

1 **Impact of subgroup distribution on seasonality of human respiratory syncytial**  
2 **virus: A global systematic analysis**

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29 **Abstract**

30 **Introduction**

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

36 **Methods**

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38 supplemented with unpublished data shared by international collaborators.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

44 **Results**

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

51 both RSV subgroup distribution and meteorological factors only jointly explained 2–4% of  
52 the variations in RSV season onset and offset.

53 **Conclusion**

54 Globally, RSV subgroup distribution had negligible impact on the RSV seasonal  
55 characteristics. RSV subgroup distribution and meteorological factors jointly could only  
56 explain limited year-on-year variations in RSV season onset and offset. The role of  
57 population susceptibility, mobility, and viral interference should be examined in future  
58 studies.

## 59 Introduction

60 Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory infections  
61 among young children and the elderly, resulting in considerable burden on healthcare  
62 systems [1-3]. There are no vaccines or antivirals for RSV infection; only monoclonal  
63 antibodies can be used for passive immunisation [4,5]. Palivizumab has been available for  
64 over 2 decades but its use is limited to infants at extremely high risk of severe RSV infection  
65 and almost exclusively in high-income countries [6]. Nirsevimab has recently been approved  
66 by the European Medicines Agency for wide use in all infants [7]. As various RSV  
67 prophylactic products available and currently in clinical development may have relatively  
68 short time windows for protection (i.e., up to six months), the implementation of RSV  
69 immunisation requires a clear understanding of RSV seasonality for optimal effectiveness  
70 [4,5,7,8].

71  
72 A systematic analysis of global RSV seasonality showed that RSV has clear seasonal  
73 epidemics in both temperate and tropical regions; RSV season usually starts in late-summer  
74 months in the tropics of each hemisphere and starts in late autumn or early winter in most  
75 temperate regions [9]. Although RSV seasonality is found to be highly correlated with  
76 geographic location (e.g., latitude and longitude) [9] as well as meteorological factors (e.g.,  
77 temperature, humidity, and rainfall) [10-12], variations in local year-on-year RSV seasonality  
78 remain largely unexplained. A study in Beijing, China reported that the dominant RSV  
79 subgroup (i.e., subgroup A or B) might explain the year-on-year variations in RSV season  
80 onset and duration; RSV seasons occurred 3–5 weeks earlier and lasted 6 weeks longer in

81 RSV subgroup A-dominant years than in subgroup B-dominant years [13]. If generalisable,  
82 this would have important implications for RSV prevention and surveillance — knowing the  
83 predominant RSV subgroup could help explain the year-on-year changes in RSV seasonality.  
84 To that end, surveillance systems around the world would need to monitor and report RSV  
85 subgroup data, which is not a routine practice in most regions at present. In addition, it is  
86 relevant to the implementation of RSV prophylactic products that might have varied efficacy  
87 by RSV subgroup [14]. However, despite using the same methodology, a subsequent study  
88 reporting data from four temperate countries did not observe any associations between the  
89 predominant RSV subgroup and RSV seasonality [15]; the research group also noted that  
90 subgroup dominance was rare in most RSV seasons [16]. The inconsistent findings above led  
91 to a series of questions such as whether the reported association between predominant RSV  
92 subgroup and RSV seasonality in Beijing was a chance finding, whether the reported  
93 association only exists for certain geographic locations, and whether any meteorological  
94 factors (not being accounted for in either of the two studies) could help explain the year-on-  
95 year variations. Moreover, it is not yet known whether the association holds for the tropics  
96 and subtropics where RSV seasonality was clear.

97

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

102

## 103 **Methods**

### 104 **Systematic literature review**

105 A systematic literature review (PROSPERO: CRD42022313722) was conducted using  
106 electronic databases of MEDLINE, EMBASE, and Web of Science (search strategy in Text S1)  
107 to identify studies with eligible data on RSV seasonality and subgroup distribution (detailed  
108 inclusion criteria in Text S2), without language restrictions. For included studies, we used a  
109 tailored extraction sheet to collect information related to study characteristics (location,  
110 period, subject age, case definition and source, clinical specimen, testing and subgrouping  
111 methods, subgroup information, sample size) and RSV activity (monthly or weekly number  
112 of RSV-positive cases). Two authors (SD and LG) independently performed the literature  
113 search, screening, and extraction. Disagreements were resolved through discussion or  
114 arbitrated by YL.

