Open Forum Infectious Diseases

MAJOR ARTICLE

The Global Epidemiology of RSV in Community and Hospitalized Care: Findings From 15 Countries

Lisa Staadegaard,[1] Saverio Caini,[1] Sonam Wangchuk,[2] Binay Thapa,[2] Walquiria Aparecida Ferreira de Almeida,[3] Felipe Cotrim de Carvalho,[3] Richard Njouom,[4] Rodrigo A. Fasce,[5] Patricia Bustos,[6] Jan Kyncl,[7,8] Ludmila Novakova,[9] Alfredo Bruno Caicedo,[10,11] Domenica Joseth de Mora Coloma,[10] Adam Meijer,[12] Mariëtte Hooiveld,[1] Sue Huang,[13] Tim Wood,[13] Raquel Guiomar,[14] Ana Paula Rodrigues,[14] Daria Danilenko,[15] Kirill Stolyarov,[15] Vernon Jian Ming Lee,[16,17] Li Wei Ang,[16,18] Cheryl Cohen,[19,20] Jocelyn Moyes,[19,20] Amparo Larrauri,[21] Concepción Delgado-Sanz,[21] Mai Quynh Le,[22] Phuong Vu Mai Hoang,[22] Clarisse Demont,[23] Mathieu Bangert,[23] Jojanneke van Summeren,[1] Michel Dückers,[1,24,25] and John Paget[1]

[1]Nivel (Netherlands Institute for Health Services Research), Utrecht, the Netherlands, [2]Royal Centre for Disease Control, Ministry of Health, Thimphu, Bhutan, [3]Ministry of Health, Brasilia, Brazil, [4]Service de Virologie, Centre Pasteur du Cameroun, Yaounde, Cameroon, [5]Subdepartamento Enfermedades Virales, Instituto de Salud Pública de Chile, Santiago, Chile, [6]Sección Virus Respiratorios, Subdepartamento Enfermedades Virales, Instituto de Salud Publica de Chile, Santiago, Chile, [7]Department of Infectious Diseases Epidemiology, National Institute of Public Health, Prague, Czech Republic, [8]Department of Epidemiology and Biostatistics, Third Faculty of Medicine, Charles University, Prague, Czech Republic, [9]National Reference Laboratory for Influenza and Other Respiratory Viruses, National Institute of Public Health, Prague, Czech Republic, [10]Instituto Nacional de Investigación en Salud Pública (INSPI), Centro de Referencia Nacional de Influenza y otros Virus Respiratorios, Guayaquil, Ecuador, [11]Universidad Agraria del Ecuador, Guayaquil, Ecuador, [12]National Institute for Public Health and the Environment, Bilthoven, the Netherlands, [13]Institute of Environmental Science and Research Limited (ESR), National Centre for Biosecurity and Infectious Disease (NCBID), Upper Hutt, New Zealand, [14]Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisbon, Portugal, [15]Smorodintsev Research Institute of Influenza, Saint Petersburg, Russian Federation, [16]Ministry of Health, Singapore, [17]Saw Swee Hock School of Public Health, Singapore, [18]National Centre for Infectious Diseases, Singapore, [19]Centre for Respiratory Disease and Meningitis, National Institute for Communicable Diseases, Johannesburg, South Africa, [20]School of Public Health, University of Witwatersrand, Johannesburg, South Africa, [21]National Centre of Epidemiology, CIBER Epidemiología y Salud Pública (CIBERESP), Institute of Health Carlos III (ISCIII), Madrid, Spain, [22]National Institute of Hygiene and Epidemiology, Hanoi, Vietnam, [23]Sanofi Pasteur, Lyon, France, [24]ARQ National Psychotrauma Centre, Diemen, the Netherlands, and [25]Faculty of Behavioural and Social Sciences, University of Groningen, Groningen, the Netherlands

Background. Respiratory syncytial virus (RSV) is one of the leading causes of acute respiratory tract infections. To optimize control strategies, a better understanding of the global epidemiology of RSV is critical. To this end, we initiated the Global Epidemiology of RSV in Hospitalized and Community care study (GERi).

Methods. Focal points from 44 countries were approached to join GERi and share detailed RSV surveillance data. Countries completed a questionnaire on the characteristics of their surveillance system.

Results. Fifteen countries provided granular surveillance data and information on their surveillance system. A median (interquartile range) of 1641 (552–2415) RSV cases per season were reported from 2000 and 2020. The majority (55%) of RSV cases occurred in the <1-year-olds, with 8% of cases reported in those aged ≥65 years. Hospitalized cases were younger than those in community care. We found no age difference between RSV subtypes and no clear pattern of dominant subtypes.

Conclusions. The high number of cases in the <1-year-olds indicates a need to focus prevention efforts in this group. The minimal differences between RSV subtypes and their co-circulation implies that prevention needs to target both subtypes. Importantly, there appears to be a lack of RSV surveillance data in the elderly.

Keywords. epidemiology: RSV: respiratory infections; surveillance.

Respiratory syncytial virus (RSV) is one of the leading causes of acute respiratory tract infections (ARIs) in both children and adults [1, 2]. The 2016 Global Burden of Disease (GBD) study estimated that RSV is responsible for 24.8 million ARI episodes and 76 600 deaths each year [3]. By the age of 1, ~60%–70% of children have been infected with RSV, and 2%–3% of these infections result in hospitalization, making RSV a leading cause of mortality and morbidity in children age <5, particularly in low- and median-income countries [4, 5]. Although the incidence of RSV infection is generally lower in adults compared with young children [6], RSV has been increasingly recognized as an important cause of respiratory disease in adults. High hospitalization and mortality rates associated with RSV have been reported in the elderly and in high-risk adults [2, 7].

Over 30 potential vaccines and new monoclonal antibodies (mAbs) are currently being evaluated, and new prevention methods are anticipated in the coming years [8]. For an effective implementation of these preventive measures, a clear understanding of the epidemiology of RSV is required. Several studies have previously reported and compared epidemiological metrics on a regional or global level [1, 3, 9]. However, studies transcending the national level do not leverage national surveillance data, and few studies have focused on the overall

Received 17 January 2021; editorial decision 24 March 2021; accepted 25 March 2021.

