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SUPPLEMENT ARTICLE

Impact of Subgroup Distribution on Seasonality of Human Respiratory Syncytial Virus: A Global Systematic Analysis

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Background. Previous studies reported inconsistent findings regarding the association between respiratory syncytial virus (RSV) subgroup distribution and timing of RSV season. We aimed to further understand the association by conducting a global-level systematic analysis.

Methods. We compiled published data on RSV seasonality through a systematic literature review, and unpublished data shared by international collaborators. Using annual cumulative proportion (ACP) of RSV-positive cases, we defined RSV season onset and offset as ACP reaching 10% and 90%, respectively. Linear regression models accounting for meteorological factors were constructed to analyze the association of proportion of RSV-A with the corresponding RSV season onset and offset.

Results. We included 36 study sites from 20 countries, providing data for 179 study-years in 1995–2019. Globally, RSV subgroup distribution was not significantly associated with RSV season onset or offset globally, except for RSV season offset in the tropics in 1 model, possibly by chance. Models that included RSV subgroup distribution and meteorological factors explained only 2%–4% of the variations in timing of RSV season.

Conclusions. Year-on-year variations in RSV season onset and offset are not well explained by RSV subgroup distribution or meteorological factors. Factors including population susceptibility, mobility, and viral interference should be examined in future studies.

Keywords. meteorological factors; respiratory syncytial virus; seasonality; subgroup.

Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory infections among young children and older people, resulting in considerable burden on health care systems [1–3]. There are no vaccines or antivirals for RSV infection; only monoclonal antibodies can be used for passive immunization [4, 5]. Palivizumab has been available for over 2 decades but its use is limited to infants at extremely high risk of severe RSV infection and almost exclusively in high-income countries [6]. Nirsevimab has recently been approved by the European Medicines Agency for wide use in all infants [7]. As various RSV prophylactic products available and currently in clinical development may have relatively short time windows for protection (ie, up to 6 months), the implementation of RSV immunization requires a clear understanding of RSV seasonality for optimal effectiveness [4, 5, 7, 8].

A systematic analysis of global RSV seasonality showed that RSV has clear seasonal epidemics in both temperate and tropical regions; RSV season usually starts in late-summer months in the tropics of each hemisphere and starts in late autumn or early winter in most temperate regions [9]. Although RSV seasonality is found to be highly correlated with geographic location (eg, latitude and longitude) [9] as well as meteorological factors (eg, temperature, humidity, and rainfall) [10–12], variations in local year-on-year RSV seasonality remain largely unexplained. A study in Beijing, China reported that the dominant RSV subgroup (ie, subgroup A or B) might explain the year-on-year variations in RSV season onset and duration; RSV seasons occurred 3–5 weeks earlier and lasted 6 weeks longer in RSV subgroup A-dominant years than in subgroup B-dominant years [13]. If generalizable, this would have important implications for RSV prevention and surveillance—knowing the predominant RSV subgroup could help explain the year-on-year changes in RSV seasonality. To that end, surveillance systems around the world would need to monitor and report RSV subgroup data, which is not a routine practice in most regions at present. In addition, it is relevant to the implementation of RSV prophylactic products that might

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have varied efficacy by RSV subgroup [14]. However, despite using the same methodology, a subsequent study reporting data from 4 temperate countries did not observe any associations between the predominant RSV subgroup and RSV seasonality [15]; the research group also noted that subgroup dominance was rare in most RSV seasons [16]. The inconsistent findings above led to a series of questions such as whether the reported association between predominant RSV subgroup and RSV seasonality in Beijing was a chance finding, whether the reported association only exists for certain geographic locations, and whether any meteorological factors (not being accounted for in either of the 2 studies) could help explain the year-on-year variations. Moreover, it is not yet known whether the association holds for the tropics and subtropics where RSV seasonality was clear.

Here, using a compiled RSV seasonality dataset covering 36 sites from 20 countries, we aimed to systematically analyze the impact of subgroup predominance on RSV seasonal characteristics, including RSV season onset, offset, and duration, while accounting for meteorological factors.

