antibodies are in various stages of development as prophylactic interventions.9 To formulate appropriate intervention strategies, a standardized global RSV surveillance system is needed to better describe the epidemiological characteristics of RSV disease, including seasonal variations in incidence in different geographic settings. In several high-income countries, surveillance of RSV has been integrated within their routine influenza surveillance9; however, there is a paucity of data from low- and middle-income countries (LMICs), where the RSV disease burden is likely the highest.

The World Health Organization (WHO) Global Influenza Surveillance and Response System (GISRS) has been monitoring influenza viruses for over six decades. GISRS operates through a worldwide network of laboratories that provides real-time surveillance information on the circulation and evolution of influenza viruses. Most of the countries participating in GISRS use a case definition of severe acute respiratory infection (SARI), influenza-like illness (ILI), and/or acute respiratory infection (ARI), to identify potential influenza cases for laboratory testing, a surveillance system which could be leveraged to build global RSV surveillance. Following several meetings with influenza and RSV experts from different countries, it was agreed to assess the feasibility of establishing RSV surveillance as a pilot using the existing GISRS platform. The pilot would also assess the possibility of compromise to influenza surveillance resulting from the integration of RSV through GISRS.10 One of the primary objectives of the RSV pilot was to analyze the seasonal patterns of RSV disease in different countries in varied geographical regions. Fourteen countries, in six WHO regions, which were already members of GISRS, were selected and invited for the pilot.

This paper aims to describe RSV seasonality in countries participating in the WHO RSV pilot surveillance programme during the period January 2017 to April 2019, compared to the seasonality of influenza. Other aspects of the pilot initiative are being published in separate papers.

2 MATERIALS AND METHODS

2.1 Study sites

Fourteen countries, in six WHO regions, which were already participating in GISRS, were invited to participate in the pilot (Figure 1). In each of these countries, there was a recognized National Influenza Center and/or a national public health laboratory with ongoing influenza surveillance and laboratory capacity for RSV testing using

Conclusion: Early findings from the WHO RSV surveillance pilot based on the GISRS suggest annual seasonal patterns for RSV circulation that overlap with influenza. RSV surveillance needs to be continued for several more seasons to establish seasonality patterns to inform prevention and control strategies.

KEYWORDS
Global Influenza Surveillance and Response network, human respiratory syncytial virus, influenza, seasonality
molecular methods and a history of successful past performance in the WHO EQA for the molecular detection of influenza. All these laboratories/countries regularly provide influenza surveillance data to WHO via the FluNet platform.

2.2 Selection of sentinel sites and case definition

The number and type of sentinel hospitals (secondary- and tertiary-level care) and clinics included in the RSV Surveillance Pilot varied among the countries (Table 1). The selection of sentinel hospitals and clinics was largely based on patient load and convenience. These sites were not necessarily nationally representative. For clinic- and hospital-based surveillance, countries chose sentinel sites that were able to comply with the required minimum sample size. Hospitals with inpatient care and intensive care units providing adult and pediatric care were preferentially selected. At these sites, patients across all ages who presented with extended SARI were eligible for inclusion. The SARI case definition requires cough and hospitalization plus the presence, or a history, of fever, whereas the extended SARI definition does not require fever. In addition, infants less than 6 months presenting with sepsis or apnea were also eligible for inclusion, as RSV illness frequently presents with these conditions in this age group. For outpatient-based surveillance, the WHO ARI case definition was used at these sites.

2.3 Sampling of cases

Argentina, Brazil, Chile, Egypt, the Russian Federation, and South Africa screened patients from all age groups admitted to sentinel hospitals, whereas Australia and Canada screened pediatric hospital admissions only. Côte d’Ivoire, India, Mongolia, Mozambique, and Thailand screened patients from all age groups in both sentinel hospitals and clinics. The United Kingdom screened pediatric patients attending sentinel general practitioner clinics in England (Table 1).

