Respiratory syncytial virus seasonality, transmission zones, and implications for seasonal prevention strategy in China: a systematic analysis

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Summary

Background Respiratory syncytial virus (RSV) represents a substantial global health challenge, with a disproportionately high disease burden in low-income and middle-income countries. RSV exhibits seasonality in most areas globally, and a comprehensive understanding of within-country variations in RSV seasonality could help to define the timing of RSV immunisation programmes. This study focused on China, and aimed to describe the geographical distribution of RSV seasonality, identify distinct RSV transmission zones, and evaluate the potential suitability of a seasonal RSV prevention strategy.

Methods We did a systematic analysis of RSV seasonality in China, with use of data on RSV activity extracted from a systematic review of studies published on Embase, MEDLINE, Web of Science, China National Knowledge Infrastructure, Wanfang Data, Chongqing VIP Information, and SinoMed, from database inception until May 5, 2023. We included studies of any design in China reporting at least 25 RSV cases, which aggregated RSV case number by calendar month or week at the province level, and with data covering at least 12 consecutive months before the year 2020 (prior to the COVID-19 pandemic). Studies that used only serology for RSV testing were excluded. We also included weekly data on RSV activity from open-access online databases of the Taiwan National Infection Disease Statistics System and Hong Kong Centre for Health Protection, applying the same eligiblity requirements. Across all datasets, we excluded data on RSV activity from Jan 1, 2020, onwards. We estimated RSV seasonal epidemic onset and duration using the annual average percentage (AAP) approach, and summarised seasonality at the provincial level. We used Pearson's partial correlation analysis to assess the correlation between RSV season duration and the latitude and longitude of the individual provinces. To define transmission zones, we used two independent approaches, an infant-passive-immunisation-driven approach (the moving interval approach, 6-month interval) and a data-driven approach (*k*-means), to identify groups of provinces with similar RSV seasonality. The systematic review was registered on PROSPERO, CRD42022376993.

Findings A total of 157 studies were included along with the two online datasets, reporting data on 194 596 RSV cases over 442 study-years (covering the period from Jan 1, 1993 to Dec 31, 2019), from 52 sites in 23 provinces. Among 21 provinces with sufficient data (≥100 reported cases), the median duration of RSV seasonal epidemics was 4·6 months (IQR 4·1–5·4), with a significant latitudinal gradient (r=–0·69, p<0·0007), in that provinces on or near the Tropic of Cancer had the longest epidemic duration. We found no correlation between longitude and epidemic duration (r=–0·15, p=0·53). 15 (71%) of 21 provinces had RSV epidemics from November to March. 13 (62%) of 21 provinces had clear RSV seasonality (epidemic duration ≤5 months). The moving interval approach categorised the 21 provinces into four RSV transmission zones. The first zone, consisting of five provinces (Fujian, Guangdong, Hong Kong, Taiwan, and Yunnan), was assessed as unsuitable for seasonal RSV immunisation strategies; the other three zones were considered suitable for seasonal RSV immunisation strategies with the optimal start month varying between September (Hebei), October (Anhui, Chongqing, Henan, Hubei, Jiangsu, Shaanxi, Shandong, Shanghai, Sichuan, and Xinjiang), and November (Beijing, Gansu, Guizhou, Hunan, and Zhejiang). The *k*-means approach identified two RSV transmission zones, primarily differentiated by whether the province was on or near the Tropic of Cancer (Fujian, Guangdong, Hong Kong, Taiwan, Yunan, and Hunan) or not (the remaining 15 provinces).

Interpretation Although substantial variations in RSV seasonality were observed across provinces of China, our study identified distinct transmission zones with shared RSV circulating patterns. These findings could have important implications for decision making on RSV passive immunisation strategy. Furthermore, the methodological framework in this study for defining RSV seasons and identifying RSV transmission zones is potentially applicable to other countries or regions.

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For the Chinese translation of the abstract see **Online** for appendix 1

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Research in context

Evidence before this study

We searched PubMed for studies published from database inception up to Nov 6, 2023, that reported RSV seasonality in China, using the search terms "(RSV OR respiratory syncytial virus) AND (seasonal* OR activity) AND (China)". No language restriction was applied. We identified eight studies reporting the seasonality of RSV in China, including two systematic reviews and six multiprovincial primary studies. All eight studies showed seasonal circulating patterns of RSV at the national level, with increased activity seen in winter and spring. Although the existing studies showed that RSV seasonality differed between the north and south of China, no studies provided a detailed analysis at the provincial level or provided a granular geographical breakdown.

Added value of this study

Using a uniform analytical method, we analysed the within-country variations of RSV seasonality in China. We discerned two distinct patterns of RSV seasonality among 21 provinces: a clear and stable pattern where RSV activity was concentrated within 5 months and minor year-on-year variations and within-province variations were observed, and a not clear or stable pattern where RSV activity was more dispersed and substantial year-on-year and within-province variations were observed. The two approaches for ascertaining RSV transmission zones yielded complementary results, overall differentiating provinces by suitability of RSV seasonal prevention strategies.

Implications of all the available evidence

The long-acting monoclonal antibody nirsevimab received licensure by the National Medical Products Administration of China in December, 2023, and is expected to enter the Chinese market for the 2024–25 RSV season. The RSV seasonality patterns in different provinces of China as characterised in this study address a crucial knowledge gap and provide evidence for the formulation of seasonal prevention strategies. Furthermore, the methodological framework for defining RSV seasons and identifying RSV transmission zones in this study could be applicable to other countries or regions that need to understand the geographical distribution of RSV seasonality and its relevance to RSV immunisation strategy.

Introduction

Respiratory syncytial virus (RSV) is one of the major pathogens that causes acute lower respiratory infections.[1] Young children are at increased risk of severe RSV diseases.[2] Globally in 2019, RSV was associated with 33·0 million acute lower respiratory infection episodes and 101 400 deaths in children younger than 5 years, with more than 95% of the morbidity and mortality burden across all age groups occurring in low-income and middle-income countries (LMICs).[3]

RSV epidemics show distinct seasonal patterns in most areas around the world. In temperate regions, RSV epidemics typically last for 2–5 months, with the peak commonly occurring during winter months. In the tropics, RSV seasonality varies considerably and can have longer durations than in temperate regions, but the peak typically aligns with the rainy season.[4,5] RSV seasonality patterns are substantially influenced by geographical factors (eg, latitude and altitude)[6] and meteorological factors (eg, temperature and relative humidity).[7,8]

Recently licensed RSV passive immunisation products targeting protection in infants (including the long-acting monoclonal antibody nirsevimab and maternal RSV bivalent prefusion F vaccine)[9] are expected to provide protection for approximately 6 months.[10,11] As such, comprehensive understanding of regional RSV seasonality is imperative to help define the timing of RSV immunisation programmes. We previously showed that most LMICs had clear RSV seasonality and could potentially consider seasonal administration programmes for RSV passive immunisation to maximise the per-dose effectiveness.[12] However, within-country variations in RSV seasonality could exist in some of these LMICs, such as Brazil,[13] China,[14] and Kenya,[15] possibly due to within-country variability in geographical and meteorological characteristics; as a result, the optimal RSV immunisation strategy in these countries might differ regionally. Therefore, further evidence-based evaluation is needed to understand the within-country geographic distribution of RSV seasonality, which part of the country would be potentially suitable for a seasonal administration programme, and when to begin a seasonal administration programme.