METHODS

Systematic Literature Review

A systematic literature review (PROSPERO, CRD42022313722) was conducted using electronic databases of MEDLINE, EMBASE, and Web of Science (search strategy in Supplementary Material) to identify studies with eligible data on RSV seasonality and subgroup distribution (detailed inclusion criteria in Supplementary Material), without language restrictions. This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (checklist in Supplementary Material). For included studies, we used a tailored extraction sheet to collect information related to study characteristics (location, period, subject age, case definition and source, clinical specimen, testing and subgrouping methods, subgroup information, sample size) and RSV activity (monthly or weekly number of RSV-positive cases). Two authors (S. D. and L. G.) independently performed the literature search, screening, and extraction. Disagreements were resolved through discussion or arbitrated by Y. L.

Unpublished RSV Data

In addition to the published literature, we collected unpublished weekly RSV activity data from datasets shared by collaborative research groups who published RSV epidemiology studies [9, 12, 17–19] and the Global Epidemiology of RSV in Community and Hospitalized Care (GERi) project [16]. Where available, the RSV activity data were also collected by the 3 predefined age groups: < 18 years, 18–64 years, and 65 years or older. All received data were cross-checked by S. D. and Y. L. for completeness and consistency before being included in the analysis.

External RSV Subgroup Data From GISAID

For those national studies that did not provide RSV subgroup information, we extracted RSV subgroup data from the GISAID EpiRSV database [20] and aggregated the number of each RSV subgroup by season and country. We excluded data from EpiRSV in sensitivity analysis given that they might not be fully representative.

Meteorological Data

For each study site, we extracted the coordinates of site's centroid from Google Maps and identified the nearest weather station with available meteorological data. The median of distances between sites and weather stations was 15.0 (interquartile range [IQR], 8.5–26.0) kilometers. We then extracted the daily average meteorological data from the Global Surface Summary of the Day dataset provided by the US National Centers for Environmental Information, via the R package "GSODR".

Quality Assessment

Two authors (S. D. and L. G.) assessed the quality of included studies using a brief rating scale which incorporated 3 questions regarding representativeness of subjects, stability of testing methods and practice, and timeliness of positive case reports (detailed in Supplementary Tables 1 and 2) [9]. Each question was rated on a scale of 1–3 points for the included studies, indicating quality from poor to good.

Data Analysis

Defining RSV Season

As in our previously published analysis on RSV seasonality [21], RSV season was defined by calculating the annual cumulative proportion (ACP) of RSV-positive cases (determined by any diagnostic tests except serology alone) retrospectively for each season per study site. In brief, the onset of RSV season was defined as the month/week when the ACP reached 10% (ie, the time when 10% of the annual RSV cases have occurred); the offset of RSV season was defined as when the ACP reached 90%; the duration of RSV season was defined as the time difference between onset and offset, capturing 80% of the annual RSV cases. For defining RSV season onset and offset, our calculation allowed noninteger estimates by applying linear interpolation of ACP (eg, the onset of RSV season could be week 4.5 or month 1.2). We conducted sensitivity analyses that used different ACP cutoffs for onset and offset.

Defining Year-on-Year Variation

Our primary outcomes of interest, determined a priori, were the year-on-year variations in RSV season onset, offset, and duration for each study site. To ensure that the year-on-year variations from different study sites were comparable, we first obtained the median RSV season onset, offset, and duration

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as the reference for each site and then calculated the differences in RSV season onset, offset, and duration between each of the study-years and the reference. As a result, the year-on-year variations in onset, offset, and duration for each site can be interpreted as the variation compared with the median value from that site, with positive values indicating later-than-usual onset or offset, or longer-than-usual duration.

