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Impact of subgroup distribution on seasonality of human respiratory syncytial virus: a global systematic analysis

Shuyu Deng[1], Ling Guo[1], Cheryl Cohen[2,3], Adam Meijer[4], Jocelyn Moyes[2], Siripat Pasittungkul[5], Yong Poovorawan[5], Anne Teirlinck[4], Michiel van Boven[4], Nasamon Wanlapakorn[5], Nicole Wolter[2,3], John Paget[6], Harish Nair[7,3*†], You Li[1,7*†]

1 School of Public Health, Nanjing Medical University, Nanjing, China;
2 Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, Johannesburg, South Africa;
3 Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa;
4 National Institute for Public Health and the Environment (RIVM) - Centre for Infectious Disease Control, Bilthoven, the Netherlands;
5 Centre of Excellence in Clinical Virology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand;
6 Netherlands Institute for Health Services Research (Nivel), Utrecht, the Netherlands;
7 Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, United Kingdom
† Joint senior authors

Abstract

Introduction: Previous studies reported inconsistent findings regarding the association between respiratory syncytial virus (RSV) subgroup distribution and timing of RSV seasonal epidemics, possibly due to not accounting for confounders such as meteorological factors. We aimed to improve the understanding of the association through a global-level systematic analysis that accounted for these potential confounders.

* Correspondence to: Prof. You Li (You.Li@njmu.edu.cn), School of Public Health, Nanjing Medical University, 101 Longmian Avenue, Nanjing, China 211166; Prof. Harish Nair (Harish.Nair@ed.ac.uk), Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, United Kingdom EH8 9AG.

Methods: We compiled published data on RSV seasonality through a systematic literature review, and supplemented with unpublished data shared by international collaborators. RSV seasonal characteristics were defined for each study-year based on the annual cumulative proportion (ACP) of RSV-positive cases, with ACP of 10% and 90% being defined as season onset and offset, respectively. Linear regression models with study-level clustered standard errors were conducted to analyse the association of proportion of RSV-A with the corresponding RSV season onset and offset separately, while accounting for meteorological factors.

Results: We included a total of 36 studies from 36 sites in 20 countries, which cumulatively provided data for 179 study-years in 1995-2019. Overall, year-on-year variations in RSV season onset, offset, and duration were generally comparable among tropical, sub-tropical, and temperate regions. Regression analysis by latitude groups showed that RSV subgroup distribution was not significantly associated with RSV season onset or offset globally; the only exception was for RSV season offset in the tropics in one model, possibly by chance. Models that included both RSV subgroup distribution and meteorological factors only jointly explained 2-4% of the variations in RSV season onset and offset.

Conclusion: Globally, RSV subgroup distribution had negligible impact on the RSV seasonal characteristics. RSV subgroup distribution and meteorological factors jointly could only explain limited 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.

Introduction

Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory infections among young children and the elderly, resulting in considerable burden on healthcare systems [1-3]. There are no vaccines or antivirals for RSV infection; only monoclonal antibodies can be used for passive immunisation [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 highincome 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 (i.e., up to six months), the implementation of RSV immunisation 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 (e.g., latitude and longitude) [9] as well as meteorological factors (e.g., 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 (i.e., 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 generalisable, this would have important implications for RSV prevention and surveillance — knowing the predominant RSV subgroup could help explain the ear-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 have varied efficacy by RSV subgroup [14]. However, despite using the same methodology, a subsequent study reporting data from four 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 two 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 analyse 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 Text S1) to identify studies with eligible data on RSV seasonality and subgroup distribution (detailed inclusion criteria in Text S2), without language restrictions. 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 (SD and LG) independently performed the literature search, screening, and extraction. Disagreements were resolved through discussion or arbitrated by YL.