In this study we focused on China. We aimed to describe RSV seasonality; gain insights into the within-country variations of RSV seasonality by identifying transmission zones; and assess the potential suitability of RSV seasonal immunisation programmes in different regions of China.

Methods

Search strategy and selection criteria

We did a systematic analysis of RSV seasonality in China, which first required a systematic literature review to identify published data on RSV activity. We searched seven electronic databases (Embase, MEDLINE, Web of Science, China National Knowledge Infrastructure, Wanfang Data, Chongqing VIP Information, and SinoMed) for studies published from database inception until May 5, 2023, without language restrictions. The search strategy was developed on the basis of a previously published global systematic review;[6] the following keywords (plus closely related words and synonyms) were used as the search terms: "respiratory syncytial virus", "bronchiolitis", "respiratory infection", "seasonality", "surveillance", "periodicity", "temporal", and "China". The detailed search strategy is presented in appendix 2 (pp 1–2). We included studies of any design done in China (including Hong Kong, Macao, and Taiwan) reporting at least 25 RSV cases (as the minimum threshold used in a previous study on seasonality of respiratory viruses[6]), with available aggregated data on RSV case number by calendar month or week; the reported data were also required to cover at least 12 consecutive months before the year 2020 (as RSV seasonality was reportedly affected by the COVID-19 pandemic).[16] Studies only reporting nosocomial infections or respiratory infections only among people with specific medical conditions (eg, patients infected with HIV) were excluded. For multiple studies from the same site (eg, same hospital), we included the study with the highest number of RSV cases. Although we had no criteria regarding laboratory testing approach, studies were excluded if RSV cases were confirmed solely by serological tests. Studies that reported only aggregated data across multiple provinces were excluded. Studies identified by expert recommendation were also considered according to the inclusion criteria.

For eligible studies, we used a tailored data extraction sheet in Microsoft Excel 2021 to collect information about study characteristics (including location and setting, study period, age range, case definition, clinical specimen, and testing approach) and weekly or monthly data on RSV activity. We used the software WebPlotDigitizer (version 4.6) to read and extract data reported in graphs. The literature search, screening, and extraction were all done independently by two authors (LG and SD), with any disagreements arbitrated by YL.

To supplement the published literature, we included open-access data on weekly RSV cases from the Nationwide Weekly Respiratory Virus Positive Isolates database of the Taiwan National Infection Disease Statistics System, and from the Detection of Pathogens from Respiratory Specimen database of the Hong Kong Centre for Health Protection. The same eligibility criteria as in the systematic review applied to these additional data sources.

Quality assessment

Before the formal quality assessment, we did preliminary quality screening for each potentially eligible study and for the online datasets using a self-designed screening form, as previously detailed (appendix 2 p 3).[6] Only studies and datasets that passed the preliminary quality screening were included in the analysis and subsequently underwent a formal quality assessment process with a Joanna Briggs Institute critical appraisal tool. The Joanna Briggs Institute checklist for prevalence or incidence studies[17] was used, which consists of nine questions (appendix 2 p 4). For each question, the answer of "yes" indicated high quality; overall quality score was defined as the number of questions receiving a "yes" for each study.

Studies and datasets were categorised into one of four quality levels depending on the overall quality score, defined for the present study as high quality (8–9 points), moderate quality (6–7 points), low quality (4–5 points), and very low quality (0–3 points). Two reviewers (LG and SD) independently did the preliminary quality screening and formal quality assessment with any disagreements arbitrated by YL.

See **Online** for appendix 2

Data analysis

To aggregate data, weekly numbers of RSV cases were first converted to monthly data (calendar months) with use of the R package wktmo before they were processed further. For each study site, we totalled the number of RSV cases by calendar month across study years. By doing this, we hypothesised that RSV seasonal pattern was relatively stable from year to year at each site (we tested this hypothesis in a prespecified exploratory year-on-year analysis that analysed each year separately among studies that reported data for at least 5 years). Across all datasets, we excluded data on RSV activity from Jan 1, 2020, onwards, to avoid the effects of the COVID-19 pandemic.

As in previous studies,[6,7,18] an RSV season was defined with use of the annual average percentage (AAP) approach, with the following formula:

$$\mathrm{AAP}_i = \frac{n_i}{\sum_1^{12} n_i} \times 100\%$$

Where i denotes each month and n denotes the number of RSV cases for month i.

For **WebPlotDigitizer** see https://automeris.io/WebPlotDigitizer

First, the AAP for each calendar month was calculated and the months were sorted in descending order according to their AAP. Then, the cumulative sum of the AAP was calculated sequentially in descending order until the cumulative sum of the AAP reached 75%. Each month that contributed to the cumulative sum of the AAP (of ≥75%) was defined as an epidemic month; if the cumulative sum of the AAP exceeded 75% with the addition of the last epidemic month (ie, month m), then only a proportion of that month was considered an epidemic month, determined by the formula:

For the **data from the Taiwan National Infection Disease Statistics System** see https://nidss.cdc.gov.tw/en/Home/Index

For the **data from the Hong Kong Centre for Health Protection** see https://www.chp.gov.hk/en/statistics/data/10/641/642/2274.html

$$\mathrm{EP}_m = \frac{0{\cdot}75 - \mathrm{cumAAP}_{m-1}}{\mathrm{AAP}_m}$$

Where cumAAP denotes cumulative AAP per month, and EP_m denotes the epidemic proportion of month m (numeric example available in appendix 2 [p 5]).

The total duration of RSV seasonal epidemics (in months) was calculated with the formula $m-1+\mathrm{EP}_m$. The AAP method was previously shown to have consistent results with other common methods,[19] and was not dependent on the RSV testing approach in this analysis. As in our previously published analysis,[12] we defined sites with a maximum epidemic duration of

5 months (ie, any duration spanning >0 to 5 months inclusive) as having clear RSV seasonality, and longer than 5 months as no clear RSV seasonality.

We defined individual RSV seasons as clusters of consecutive epidemic months for all provinces with or without clear seasonality. Since epidemic months could either be consecutive or separated, there might be one or multiple RSV seasons in a year. We defined the onset of an RSV season by the beginning month of consecutive epidemic months. As a special case, any standalone RSV epidemic month formed an individual RSV season. An RSV season with the highest number of RSV cases in a year was defined as the primary season. Our prespecified year-on-year exploratory analysis assessed differences in primary season onset over consecutive study years (among studies reporting data for ≥5 years) between provinces with and without clear RSV seasonality. For each site, the absolute difference between the primary season onset determined in a single year and across all study years was calculated; the mean and 95% CI of the absolute differences across different study years was reported as the measure of year-on-year variation.