Correspondence: Lisa Staadegaard, MSc, Nivel, Otterstraat 118, 3513CR, Utrecht, the Netherlands (l.staadegaard@nivel.nl).

Open Forum Infectious Diseases®2021

DOI: 10.1093/ofid/ofab159

age distribution of RSV. Though studies have reviewed the epidemiology of RSV subtypes [10], few studies have done so at global level [11].

An important challenge to understand the epidemiology of RSV is a lack of publicly available data [12]. While most influenza-endemic countries have an influenza surveillance system publicly available data, dedicated surveillance systems for RSV are lacking [13]. RSV cases are therefore mostly captured through influenza surveillance systems, which has inherent challenges, and no public platform consolidating these data exists. In 2016, the World Health Organization initiated a pilot study to evaluate the feasibility of incorporating RSV surveillance into the Global Influenza Surveillance and Response System (GISRS) platform [13]. Two studies that emerged from this initiative compared the seasonality of RSV and influenza and described clinical characteristics as well as the performance of case definitions [13, 14].

Although RSV data collected through influenza surveillance systems are not perfectly sensitive or specific for capturing RSV cases [14], they can be a valuable source to predict the timing and duration of RSV epidemics as well as help define risk groups. Therefore, the Global Epidemiology of RSV (GERi) network was launched in 2019 to examine the global epidemiology and timing of RSV epidemics based on virological surveillance data [15]. Here, we describe the surveillance systems used to collect RSV data in 15 countries. Importantly, through access to national surveillance data, we analyze the age distribution of RSV cases overall and examine whether they are differently distributed across care levels or RSV subtypes. Lastly, to better define the epidemiology of RSV, we explore the role of RSV A and B in terms of overall patterns (dominant seasons), per country, and per level of care.

METHODS

Collection of Surveillance Data

Focal points of 44 countries across the world (usually based at national influenza centers) were approached between January 2019 and January 2020 to identify whether the respective country conducted RSV surveillance, and if so, they were invited to participate in the GERi network. Those who agreed to participate were sent an Excel data collection template and were asked to provide national RSV surveillance data from 2000 onwards. Data requested included: weekly number of RSV cases, age of the cases, number of specimens tested, and, if available, the RSV subtype. In addition, countries were asked to stratify cases by the level of care from which cases were reported.

Initially our data collection template differentiated between 3 levels of care: primary, secondary, and tertiary care. Primary care was defined as day-to-day health care, that is, the first contact and principal point of continuing care within the health care system. This typically includes general practitioners (GPs) or pediatricians. Secondary care was defined as acute care that required treatment for a short period of time, usually being the emergency department (ED) or the intensive care unit (ICU). Lastly, tertiary care was defined as more specialized consultative health care, which usually concerns inpatients and is provided on referral from primary or secondary care providers. We merged secondary and tertiary care into 1 category (referred to henceforth as "hospitalized care"), with primary care referred to as "community care" from this point forward.

Participating countries were also given a questionnaire (Supplementary Data) focused on the functioning of their respective surveillance system(s). In addition, they were asked for supplementary literature outlining their surveillance system(s). Through this mechanism, information on case definitions, definitions of different levels of care, type of laboratory testing, and representativeness of the data were obtained.

Data Analysis

To be included in the analysis, each season was required to contain at least 50 cases. Seasons north of the Tropic of Cancer were defined as ranging from week 27 to week 26 of the next calendar year. For countries south of the Tropic of Cancer, seasons were defined as ranging from week 1 through week 52 of the same calendar year.

The age distribution of RSV cases was investigated by calculating a median and interquartile range (IQR) at the country level, per level of care, and per RSV subtype. Differences in median were tested for significance using a 2-sample Wilcoxon rank sum. At the country level, age was expressed in the form of a relative illness ratio (RIR). The RIR, used to account for different age structures between countries, was calculated as follows:

$$RIR = (\frac{C_i}{\sum C_i})/(\frac{N_i}{\sum N_i})$$

Here, C_i represents the number of cases in a given age group (i), and N_i represents the population size in a given age group [16]. Age-specific population data were obtained from the United Nations population division [17].

A meta-analysis was performed to pool results on the proportion of specimen testing positive for RSV each season and per country to estimate this proportion per care level using the R package "metafor" [18]. Pooled estimates were calculated using logit transformation and the DerSimonian-Laird estimator for random effects.

Lastly, the distribution of RSV A and B cases across seasons was analyzed for both community and hospitalized care. Differences in proportions were tested using a z test.

The occurrence of RSV A or B dominant seasons was explored using a ≥60% threshold to define a subtype as being dominant. All analyses were performed and figures created using the statistical program R, version 3.6.1 [19].

Table 1. Description of the RSV Surveillance Systems by Level of Care (eg, Mix, Community, or Hospitalized Care) of the 15 Participating Countries on the Basis of a Questionnaire