At all sentinel sites, physicians and nurses were trained to screen patients meeting the extended SARI case definition for hospital-based surveillance and ARI for clinic surveillance. Patients were screened for eligibility all year-round, except for Canada where the RSV pilot ran annually from the beginning of November (epidemiological week 44) through to the end of May (epidemiological week 22). Countries were required to test a minimum of 1000 samples annually for RSV (250 patients in each of four age groups—less than 6 month, 6 months to <5 years, 5 years to <65 years, and 65 years or over). If there were inadequate numbers of eligible patients for RSV surveillance in any age group, countries had the option to make up the shortfall by enrolling patients from the ongoing routine influenza surveillance where the SARI and ARI/ILI case definitions were being used or based on the patient load at the sentinel site. The sampling strategy varied across countries and ranged from screening of all eligible patients...
to screening of eligible patients on certain days of the week. While the required minimum number of samples per week was 20, some countries received more samples during the influenza season while others received less than the expected samples per week due to lesser number of case-patients with respiratory illness. In addition, some countries enhanced laboratory testing during periods of increased proportion of RSV-positive specimens.

### 2.4 Collection of clinical samples and detection of RSV

Clinical specimen collection, transport, and storage of clinical samples were done as per WHO guidelines. Oropharyngeal, nasal or nasopharyngeal respiratory specimens (according to age) were collected and transported in viral transport media to the National Influenza Centre or the national public health laboratory for testing for RSV and influenza virus. Before initiating testing of clinical samples, all countries successfully participated in an external molecular quality assurance panel for the detection of RSV, which was developed by the United States Centers for Disease Control and Prevention (US CDC). Clinical specimens were batch tested in their respective countries. All laboratories used real-time reverse transcription-polymerase chain reaction (RT-PCR) for RSV detection; while most laboratories used an assay developed by the US CDC, which was a monoplex RT-PCR assay that detected the conserved regions of the RSV matrix protein gene. A few laboratories opted to continue using commercial or in-house developed RT-PCR assays after validation against the US CDC assay. Reagents were supplied by the US CDC through the influenza Reagent Resource (IRR; https://www.internationalreagentresource.org). Seven countries (Argentina, Australia, Canada, India, South Africa, Thailand, and the United Kingdom) used multiplex RT-PCR to further subtype all or a representative sample of RSV-positive specimens as RSV-A and RSV-B. All countries also tested specimens for influenza.

### 2.5 Duration of surveillance

During the pilot, RSV surveillance was conducted year-round by all countries even though seasonality was already well-established in some temperate countries, except for Canada where the RSV pilot ran within the timeframe of well-established seasonality from the beginning of November (epidemiological week 44) through to the end of May (epidemiological week 22; Table 1).

### 2.6 Data collection and analysis

Data from surveillance sites were uploaded to the WHO’s web-based FluMart data platform by the respective countries. To analyze RSV seasonality, the date of specimen collection was used to aggregate by epidemiologic week (EW). When the date of specimen collection was missing, the date of onset of symptoms was used instead. Since date of onset was missing in 6560 cases and date of specimen collection was most definitive, it was used for construction of the epi curve. All specimens collected using the SARI, extended SARI and ARI/ILI case definition were pooled per country for the RSV seasonality graphs. Temporal plots of RSV and influenza activity were smoothed using the

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**TABLE 1** Site profile, WHO RSV surveillance, 2017-19