We selected province as the geographical unit for the analysis of RSV seasonality. There are 34 provincial administrative units in China, with Hong Kong, Macao, and Taiwan individually included. We assumed small within-province variations in RSV seasonality compared with between-province variations. When multiple studies were available from the same province, the number of RSV cases was summed for each calendar month across these studies. There were no restrictions on the number of study-years per province. As a threshold for insufficient data,[6] provinces with a total number of RSV cases fewer than 100 were excluded from further analysis that compared RSV epidemic season onset and duration across provinces, and that identified transmission zones, although monthly RSV activity was summarised for all provinces with study data. We did a prespecified within-province exploratory analysis that compared municipality-level results in provinces that had available RSV data for three or more municipalities; as an ad-hoc analysis, we did a municipality-level analysis for Fujian province that had shown two RSV epidemic seasons in a year at the province level. We also did an ad-hoc within-municipality exploratory analysis that compared study-level results in municipalities with available RSV data from five or more studies, in which we calculated the difference between the RSV season onset month identified in each study and that identified from aggregated data across studies for the same municipality, and reported the mean and 95% CI of the absolute differences across studies as the measure of within-municipality variation. In within-province and within-municipality analyses, we did prespecified comparisons of areas with and without clear RSV seasonality.

In the main analysis of RSV seasonality, we described the province-level primary season onset month, distribution of epidemic months, and duration of RSV epidemics, and described how these varied across provinces. We used Pearson's partial correlation analysis to assess the correlation between RSV season duration and the latitude and longitude of the individual provinces (taking the provinces' centroids). As ad-hoc sensitivity analyses, we did the same Pearson's partial correlation analysis with varied restrictions regarding the number of study-years (excluding provinces with <5 study-years or <10 study-years) and the number of RSV cases (excluding provinces with <1000 RSV cases or <2000 RSV cases) per province. We also did prespecified sensitivity analyses to investigate how RSV seasonality varied when changing the threshold to define RSV seasons, from a cumulative AAP of 75% to a lower threshold of 70% and higher threshold of 80%; and when excluding studies reporting RSV activity data in the first RSV season following the onset of the 2009 influenza pandemic (defined as July 1, 2009, to June 30, 2010).[20] As a further prespecified sensitivity analysis, we excluded studies or datasets of low or very low quality.

To identify transmission zones, which were defined for this study as groups of provinces with similar RSV seasonality where a universal RSV intervention strategy could be applied, we used two independent approaches: an infant-passive-immunisation-driven approach (moving interval approach; a self-designed clustering approach based on the possible scenarios regarding infant passive immunisation) and a data-driven approach (*k*-means approach[21]).

In the moving interval approach, we grouped provinces on the basis of whether a seasonal RSV immunisation programme would be suitable, and (if suitable) from which month of the year that seasonal programme might start to have maximum effectiveness. On the basis of published clinical trial results on the long-acting monoclonal antibody nirsevimab[10] and maternal RSV bivalent prefusion F vaccine,[11] we assumed a protection period of 6 months and calculated cumulative AAP in a 6-month-moving interval for each province, yielding 12 different totals. Although a seasonal immunisation programme would have higher per-dose effectiveness than a year-round programme, the total effectiveness would be lower as not all months of a year would be covered in a seasonal programme. Therefore, to help establish the suitability of a seasonal programme, the total effectiveness in a seasonal programme relative to the year-round programme should stay above a threshold. We used a threshold of 80% for the purpose of this study; if the maximum total AAP in the 6-month moving interval of a province was more than 80%, then the beginning month of the interval would be regarded as the optimal starting month of an RSV immunisation programme; if no 6-month moving interval had a cumulative AAP greater than 80%, the province would be regarded as being not suitable for a seasonal immunisation programme. As prespecified sensitivity analyses, we changed the threshold of 80% to 70% and 90%. As ad-hoc exploratory analyses, we assessed within-municipality variation by comparing the optimal beginning months as determined by each study with the optimal beginning months as determined by the aggregated data over all studies from the same municipality; and the year-on-year variation by comparing the optimal beginning months as determined for each year and from the aggregated data over all study years for the same site.

In the *k*-means approach, we applied the *k*-means algorithm to the monthly AAP of each province, where *k* denotes the number of clusters, defined as individual groups of provinces that had similar monthly AAP. This algorithm was based on minimising the sum of squares of the Euclidean distances (of monthly AAP) from the provinces to the centroid of the cluster. Both the elbow method[22] and the gap statistics method[23] were used to identify the optimal value of *k* with use of the R package factoextra. In addition, we set *k* arbitrarily to 4 and 6 for comparison as sensitivity analyses. In a further prespecified sensitivity analysis, we explored hierarchical clustering as an alternative approach to the *k*-means approach with results presented in a dendrogram.

All data analysis and visualisation were done in R software (version 4.2.2). Figures were generated with the R package ggplot2.

The systematic review of the literature was registered with PROSPERO, CRD42022376993. The PRISMA checklist is presented in appendix 2 (pp 54–57).

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In the systematic literature search, we identified 9157 records. After the exclusion of duplicates, 5889 records were screened, and subsequently 1238 full-text reports were assessed for eligibility, of which 156 studies met the eligibility criteria. The addition of one more published study identified from expert recommendation gave a total of 157 studies, along with the two online datasets from the Taiwan National Infection Disease Statistics System and Hong Kong Centre for Health Protection. All studies and datasets passed the preliminary quality screening and were subsequently included (figure 1, appendix 2 pp 22–26). Summary information on the included studies and datasets is provided in appendix 2 (pp 7–21). In the formal quality assessment process, 61 (39%) of 157 studies were rated as high quality and 88 (56%) were rated as moderate quality; the remaining eight (5%) studies were rated as low quality. The Hong Kong Centre for Health Protection dataset was rated as moderate quality and the Taiwan National Infection Disease Statistics System dataset as low quality (appendix 2 pp 27–34).

The 157 studies and two online datasets reported data on a total of 194 596 RSV cases over 442 study-years (covering the period from Jan 1, 1993 to Dec 31, 2019),