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 Hospitalised Care (GERi) project [16]. Where available, the RSV activity data were also collected by the three predefined age groups: <18 years, 18–64 years, and 65 years or above. All received data were cross-checked by SD and YL 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 and interquartile range (IQR) of distances between sites and weather stations was 15.0 (8.5–26.0) kilometres. 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 (SD and LG) assessed the quality of included studies using a brief rating scale which incorporated three questions regarding representativeness of subjects, stability of testing methods and practice, and timeliness of positive case reports (detailed in Tables S1–S2) [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% (i.e., 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 non-integer estimates by applying linear interpolation of ACP (e.g., the onset of RSV season could be week 4.5 or month 1.2). We conducted sensitivity analyses that used different ACP cut-offs 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 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 one to three days before site's median RSV season onset or the past one to three 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 (e.g., 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 five or more seasons were included in the main analysis (we lifted this restriction in one of 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), sub-tropical 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 bi-variable models with RSV-A proportion and one of four meteorological factors (temperature, relative humidity, dew point, and wind speed) as covariates. We also conducted tri-variable models (which included two of the four meteorological factors, in addition to the RSV subgroup predominance, as covariates) for checking the robustness of our main (bi-variable) 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 timevarying 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 one condition in the main analysis each time (the complete list can be found in Text S3). Moreover, for individual studies that quantitatively assessed the association between RSV seasonal characteristics and subgroup distribution, we reanalysed the study data using our own definition and methodology and compared the results.

Data were analysed 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 five or more seasons: three from tropical regions, four from subtropical regions, and nine from temperate regions. A total of 30 sites reported data on RSV subgroup; for the rest 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 the appendix (Figure S1).

Subgroup distribution and seasonality

Year-on-year variations in RSV season onset, offset, and duration were generally comparable among tropical, sub-tropical, and temperate regions (Figure 3A); variations in RSV season onset, offset, and duration were within two weeks of the site's median level for over half of the studyyears (51–71%, 60–71%, and 57–64% of the study-years, respectively). Results from Pearson's 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 five or more seasons or in all sites (Figure 3B–D).

Overall, our main bi-variable models that accounted for RSV-A proportion and one of the meteorological factors could 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 one model, with a 4-day delay in offset per 10% increase in RSV-A proportion (Figure 4). Consistent results were observed in tri-variable analyses (Figure S2), 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 season were defined separately for each site per study-year, no significant differences were found in the onset, offset, and duration of the two RSV-subgroup specific seasons (Figure S3). The results were consistent when the characteristics of RSV seasonality in different age groups were compared (Figure S4).

The results of sensitivity analyses were generally consistent with those from the main analysis (Figures S5–S12). Using our definition and methodology, we reanalysed studies that reported the association between subgroup distribution with RSV seasonal characteristics, which yielded consistent results in direction with the original findings (Table S3).

Meteorological factors and seasonality

Based on the main bi-variable 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 (3–11). In the temperate regions, for each 1° C increase in temperature, RSV season onset was 2 days (0–3) earlier (Figure 4).

Discussion

To our knowledge, this is the first global-level study covering tropical, sub-tropical, and temperate regions to analyse 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 one of the four models (possibly by chance). Stratified analysis by RSV subgroup within a season did not show any statistical differences in the circulating timing between the two subgroups. Overall, RSV subgroup 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 since a similar local-level finding for each of the previous studies was obtained after reanalysing 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 under-researched. 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 analyse 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 five seasons (i.e., three or four seasons). As we focused on the year-on-year variations, it was important to include a fairly 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 three and four 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 six 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 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 (e.g. influenced by non-pharmacological 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 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 SARS-CoV-2 virus circulation and the potential changes in population behaviours 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.