<table>
<thead>
<tr>
<th>Country</th>
<th>Duration of surveillance</th>
<th>No. of sentinel sites</th>
<th>Patients under surveillance</th>
<th>Number of clinical samples considered for analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>2017 Week 1-2019 Week 14</td>
<td>6</td>
<td>Inpatient</td>
<td>1660</td>
</tr>
<tr>
<td>Australia</td>
<td>2017 Week 31-2019 Week 17</td>
<td>1</td>
<td>Inpatient</td>
<td>2005</td>
</tr>
<tr>
<td>Brazil</td>
<td>2017 Week 3-2019 Week 7</td>
<td>2</td>
<td>Inpatient + outpatient</td>
<td>756</td>
</tr>
<tr>
<td>Canada</td>
<td>2017 Week 44-2018 Week 22; and 2018 Week 44-2019 Week 22</td>
<td>12</td>
<td>Inpatient</td>
<td>4892</td>
</tr>
<tr>
<td>Chile</td>
<td>2017 Week 1-2019 Week 13</td>
<td>2</td>
<td>Inpatient</td>
<td>1134</td>
</tr>
<tr>
<td>Côte d’Ivoire</td>
<td>2017 Week 1-2019 Week 1</td>
<td>9</td>
<td>Inpatient + outpatient</td>
<td>3362</td>
</tr>
<tr>
<td>Egypt</td>
<td>2017 Week 1-2019 Week 14</td>
<td>6</td>
<td>Inpatient</td>
<td>1688</td>
</tr>
<tr>
<td>India</td>
<td>2017 Week 1-2019 Week 9</td>
<td>11</td>
<td>Inpatient + outpatient</td>
<td>1998</td>
</tr>
<tr>
<td>Mongolia</td>
<td>2017 Week 2-2019 Week 15</td>
<td>7</td>
<td>Inpatient + outpatient</td>
<td>1803</td>
</tr>
<tr>
<td>Mozambique</td>
<td>2017 Week 1-2019 Week 3</td>
<td>4</td>
<td>Inpatient + outpatient</td>
<td>1329</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>2017 Week 1-2019 Week 15</td>
<td>18</td>
<td>Inpatient</td>
<td>2067</td>
</tr>
<tr>
<td>South Africa</td>
<td>2017 Week 1-2019 Week 18</td>
<td>5</td>
<td>Inpatient</td>
<td>6002</td>
</tr>
<tr>
<td>Thailand</td>
<td>2017 Week 1-2019 Week 5</td>
<td>11</td>
<td>Inpatient + outpatient</td>
<td>3106</td>
</tr>
<tr>
<td>United Kingdom*</td>
<td>2017 Week 39-2019 Week 12</td>
<td>70 GP</td>
<td>Outpatient</td>
<td>4250</td>
</tr>
</tbody>
</table>

Abbreviation: GP, General practitioners.

*Surveillance restricted to England only.
3-week moving average in R version 3.5.3 (R Foundation for Statistical Computing). Data points where only one specimen was tested in the week were removed from the analysis. Seven countries (Brazil, Chile, Egypt, India, Mozambique, South Africa, and the United Kingdom) described their seasons. For the remaining countries, seasons were derived from the World Meteorological Organization website or were taken from the official web site of the country. For analyzing seasonality, a threshold of 10% RSV positivity for two consecutive weeks was used to indicate the onset of the RSV season and similarly a percent positivity of <10% for two consecutive weeks was used to indicate the end of the season. For Canada, the number of RSV-positive cases was used to analyze seasonality as the total number of specimens tested was not reported. In countries with multiple sentinel sites, data were pooled for each country’s seasonality analysis. For countries which typed RSV cases (Argentina, Australia, Canada, India, Thailand, South Africa, and the UK), data were also analyzed by RSV subtypes.

3 | RESULTS

Fourteen countries provided data for the seasonality analysis (Table 1). Nine of 14 countries initiated surveillance from EW 01 of 2017 through a variable period in 2019 (EW 01-25) (Table 1). Data for two RSV seasons were captured across all countries except for Côte d’Ivoire. A total of 245 of 33 583 samples (0.73%) had both date of specimen collection and onset of symptom missing and were excluded from analysis.