A similar median-based approach was used for year-on-year variations in meteorological factors. For each study site, we estimated how different meteorological factors varied across different study-years for the same days of the year; here, the same days under comparison are defined as the past 1 to 3 days before site's median RSV season onset or the past 1 to 3 days before site's median RSV season offset. In this way, we would be able to assess the role of varying meteorological factors in the variations in RSV seasonal characteristics (eg, whether colder-than-usual weather was associated with an earlier-than-usual or later-than-usual RSV season onset).

Main Analysis

As our analysis focused on determinants of year-on-year variations, only studies contributing 5 or more seasons were included in the main analysis (we lifted this restriction in 1 of the sensitivity analyses). As large variations in RSV seasonality and its determinants across latitudes were anticipated, we classified study sites into tropical region (defined as latitude between −23.5 and 23.5 degrees), subtropical region (latitude between 23.5 and 35 degrees or between −35 and −23.5 degrees), and temperate region (latitude above 35 degrees or below −35 degrees), based on site's centroid, and conducted analyses for each of the regions separately.

We modelled the year-on-year variations in RSV season onset or offset as outcomes (we did not model RSV duration, as it was determined by onset and offset) using linear regression models with clustered standard errors to account for the potential clustering of individual site estimates. Our main factor of interest, RSV subgroup predominance, was included as a continuous independent variable, quantifying the proportion of RSV-A subgroup among cases with subgroup information in each season per site. To test whether meteorological factors play a role in year-on-year variations in RSV season, we considered bivariable models with RSV-A proportion and 1 of 4 meteorological factors (temperature, relative humidity, dew point, and wind speed) as covariates. We also conducted trivariable models (which included 2 of the 4 meteorological factors, in addition to the RSV subgroup predominance, as covariates) for checking the robustness of our main (bivariable) models.

Secondary Analysis

For study-years that provided at least 25 cases for each RSV subgroup, we determined the RSV season onset, offset, and duration separately by RSV subgroup. We then calculated the differences in RSV season onset, offset, and duration between RSV-A and RSV-B for each study-year. This approach automatically accounted for meteorological factors among other time-varying confounders.

As exploratory analysis, we repeated the same approach as above stratified by age groups (<18, 18–64, and >64 years) to understand whether there are any asynchronous circulating patterns of RSV among age groups within each study-year (the age group of <18 years was regarded as the reference for comparisons among different age groups).

Sensitivity Analysis

Multiple sensitivity analyses were performed by changing 1 condition in the main analysis each time (the complete list can be found in Supplementary Material). Moreover, for individual studies that quantitatively assessed the association between RSV seasonal characteristics and subgroup distribution, we reanalyzed the study data using our own definition and methodology and compared the results. Data were analyzed and visualized with the R software (version 4.1.2).

RESULTS

After removing duplicates, a total of 4034 records were screened, of which 32 met the inclusion criteria (Figure 1). After adding 4 records from the unpublished datasets shared by collaborators, the analysis included a total of 36 studies from 36 sites in 20 countries, providing data for 179 study-years in 1995–2019 (Figure 2). Among them, 16 sites contributed 5 or more seasons: 3 were from tropical regions, 4 from subtropical regions, and 9 from temperate regions. A total of 30 sites reported data on RSV subgroup; for the other 6 sites without RSV subgroup data, we obtained RSV subgroup data externally from the GISAID EpiRSV database. Detailed RSV seasonal characteristics and subgroup distribution for each season in each site are presented in Supplementary Figure 1.

Subgroup Distribution and Seasonality

Year-on-year variations in RSV season onset, offset, and duration were generally comparable among tropical, subtropical, and temperate regions (Figure 3*A*); variations in RSV season onset, offset, and duration were within 2 weeks of the site's median level for over half of the study-years (51%–71%, 60%–71%, and 57%–64% of the study-years, respectively). Results from Pearson correlation analysis showed that the proportion of RSV-A subgroup was not significantly correlated with year-on-year variations in RSV season onset, offset, or duration for any regions, either in sites that contributed 5 or more seasons or in all sites (Figure 3*B*–3*D*).