Notes

Respiratory Virus Global Epidemiology Network investigators. Shuyu Deng, Ling Guo, You Li (Nanjing Medical University, Nanjing, China); Cheryl Cohen, Jocelyn Moyes, Nicole Wolter, Anne von Gottberg (National Institute for Communicable Diseases, Johannesburg, South Africa); Adam Meijer, Anne Teirlinck, Michiel van Boven (National Institute for Public Health and the Environment, Bilthoven, the Netherlands); Siripat Pasittungkul, Yong Poovorawan, Nasamon Wanlapakorn (Chulalongkorn University, Bangkok, Thailand); John Paget (Netherlands Institute for Health Services Research (Nivel), the Netherlands); Harish Nair (University of Edinburgh, Edinburgh, UK).
PROMISE investigators. Jeroen Aerssens, Gabriela Ispas (Janssen, Beerse, Belgium); Bahar Ahani (AstraZeneca, Gaithersburg, Maryland, USA); Jessica Atwell, Elizabeth Begier, Tin Tin Htar (Pfizer, Paris, France); Mathieu Bangert, Rolf Kramer, Charlotte Vernhes (Sanofi Pasteur, Lyon, France); Philippe Beutels (University of Antwerp, Antwerpen, Belgium); Louis Bont (University Medical Centre Utrecht, Utrecht, the Netherlands); Harry Campbell, Harish Nair, You Li, Richard Osei-Yeboah, Xin Wang (University of Edinburgh, Edinburgh, UK); Rachel Cohen, Gael Dos Santos, Theo Last (GlaxoSmithKline, Wavre, Belgium); Veena Kumar (Novavax, Gaithersburg, Maryland, USA); Nuria Machin (Teamit Research, Barcelona, Spain); Hanna Nohynek (Finnish National Institute for Health and Welfare, Helsinki, Finland); Peter Openshaw (Imperial College London, London, UK); John Paget (Netherlands Institute for Health Services Research, Utrecht, the Netherlands); Andrew Pollard (University of Oxford, Oxford, UK); Anne Teirlinck (National Institute for Public Health and the Environment, Bilthoven, the Netherlands).

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Author contributions

YL conceptualised the study; SD led the data acquisition with substantial contributions from LG, CC, AM, JM, SP, YP, AT, MvB, NWa, NWo and JP. YL and SD jointly led the data analysis and visualisation; SD, YL and HN led data interpretation with input from LG, CC, AM, JM, SP, YP, AT, MvB, NWa, NWo and JP. SD wrote the first draft of the report with substantial input from YL. All co-authors reviewed the draft for intellectual content and approved the final report

Disclaimer

This manuscript reflects only the authors' view and the Joint Undertaking is not responsible for any use that may be made of the information it contains herein.