The percentages of specimens testing positive for RSV and influenza during each epidemiological week of surveillance are shown in Figure 2. In several temperate countries (Argentina, Australia, Chile, Canada, Mongolia, Russian Federation, and the UK), RSV activity tended to be greatest in the cooler months of the year, but there was substantial variability in timing between countries, and some year-to-year variation within countries. As shown in Figure 2A, the RSV activity in Argentina in 2017/2018 began in early autumn and peaked in winter. However, in 2018/19 RSV activity continued in the spring and summer seasons (RSV season duration 2017/18 = 28 weeks; 2018/19 = 50 weeks). In Australia, there was some RSV activity in the summer months, but it peaked in the winter (RSV season duration; 2018/19 = 52 weeks). In Chile, the RSV season started in late autumn-early winter in both years and ended in spring (RSV season duration 2017 = 22 weeks; 2018 = 18 weeks). In South Africa, RSV activity started in late summer in each of the 3 years of surveillance, peaked in autumn/winter, and ended in spring (RSV season duration 2017 = 28 weeks; 2018 = 27 weeks).

In Canada, no RSV surveillance was conducted in the summer; RSV activity started in the late autumn and continued through to spring, with peak activity during winter (RSV season duration 2017/18 = 17 weeks; 2018/19 = 16 weeks). In Mongolia, RSV activity started in early winter and ended by spring (RSV season duration 2017/18 = 10 weeks; 2018/19 = 17 weeks). In Russia, relatively smaller numbers of specimens tested positive for RSV, compared to most other countries, with highest RSV activity in winter and spring (RSV season duration 2017/18 = 7 weeks; 2018/19 = 10 weeks). The UK also had relatively low RSV positivity rates, with activity starting in mid-autumn and ending by mid-winter (RSV season duration 2017/18 = 7 weeks; 2018/19 = 10 weeks).

Six countries had a subtropical/tropical climate (Figure 2C). In Brazil, in both years of surveillance RSV activity started in early autumn and finished toward the end of winter (RSV season duration 2017 = 21 weeks; 2018 = 27 weeks). In Egypt, RSV activity started in early winter and finished in early spring (RSV season duration 2017/18 = 17 weeks; 2018/19 = 18 weeks).

In Côte d’Ivoire, seasonality was less clear, but most RSV activity was detected toward the end of the hot and dry season, through to the hot and wet season and declined at the beginning of the warm and dry season (RSV season duration 2017 = 30 weeks). In India, activity began in the rainy season and continued to the beginning of winter, though the patterns in 2017 and 2018 differed (RSV season duration 2017 = 13 weeks; 2018 = 12 weeks). In Mozambique, RSV activity started toward the end of the rainy season and finished in late spring or early winter (RSV season duration 2017 = 10 weeks; 2018 = 17 weeks). Thailand had RSV activity starting in the early part of the rainy season and ended toward the end of the rainy season in the first year with activity beginning earlier in the second year of surveillance (RSV season duration 2017 = 6 weeks; 2018 = 20 weeks).

Respiratory syncytial virus seasonality when compared with that of influenza showed different patterns across various countries. Influenza and RSV activity peaks were observed during the same period in some countries (eg, Australia, Brazil, Canada, Egypt, and Russia). The RSV season preceded the influenza season by 6-9 weeks in Argentina, Mongolia South Africa, and the UK. In countries, where the RSV season preceded the influenza season, the end of RSV activity varied. In Argentina and South Africa, which were both temperate regions, RSV season ended with the start of the influenza season. In the UK, the RSV season ended before influenza activity peaked. In Mozambique, the 2017 RSV season ended before influenza activity commenced while in 2018, both RSV and influenza activity overlapped but had different peaks. However, influenza was not observed after week 16 and by week 20, a downward trend was observed in RSV activity. Year-round baseline activity of influenza was observed in Côte d’Ivoire, India, and Thailand but RSV was distinctly heightened during the rainy season. In 2017, India observed influenza year-round and RSV was predominantly observed during the rainy season and continuing through the winter of 2017-18 and summer of 2018. In 2018 in India, influenza was not observed during summer but was circulating in the rainy season. Although there was some similarity with respect to the timings of the periods of high positivity for RSV and influenza, there was considerable variation among the participating countries.