Overall, our main bivariable models that accounted for RSV-A proportion and 1 of the meteorological factors could

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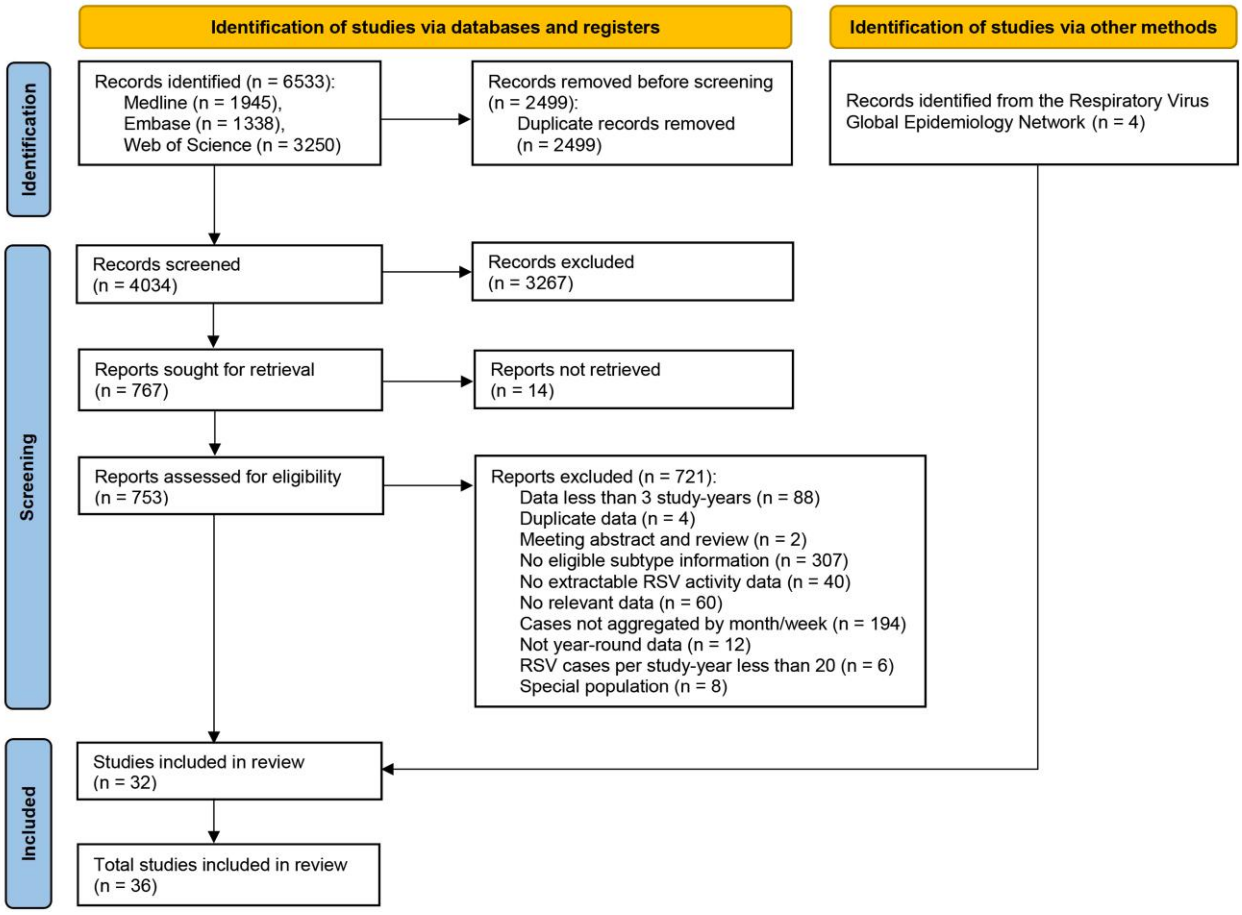

Figure 1. PRISMA 2020 flow diagram of study inclusion. Abbreviation: RSV, respiratory syncytial virus.

