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Change in Age profile of Respiratory Syncytial Virus disease over the course of annual epidemics: a multi-national study

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SUMMARY

Objectives: We aimed to study whether the percentwise age distribution of RSV cases changes over time during annual epidemics.

Methods: We used surveillance data (2008–2019) from the Netherlands, Lyon (France), Portugal, Singapore, Ecuador, South Africa, and New Zealand. In each country, every season was divided into "epidemic quarters", i.e. periods corresponding to each quartile of RSV cases. Multinomial logistic regression models were fitted to evaluate whether the likelihood of RSV cases being aged < 1 or ≥5 years (vs. 1 to < 5) changed over time within a season.

Results: In all countries, RSV cases were significantly more likely to be aged < 1 year in the 4th vs. 1st epidemic quarter; the relative risk ratio [RRR] ranged between 1.35 and 2.56. Likewise, RSV cases were significantly more likely to be aged ≥5 years in the 4th vs. 1st epidemic quarter (except in Singapore); the RRR ranged from 1.75 to 6.70. The results did not change when stratifying by level of care or moving the lower cut-off to 6 months.

Conclusions: The age profile of RSV cases shifts within a season, with infants and adolescents, adults, and the elderly constituting a higher proportion of cases in the later phases of annual epidemics. These findings may have implications for RSV prevention policies with newly approved vaccines.

Introduction

Respiratory syncytial virus (RSV) is highly contagious and most children become infected in their first months of life, but reinfections occur frequently throughout early childhood.[1–4] The risk of RSV-associated severe disease and hospitalization is highest among infants younger than 6 months as well as seniors and subjects with specific comorbidities.[5] A modeling study using US data suggested that children less than 10 years of age (and especially those aged 3–6 years) play a prominent role in propagating RSV epidemics, because of high susceptibility and/or contact rates.[6] This encompasses toddlers (2–3 years), pre-schoolers (3–5 years), and children in middle childhood (6–8 years).[7] Indeed, RSV can spread rapidly within preschools, kindergartens and day-care centers,[8] and

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a substantial proportion of infections in children in their first year of age are caused by transmission from older school-going siblings.[9–12]

Taken together, these data suggest that a common chain of transmission of RSV consists of children in their early childhood becoming infected at pre-schools, kindergartens, and early primary school (where many susceptible young individuals congregate, thus allowing a sustained viral circulation) and then introducing the virus into their household, where co-occupants (younger siblings including infants, as well as older siblings, parents, and grandparents) get infected. Differences in country demographics, household size and social structuring will affect the importance of this transmission chain.[13] If this type of transmission dynamics are indeed prominent, however, one could expect to see a shift in the age of RSV cases over the course of an epidemic, with toddlers, pre-schoolers, and children in middle childhood as the predominantly infected group at the start of the epidemic, and younger (infants) and older individuals (older children, adolescents, adults, seniors) progressively more represented as time passes. In terms of preparedness, this would imply that the peak of RSV cases requiring hospitalizations would not be synchronized, but rather delayed, relative to the overall epidemic peak (i.e. the peak of all RSV cases, both mild and severe), since infants and the elderly would comprise a higher proportion of RSV infections in the later phases of epidemics.

Given the public health relevance of the above (also in the light of the newly approved RSV vaccines for adults 60 years or older and pregnant women), we set out to study whether the age distribution of RSV cases varies over time in the course of annual epidemics by using pre-COVID-19 respiratory virus surveillance data gathered for the Global Epidemiology of RSV in Hospitalized and Community care (GERi) study.

Materials and Methods

The GERi study

The GERi study database assembled RSV surveillance data from 16 countries.[14] Collected data includes information on the weekly number of respiratory specimens collected within the respiratory viruses surveillance system, the number of those testing positive for RSV, the age of every case, and the level of care from which cases were reported, either “primary” care (outpatients mostly seen by general practitioners or pediatricians) or “secondary” care (subjects seen at hospitals, emergency departments, intensive care units, or more specialized healthcare settings). Information was also collected regarding the case definitions, laboratory procedures and methods, and representativeness of the data (Supplementary Table 1; more information is available in previous publications[14,15]).