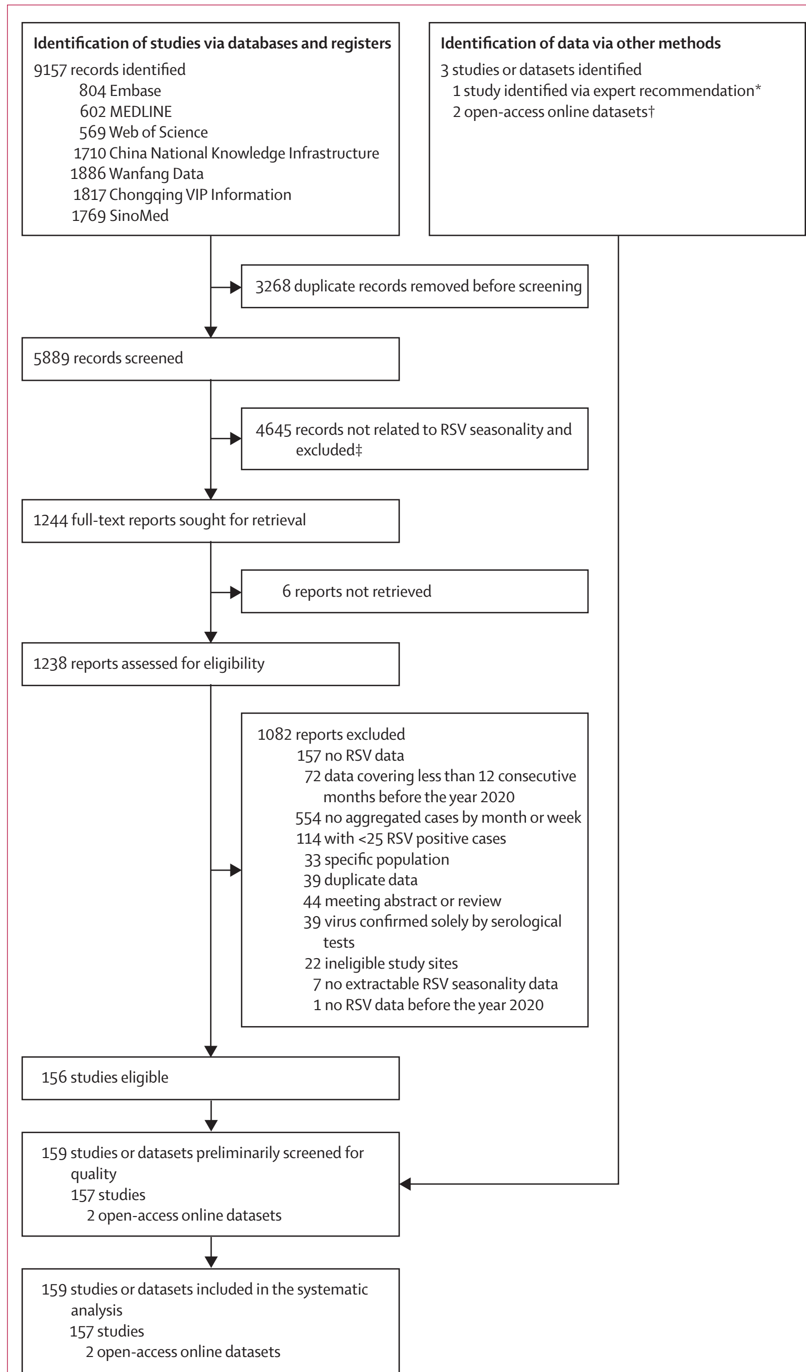

Figure 1: **PRISMA flow diagram of the systematic literature search**
*Identified from expert recommendation, which was deemed eligible per inclusion requirements despite not being identified in the search. †The same inclusion crtieria as in the systematic review was applied to these datasets. ‡Evident from titles or abstracts that the records did not contain data on RSV seasonality.

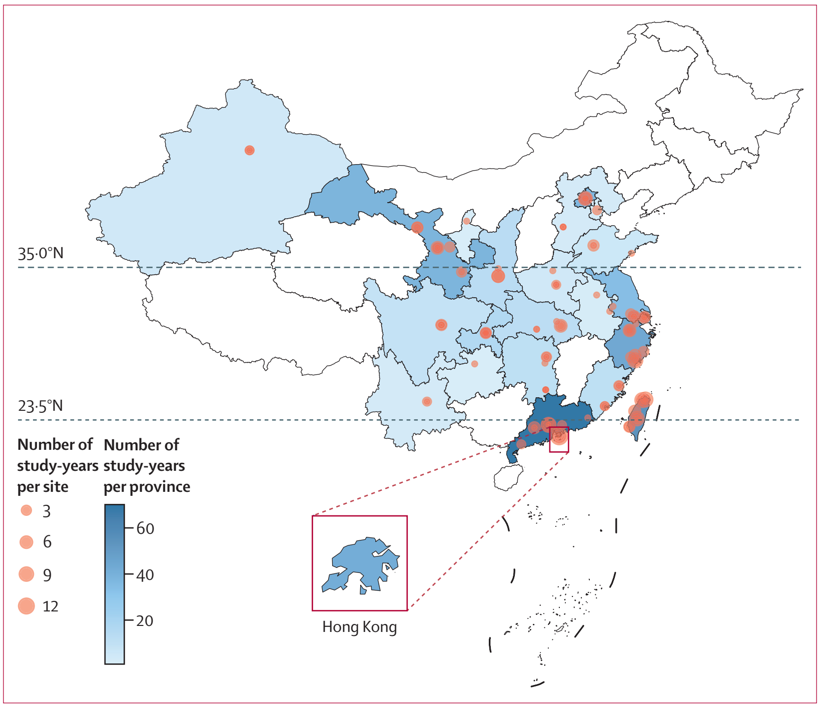

Figure 2: **Distribution of respiratory syncytial virus activity data in the study**
Provinces without data are shown in white. 23·5°N denotes the Tropic of Cancer, separating the tropics and subtropics; 35·0°N separates the subtropical and temperate regions in the northern hemisphere. No data were identified from the South China Sea Islands (excluded from the analysis).

from 52 sites in 23 provinces (figure 2). The study periods ranged from 1 year (in Guizhou, Shaanxi, and Ningxia) to 69 years (in Guangdong), with a median study duration of 11 years (IQR 4·0–35·5). The number of RSV cases ranged from 29 (in Tianjin) to 64 010 (in Hong Kong), with a median case number of 2642 (IQR 424–7565; appendix 2 pp 36–37). Two provinces (Ningxia and Tianjin) did not meet the sample size threshold for comparisons of seasonality between provinces and transmission zone analysis (each having <100 cases); the results for the two provinces are summarised in appendix 2 (p 39).

Substantial variations in the duration of RSV seasonal epidemics were observed across provinces (figure 3, appendix 2 pp 36–37). Among the 21 provinces with sufficient data, the median epidemic duration was 4·6 months (IQR 4·1–5·4). We observed a latitudinal gradient in the length of duration (r=–0·69, p<0·0007), in that provinces at the lowest latitudes (on or near the Tropic of Cancer) had the longest epidemic duration (from lowest to highest duration, Yunnan, Fujian, Guangdong, Hong Kong, and Taiwan; range 6·4–7·4 months). No significant correlation was identified between longitude and duration (r=–0·15, p=0·53). Similar correlation results were observed in sensitivity analyses that restricted the number of study-years and the number of RSV cases in the provinces (appendix 2 p 48). 13 (62%) of 21 provinces had clear RSV seasonality, as defined by having a maximum epidemic duration of 5 months (figure 3, appendix 2 pp 36–37). In sensitivity analysis, three additional provinces (16 [76%] overall) were identified as having clear RSV seasonality when making the threshold to define RSV seasons less strict (ie, 70% of cumulative AAP instead of 75%; appendix 2 p 49). When making the threshold stricter (ie, 80% of cumulative AAP), the number of provinces with clear RSV seasonality was reduced to nine (43%). The results of the sensitivity analysis excluding low-quality studies and the sensitivity analysis that excluded studies reporting data from the 2009 influenza pandemic period were generally similar with that of the main analysis (appendix 2 p 49).