Potential conflicts of interest

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Figures

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

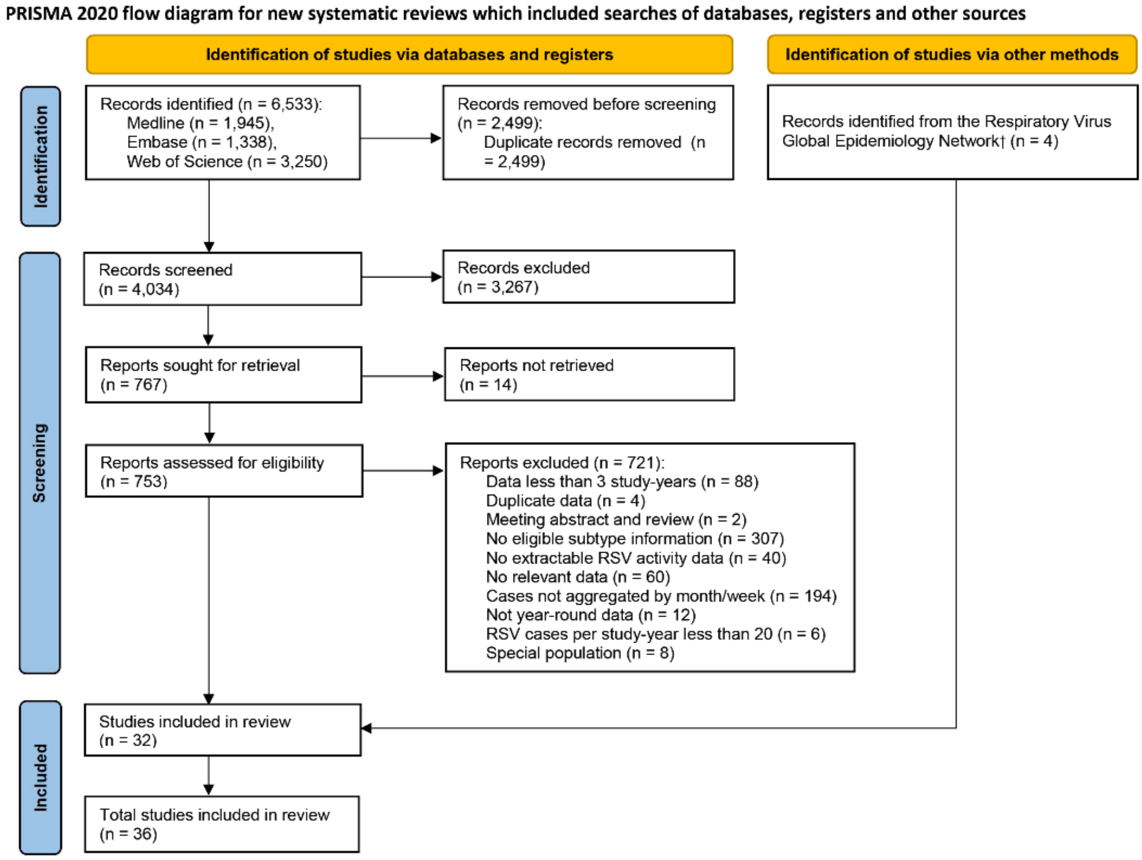


Figure 2. World map showing study sites included

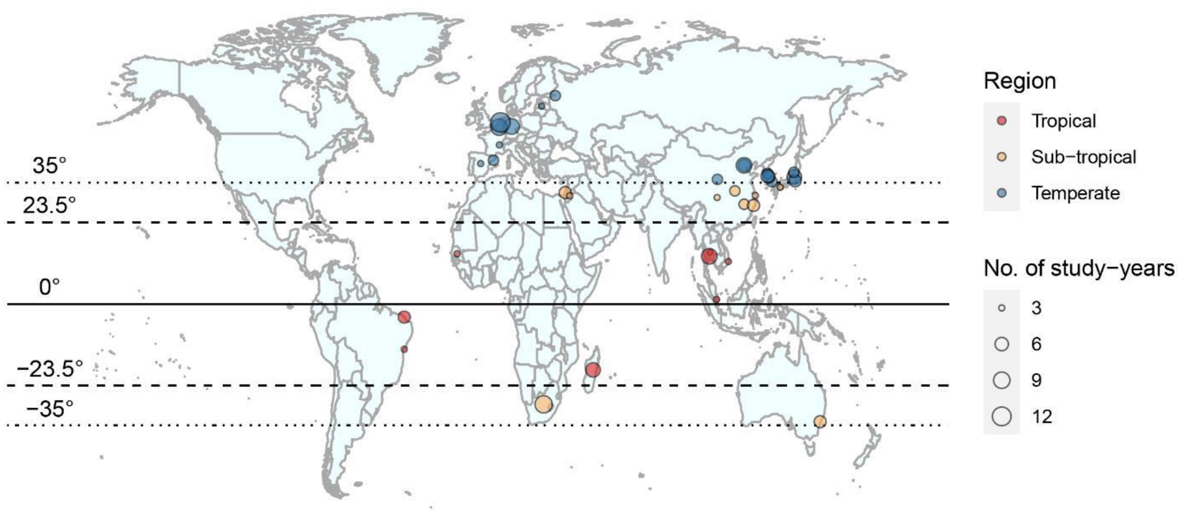


Figure 3. RSV-A proportion and year-on-year variations of RSV seasonality. (A) Year-on-year variations in RSV season onset, offset, and duration. The median of differences was zero, as the annual RSV seasonal characteristics of each site were compared with the site's median. (B–D) RSV-A proportion and year-on-year variations of RSV season onset, offset, and duration. Red indicated sites contributing five or more seasons, and grey indicated all included sites. Lines indicated fitted regression lines, and shaded sections indicated 95% confidence intervals. Abbreviation: RSV, respiratory syncytial virus.