	Care Level[a]	Regional Stratification	Timing	Type of Surveillance	Care Level Definition	Case Definition	Methods Detection	Representativeness
Cameroon	Mix	No	Year round	Sentinel surveillance system in outpatient and hospitalized patients	NA	Outpatient: ILIHospitalized: SARI	Real-time RT-PCR	Data from 6 different regions out of 10
Portugal	Mix	Yes	Seasonal (~weeks 40–18)	Nonsentinel, laboratory surveillance[#]	Outpatients & hospitalized patients	None	Real-time RT-PCR + antigen detection	No hospitals in the southern region
United States of America	Mix	Yes	Year round	Passive national laboratory surveillance (NREVSS)	NA	NA	NA	10 HHS regions, with data from >500 state and local public health laboratories, commercial labs, and hospitals/universities
The Czech Republic	Community care	No	Seasonal (weeks 40–20)	Sentinel surveillance	GPs for adults and GPs for children	ILI/ARI	Antigen detection, virus isolation, and other; Biomerieaux	0.37% of GPs and all regions are covered
The Netherlands	Community care	No	Year round	Sentinel surveillance—subset of patients; at least 2 per week and GP sentinel practice, 1 of which should be a child age <10	GPs in a sentinel network	ILI/ARI	Real-time RT-PCR	0.8% of the Dutch population
New Zealand	Community care	No	Seasonal (~weeks 18–40)	Sentinel surveillance—subset of patients: all ILIs in Auckland and Wellington and the first patient with ILI from Monday to Wednesday for the rest of NZ	GP-based surveillance	ILI	Real-time RT-PCR: US CDC protocol	80–90 GP practices covering the whole of NZ; previously (<2015) only Auckland region was included
Portugal	Community care	Yes	Seasonal (~weeks 40–18)	Sentinel surveillance[+]	GP at health care centers or patients attending at emergency rooms	ILI	Real-time RT-PCR	All regions
Russian Federation	Community care	Yes	Year round	Sentinel surveillance	Patients attended a polyclinic	ILI	Multiplex PCR	Facilities in 10 cities, each in every federal district; this population compromises 16.2% of the population
Singapore	Community care	No	Year round	Sentinel surveillance[+]	Government-funded primary clinics (20) & private GPs (30) covering all regions of the country	ARI + fever ≥38°C and cough	Antigen detection, gel-based RT-PCR, or multiplex syndromic panels	All regions are covered
South Africa	Community care	No	Year round	Sentinel surveillance[#]	Primary health care clinic in the community	ILI	Real-time RT-PCR assay, Fast Track Diagnostics Flu/RSV	Conducted at 2 clinics in the country
Bhutan	Hospitalized care	Yes	Year round	Sentinel surveillance[#]	Hospitalized patients	SARI	Real-time RT-PCR	Nationally
Brazil[b]	Hospitalized care	Yes	NA	NA	NA	NA	NA	NA
Chile	Hospitalized care	No	Year round	Sentinel surveillance[#]	Cases are in hospitalized patients, may consult at ER	SARI	Immunofluorescence assay or RT-PCR	Cities located in regions with the highest proportion of the population (80%)

Table 1. Continued

	Care Level[a]	Regional Stratification	Timing	Type of Surveillance	Care Level Definition	Case Definition	Methods Detection	Representativeness
The Czech Republic	Hospitalized care	No	Seasonal (weeks 40–20)	Nonsentinel/routinely—subset: ~500–700 swabs each epidemic season	Local (district) hospitals and regional hospitals + university hospitals	NA	Antigen detection, virus isolation, and other; Biomerieaux	All regions
Ecuador	Hospitalized care	No	Year round	Sentinel surveillance#	National sentinel surveillance hospitals	SARI	Antigen detection	Nationally
Spain[b]	Hospitalized care	No	NA	NA	NA	NA	NA	NA
The Netherlands	Hospitalized care	No	Year round	Passive national laboratory surveillance (virologische weekstaten)	Testing requested by GPs, clinical departments in hospitals, and outpatient clinics	NA	Rapid antigen test, PCR	14–21 laboratories across the Netherlands, covering 29%–44% of the population
New Zealand	Hospitalized care	No	Seasonal (~weeks 18–40)	Sentinel surveillance#	Hospital-based surveillance + ICU	SARI	Real-time RT-PCR	4 hospitals in Auckland (20% of NZ population)
Russian Federation	Hospitalized care	Yes	Year round	Sentinel surveillance#	Hospitalized patients (special infectious disease hospitals)	SARI	Multiplex PCR	10 cities, each in every federal district; this population compromises 16.2% of the population
Singapore	Hospitalized care	No	Year round	NA	Two pediatric departments in public acute care hospitals	SARI	Antigen detection, gel-based RT-PCR or multiplex syndromic panels	All regions are covered
Vietnam	Hospitalized care	No	Year round	NA	Hospitalized patients	SARI	Gel-based RT-PCR	North of Vietnam only
South Africa	Hospitalized care	No	Year round	Sentinel surveillance system#	Hospitalized care & tertiary care facilities	SARI (>5-y), LRTI (>2 d–<5 y)	Real-time RT-PCR assay, Fast Track Diagnostics Flu/RSV	Conducted at 7 hospitals in 5 out of 9 provinces

Symbols: #, surveillance aimed at testing all patients fitting the case definition reporting to the included facilities; +, only samples that were negative for influenza were tested for RSV.

Abbreviations: ARI, acute respiratory infection; GP, general practitioner; HHS, US Department of Health & Human Services; ICU, intensive care unit; ILI, influenza-like-illness; LRTI, lower respiratory tract infection; NA, not available; NREVSS, the National Respiratory and Enteric Virus Surveillance System (USA); PCR, polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; SARI, severe acute respiratory infection.

[a]Care level definitions: community care = day-to-day health care usually provided by the first contact within the health care system, hospitalized care = both acute care received in the emergency department or intensive care unit and more specialized consultative health care usually concerning inpatients, mix = a combination of the 2.

[b]Brazil and Spain did not return the questionnaire.

RESULTS

Structure of RSV Surveillance in Participating Countries

Of the 44 invited countries, 15 countries (Supplementary Figure 1) provided data, and 13 of these completed the questionnaire (Supplementary Data). A summary of questionnaire results can be found in Table 1. Seven countries provided community care surveillance data, 12 provided data from hospitalized care, and 4 provided data on a combination of both. Cases were recorded as part of sentinel surveillance for all 7 countries providing data on community care and 6 out of 12 countries providing data on hospitalized care. The remaining countries recording cases in hospitalized care take a more passive and voluntary approach, where testing is usually driven by diagnostic needs. Definitions of community and hospitalized care largely overlapped on a country level. Most of the community care data are provided by GPs; however, the data from Portugal included emergency room visits. In some countries, data could not be categorized into level of care. The data from the United States, for example, stemmed from national laboratories that receive data from a variety of public health institutions, and some data from Portugal and Cameroon included both out- and inpatients [20].

The predominant case definition used to capture RSV was influenza-like illness (ILI) in community care and severe acute respiratory infection (SARI) in hospitalized care, with the exception of the Netherlands and Portugal, where ILI was combined with other acute respiratory infection (ARI) in community care. In most countries, RSV is 1 of several respiratory infections tested for by real-time RT-PCR.