Among the pilot countries that performed RSV sub-typing, in 2017, RSV-A circulation predominated in Argentina (91% of 237 RSV positives) and the UK (62.5% of 104), whereas RSV-B predominated in Australia (75% of 101), India (98% of 54), South Africa (64.4% of 605), and Thailand (57% of 148). In the 2018 season, RSV-B was the predominantly circulating type in all countries: Argentina (93% of 215),...
Australia (54% of 326), India (100% of 85), Thailand (61% of 111), and
the UK (73% of 33), except South Africa where RSV-A predominated
(61% of 727). In Canada, RSV-A and RSV-B co-circulated (50% RSV of
105) predominantly RSV-B (66% of 64) at the western sentinel and
RSV-A (76% of 41) at the eastern sentinel. Predominance of subtype
did not affect the timing of RSV activity peaks in any of the countries.

4 | DISCUSSION

We describe the RSV seasonality in fourteen countries participating
in the WHO RSV surveillance. This is the first time the GISRS plat-
form has included additional pathogen surveillance using a broader
case definition and which allowed standardization of RSV surveil-
ance protocols and facilitated the description of RSV seasonality in
participating countries. Intervention strategies for RSV may need to
account for the seasonal nature of RSV, as the protection conferred
by monoclonal antibodies or maternal immunization may be short
lasting. Knowledge of the local seasonality patterns of RSV will
help target intervention strategies for RSV, saving costs and allow-
ing maximum benefit.

Distinct annual peaks of RSV detection were observed across all the
study sites. The magnitude of the peak and the duration of increased
activity varied across countries, and there was some year-to-year vari-
ation within countries. RSV activity observed among countries may
be influenced by weather pattern. While it was possible to com-
pare/group some countries, there was still considerable variation even
among countries with similar climate zones. In the temperate regions
in both hemispheres, the main RSV season period occurred during the
colder months (Argentina, Australia, Canada, Chile, Mongolia, Russian
Federation, and the UK). Associations between low temperatures and
widespread RSV circulation in temperate climates have been well de-
dcribed. Although South Africa lies in the temperate zone, RSV
activity varied: RSV peak was observed in autumn of 2017 and 2018,
which was not the coldest period of the year. This temperature-depen-
dent pattern appears to be independent of precipitation patterns. In
subtropical countries with lower annual temperatures like Brazil and
Egypt, RSV peaks occurred in the cooler months of the year. These
findings are consistent with previous studies.

In the tropics, while RSV peaks were observed primarily during rainy seasons (Côte d'Ivoire, India, Mozambique, and Thailand), residual viral activity was seen throughout the year. Other studies in tropical areas have reported RSV seasons occurring during periods of high precipitation. Similarly, earlier studies from Calcutta and The Gambia have reported outbreaks mainly during rainy season. This could support the hypothesis that due to increased precipitation there is more indoor crowding, facilitating RSV transmission in the tropics.

The timing of the RSV season was not dependent on subtype (type A or type B) that occurred, or the proportions of A/B seen in that sea-
son in countries that performed this typing. This aspect will be further studied in the next phase of the WHO RSV surveillance program.

Respiratory syncytial virus had broader distribution of peak
timings, relative to that of influenza, even within the temperate
zone. Although most countries in our study experienced distinct respiratory virus seasons, it is noteworthy that there was a bi-an-
nual influenza peak in Chile in 2017. Although distinct RSV sea-
sonality was observed in tropical countries, that is, Brazil, Côte
d'Ivoire, India, Mozambique, and Thailand, Influenza activity
was observed year-round, which is consistent with previous re-
ports. This could influence the country-specific RSV vacci-
nation strategies and timing in relation to influenza vaccination.
However, additional years of surveillance data are required for
better understanding of the variability in the distribution of RSV
timing relative to influenza and whether RSV–A and RSV-B sub-
types have any role to play in multi-year periodicity of RSV com-
pared to Influenza.