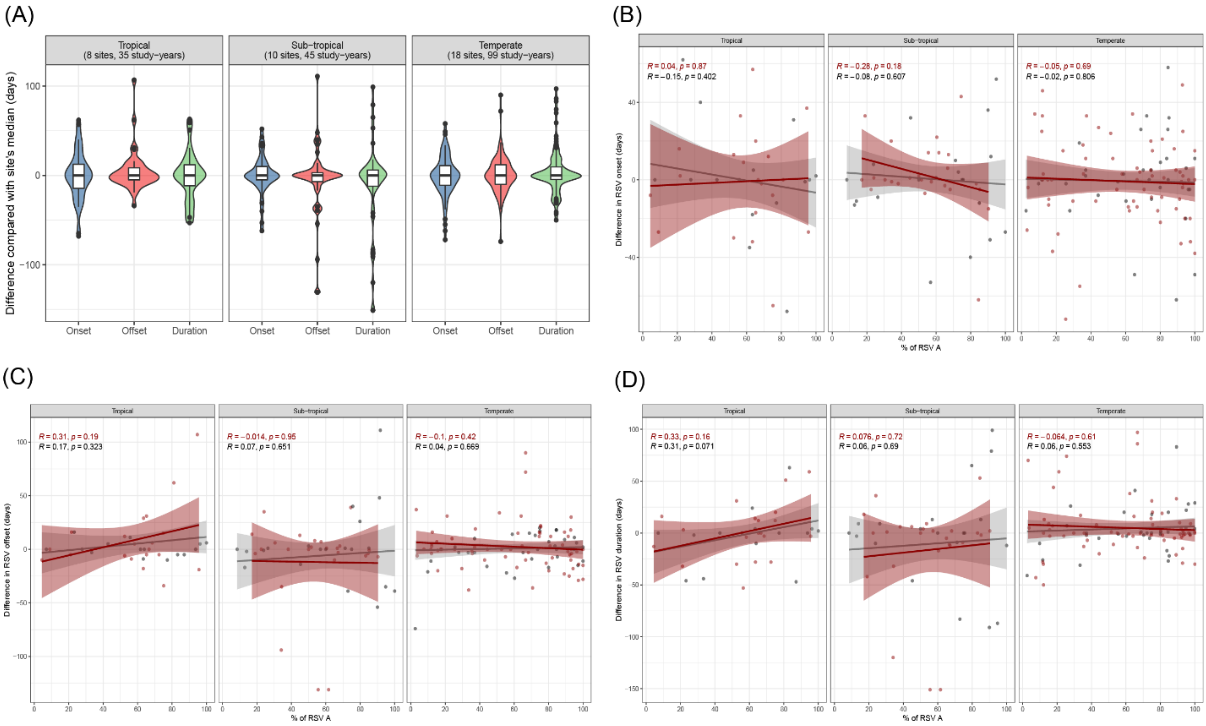
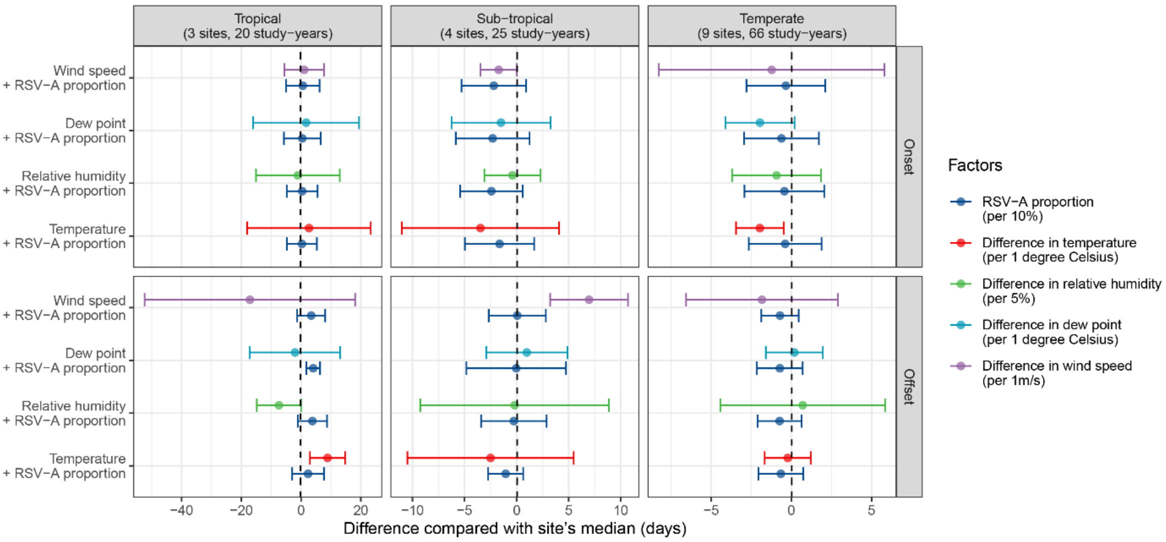
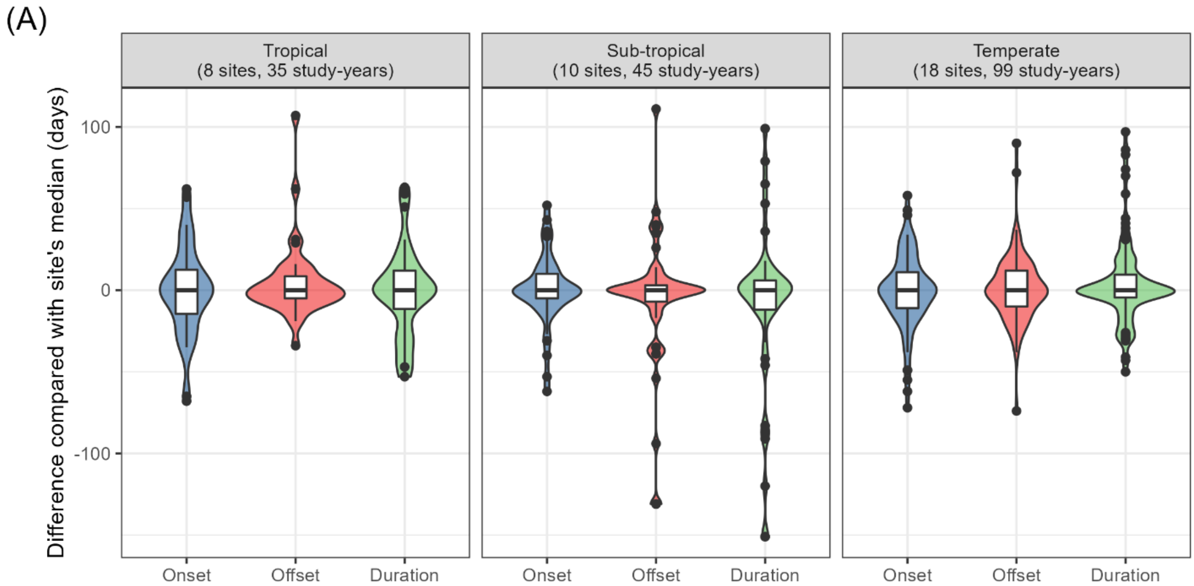