In this study, we included the countries participating in the GERi study for which there were ≥50 reported RSV cases per season for at least five consecutive seasons (for large countries with geographically stratified data, these requirements applied to each region/surveillance site), in order to ensure greater robustness of the results. Data included in our analysis were from the Netherlands, the city of Lyon in France (which associated to the GERi study later and was therefore not included in the previous publications[16]; for brevity, we will refer to it as “France” henceforth), Portugal, Singapore, Ecuador, South Africa, and New Zealand. The age distribution of RSV cases was provided by individual years of age for the Netherlands, France, Ecuador, South Africa, and New Zealand, and by age group for Portugal (0–4, 5–14, 15–44, 45–64, and ≥65 years) and Singapore (< 1, 1–2, 3–4, 5–17, 18–39, 40–64, and ≥65 years).

Statistical analysis

The age distribution of RSV cases was depicted by meanAge profile of Respiratory Syncytial Virus disease over the course of annual epidemics: a multi-national study of histograms. Smoothed time series of RSV cases (using a 3-week moving average) were used to show the seasonality of epidemics in each country.

Our starting hypothesis was that children attending pre-schools, kindergartens, and early primary school would make a larger proportion of RSV cases in the early phases of annual epidemics, while younger and older individuals would be progressively more represented later in the season. For comparability purposes, we considered it important to apply the same age cut-offs to all countries (although the age at which children start spending a substantial part of their time outside of the family setting may differ across countries), and this implied that the choice of the age cut-offs was partly driven by data availability. In detail, the age cut-offs were set at 1 and 5 years of age, and the analyses were conducted to investigate whether the likelihood of a RSV case being < 1 year or ≥5 years of age (with subjects aged 1 to < 5 years taken as the referent) increased over time in the course of the epidemic season. The lower cut-off was set to 1 year because (a) around half to nearly two thirds of all RSV cases were < 1 year of age in four of the seven countries in this study (see Results), and (b) < 1 year was the lowest age group for Singapore. The upper cut-off was set to 5 years so that we could use the same cut-off for all countries, including those (Portugal and Singapore) which reported RSV cases’ age in pre-defined categories. In order to check the robustness of our findings against the choice of the age cut-off, we replicated the analyses (for the countries for which the exact age was available) by moving the lower cut-off to 6 months of age.

The analyses were conducted separately in each of the countries included in our study. First, for each season, we divided the RSV epidemic into four periods (called “epidemic quarters” henceforth) corresponding to the weeks in which the first, second, third, and fourth quartile of all cases in the season were reported. Given the well-known relationship between a country’s latitude and the timing of RSV circulation,[15] a “season” was defined as the period from July to next-year June in the Northern hemisphere, and as the calendar year (January to December) in the tropics and the Southern hemisphere.

We fitted multilevel multinomial logistic regression models with season as higher-level variable to investigate whether the likelihood of RSV cases being aged < 1 or ≥5 years (vs. 1 to < 5 years, taken as referent) differed in the second, third and fourth epidemic quarter compared to the first epidemic quarter. In multinomial logistic regression, the regression coefficients are expressed as relative risk ratios (RRR, with corresponding 95% confidence intervals [CI]), whose interpretation is illustrated by the following hypothetical example: an RRR of 1.75 in the second epidemic quarter for the ≥5 years age group means that the relative risk of being ≥5 years (instead of 1 to < 5 years) is 75% higher in the second than in the first epidemic quarter. For Portugal, the lowest age group was < 5 years, which made it impossible to use three age categories as for the other countries. Hence, we fitted multilevel logistic regression models to estimate the odds ratio (OR, and corresponding 95% CI) of being aged ≥5 vs. < 5 years (referent group) in the second, third, and fourth epidemic quarters compared to the first epidemic quarter. The weekly overall positivity rate for RSV (defined as the percentage of all specimens tested positive for RSV) was entered as covariate into all models. The addition of random slopes to the models did not improve their fit, thus the results reported are from models with random intercepts only. Analyses stratified by care setting (primary vs. secondary care) were conducted for countries where RSV cases were reported from both settings.