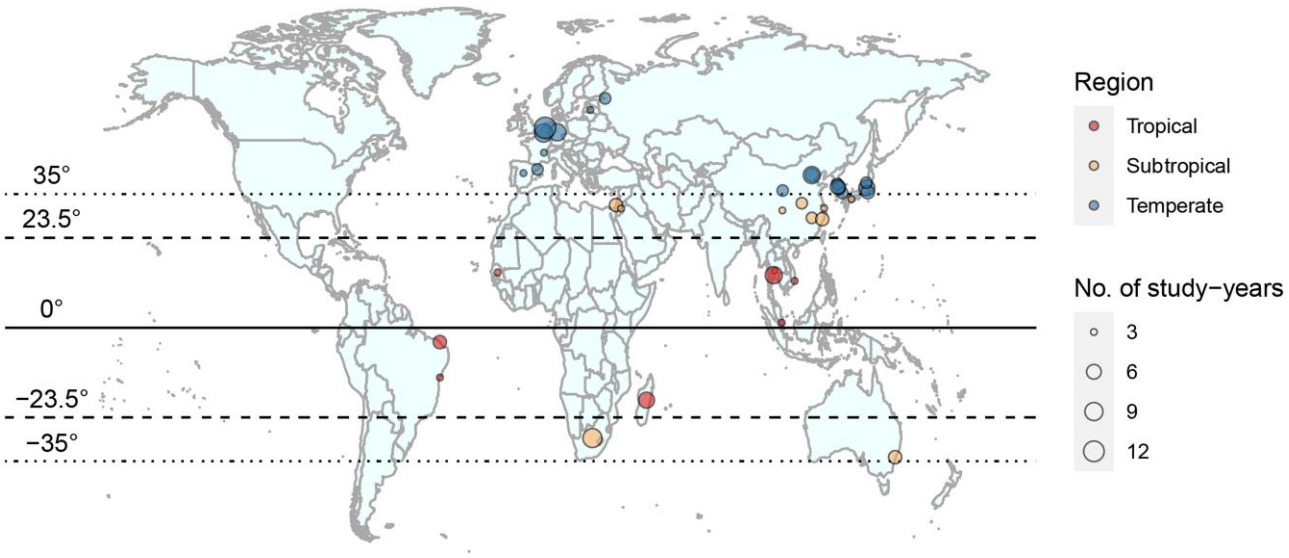

Figure 2. World map showing study sites included.

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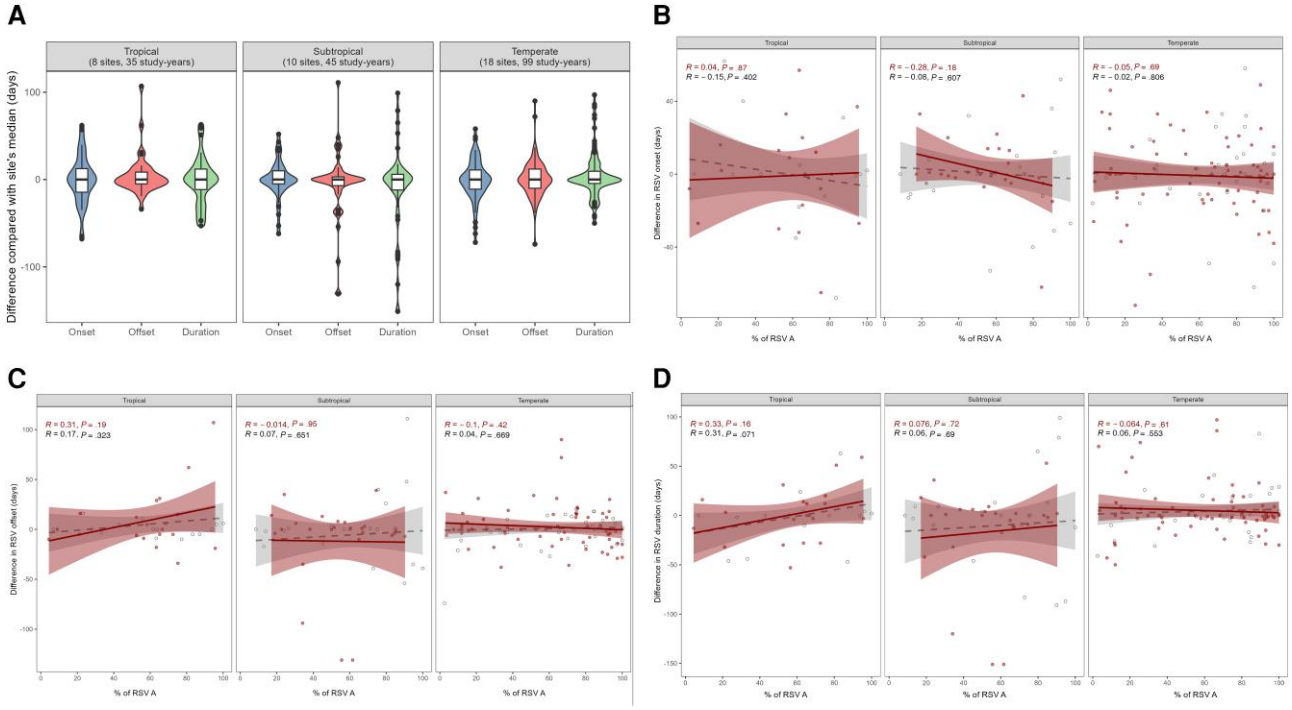