The largest variation between countries was seen when comparing representativeness by country. Most of the countries provided data at the national level, with the exception of Chile, Portugal, and New Zealand. Four countries provided regional data (Bhutan, Brazil, Portugal, and the United States). Another factor influencing the representativeness of the data and comparability across countries was testing policy. Where some countries test a predetermined subset of patients (eg, 1 child and 1 adult per week) presenting with ILI or SARI (the Netherlands: community care; New Zealand: community care; and Portugal: mix), others test all patients presenting with ILI or SARI symptoms (Cameroon, the Czech Republic, Portugal: community care; Russian Federation, South Africa, Bhutan, Chile, Ecuador, New Zealand: hospitalized care). In 2 out of 15 countries, specimens collected are first tested for influenza, and testing for other respiratory viruses only occurs if negative for influenza (Portugal and Singapore). However, most surveillance data were collected year-round.

Overview RSV Surveillance Data

Surveillance data shared by the 15 participating countries are summarized in Table 2. Supplementary Figures 2 and 3 show the available national surveillance data over time. Countries provided data for a median (range) of 7 (1–19) seasons, with a median (IQR) of 1641 (552–2415) RSV cases per season. Apart from Brazil, all countries provided a weekly number of specimens tested, with a median (IQR) of 6420 (3473–22 777) specimens tested per season. The majority of cases (97%) were recorded in hospitalized care, both overall and in countries with data available from both community and hospitalized surveillance. For the United States, no age data were available.

The percentage of RSV-positive cases varied widely across countries. The proportions are consistent from season to season at a country level in community care, but there was great variation in hospitalized care. Overall, the percentage of positive cases was higher in hospitalized care (SARI; 12%; 95% CI, 11%–13%; I^2 = 99%) than in community care (ILI or ARI; 6%; 95% CI, 5%–6%; I^2 = 91%). Forest plots on RSV positivity in community and hospitalized care are shown in Supplementary Figures 4 and 5, respectively.

Age Distribution of RSV Cases

The median age of RSV cases was available for 10 countries, and 4 countries provided cases per age category (Table 3). Portugal provided both exact and categorical age data; however, due to the small number of cases with the exact age (105/4902), Table 3 only presents the categorical data. Spain, not presented in Table 3, provided data stratified as <15- and ≥15-year age categories.

Overall, the median age (IQR) was 0.78 (0.3–2.6), but this differed greatly across countries (Table 3). The RIR was consistently higher in the youngest age category compared with the ≥5-year age category, where the RIR remained consistently below 1 (~20–800 fold). For Spain, the RIR showed a similar pattern, with the highest RIR (IQR), 5.4 (4.9–6.2), in the <15-year-old age category, compared with 0.2 (0.1–0.3) in the ≥15-year-old age category. All countries included RSV cases in those aged 65 or older, comprising ~8% of all cases. This proportion ranged from 1% in Chile, Ecuador, Portugal, and South Africa to 20% in Portugal.

As the majority of cases (n = 9287, 55%) were found in the <1-year-old category, we decided to focus on this group. The monthly age distribution for this category in community and hospitalized care is depicted in Figure 1A–B. In hospitalized care (1B), the number of cases peaked in the 1–2-month age group, after which the number of cases declined for older age groups. In this age category and setting, 70% of cases were ≤6 months of age. The sample size for the <1-year-old age category in community care was substantially smaller (n = 422) than in hospitalized care (n = 8864). The age distribution found in hospitalized care did not appear to repeat itself in the community care setting for cases aged <1 year (Figure 1A).

Three countries (New Zealand, Russian Federation, and South Africa) provided exact age data for both levels of care, representing 16 934 RSV cases (Supplementary Figure 6). The median age among community care cases (IQR) was 5.5 (1.9–43.6) years, substantially and significantly higher than

Table 2. Summary of Available Surveillance Data of the 15 Participating Countries; Data Are Summarized on a Country Level and Further Specified for Level of Care (eg, Community or Hospitalized)

	Country	Seasons, No.	Subtyped Data, %	Median Cases per Season (IQR)	Care Level	Cases per Season, Median (IQR)	Average % Positive
Africa	South Africa	10 (2009–2018)	36	604 (524–824)	Community	81 (80–95)	6
					Hospitalized	693 (515–824)	14
	Cameroon	1 (2018–2019)	0	22	Community	22	13
					Hospitalized	NA	NA
Americas	United States of America	14 (2005/2006–2018/2019)	0	18 007 (5510–37 834)	Community	NA	NA
					Hospitalized	NA	NA
	Chile	7 (2012–2018)	0	4923 (4846–5490)	Community	138 (124–146)	8
					Hospitalized	4773 (4722–5361)	17
	Ecuador	7 (2012–2018)	0	482 (365–615)	Community	NA	NA
					Hospitalized	482 (365–615)	13
	Brazil	5 (2014–2018)	0	2208 (1337–2520)	Community	NA	NA
					Hospitalized	2208 (1337–2520)	NA
Europe	Portugal	8 (2011/2012–2018/2019)	14	529 (247–783)	Community	13 (7–13)	4
					Hospitalized	NA	NA
	The Netherlands	19 (2000/2001–2018/2019)	100	1980 (1766–2219)	Community	73 (53–98)	4
					Hospitalized	1959 (1732–2195)	NA
	The Czech Republic	4 (2014/2015–2017/2018)	3	233 (202–345)	Community	22 (17–26)	4
					Hospitalized	213 (189–319)	3
	Spain	13 (2006/2007–2018/2019)	0	2060 (1638–2969)	Community	NA	NA
					Hospitalized	2060 (1638–2969)	13
	Russian Federation	5 (2014/2015–2018/2019)	0	133 (104–176)	Community	66 (48–88)	4
					Hospitalized	67 (56–78)	6
South East Asia	Bhutan	3 (2015/2016–2017/2018)	0	98 (82–218)	Community	NA	NA
					Hospitalized	41 (33.5–64)	38
Western Pacific	Singapore	8 (2011–2018)	4	1786 (1647–2076)	Community	90 (75–105)	7
					Hospitalized	1710 (1574–1968)	10
	New Zealand	6 (2013–2018)	39	610 (533–682)	Community	101 (82–128)	7
					Hospitalized	466 (450–566)	16
	Vietnam	2 (2017–2018)	0	39 (26–41)	Community	39 (26–41)	10
					Hospitalized	NA	NA
Average	Average	7	-	1463 (512–2335)	Community	78 (37–110)	8
					Hospitalized	747 (435–1807)	17

Abbreviations: IQR, interquartile range; NA, not available.