All analyses were conducted using Stata software version 17.0 (StataCorp LLC, College Station, TX). All statistical tests were two-sided and significance was taken as p-value < 0.05.

Results

The study database included 27,391 RSV cases (Table 1). The median number of cases per season ranged from 75 for the

Table 1
Number of reported RSV cases by season (and overall) in the countries included in the analysis.

Season[a]	Country (N reported RSV cases)						
	Netherlands	France (Lyon)	Portugal	Singapore	Ecuador	South Africa	New Zealand
2008	44						
2009	100					518	
2010	80					650	
2011	53	784	28	61		719	
2012	60	868	93	73	769	905	439
2013	72	762	300	76	706	534	618
2014	73	359	411	102	482	279	694
2015	110	708	640	75	474	552	703
2016	122	716	682	117	525	727	505
2017	75	777	1084	109	248	848	616
2018	98	1059	1661	103	157	914	421
2019		853					
Total	**887**	**6886**	**4899**	**716**	**3361**	**6646**	**3996**

[a] A season corresponds to the calendar year in Singapore, Ecuador, South Africa, and New Zealand, and to the period between July and June of the following year (e.g. from July 2011 to June 2012 for the season labeled as 2011) in the Netherlands, France, and Portugal, which are in the Northern hemisphere.

Netherlands to 777 for France, and the number of seasons ranged from seven for Ecuador and New Zealand to 11 for the Netherlands. All reported cases were from the primary care setting in the Netherlands and Singapore; in the other countries, the totality (France and Ecuador) or the large majority (97.9% in Portugal, 91.1% in South Africa, and 84.5% in New Zealand) of cases were from the secondary care setting. The temporal distribution of reported RSV cases by country is depicted in Supplementary Fig. 1. Annual epidemics mostly occurred in late fall and winter months in the Netherlands, France, Portugal, and New Zealand, with very limited viral circulation in spring and summer. In Ecuador, there was one clear peak each year, which took place in different months of the year. In South Africa, the peaks were mostly seen in March to May (southern hemisphere autumn) but the duration of epidemics was generally longer than in Northern hemisphere countries and RSV cases were reported throughout the year. In Singapore, there was year-round circulation.

The country-specific age distribution of RSV cases is in Supplementary Fig. 2. In the Netherlands, RSV cases were predominantly young children (15.9% were < 1 year, and 41.9% aged 1 to < 5 years). In France, Ecuador, South Africa, and New Zealand, a large proportion of RSV cases were aged < 1 year (63.1%, 64.8%, 66.5%, and 49.8% years, respectively), while those aged ≥5 years constituted 21.9%, 3.9%, 12.7%, and 25.3% of all cases, respectively. The median age and interquartile range (IQR) were 0.4 years (0.1–3.0) for France, 0.6 years (0.2–1.0) for Ecuador, 0.5 year (0.2–1.5) for South Africa, and 1.0 year (0.2–5.2) for New Zealand. In Portugal, the median age was in the 0–4 years group (which accounted for 61.5% of all reported cases), and around 20% of cases were aged ≥65 years. In Singapore, 16.5% of cases were < 1 year and 30.0% were ≥5 years of age; the median age was in the 1–2 years group, and the elderly (≥65 years) comprised 3.6% of the cases. The median duration of each epidemic quarter, and the total number of RSV cases (by age group) occurred in each epidemic quarter, were reported for each country in Supplementary Table 2.