Figure 3. RSV-A proportion and year-on-year variations of RSV seasonality. *A*, Year-on-year variations in RSV season onset, offset, and duration. The box inside the violin plot indicates the IQR of the differences, the horizontal line denotes the median, the whiskers are 1.5 times the IQR, and the dots outside the whiskers show the outliers. The median of differences was zero, as the annual RSV seasonal characteristics of each site were compared with the site's median. *B–D*, RSV-A proportion and year-on-year variations of RSV season onset, offset, and duration. Circles indicate all study sites included, with solid circles indicating sites contributing 5 or more seasons and hollow circles indicating sites contributing 3 or 4 seasons. Lines denote fitted regression lines, with solid lines corresponding to data from sites contributing 5 or more seasons and dashed lines corresponding to data from all sites. Shaded areas represent 95% confidence intervals. Correlation coefficients and significance levels are shown in the upper left corner (the first row corresponds to the solid line). Abbreviation: RSV, respiratory syncytial virus; IQR, interquartile range.

explain a median of 2% (IQR, 1%–9%) of the variations in RSV season onset and offset. RSV-A proportion was not significantly associated with RSV season onset or offset globally; the only exception was for RSV season offset in the tropics in 1 model, with a 4-day delay in offset per 10% increase in RSV-A proportion (Figure 4). Consistent results were observed in trivariable analyses (Supplementary Figure 2), which explained a median of 4% (IQR, 2%–17%) of the variations in RSV season onset and offset.

When the RSV-A and RSV-B seasons were defined separately for each site per study-year, no significant differences were found in the onset, offset, and duration of the 2 RSV-subgroup–specific seasons (Supplementary Figure 3). The results were consistent when the characteristics of RSV seasonality in different age groups were compared (Supplementary Figure 4).

The results of sensitivity analyses were generally consistent with those from the main analysis (Supplementary Figures 5–12). Using our definition and methodology, we reanalyzed studies that reported the association between subgroup distribution with RSV seasonal characteristics, which yielded consistent results in direction with the original findings (Supplementary Table 3).

Meteorological Factors and Seasonality

Based on the main bivariable model, in the tropics, temperature was significantly associated with RSV season offset, with each 1°C increase in temperature delaying RSV season offset by 9 days (95% confidence interval [CI], 3–15). In the subtropics, high wind speed was significantly correlated with the delay in RSV season offset, with wind speed increasing by 1 m/s and RSV season offset delaying by 7 days (95% CI, 3–11). In the temperate regions, for each 1°C increase in temperature, RSV season onset was 2 days (95% CI, 0–3) earlier (Figure 4).