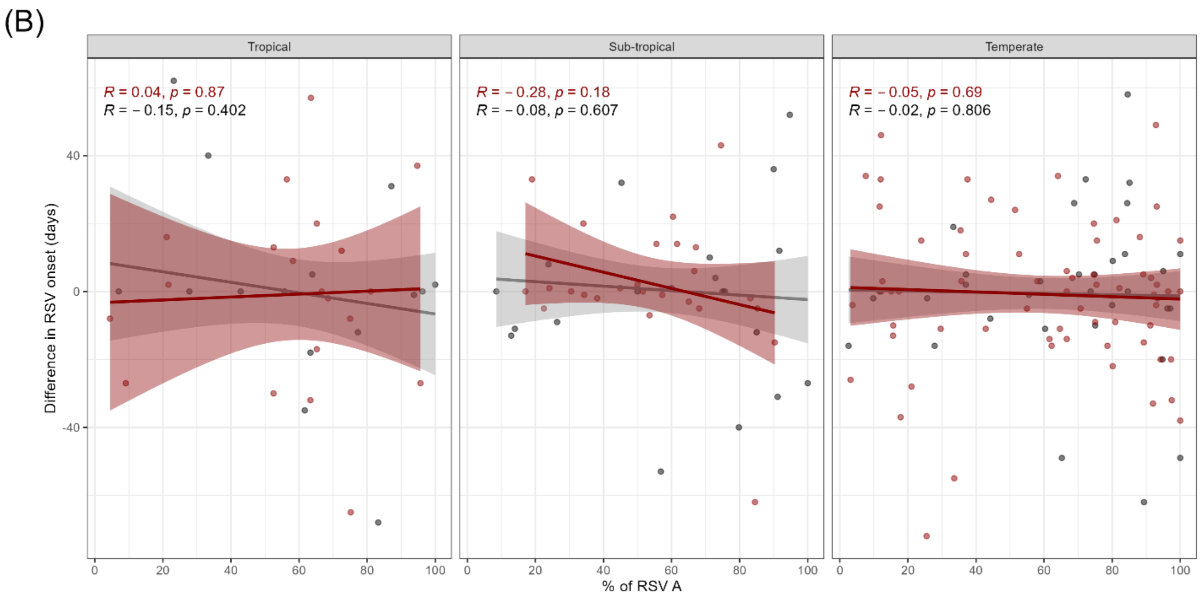
Figure 4. Bi-variable linear regression model for year-on-year variations of RSV season onset and offset in tropical, sub-tropical, and temperate regions. Abbreviation: RSV, respiratory syncytial virus.