In all the countries, the likelihood of RSV cases aged < 1 or ≥5 years (vs. 1 to < 5 years) to make a large proportion of total cases tended to increase over time within a season (Table 2). In the Netherlands and France, this tendency was already evident in the second epidemic quarter for RSV cases ≥5 years of age, and not before the third or fourth quarter for infants (< 1 year). In South Africa and New Zealand, the shift of RSV cases towards younger or older than those aged 1 to < 5 years (in percent over the totality of cases) appeared in the second epidemic quarter and was maintained until the end of the RSV epidemic. The same held for Portugal, limited to the ≥5 year age category. In Ecuador, RSV-positive infants were more likely to be found in the second to fourth epidemic quarter than at the beginning of the epidemic, while the shift towards those aged ≥5 years was evident only in the fourth quarter (RRR 1.75, 95% CI 1.07–2.86). In Singapore, the percentwise change in the age distribution of RSV cases within a season was least evident: only in the last epidemic quarter was there a significant shift towards infants (RRR 2.32, 95% CI 1.29–4.15), while no shift towards cases ≥5 years of age was observed at any point.

When stratifying by the type of care setting, there were no differences in the direction of the RRRs, and mostly only moderate differences in their magnitude, when comparing the results of the analyses stratified by type of care setting (Table 3). Moving the lower cut-off to 6 months of age altered the magnitude of the RRRs only marginally and did not affect their overall interpretation (Table 4).

Discussion

We found that the age of RSV cases detected within surveillance systems shift over time (in % over the total of cases) within the course of the annual RSV epidemics. More specifically, young children tend to make up a larger proportion of total detections at the beginning of the season, while infants and older individuals are progressively more represented over time during the season. This trend was observed consistently across countries and in data originating from different settings, and were robust to changes in model specifications and consistent in analyses stratified by care setting. Differences seem to exist according to the country latitude: for example among infants, the rise in the RRR was already evident in the 2nd epidemic quarter in the two Southern hemisphere countries (New Zealand and South Africa) as well as Ecuador, but only in the 3rd or 4th quarter in Singapore and in the Northern hemisphere (Netherlands and France). Of note, the trend towards a large proportion of RSV cases being < 1 year of age in the later phases of annual epidemics emerged also in the two tropical countries included in the analyses, while the results were less clear-cut for individuals aged ≥5 years. This may seem surprising, considering that respiratory viruses often circulate year-round, with limited or no seasonality, in tropical countries, but previous findings from the same database showed that Singapore and Ecuador do indeed show some seasonality in the circulation of RSV.[15] The pattern we observed in the age distribution of RSV cases over time during a calendar year might also be due to factors unrelated to climate (e.g. the timing of school terms, holidays, and school closures; these factors may have a role also in non-tropical countries), although data on this issue from the pre-COVID-19 period were not always consistent.[17,18] Further analyses are needed to establish whether this pattern can be observed in other tropical countries beyond those included in the present analysis.

Table 2

Relative risk ratio (RRR) and 95% confidence intervals (CI) for the risk of an RSV case to be aged < 1.0 year or ≥5.0 years (instead of 1.0–4.9 years, referent group) in the 2nd, 3rd, and 4th epidemic quarter compared to the 1st epidemic quarter (see text for details). Multilevel multinomial logistic regression models adjusted by the weekly RSV positivity rate, with season as higher-level variable.