115

### 116 **Unpublished RSV data**

117 In addition to the published literature, we collected unpublished weekly RSV activity data  
118 from datasets shared by collaborative research groups who published RSV epidemiology  
119 studies [9,12,17-19] and the Global Epidemiology of RSV in Community and Hospitalised  
120 Care (GERi) project [16]. Where available, the RSV activity data were also collected by the  
121 three predefined age groups: <18 years, 18–64 years, and 65 years or above. All received  
122 data were cross-checked by SD and YL for completeness and consistency before being  
123 included in the analysis.

124

125 **External RSV subgroup data from GISAID**

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

130

131 **Meteorological data**

132 For each study site, we extracted the coordinates of site’s centroid from Google Maps and  
133 identified the nearest weather station with available meteorological data. The median and  
134 interquartile range (IQR) of distances between sites and weather stations was 15.0 (8.5–  
135 26.0) kilometres. We then extracted the daily average meteorological data from the Global  
136 Surface Summary of the Day dataset provided by the US National Centers for Environmental  
137 Information, via the R package “GSODR”.

138

139 **Quality assessment**

140 Two authors (SD and LG) assessed the quality of included studies using a brief rating scale  
141 which incorporated three questions regarding representativeness of subjects, stability of  
142 testing methods and practice, and timeliness of positive case reports (detailed in Tables S1–  
143 S2) [9]. Each question was rated on a scale of “1–3” points for the included studies,  
144 indicating quality from poor to good.

145

146 **Data analysis**

147 **Defining RSV season**

148 As in our previously published analysis on RSV seasonality [21], RSV season was defined by  
149 calculating the annual cumulative proportion (ACP) of RSV-positive cases (determined by  
150 any diagnostic tests except serology alone) retrospectively for each season per study site. In  
151 brief, the onset of RSV season was defined as the month/week when the ACP reached 10%  
152 (i.e., the time when 10% of the annual RSV cases have occurred); the offset of RSV season  
153 was defined as when the ACP reached 90%; the duration of RSV season was defined as the  
154 time difference between onset and offset, capturing 80% of the annual RSV cases. For  
155 defining RSV season onset and offset, our calculation allowed non-integer estimates by  
156 applying linear interpolation of ACP (e.g., the onset of RSV season could be week 4.5 or  
157 month 1.2). We conducted sensitivity analyses that used different ACP cut-offs for onset and  
158 offset.

159

160 **Defining year-on-year variation**

161 Our primary outcomes of interest, determined a priori, were the year-on-year variations in  
162 RSV season onset, offset, and duration for each study site. To ensure that the year-on-year  
163 variations from different study sites were comparable, we first obtained the median RSV  
164 season onset, offset, and duration as the reference for each site and then calculated the  
165 differences in RSV season onset, offset, and duration between each of the study-years and  
166 the reference. As a result, the year-on-year variations in onset, offset, and duration for each

167 site can be interpreted as the variation compared with the median value from that site, with  
168 positive values indicating later-than-usual onset or offset, or longer-than-usual duration.

169

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

178

### 179 **Main analysis**

180 As our analysis focused on determinants of year-on-year variations, only studies  
181 contributing five or more seasons were included in the main analysis (we lifted this  
182 restriction in one of sensitivity analyses). As large variations in RSV seasonality and its  
183 determinants across latitudes were anticipated, we classified study sites into tropical region  
184 (defined as latitude between -23.5 and 23.5 degrees), sub-tropical region (latitude between  
185 23.5 and 35 degrees or between -35 and -23.5 degrees), and temperate region (latitude  
186 above 35 degrees or below -35 degrees), based on site's centroid, and conducted analyses  
187 for each of the regions separately.