Table 3. Number of Cases, Median Age, and Age Distribution Expressed as a Relative Illness Ratio of RSV Cases per Country

			Age Category						
			<1 y		1–4 y		≥5 y		
	No. of Cases	Median Age (IQR), y	No. of Cases	Median RIR (IQR)	No. of Cases	Median RIR (IQR)	No. of Cases	Median RIR (IQR)	No. of Years
Bhutan	320	1.00 (0.42–2.00)	156	28.5 (22.4–29.8)	125	5.6 (4.8–6.5)	39	0.1 (0.1–0.1)	3
Cameroon	35	1.00 (0.33–4.50)	15	NA	11	NA	9	NA	0
Chile	358	0.92 (0.42–1.00)	189	42.8 (42.6–43.1)	137	7.3 (7.1–7.6)	32	0.1 (0.1–0.1)	2
The Czech Republic	141	6.00 (3.00–43.00)	13	NA	46	NA	82	NA	0
Ecuador	3361	0.58 (0.25–1.00)	2179	31.7 (29.0–33.1)	1051	4.0 (3.8–4.6)	131	0.0 (0.0–0.1)	7
The Netherlands	975	14.82 (1.64–55.66)	157	14.3 (11.9 –18.2)	253	6.2 (5.8–7.0)	565	0.6 (0.5–0.6)	13
New Zealand	3996	1.00 (0.25–5.17)	1992	38.4 (35.8–44.5)	994	4.6 (4.0–5.0)	1010	0.3 (0.1–0.3)	7
Russian Federation	781	3.00 (1.00–8.00)	160	13.8 (6.7–16.5)	371	9.4 (9.0–9.5)	250	0.4 (0.3–0.4)	6
South Africa	6646	0.51 (0.21–1.53)	4416	28.9 (16.5–35.0)	1385	2.4 (2.3–2.5)	845	0.1 (0.1–0.2)	10
Vietnam	78	2.00 (1.50–4.00)	10	NA	50	NA	18	NA	0
Countries With Information on Age Provided Only in Categories					<5 y		≥5 y		No. of Years
					No. of Cases	Median RIR (IQR)	No. of Cases	Median RIR (IQR)	
Brazil	11 460	<2 y#	NA	NA	10 318	12.7 (12.6–12.7)	1142	0.1 (0.1–0.1)	5
Portugal	4902	0–4	NA	NA	2973	7.3 (0.7–18.6)	1859	0.4 (0.2–0.6)	7
Singapore	716	1–2	NA	NA	523	18.6 (18.1–19.9)	193	0.3 (0.1–0.3)	8

Symbol: #, median age category, as exact ages were not available.

Abbreviations: IQR, interquartile range; NA, not available; RIR, relative illness ratio; RSV, respiratory syncytial virus.