Substantial variations were noted in the distribution of RSV epidemic months across different provinces (figure 4, appendix 2 p 35). Despite these variations, 15 (71%) of 21 provinces had RSV epidemics from November to March. 14 (67%) provinces had RSV season onset in October or November. All provinces had one RSV season in a year except for Fujian (two seasons). An ad-hoc subgroup analysis within Fujian province showed two RSV seasons in Xiamen and one RSV season in Fuzhou (appendix 2 p 53).

Exploratory analysis showed minor year-on-year variation in the month of RSV season onset in provinces with clear RSV seasonality (appendix 2 p 45); the mean absolute difference from the average season onset month was 0·6 months (95% CI 0·4–0·9) across years (based on 32 study-years of data from six studies and four provinces). Conversely, the year-on-year variation in provinces without clear RSV seasonality was higher (appendix 2 p 45); the mean absolute difference was 1·4 months (0·8–2·0; 17 study-years of data from three studies and two provinces). Consistent findings were observed when replacing RSV onset month by the optimal beginning month of a seasonal immunisation programme by the moving interval approach (appendix 2 p 46).

Seven provinces with available data for three or more municipalities (Gansu, Guangdong, Hubei, Hunan, Jiangsu, Taiwan, and Zhejiang) were assessed in an exploratory analysis to understand within-province variations in RSV activity (figure 5, appendix 2 pp 40–42). For provinces with clear RSV seasonality (Gansu, Hubei, Hunan, Jiangsu, and Zhejiang), a small amount of within-province variation was observed. For the other two provinces (Guangdong and Taiwan), a greater amount of within-province variation was noted. For example, in Guangdong, four of the six municipalities had two RSV seasons in a year; jointly at the province level, these separated epidemic months formed a consecutive (and long) RSV season. In the municipality of Huizhou, the onset month of the epidemic differed considerably from the onset month in other municipalities in the region (figure 5).

When multiple studies (≥5) reported RSV seasonality for the same municipality, our exploratory analysis showed small variations in the month of RSV season onset both in municipalities with clear RSV seasonality and those without (appendix 2 p 43). Across studies, the mean absolute difference from the corresponding municipality-level estimate of onset was 0·6 months (95% CI 0·3–1·0; based on 106 study-years of data from 32 studies) for three municipalities with clear RSV seasonality, and 0·9 months (0·3–1·5; based on 54 study-years of data from 14 studies) for two municipalities without clear RSV seasonality. Similarly, small variations were observed when replacing RSV onset month by the optimal beginning month of a seasonal immunisation programme by the moving interval approach (appendix 2 p 44).

According to the moving interval approach, the 21 included provinces were categorised into four transmission zones (figure 6A). Five provinces (Fujian, Guangdong, Hong Kong, Taiwan, and Yunnan) were identified as not being suitable for seasonal infant immunisation programmes, with the maximum AAP in 6-month intervals between 59% and 72% across these provinces. Among the remaining 16 provinces, Hebei was suitable for a seasonal programme beginning in September (2 months before the season onset) and all other provinces were suitable for a seasonal programme beginning in either October (Anhui, Chongqing, Henan, Hubei, Jiangsu, Shaanxi, Shandong, Shanghai, Sichuan, and Xinjiang) or November (Beijing, Gansu, Guizhou, Hunan, and Zhejiang; 0–1 month before the season onset; appendix 2 p 38). The sensitivity analysis that used a less strict criterion (ie, 70% of cumulative AAP in the 6-month interval instead of 80%) resulted in the addition of Yunnan to the list of provinces suitable for a seasonal programme (starting in July, the month of onset); the sensitivity analysis that used a stricter criterion (ie, 90% of cumulative AAP in the 6-month interval) categorised most of the provinces into not being suitable for a seasonal programme; the provinces that remained suitable for a seasonal programme were Beijing, Guizhou, Hebei, Henan, Shandong, and Xinjiang (appendix 2 p 50). For both sensitivity analyses, the optimal beginning months for seasonal programmes did not differ from those identified in the main analysis.

With the *k*-means approach, the elbow method and gap statistic method both indicated that the optimal number of clusters was two (ie, two transmission zones; appendix 2 p 47). Transmission zone one included six provinces: Fujian, Guangdong, Hong Kong, Hunan Taiwan, and Yunnan (figure 6B). These six provinces were those that were on or near the Tropic of Cancer. The remaining 15 provinces were in transmission zone two. Sensitivity analysis that used hierarchical clustering yielded the same clustering results, with the six aforementioned provinces having increased Euclidean distance (the root of the summed squared differences in monthly AAP between different provinces) from the remaining provinces (appendix 2 p 51). Sensitivity analysis that set *k* to a value of 4 or 6 did not return meaningful clustering results due to the limited total number of provinces (n=21) relative to the number of clusters (appendix 2 p 52).

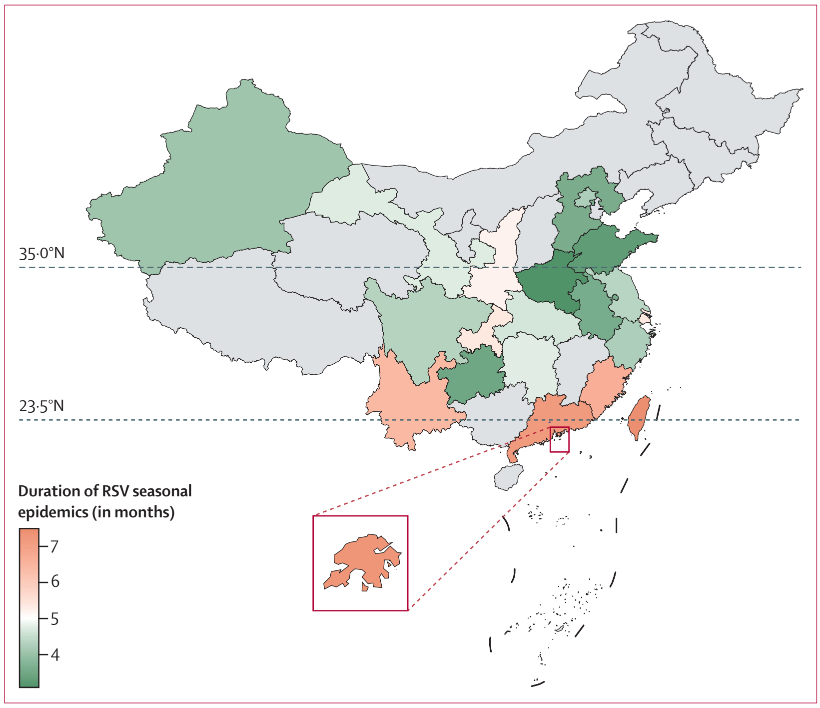

Figure 3: **Distribution of duration of RSV seasonal epidemics**
Provinces with no data or without sufficient data (<100 cases; Ningxia and Tianjin) are shown in grey. 23·5°N denotes the Tropic of Cancer, separating the tropics and subtropics; 35·0°N separates the subtropical and temperate zones in the northern hemisphere. RSV=respiratory syncytial virus. The South China Sea Islands were excluded from the analysis.