There are several limitations to be noted. First, the duration
of surveillance varied between countries and covered only two
seasons. It is not possible to establish reliably the consistency of
seasonal patterns of RSV from year-to-year in these countries.
Second, we did not consider detailed meteorological data for each
country during the actual period of surveillance and, as such, sea-
sons were used descriptively for our assessment based on usual
patterns. Third, RSV activity observed was limited to the catch-
ment areas of participating surveillance sites within the countries
and may not be representative of the whole country, especially
in countries with a large latitudinal spread with multiple climate
zones. Some of these limitations will be addressed in the second
phase of global RSV surveillance initiative. Surveillance needs to
be conducted over a longer period, using uniform case definition
and sampling strategies and ensuring geographical representative-
ness in larger countries. It would also be useful to evaluate the
threshold of 10% RSV positivity to describe onset and offset of
the seasonal RSV epidemic. With more data available other meth-
ods of analyzing seasonal data may be used. Despite its limita-
tions, this pilot provides a better understanding of the seasonality
of RSV circulation globally. Additional years of RSV surveillance
data from different geographical regions within the same country
will provide more robust RSV seasonality patterns.

In conclusion, we observed distinct annual peak activity of RSV
in different regions of the world. Timing of RSV epidemics varied
among participating countries, and it generally overlapped with sea-
sonal influenza epidemics in most countries. The GISRS platform
can be leveraged for generating standardized and quality data on RSV
circulation. These data will be useful for deciding the best time for
targeting interventions such as future RSV vaccination and the use
of monoclonal antibodies.

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ORCID
Siddhivinayak Hirve  https://orcid.org/0000-0002-9651-7789
Sandra Jackson  https://orcid.org/0000-0002-1042-8882

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APPENDIX

WHO RSV Surveillance Group: Amal Barakat (Eastern Mediterranean Region Office, World Health Organization, Cairo, Egypt), Sumit Bhardwaj (National Institute of Virology, Indian Council of Medical Research, Pune, India), Shobha Broor (Medicine and Health Sciences, Shree Guru Gobind Singh Tricentenary University, Gurugram, India), Alyeksandr Burmaa (National Influenza Surveillance Division, National Center for Communicable Diseases, Ministry of Health, Ulaanbaatar, Mongolia), Harry Campbell (Usher Institute of Population Health Research and Informatics, University of Edinburgh, Edinburgh, United Kingdom), Daouda Coulibaly (Epidemiological Surveillance and Research, Institut National de l’Hygiène Publique, Abidjan, Côte d’Ivoire), Nigel Crawford (Royal Children’s Hospital, Melbourne, Australia), Manal Fahim (Department of Surveillance and Epidemiology, Ministry of Health and Population, Cairo, Egypt), Belinda Herring (African Region Office, World Health Organization, Brazzaville, Republic of Congo), Harish Nair (Usher Institute of Population Health Research and Informatics, University of Edinburgh, Edinburgh, United Kingdom), Rakhee Palekar (Pan American Health Organization, Washington DC, United States), Richard Pebody (Flu Surveillance, Public Health England, London, United Kingdom), Soatlana Rajatonirina (African Region Office, World Health Organization, Brazzaville, Republic of Congo), Marilda Siqueira (Instituto Oswaldo Cruz/FIOCRUZ, Rio de Janeiro, Brazil), Peter G. Smith (MRC Tropical Epidemiology Group, London School of Hygiene and Tropical Medicine, London, United Kingdom), Elizaveta Smorodintseva (Laboratory for studying risk factors of Influenza and ARVI, Smorodintsev Research Institute of Influenza, Ministry of Health of the Russian Federation, St. Petersburg, Russian Federation), Viviana Sotomayor (Division de Planificacion Sanitaria, Ministerio de Salud Chile, Santiago, Chile), Florette Treurnicht (Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, Johannesburg, South Africa), Miquelina Vaz (Laboratório de Isolamento Viral, Instituto Nacional de Saúde, Maputo, Mozambique), Marietjie Venter (Center for Viral Zoonosis, Department of Medical Virology, University of Pretoria, South Africa), Niteen Wairagkar (Bill and Melinda Gates Foundation, Seattle, United States), Maria Zambon (Virus Reference Department, Public Health England, London, United Kingdom).