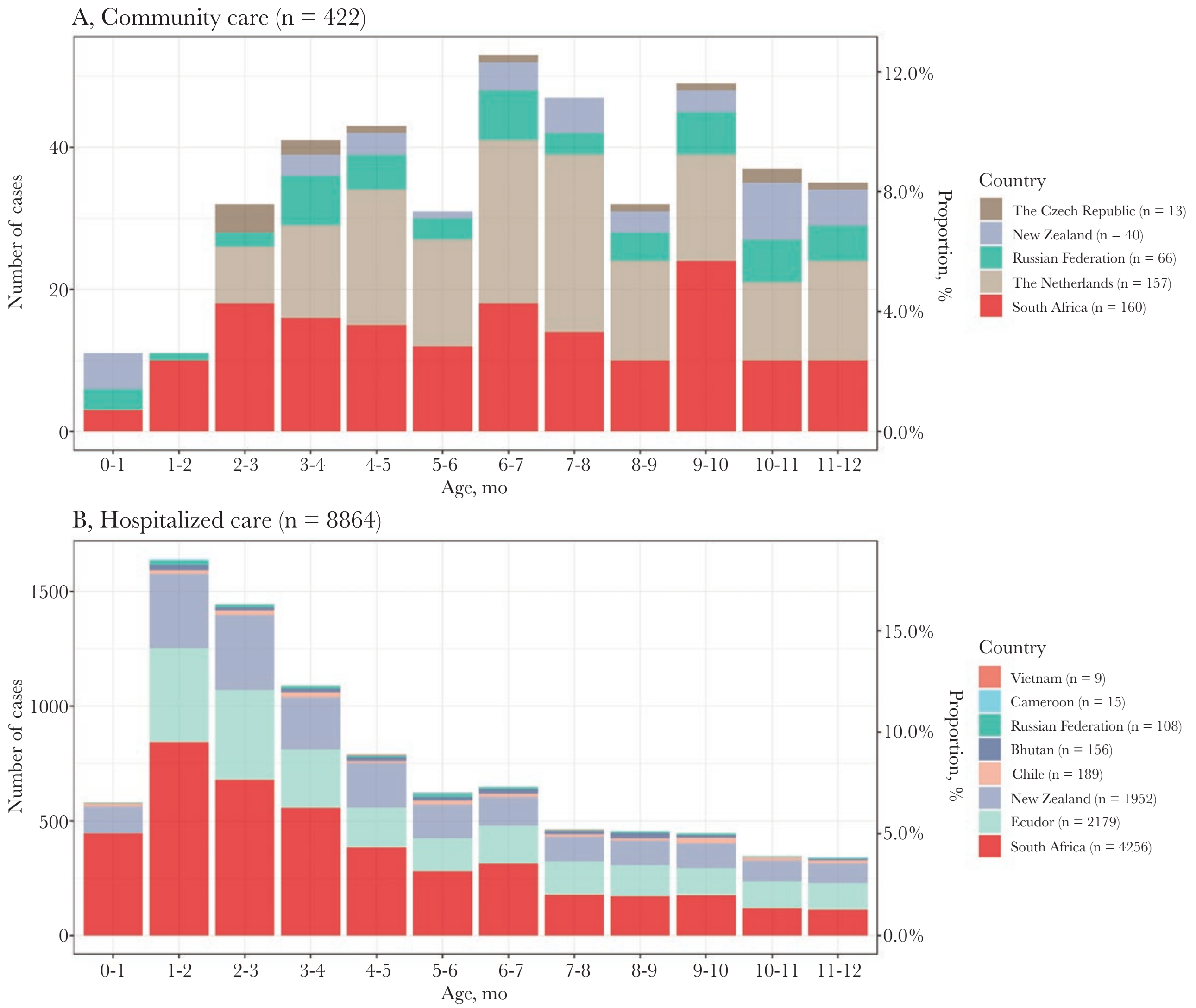

Figure 1. A–B, Number of RSV cases per month in the <1-year-old age category in community and hospitalized care. "Age, mo" on the x-axis refers to the age of the child. The overall number of cases in the <1-year-old category was taken to calculate the proportion of cases in a given month. Abbreviation: RSV, respiratory syncytial virus.

the median age (IQR) in hospitalized care (0.6 [0.2–1.4] years; $P < .001$). The same level of significance ($P < .001$) was found when comparing age per care level on the individual country level.

RSV Subtype Distribution

Six countries (the Czech Republic, the Netherlands, New Zealand, Portugal, Singapore, and South Africa) provided subtyped RSV data. In the Netherlands, Singapore, and South Africa, ≥90% of RSV cases were typed, whereas this was 3%, 14%, and 39% for the Czech Republic, Portugal, and New Zealand, respectively. These countries reported a total of 6148 RSV subtyped cases, of which 3155 were typed as RSV A cases (51%) and 2993 were typed as RSV B cases (49%). There were 34 seasons containing sufficient subtyped RSV cases to be included in the analysis. The distributions of RSV subtypes for these seasons (from 2010 to 2019) stemmed from 5 countries (the Netherlands, New Zealand, Portugal, Singapore, and South Africa) and are summarized in Figure 2. The figure shows a slightly higher median (IQR) for RSV A (54% [38%–65%]) compared with RSV B (46% [35%–62%]).

There were 12 out of 34 seasons where RSV A was dominant and 10 seasons where RSV B was dominant. Subtype dominance reached ≥80% twice in the Netherlands for RSV B for the 2017/2018 and 2018/2019 seasons, once in New Zealand for RSV A in the 2012 season, and once in Portugal for RSV B in the 2014/2015 season.

For 2 countries (New Zealand and South Africa), subtyped RSV data (n = 2180) were available in both community and hospitalized care. Overall the proportion of RSV A was lower in community care (46%, 264/570) compared with hospitalized care (53%, 859/1610; $P < .001$). At the country level, the

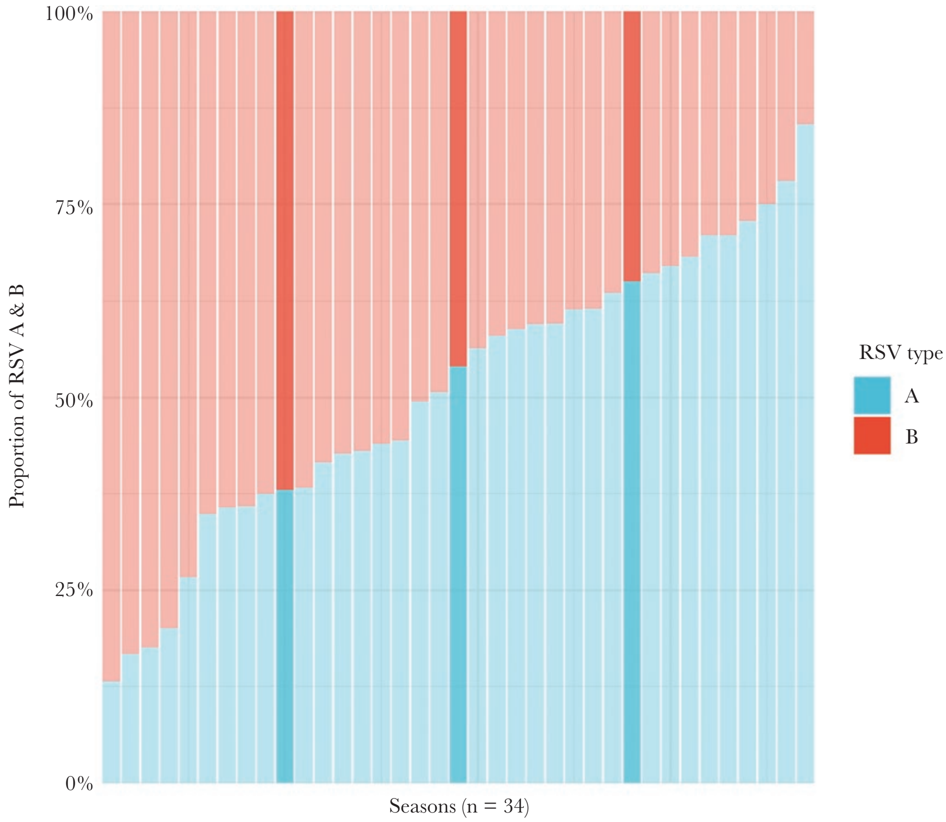

Figure 2. Proportion of RSV A & B cases per season (n = 34; seasons ordered by increasing proportion RSV A) among subtyped results. Countries included were the Netherlands, New Zealand, Portugal, South Africa, and Singapore, and data from both community and hospitalized care are combined. Proportion distribution was calculated by country for all included seasons. The dark line in the middle indicates the median proportion of both RSV A and B per season, and the dark lines on the left and right indicate the interquartile range. Abbreviation: RSV, respiratory syncytial virus.

proportion of RSV A was 40% (107/269) in community care in South Africa and 54% (232/433) in hospitalized care ($P < .001$); in New Zealand this difference was 52% (157/301) compared with 53% (627/1177; $P = .78$) in community and hospitalized care, respectively.