DISCUSSION

To our knowledge, this is the first global-level study covering tropical, subtropical, and temperate regions to analyze the relationship between RSV subgroup distribution and RSV seasonality. We found RSV-A proportion was not significantly associated with RSV season onset or offset; the only exception was for RSV season offset in the tropics in 1 of the 4 models (possibly by chance). Stratified analysis by RSV subgroup within a season did not show any statistical differences in the circulating timing between the 2 subgroups. Overall, RSV subgroup

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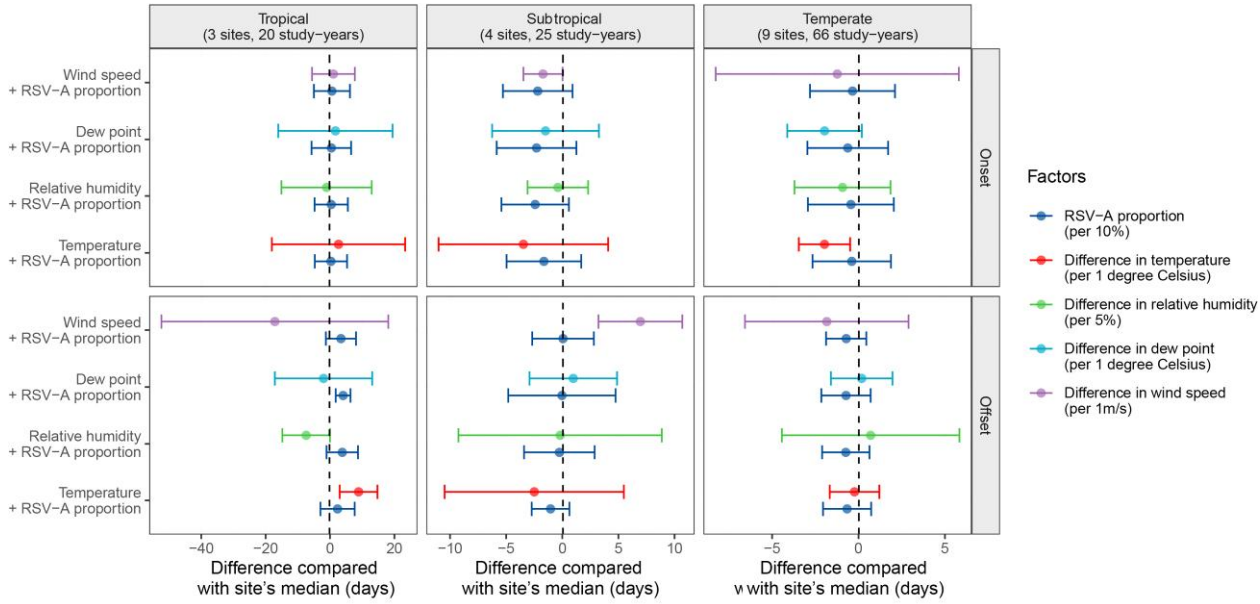

Figure 4. Bivariable linear regression model for year-on-year variations of RSV season onset and offset in tropical, subtropical, and temperate regions. Abbreviation: RSV, respiratory syncytial virus.

distribution has negligible impact on the year-on-year variations of RSV seasonality. Even when meteorological factors were further considered, the overall model explained only a small proportion of the variations.

Our main results in temperate regions complemented those of Staadegaard et al [15], while differed from several previous local-level findings reporting the association between subgroup distribution with RSV seasonal characteristics [13, 15, 19, 22], but such inconsistencies were not a result of different methodologies or definitions because a similar local-level finding for each of the previous studies was obtained after reanalyzing the study data using our methodology and definition.