Country	RSV epidemic quarter (referent: 1st quarter)	< 1.0 year vs. 1.0-4.9 years (referent)			≥5.0 years vs. 1.0-4.9 years (referent)		
		RRR	95% CI	p-value	RRR	95% CI	p-value
Netherlands	2nd	1.08	(0.61–1.90)	0.793	1.45	(0.95–2.21)	0.084
	3rd	1.64	(0.92–2.94)	0.095	2.94	(1.89–4.56)	***< 0.001***
	4th	2.56	(1.22–4.18)	***0.010***	3.72	(2.29–6.02)	***< 0.001***
France (Lyon)	2nd	1.04	(0.85–1.29)	0.678	2.51	(1.86–3.37)	***< 0.001***
	3rd	1.64	(1.34–2.01)	***< 0.001***	6.15	(4.70–8.06)	***< 0.001***
	4th	1.35	(1.10–1.65)	***0.004***	6.70	(5.11–8.77)	***< 0.001***
Portugal[a]	2nd	-			2.17	(1.79–2.64)	***< 0.001***
	3rd				2.61	(2.12–2.21)	***< 0.001***
	4th				2.79	(2.31–3.37)	***< 0.001***
Singapore	2nd	1.05	(0.56–1.95)	0.887	0.85	(0.52–1.39)	0.508
	3rd	1.20	(0.64–2.25)	0.562	1.09	(0.67–1.78)	0.736
	4th	2.32	(1.29–4.15)	***0.005***	1.45	(0.89–2.36)	0.134
Ecuador	2nd	1.78	(1.44–2.21)	***< 0.001***	1.01	(0.57–1.79)	0.974
	3rd	2.07	(1.67–2.56)	***< 0.001***	1.45	(0.85–2.45)	0.172
	4th	1.52	(1.23–1.87)	***< 0.001***	1.75	(1.07–2.86)	***0.027***
South Africa	2nd	1.48	(1.23–1.79)	***< 0.001***	1.38	(1.04–1.82)	***0.026***
	3rd	1.86	(1.56–2.21)	***< 0.001***	1.88	(1.47–2.40)	***< 0.001***
	4th	2.32	(1.93–2.80)	***< 0.001***	1.75	(1.35–2.27)	***< 0.001***
New Zealand	2nd	1.43	(1.14–1.80)	***0.002***	1.92	(1.45–2.54)	***< 0.001***
	3rd	1.44	(1.15–1.80)	***0.001***	2.50	(1.92–3.25)	***< 0.001***
	4th	2.15	(1.70–2.72)	***< 0.001***	2.29	(1.74–3.01)	***< 0.001***

Bold-italics was used for p-value < 0.05.

[a] Due to limited data availability (see text for details), RRRs and corresponding 95% CI in Portugal could only be calculated for the comparison of RSV cases aged ≥5 vs. < 5 years.

Our results may have important implications for healthcare systems. First, our findings provide indirect support to the notion that a frequent chain of transmission of RSV is from young children (those attending pre-school, kindergartens, and early primary school) to infants as well as susceptible adults and elderly individuals. This may constitute a key piece of background information when planning and implementing measures aimed at containing the virus and other targeted age-specific prevention and control interventions. In particular, our data (if confirmed) suggest that immunization of infants and toddlers (with RSV antibody, or by administering the RSV vaccine to pregnant women) may be largely ineffective to indirectly protect the elderly, since these may often become infected from older (i.e. school-going) children. Therefore, active immunization with the vaccine is likely to represent the only way to protect older adults, and is recommended especially to those at increased risk of severe illness from RSV infection. Second, infants and the elderly have the highest risk of severe illness, complicated clinical course, hospitalization, and RSV-associated death.[5] Since these age groups tend to be increasingly more represented over time during epidemics, our findings suggest that the hospital burden may progressively worsen as the annual epidemic unfolds. Furthermore, our findings support the recommendation of conducting age-stratified surveillance of RSV.[19] In particular, the circulation among children below 2 years old may not be a good proximate for RSV circulation among the elderly, which should be kept in mind when conducting excess mortality and burden analyses.

To our knowledge, this is the first epidemiological report that brings to light a shift in the age distribution of cases in the within-season time course of RSV epidemics. Indirect confirmation of our findings can be found by inspecting age-stratified RSV time series in

Table 3

Results stratified by the type of care setting (primary vs. secondary) in Portugal, South Africa, and New Zealand (in the other countries included in the analyses, all data were from the same care setting).