Discussion

In the present analysis, we collated data on RSV activity in China from a systematic literature review and online databases. For a sample of more than 190 000 RSV cases, we presented RSV seasonal patterns at the national, provincial, and, where possible, municipal levels. Although we highlighted substantial variations in RSV seasonality among different provinces, we also identified shared seasonal patterns across some provinces in terms of the onset and duration of RSV seasons. On the basis of these commonalities, we classified provinces into transmission zones. Four transmission zones were identified by the moving interval approach that assessed the suitability and optimal timing of a seasonal passive immunisation programme for infants. Two transmission zones were identified by the data-driven *k*-means approach, which appeared to classify the provinces by proximity to the Tropic of Cancer. These analyses did not only address knowledge gaps on RSV seasonality in China, but also provided a practical methodology framework for analysing and interpreting regional variations in RSV seasonality for countries with large

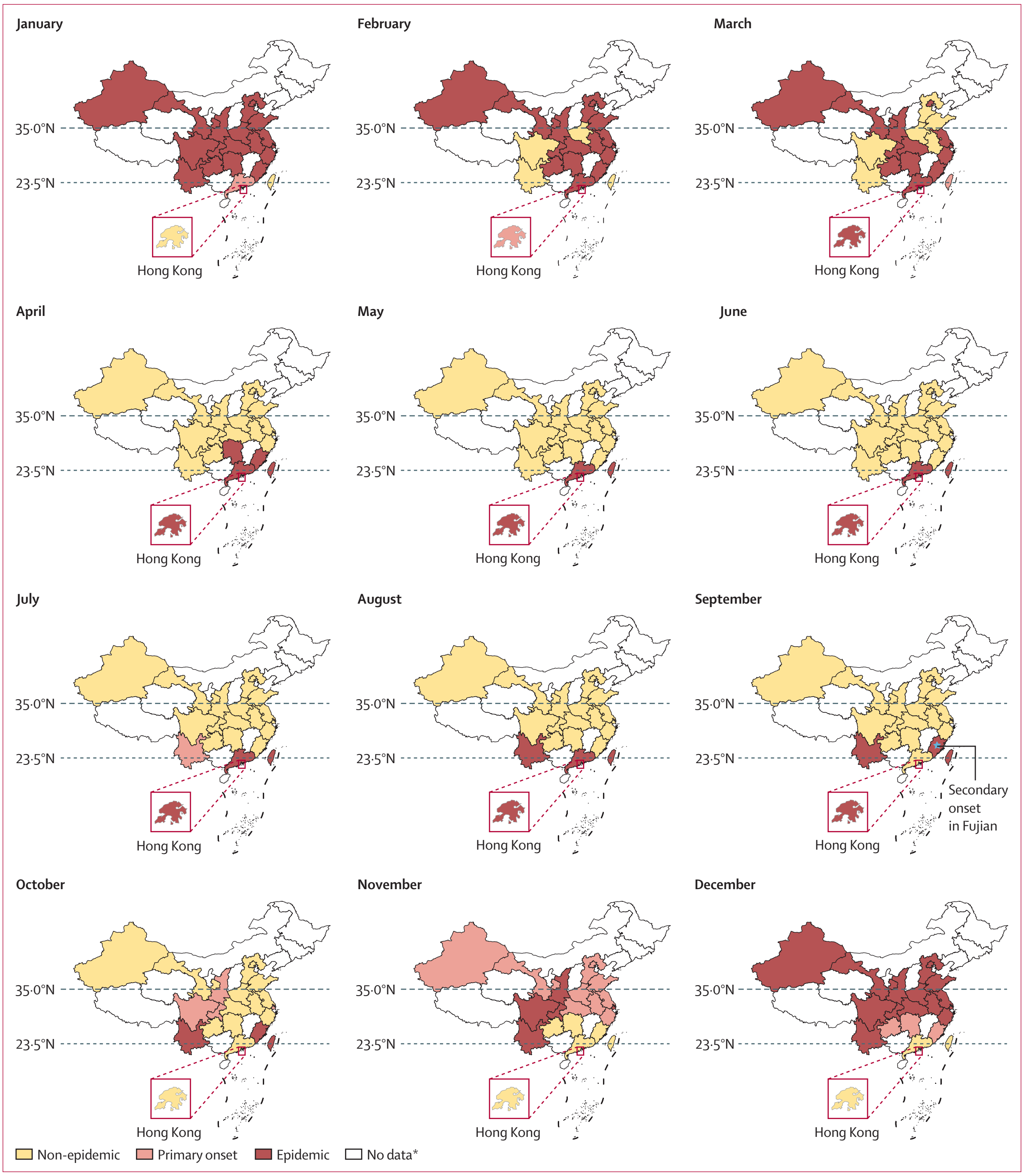

Figure 4: **Distribution of RSV epidemic months and primary onset month of the RSV season**
23·5°N denotes the Tropic of Cancer, separating the tropics and subtropics; 35°N separates the subtropical and temperate regions in the northern hemisphere. The South China Sea Islands were excluded from the analysis. RSV=respiratory syncytial virus. *Includes provinces with insufficient data (<100 cases; Ningxia and Tianjin).

geographical span or that are known to have varied RSV seasonal patterns. The resulting transmission zones could have important implications for coordinating regional efforts for the prevention and control of RSV within countries.

The two approaches complemented each other. Although the moving interval approach had direct implications for a seasonal RSV immunisation programme, it was subjective and required an arbitrary AAP threshold (80%) for establishing suitability for a seasonal RSV immunisation programme. By comparison, the *k*-means approach identified the clusters of provinces with similar RSV seasonality in an objective manner, although transmission zones detected in this way might not have a direct public health implication. Overall, the two approaches yielded similar results in that five of six provinces not suitable for a seasonal immunisation programme as indicated by the moving interval approach were all classified into one cluster by the *k*-means approach. Although the moving interval approach further grouped provinces suitable for a seasonal immunisation into three transmission zones, these provinces were not differentiated by the *k*-means approach, because the *k*-means approach tends to be conservative when the sample size (ie, number of provinces) is small.

Consistent with a previously published global analysis,[6] we observed a latitudinal gradient in RSV season duration, with provinces at the lowest latitudes having the longest seasonal epidemics. Interestingly, provinces with clear RSV seasonality generally had minor year-on-year and within-province variations (ie, clear and stable seasonality), and thus were potentially suitable for seasonal RSV immunisation programmes, as confirmed by the moving interval approach, which could maximise per-dose effectiveness.[12,24] By contrast, provinces with no clear seasonality had notable year-on-year and within-province variations (ie, not clear or stable seasonality). Similar observations were reported in a multicountry analysis of RSV surveillance by Staadegaar and colleagues;[5] countries in the tropics and subtropics had less of a seasonal pattern in RSV epidemics, with high year-on-year variation, than countries outside the tropics and subtropics.