Multiple studies have demonstrated the association between meteorological factors and RSV seasonality. Our previous global-level analyses have revealed that meteorological factors can largely explain seasonal variations among areas with different latitudes and longitudes [9, 23]; however, the role of meteorological factors in explaining year-on-year variations for the same site across the globe was underresearched. This study showed that meteorological factors, such as temperature and wind speed, could also help to explain the year-on-year variations, but to a lesser extent, which was consistent with several previous local-level studies [10, 24, 25]. However, the observed association regarding meteorological factors was not consistent across different latitude groups, likely a result of different climatic characteristics.

The strengths of our study comprise the inclusion of data from multiple countries around the world to systematically analyze the potential influencing factors of year-on-year variations in RSV seasonality, application of a uniform definition of RSV seasonality using the ACP method, which allowed us to compare associations between RSV subgroup distribution and seasonal characteristics across latitudes and with different types of data, and the use of multivariate regression models that accounted for meteorological factors as important potential confounders.

However, our study does inevitably have some limitations. First, over half (56%, 20/36) of eligible studies reported data for fewer than 5 seasons (ie, 3 or 4 seasons). As we focused on the year-on-year variations, it was important to include a sufficient number of study-years for robust results; therefore, we did not include these studies in the main analysis, resulting in limited number of studies, particularly in tropical and subtropical regions, where only 3 and 4 studies were included, respectively. Second, most data (11/16) in the main analysis were aggregated on monthly basis, which limited the time-resolution of our analysis compared with weekly data. Third, the RSV subgroup data were obtained from EpiRSV in 6 studies, which might not represent the actual subgroup distribution, although our sensitivity analysis that removed these data yielded consistent findings. Furthermore, due to insufficient data on RSV subgroup per season, we could not look into the association of RSV subgroup by the RSV season onset (rather than during the entire season) with the timing of RSV season onset. Fourth, there were substantial heterogeneities among the included studies, such as the age of subjects, methods of RSV detection, frequency of RSV reporting, and criteria for RSV testing (most studies, 33/36, were based on hospitals where RSV testing was ordered at the discretion of

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clinicians). Nevertheless, we do not consider these heterogeneities to have a major impact on our main findings given that the comparisons of RSV seasonality were made within each site across study-years. Fifth, we could not rule out residual confounding; factors such as population susceptibility [26], mobility (eg, influenced by nonpharmacological interventions including school closure) [27], and viral interference [21], may help to explain the year-on-year variations in RSV seasonality. Moreover, heterogeneity in local spread could also explain some of the variations; demographic characteristics such as population density were previously reported to contribute to the varied onset timings of RSV epidemics [28]. Finally, our analysis did not include the coronavirus disease 2019 (COVID-19) period that was reported to be associated with irregular RSV epidemics in various countries [29]. It is important to understand the role of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus circulation and the potential changes in population behaviors following the COVID-19 pandemic in shaping RSV seasonality in the coming few years.

In summary, RSV subgroup distribution in an RSV season has negligible impact on RSV seasonal characteristics. RSV subgroup distribution and meteorological factors jointly could only explain a small proportion of the year-on-year variations in RSV season onset and offset. The role of population susceptibility, mobility, and viral interference should be examined in future studies. Meanwhile, we highlight the lack of multiple-year high-quality data on RSV seasonality, which would be important for understanding RSV transmission and guiding RSV treatment, prevention, and control.

Supplementary Data

Supplementary materials are available at *The Journal of 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.

Notes

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Author contributions. Y. L. conceptualized the study. S. D. led the data acquisition with substantial contributions from L. G., C. C., A. M., J. M., S. P., Y. P., A. T., M. v B., N. Wa., N. Wo., and J. P. Y. L. and S. D. jointly led the data analysis and visualization. S. D., Y. L., and H. N. led data interpretation with input from L. G., C. C., A. M., J. M., S. P., Y. P., A. T., M. v B., N. Wa., N. Wo., and J. P. S. D. wrote the first draft of the report with substantial input from Y. L. All coauthors reviewed the draft for intellectual content and approved the final report.

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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.

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