Country	Level of care (% of RSV cases)	RSV epidemic quarter (referent: 1st quarter)	< 1.0 year vs. 1.0-4.9 years (referent)			≥5.0 years vs. 1.0-4.9 years (referent)		
			RRR	95% CI	p-value	RRR	95% CI	p-value
Portugal[a]	Primary (2.1%)	2nd	-			2.14	(0.18–25.88)	0.549
		3rd				2.20	(0.19–26.02)	0.530
		4th				-	-	-
	Secondary (97.9%)	2nd				2.12	(1.74–2.59)	***< 0.001***
		3rd				2.60	(2.10–3.22)	***< 0.001***
		4th				2.86	(2.35–3.47)	***< 0.001***
South Africa	Primary (8.9%)	2nd	1.40	(0.76–2.56)	0.279	1.26	(0.73–2.21)	0.408
		3rd	1.89	(1.02–3.50)	***0.042***	1.66	(0.94–2.93)	0.083
		4th	2.65	(1.46–4.82)	***0.001***	2.28	(1.30–3.98)	***0.004***
	Secondary (91.1%)	2nd	1.52	(1.24–1.85)	***< 0.001***	1.31	(0.95–1.81)	0.097
		3rd	1.60	(1.33–1.92)	***< 0.001***	2.00	(1.52–2.63)	***< 0.001***
		4th	2.13	(1.73–2.61)	***< 0.001***	1.90	(1.41–2.57)	***< 0.001***
New Zealand	Primary (15.5%)	2nd	1.95	(0.72–5.25)	0.188	1.21	(0.74–1.98)	0.447
		3rd	1.39	(0.49–3.96)	0.537	1.65	(1.02–2.69)	***0.043***
		4th	2.43	(0.82–7.21)	***0.109***	2.31	(1.35–3.97)	***0.002***
	Secondary (84.5%)	2nd	1.52	(1.17–1.97)	***0.002***	1.74	(1.23–2.48)	***0.002***
		3rd	1.50	(1.19–1.90)	***0.001***	2.32	(1.71–3.16)	***< 0.001***
		4th	2.21	(1.72–2.84)	***< 0.001***	2.04	(1.48–2.81)	***< 0.001***

Bold-italics was used for p-value < 0.05.

[a] Due to limited data availability (see text for details), RRRs and corresponding 95% CI in Portugal could only be calculated for the comparison of RSV cases aged ≥5 vs. < 5 years. The model did not converge in the 4th epidemic quarter because of the limited number of RSV cases coming from primary care surveillance.

Table 4
Relative risk ratio (RRR) and 95% confidence intervals (CI) for the risk of an RSV case to be aged < 0.5 year or ≥5.0 years (instead of 0.5–4.9 years, referent group) in the 2nd, 3rd, and 4th epidemic quarter compared to the 1st epidemic quarter (see text for details). Multilevel multinomial logistic regression models adjusted by the weekly RSV positivity rate, with season as higher-level variable. Only the countries for which the exact age of RSV cases was available were included.