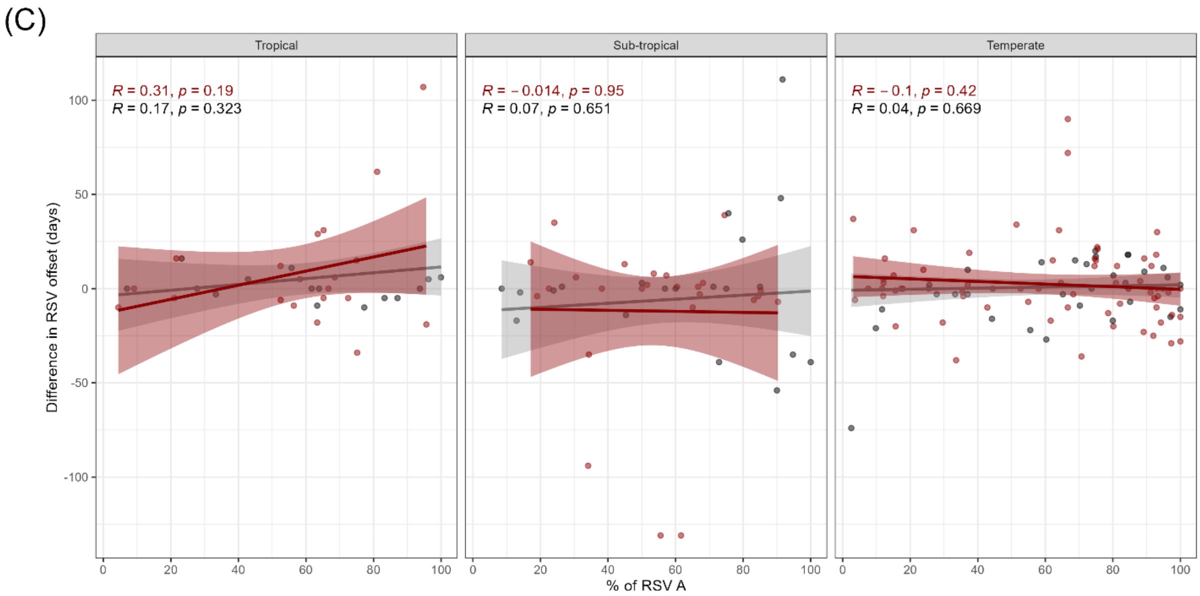
Panel A of Figure 3



Panel B of Figure 3



Panel C of Figure 3



Panel D of Figure 3