The age distribution of RSV by subtype was available for a total of 4911 cases distributed across 5 countries (the Czech Republic, the Netherlands, New Zealand, Portugal, and South Africa). The global median age for RSV A (IQR) was 0.9 (0.3–4.3) years compared with 0.9 (0.3–5.2) years for RSV B ($P = .96$). Similar results were seen at the country level, the only exception being the Netherlands, where RSV B cases had a median age (IQR) of 24.4 (1.7–58.2) years compared with 6.4 (1.6–52.8) years for RSV A cases ($P = .02$) (Supplementary Figure 7).

DISCUSSION

This study describes for the first time age- and care setting–specific surveillance data at a global level. Importantly, it also provides insight into current RSV surveillance practices at a national level. The GERi network currently encompasses 15 countries and includes 112 seasons of RSV surveillance data between 2000 and 2020. We found several differences in data collection practices and demonstrated that the highest incidence of RSV cases requiring medical attention was found in the <1-year-old age category. In addition, our data set contained very few infections in the 65+ age group (8%).

Though it is well established that RSV is an important cause of respiratory disease requiring medical attention in the very young [5], the impact of RSV on the overall population is not well studied. Though the RIR is consistently higher in the <1-year-old age category, the lack of cases in the elderly might reflect that this group is disproportionately captured by the surveillance systems. In our study, only 8% of total surveillance cases were found in the >65-year-old age category (ranging from 1% in Chile, Ecuador, Portugal, and South Africa to 20% in Portugal). Based on previously published population-based RSV estimates, we would expect this age group to represent between 19% and 33% of total surveillance cases in the United States, 37% in the United Kingdom, 25% in Canada, 16% in Thailand, and <1% in Madagascar [21–26]. Studies in the United States have also reported incidence rates of RSV in the elderly that were nearly twice that of influenza A and that RSV had a high disease severity in the elderly [2]. These data suggest that, at least for developed countries with relatively large elderly populations, surveillance systems may not be sufficiently picking up RSV cases in the ≥65-year-old age group. This could be influenced by a variety of factors, including an atypical clinical presentation in older adults or lower viral titers, which might hinder RSV detection by rapid antigen tests [27].

RSV patients in community care were older than those in hospitalized care, underlined by South Africa and New Zealand—in which all ILI as well as SARI cases are tested. Data from both countries show that cases in hospitalized care were substantially younger. This could be due to the previously demonstrated higher risk of hospitalization in younger individuals [28]. The percentage of cases testing positive for RSV was consistently higher in hospitalized patients, suggesting that RSV might play a larger role among other causes of respiratory infections in the hospitalized setting than in the community setting. Several studies found similarly high proportions of RSV positivity among hospitalized patients [29, 30].

No evidence for age differences between RSV subtypes was found. In most seasons analyzed, both RSV subtypes co-circulated (<80% threshold) and no clear pattern per country or from season to season was found. Though the RSV subtype remained unknown for a large subset of cases, this would likely not impact the proportion of RSV A or B per season found in our study. While among subtyped cases the proportion of RSV A was higher in hospitalized care compared with community care, the evidence was limited. A difference in this distribution could indicate an increased severity for those infected with RSV A [11].

The strengths of the GERi network lie in the size of the data set, the global distribution of the countries, the stratification by level of care, and additional information gained through our questionnaire. This study also comes with several limitations. Although surveillance data are an effective way to determine timing and seasonality of epidemics, it is important to note that only medically attended cases are included in the data set. In addition, influenza surveillance systems—a common foundation for RSV testing—commonly use the ILI case definition, which requires a fever, a clinical symptom not universally and globally represented in RSV cases [14]. Another limitation of the GERi network is the diversity in surveillance systems. The information gathered through the questionnaire, in combination with the size of the database, enables a better interpretation of results. Not all regions and Income categories are equally represented in the database. In line with previous studies that have assessed global data sets, high-income countries tend to provide more data and data that have greater detail [31].

Our results have important public health implications as well as implications for the development of future prevention methods. They highlight and support previous findings on the age groups that need to be targeted to prevent and control infections, with <1-year-olds being of greatest importance. The co-circulation of both RSV types also implies that for a prevention method to be effective it should target both types. This is especially relevant, as neither of the types appears to be overly represented in hospitalized cases.

CONCLUSIONS

The GERi network is the most substantial assessment of RSV surveillance data to date. Importantly, we found several differences in RSV surveillance systems across countries, underlining the need to harmonize surveillance activities for RSV around the world to make the data more comparable and to draw firmer conclusions for prevention and control measures. While our analysis found that the incidence of RSV is highest in the <1-year-old age category, more surveillance data in the elderly may be required, especially in developed countries, to support prevention efforts in this age group.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

The United States: We thank the Division of Viral Diseases (CDC) for sharing the NVRESS data. The Netherlands: We thank the Dutch Working Group for Clinical Virology (NWKV) for the use of virology diagnostic reports (nonsentinel data) and Sofie Mooij (RIVM) for providing the data. We thank the Nivel Primary Care Database team and general practitioners and their patients for their contribution to the national sentinel surveillance. The team of technicians at RIVM currently represented by Sharon van den Brink, Lisa Wijsman, and Gabriel Goderski are thanked for organizing the logistics and performing testing of the sentinel specimens.

Financial support. Sanofi Pasteur/AstraZeneca.

Potential conflicts of interest. C.D. and M.B. are Sanofi employees and may hold shares and/or stock options in the company; J.P. reports that Nivel has received RSV research grants from the Foundation for Influenza Epidemiology and Sanofi Pasteur. The remaining authors declare no competing interests. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patient consent. Our study uses routine surveillance data for which no patient consent is required.