According to the moving interval approach, four transmission zones were identified. Five of the 21 provinces (Fujian, Guangdong, Hong Kong, Taiwan, and Yunnan) were indicated to be unsuitable for seasonal passive immunisation programmes in infants. These provinces all had prolonged RSV seasons spanning more than 6 months, and 6 months is the expected duration of protection granted by infant passive immunisation products.[10,11] Furthermore, two separate RSV seasons were identified in Fujian (driven by data from Xiamen that showed two RSV seasons) and in municipalities of Guangdong and Taiwan. Among the 16 provinces where a seasonal immunisation programme was considered suitable, the optimal beginning month was around the month of October. The overall consistency in the optimal timing of an immunisation programme across these provinces supports the feasibility of implementing seasonal programmes at the national or regional level.

Comparison of the RSV seasonality observed in this study and the influenza seasonality reported previously in China[25–27] reveals both similarities and differences. For both RSV and influenza, clear annual circulating seasons were observed in high-latitude provinces, with seasons occurring primarily during winter months, although the RSV season onset (October or November) appeared to precede influenza season onset (December) by 1–2 months, in accordance with the results from a global-level analysis.[6] Although seasonality tended to be less distinct in the low-latitude provinces for both RSV and influenza, some of these provinces had two separate influenza seasons, one in the winter months and the other in the summer months (mostly associated with the H3N2 strain),[25–27] in contrast to the pattern observed for RSV. As a national recommendation has been made by the Chinese Center for Disease Control and Prevention to implement influenza immunisation programmes in each province according to local influenza seasonality,[28] the comparison of RSV and influenza seasonality could be informative for local public authorities when considering a joint seasonal vaccination campaign for influenza and RSV.

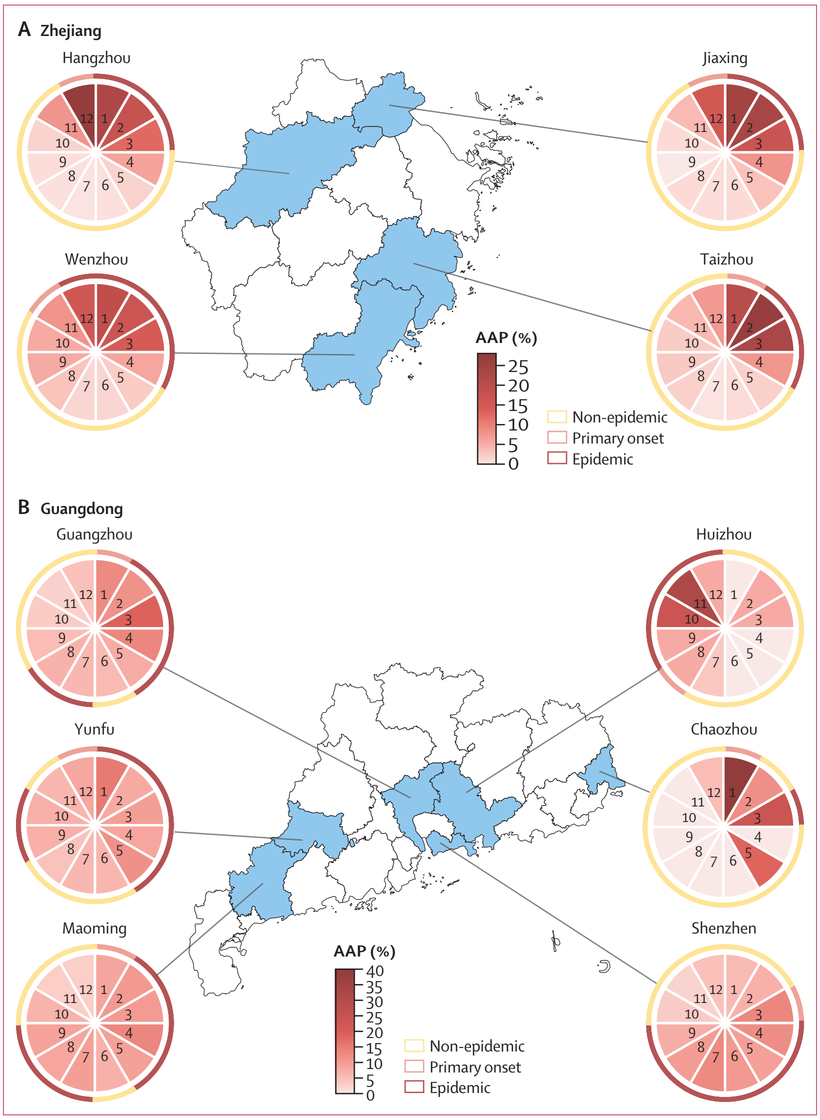

***Figure 5:* Within-province variations in respiratory syncytial virus activity in Zhejiang province (A) and Guangdong province (B)**

Municipalities without data are shown in white. Numbers 1 to 12 denote calendar month. Results for the other five provinces assessed in this exploratory analysis are available in appendix 2 (pp 40–42); Zheijiang and Guangdong had data available for the highest number of municipalities and represent provinces with and without clear RSV seasonality, respectively. AAP=annual average percentage.