188

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

200

## 201 **Secondary analysis**

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

207

208 As exploratory analysis, we repeated the same approach as above stratified by age groups  
209 (<18, 18–64, and >64 years) to understand whether there are any asynchronous circulating

210 patterns of RSV among age groups within each study-year (the age group of <18 years was  
211 regarded as the reference for comparisons among different age groups).

212

### 213 **Sensitivity analysis**

214 Multiple sensitivity analyses were performed by changing one condition in the main analysis  
215 each time (the complete list can be found in Text S3). Moreover, for individual studies that  
216 quantitatively assessed the association between RSV seasonal characteristics and subgroup  
217 distribution, we reanalysed the study data using our own definition and methodology and  
218 compared the results.

219

220 Data were analysed and visualized with the R software (version 4.1.2).

221

## 222 **Results**

223 After removing duplicates, a total of 4034 records were screened, of which 32 met the  
224 inclusion criteria (Figure 1). After adding 4 records from the unpublished datasets shared by  
225 collaborators, the analysis included a total of 36 studies from 36 sites in 20 countries,  
226 providing data for 179 study-years in 1995–2019 (Figure 2). Among them, 16 sites  
227 contributed five or more seasons: three from tropical regions, four from subtropical regions,  
228 and nine from temperate regions. A total of 30 sites reported data on RSV subgroup; for the  
229 rest 6 sites without RSV subgroup data, we obtained RSV subgroup data externally from the  
230 GISAID EpiRSV database. Detailed RSV seasonal characteristics and subgroup distribution for  
231 each season in each site are presented in the appendix (Figure S1).

232

### 233 **Subgroup distribution and seasonality**

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

242

243 Overall, our main bi-variable models that accounted for RSV-A proportion and one of the  
244 meteorological factors could explain a median of 2% (IQR: 1–9%) of the variations in RSV  
245 season onset and offset. RSV-A proportion was not significantly associated with RSV season  
246 onset or offset globally; the only exception was for RSV season offset in the tropics in one  
247 model, with a 4-day delay in offset per 10% increase in RSV-A proportion (Figure 4).

248 Consistent results were observed in tri-variable analyses (Figure S2), which explained a  
249 median of 4% (IQR: 2–17%) of the variations in RSV season onset and offset.

250

251 When the RSV-A and RSV-B season were defined separately for each site per study-year, no  
252 significant differences were found in the onset, offset, and duration of the two RSV-

253 subgroup specific seasons (Figure S3). The results were consistent when the characteristics  
254 of RSV seasonality in different age groups were compared (Figure S4).

255

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

260

### 261 **Meteorological factors and seasonality**

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

269

## 270 **Discussion**

271 To our knowledge, this is the first global-level study covering tropical, sub-tropical, and  
272 temperate regions to analyse the relationship between RSV subgroup distribution and RSV  
273 seasonality. We found RSV-A proportion was not significantly associated with RSV season  
274 onset or offset; the only exception was for RSV season offset in the tropics in one of the four

275 models (possibly by chance). Stratified analysis by RSV subgroup within a season did not

276 show any statistical differences in the circulating timing between the two subgroups.

277 Overall, RSV subgroup distribution has negligible impact on the year-on-year variations of

278 RSV seasonality. Even when meteorological factors were further considered, the overall

279 model explained only a small proportion of the variations.

280

281 Our main results in temperate regions complemented those of Staadegaard et al. [15], while

282 differed from several previous local-level findings reporting the association between

283 subgroup distribution with RSV seasonal characteristics [13,15,19,22], but such

284 inconsistencies were not a result of different methodologies or definitions since a similar

285 local-level finding for each of the previous studies was obtained after reanalysing the study

286 data using our methodology and definition.

287

288 Multiple studies have demonstrated the association between meteorological factors and

289 RSV seasonality. Our previous global-level analyses have revealed that meteorological

290 factors can largely explain seasonal variations among areas with different latitudes and

291 longitudes [9,23]; however, the role of meteorological factors in explaining year-on-year

292 variations for the same site across the globe was under-researched. This study showed that

293 meteorological factors, such as temperature and wind speed, could also help to explain the

294 year-on-year variations, but to a lesser extent, which was consistent with several previous

295 local-level studies [10,24,25]. However, the observed association regarding meteorological

296 factors was not consistent across different latitude groups, likely a result of different  
297 climatic characteristics.