Other contributors. Pedro Pechirra,[14] Inês Costa,[14] Elizaveta Smorodintseva,[15] Tze Minn Mak,[18] Lin Cui,[18] Raymond Tzer-Pin Lin,[18] Anne Von Gottberg,[19,20] Jesús Oliva Domíngue.[21]

References

1. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet **2010**; 375:1545–55.
2. Falsey AR, Hennessey PA, Formica MA, et al. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med **2005**; 352:1749–59.
3. Troeger C, Blacker B, Khalil IA, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis **2018**; 18:1191–210.
4. Obando-Pacheco P, Justicia-Grande AJ, Rivero-Calle I, et al. Respiratory syncytial virus seasonality: a global overview. J Infect Dis **2018**; 217:1356–64.

5. Shi T, McAllister DA, O'Brien KL, et al; RSV Global Epidemiology Network. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet **2017**; 390:946–58.
6. Tin Tin Htar M, Yerramalla MS, Moïsi JC, Swerdlow DL. The burden of respiratory syncytial virus in adults: a systematic review and meta-analysis. Epidemiol Infect **2020**; 148:e48.
7. Fleming DM, Taylor RJ, Lustig RL, et al. Modelling estimates of the burden of respiratory syncytial virus infection in adults and the elderly in the United Kingdom. BMC Infect Dis **2015**; 15:443.
8. PATH Vaccine Resource Library. RSV vaccine and mAb snapshot. Available at: https://vaccineresources.org/details.php?i=1562. Accessed 29 April 2020.
9. Li Y, Reeves RM, Wang X, et al; RSV Global Epidemiology Network; RESCEU investigators. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. Lancet Glob Health **2019**; 7:e1031–45.
10. Papadopoulos NG, Gourgiotis D, Javadyan A, et al. Does respiratory syncytial virus subtype influences the severity of acute bronchiolitis in hospitalized infants? Respir Med **2004**; 98:879–82.
11. Shi T, Denouel A, Tietjen AK, et al. Global disease burden estimates of respiratory syncytial virus-associated acute respiratory infection in older adults in 2015: a systematic review and meta-analysis. J Infect Dis **2019**; 222(Suppl 7): S577–83.
12. Campbell H, Bont L, Nair H. Respiratory syncytial virus (RSV) disease - new data needed to guide future policy. J Glob Health **2015**; 5:020101.
13. Chadha M, Hirve S, Bancej C, et al; WHO RSV Surveillance Group. Human respiratory syncytial virus and influenza seasonality patterns—early findings from the WHO global respiratory syncytial virus surveillance. Influenza Other Respir Viruses **2020**; 14:638–46.
14. Hirve S, Crawford N, Palekar R, Zhang W; WHO RSV Surveillance Group. Clinical characteristics, predictors, and performance of case definition—interim results from the WHO global respiratory syncytial virus surveillance pilot. Influenza Other Respir Viruses **2020**; 14:647–57.
15. Nivel. The GERI study. Available at: https://www.nivel.nl/en/geri. Accessed 29 April 2020.
16. Lemaitre M, Carrat F. Comparative age distribution of influenza morbidity and mortality during seasonal influenza epidemics and the 2009 H1N1 pandemic. BMC Infect Dis **2010**; 10:162.
17. Population Division, United Nations. World population prospects. Available at: https://population.un.org/wpp/Download/Standard/Population/. Accessed 30 April 2020.
18. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw **2010**; 36:1–48.
19. R Core Team. R: a language and environment for statistical computing. **2019**. Available at: https://www.r-project.org/. Accessed 29 April 2020.
20. Centers for Disease Control and Prevention. National Respiratory and Enteric Virus Surveillance System. Available at: https://www.cdc.gov/surveillance/nrevss/index.html. Accessed 29 April 2020.
21. Matias G, Taylor R, Haguinet F, et al. Estimates of hospitalization attributable to influenza and RSV in the US during 1997–2009, by age and risk status. BMC Public Health **2017**; 17:271.
22. Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993–2008. Clin Infect Dis **2012**; 54:1427–36.
23. Pitman RJ, Melegaro A, Gelb D, et al. Assessing the burden of influenza and other respiratory infections in England and Wales. J Infect **2007**; 54:530–8.
24. Schanzer DL, Saboui M, Lee L, et al. Burden of influenza, respiratory syncytial virus, and other respiratory viruses and the completeness of respiratory viral identification among respiratory inpatients, Canada, 2003-2014. Influenza Other Respir Viruses **2018**; 12:113–21.
25. Naorat S, Chittaganpitch M, Thamthitiwat S, et al. Hospitalizations for acute lower respiratory tract infection due to respiratory syncytial virus in Thailand, 2008–2011. J Infect Dis **2013**; 208:S238–45.
26. Rabarison JH, Tempia S, Harimanana A, et al. Burden and epidemiology of influenza- and respiratory syncytial virus-associated severe acute respiratory illness hospitalization in Madagascar, 2011–2016. Influenza Other Respir Viruses **2018**; 13:138–47.
27. Colosia AD, Yang J, Hillson E, et al. The epidemiology of medically attended respiratory syncytial virus in older adults in the United States: a systematic review. PLoS One **2017**; 12:e0182321.
28. Bont L, Checchia PA, Fauroux B, et al. Defining the epidemiology and burden of severe respiratory syncytial virus infection among infants and children in Western countries. Infect Dis Ther **2016**; 5:271–98.
29. Nokes DJ, Ngama M, Bett A, et al. Incidence and severity of respiratory syncytial virus pneumonia in rural Kenyan children identified through hospital surveillance. Clin Infect Dis **2009**; 49:1341–9.
30. Pale M, Nacoto A, Tivane A, et al. Respiratory syncytial and influenza viruses in children under 2 years old with severe acute respiratory infection (SARI) in Maputo, 2015. PLoS One **2017**; 12:e0186735.
31. Dückers MLA, Reifels L, de Beurs DP, Brewin CR. The vulnerability paradox in global mental health and its applicability to suicide. Br J Psychiatry **2019**; 215:588–93.