Country	RSV epidemic quarter (referent: 1st quarter)	< 0.5 year vs. 0.5-4.9 years (referent)			≥5.0 years vs. 0.5-4.9 years (referent)		
		RRR	95% CI	p-value	RRR	95% CI	p-value
Netherlands	2nd	0.44	(0.16–1.21)	0.113	1.35	(0.90–2.01)	0.145
	3rd	1.29	(0.56–2.99)	0.551	2.60	(1.73–3.92)	***< 0.001***
	4th	2.40	(1.07–5.39)	***0.034***	3.05	(1.98–4.70)	***< 0.001***
France (Lyon)	2nd	1.14	(0.96–1.36)	0.137	2.64	(2.01–3.46)	***< 0.001***
	3rd	1.63	(1.38–1.92)	***< 0.001***	5.76	(4.52–7.34)	***< 0.001***
	4th	1.30	(1.09–1.55)	***0.004***	6.34	(4.95–8.11)	***< 0.001***
Ecuador	2nd	1.68	(1.36–2.07)	***< 0.001***	0.85	(0.48–1.49)	0.574
	3rd	2.23	(1.82–2.74)	***< 0.001***	1.24	(0.74–2.08)	0.409
	4th	1.75	(1.42–2.16)	***< 0.001***	1.66	(1.03–2.70)	***0.039***
South Africa	2nd	1.44	(1.22–1.70)	***< 0.001***	1.25	(0.97–1.62)	0.089
	3rd	1.83	(1.57–2.13)	***< 0.001***	1.65	(1.31–2.06)	***< 0.001***
	4th	2.00	(1.70–2.35)	***< 0.001***	1.35	(1.06–1.71)	***0.013***
New Zealand	2nd	1.25	(1.00–1.55)	***0.050***	1.68	(1.30–2.17)	***< 0.001***
	3rd	1.25	(1.01–1.55)	***0.044***	2.19	(1.72–2.77)	***< 0.001***
	4th	1.62	(1.30–2.01)	***< 0.001***	1.72	(1.35–2.20)	***< 0.001***

Bold-italics was used for p-value < 0.05.

previous publications[20] or other information sources,[21] but a formal analysis, such as the one presented here, has to our knowledge not been conducted to date. A major strength of our study is the consistency of our findings across countries, and their robustness against variations in models specifications and consistency in analyses stratified by level of care. In particular, the countries included in the present analysis differ in terms of several aspects that affect viral circulation and transmission across age groups (e.g. climate, demographics, social structure, typical household size, and organization of the educational system) as well as the type and structure of surveillance system for respiratory infections.[22–24]

An important limitation of our study is the non-availability of age-specific denominators (specimens tested for RSV), hence an analysis based on age-specific RSV positivity rate was not possible. Studies specifically designed to track the transmission dynamics of RSV in a cohort setting would answer our research question in a more accurate manner. The surveillance system for RSV differs across countries, and for some of these (e.g. Singapore), only specimens testing negative for influenza are tested for RSV and other pathogens.[25] A further limitation of our analysis is that whilst the consistency of the results across different settings suggest that the observed phenomenon is real, the lack of case-level information beyond age precludes a more in-depth analysis of the role of other potential determinants (e.g. individual susceptibility and contact rates with people of different age). Testing behaviors, age group-specific testing rates, and health-seeking behaviours may also differ by country. Another limitation is that a finer categorization of RSV patients' age, with a focus on adults and the elderly, was mostly not possible due to only a small percentage of cases being > 20 years of age or to the unavailability of the information on age in a suitable format. Our data extends to as late as 2018–2019, and there is no assurance that the pattern we observed is still present after the emergence of the COVID-19 pandemic and the subsequent widespread adoption of non-pharmaceutical interventions. Finally, as explained in the Materials and Methods, the choice of the age cut-offs was largely data-driven. This is not optimal, also considering that age eligibility to pre-school and school will vary across countries. Setting the upper cut-off at 5 years seemed a reasonably good choice, as it is often in the middle of the age range of children attending pre-schools, kindergartens, and early primary school. On the other hand, the lower cut-off of 1 year of age may not be ideal, as children in some countries may start spending time outside of the family (e.g. in day care centers) earlier,[26] but reassuringly, our findings were robust when the lower cut-off was moved to 6 months of age.

In conclusion, we found that the age distribution of RSV cases detected by respiratory virus surveillance system shifts over time in the course of annual epidemics, so that individuals at greatest risk of severe disease constitute a progressively larger proportion of cases as the epidemic unfolds and progresses towards its peak and then dies out. These findings may have multiple public health implications, and could provide inputs to modeling and economic studies comparing the effectiveness and benefits of alternative age-targeted prevention and containment measures.

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Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106154.

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