298

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

306

307 However, our study does inevitably have some limitations. First, over half (56%, 20/36) of  
308 eligible studies reported data for fewer than five seasons (i.e., three or four seasons). As we  
309 focused on the year-on-year variations, it was important to include a fairly sufficient number  
310 of study-years for robust results; therefore, we did not include these studies in the main  
311 analysis, resulting in limited number of studies, particularly in tropical and subtropical  
312 regions, where only three and four studies were included, respectively. Second, most data  
313 (11/16) in the main analysis were aggregated on monthly basis, which limited the time-  
314 resolution of our analysis compared with weekly data. Third, the RSV subgroup data were  
315 obtained from EpiRSV in six studies, which might not represent the actual subgroup  
316 distribution, although our sensitivity analysis that removed these data yielded consistent  
317 findings. Furthermore, due to insufficient data on RSV subgroup per season, we could not

318 look into the association of RSV subgroup by the RSV season onset (rather than during the  
319 entire season) with the timing of RSV season onset. Fourth, there were substantial  
320 heterogeneities among the included studies, such as the age of subjects, methods of RSV  
321 detection, frequency of RSV reporting, and criteria for RSV testing (most studies, 33/36,  
322 were based on hospitals where RSV testing was ordered at the discretion of clinicians).  
323 Nevertheless, we do not consider these heterogeneities to have a major impact on our main  
324 findings given that the comparisons of RSV seasonality were made within each site across  
325 study-years. Fifth, we could not rule out residual confounding; factors such as population  
326 susceptibility [26], mobility (e.g. influenced by non-pharmacological interventions including  
327 school closure) [27], and viral interference [21], may help to explain the year-on-year  
328 variations in RSV seasonality. Moreover, heterogeneity in local spread could also explain  
329 some of the variations; demographic characteristics such as population density were  
330 previously reported to contribute to the varied onset timings of RSV epidemics [28]. Finally,  
331 our analysis did not include the COVID-19 period that was reported to be associated with  
332 irregular RSV epidemics in various countries [29]. It is important to understand the role of  
333 SARS-CoV-2 virus circulation and the potential changes in population behaviours following  
334 the COVID-19 pandemic in shaping RSV seasonality in the coming few years.

335

336 In summary, RSV subgroup distribution in an RSV season has negligible impact on RSV  
337 seasonal characteristics. RSV subgroup distribution and meteorological factors jointly could  
338 only explain a small proportion of the year-on-year variations in RSV season onset and  
339 offset. The role of population susceptibility, mobility, and viral interference should be

340 examined in future studies. Meanwhile, we highlight the lack of multiple-year high-quality  
341 data on RSV seasonality, which would be important for understanding RSV transmission and  
342 guiding RSV treatment, prevention, and control.

343

#### 344 **Notes**

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377 substantial contributions from LG, CC, AM, JM, SP, YP, AT, MvB, NWa, NWo and JP. YL and  
378 SD jointly led the data analysis and visualisation; SD, YL and HN led data interpretation with  
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396

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470 **Figures**

471 **Figure 1 (online only).** PRISMA flow diagram of study inclusion. Abbreviation: RSV,  
472 respiratory syncytial virus.

473 **Figure 2 (online only).** World map showing study sites included

474 **Figure 3 (online only).** RSV-A proportion and year-on-year variations of RSV seasonality. (A)

475 Year-on-year variations in RSV season onset, offset, and duration. The median of differences

476 was zero, as the annual RSV seasonal characteristics of each site were compared with the

477 site's median. (B–D) RSV-A proportion and year-on-year variations of RSV season onset, offset,

478 and duration. Red indicated sites contributing five or more seasons, and grey indicated all

479 included sites. Lines indicated fitted regression lines, and shaded sections indicated 95%

480 confidence intervals. Abbreviation: RSV, respiratory syncytial virus.

481 **Figure 4.** Bi-variable linear regression model for year-on-year variations of RSV season onset

482 and offset in tropical, sub-tropical, and temperate regions. Abbreviation: RSV, respiratory

483 syncytial virus.