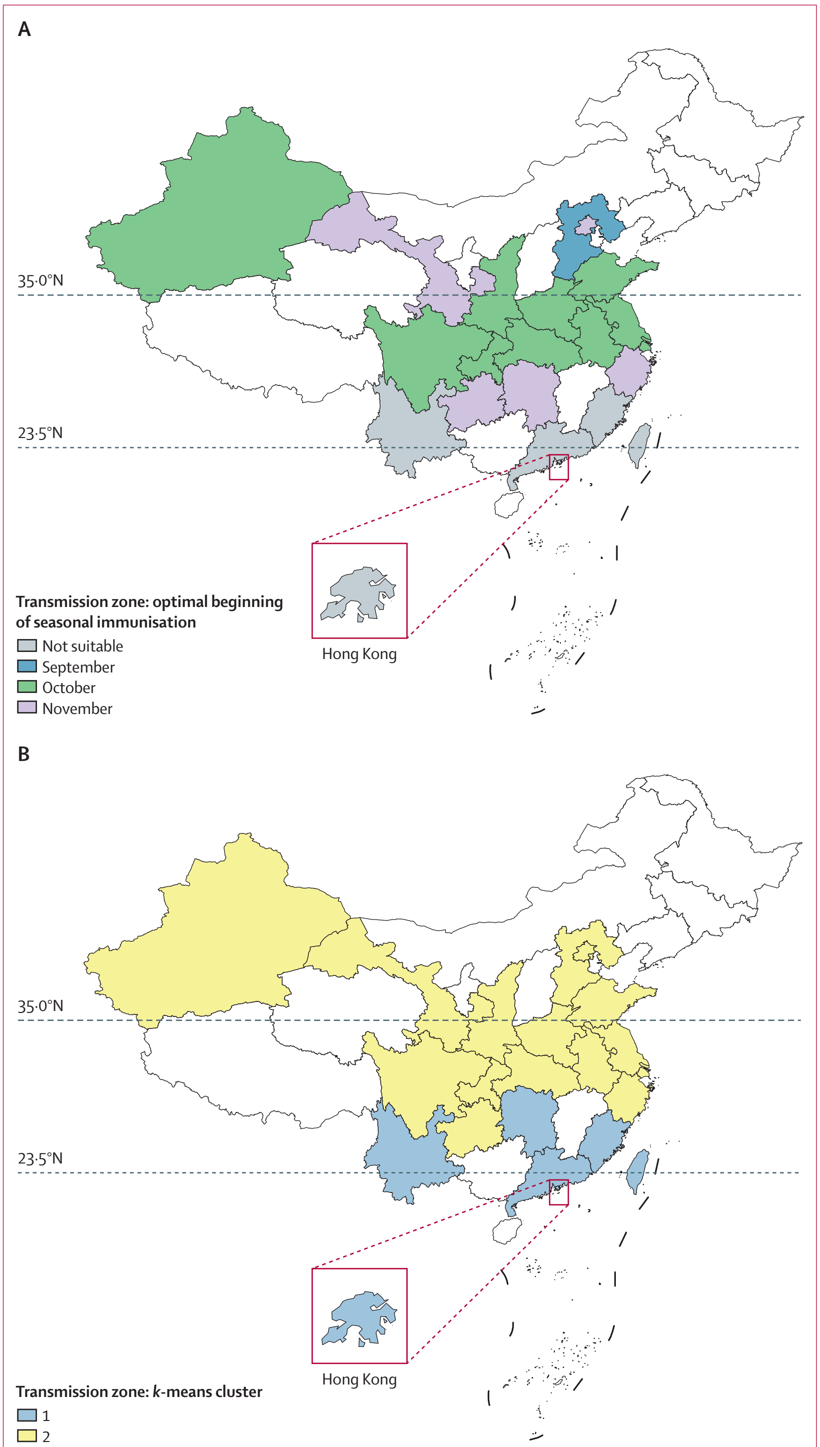

Figure 6: **Distribution of respiratory syncytial virus transmission zone identified by the moving interval approach (A) and *k*-means approach (B)**
Provinces with no data or without sufficient data (<100 cases; Ningxia and Tianjin) are shown in white. 23·5°N denotes the Tropic of Cancer, separating the tropics and subtropics; 35°N separates the subtropical and temperate regions in the northern hemisphere. The South China Sea Islands were excluded from the analysis.

We acknowledge several limitations in this study. First, because of the absence of nationwide RSV surveillance in China (as in other LMICs), RSV activity data were extracted from published reports and two province-level databases. The various data used potentially led to heterogeneities in the seasonality results that could arise from differences in study population, eligibility for RSV testing, clinical specimens, and diagnostic testing approaches. To help reduce heterogeneities, we selected the AAP approach for defining RSV season, which is insensitive to the variations in testing approaches in individual studies. We also did an exploratory analysis to estimate between-study variations within the same municipality, and found small variations between studies, both in municipalities with and without clear seasonality. However, the inclusion of published data from various sources raises concerns about quality of the data. To address these concerns, we did a preliminary quality screening to exclude studies that did not meet the minimum quality threshold, followed by a formal quality assessment. We showed that most of the included studies (149 [95%] of 157) were moderate to high quality, and the Hong Kong Centre for Health Protection dataset was rated as moderate quality, providing reassurance on overall data quality. Furthermore, our sensitivity analysis that excluded low-quality studies or datasets yielded findings similar to the main analysis.

Second, we acknowledge limitations regarding data availability. The data in our study did not represent provinces in the north-eastern part of China or the two provinces in the west at high altitudes (Tibet and Qinghai); we therefore cannot exclude the possibility that these provinces have unique RSV seasonal patterns that do not fall into any of the transmission zones identified in our study. Monthly RSV activity data were used in the analysis, rather than weekly aggregated data as used in other surveillance data-based studies,[5,7] which would have affected the precision of our estimates. Furthermore, we did not formally assess publication bias of these data, although publication bias might not be substantial given the focus of the systematic review was studies describing RSV seasonality rather than association analyses.

Third, the transmission zones identified by the moving interval approach that assessed suitability for a seasonal passive immunisation programme should be interpreted in the context of its underlying assumptions. The approach was based only on historical data of RSV activity (quantity and quality of data varied across provinces), and applied an arbitrary cutoff of 80% of cumulative AAP for establishing suitability. As shown in the sensitivity analysis, changes in the cutoff could yield different classification results. Furthermore, it was beyond the scope of this analysis to compare different variations in seasonal immunisation programmes (eg, immunisation in the beginning month of the season only versus immunisation in all months of the season). Also, province-specific programme suitability of a seasonal immunisation programme, such as accessibility, acceptability, and infrastructure, was not evaluated. Therefore, although the moving interval approach can help in understanding the overall RSV transmission zones in China, the results should not be interpreted as a recommendation for individual provinces.

Finally, considering the impact of the COVID-19 pandemic and its related non-pharmaceutical interventions on the seasonality of RSV,[16] we chose not to include data after the onset of the COVID-19 pandemic as our focus was on the normal seasonal pattern of RSV and its relevance to a prevention strategy. Recently published studies from other countries show that RSV seasonality in the post-pandemic era gradually returned to its pre-pandemic normality,[29,30] supporting the use of pre-COVID-19 pandemic data in our study. However, we cannot exclude the possibility that RSV seasonality will continue to exhibit distinctions from the pre-pandemic period in the next 3–5 years. Therefore, RSV surveillance needs to be established in China as well as in other countries to monitor the changes in RSV circulation in the future.

Notwithstanding these limitations, our study used a uniform analytical method to provide an overview of the distribution of RSV seasonality in different parts of China. By categorising provinces into different RSV transmission zones, we present the suitability and optimal timings of a seasonal infant passive immunisation programme. To date, the long-acting monoclonal antibody nirsevimab is the only agent to have been approved by the National Medical Products Administration of China (in December, 2023), and is expected to enter the Chinese market for the 2024–25 RSV season.[31] Our findings could have important implications for decision making on an RSV passive immunisation strategy, regionally and nationally. The methodological framework for defining RSV seasons and identifying RSV transmission zones in this study is also potentially applicable to other countries or regions that need to understand the geographical distribution of RSV seasonality and its relevance to RSV immunisation strategy.

Contributors

YL and XW conceptualised the study. LG and SD co-led the data collection with input from SS. LG led the data analysis with substantial contributions from SD and YL. SD, LG, YL, and XW interpreted the data. LG wrote the first draft of the manuscript with substantial input from SD, YL, XW, and SS. All authors read and approved the final draft for submission. LG and SD verified the aggregated study data for analysis in this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

XW reports grants from GSK, outside the submitted work. YL reports grants from WHO, the Wellcome Trust, and GSK, and personal fees from Pfizer, outside the submitted work. All other authors declare no competing interests.

Data sharing

All study data included in the analysis are in the public domain and have been properly cited. The extracted data and R codes for identifying respiratory syncytial virus seasonal epidemics can be found on GitHub (https://github.com/Glinnnng/RSVseasonality_China).

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Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps and tables.

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