



Time series analysis of RSV and bronchiolitis seasonality in temperate and tropical Western Australia



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ARTICLE INFO

Article history:

Received 3 February 2016

Received in revised form 8 May 2016

Accepted 9 May 2016

Available online 25 May 2016

Keywords:

Respiratory syncytial virus

Bronchiolitis

Complex demodulation

Seasonality

Fourier analysis

ABSTRACT

Respiratory syncytial virus (RSV) causes respiratory illness in young children and is most commonly associated with bronchiolitis. RSV typically occurs as annual or biennial winter epidemics in temperate regions, with less pronounced seasonality in the tropics. We sought to characterise and compare the seasonality of RSV and bronchiolitis in temperate and tropical Western Australia. We examined over 13 years of RSV laboratory identifications and bronchiolitis hospitalisations in children, using an extensive linked dataset from Western Australia. We applied mathematical time series analyses to identify the dominant seasonal cycle, and changes in epidemic size and timing over this period. Both the RSV and bronchiolitis data showed clear winter epidemic peaks in July or August in the southern Western Australia regions, but less identifiable seasonality in the northern regions. Use of complex demodulation proved very effective at comparing disease epidemics. The timing of RSV and bronchiolitis epidemics coincided well, but the size of the epidemics differed, with more consistent peak sizes for bronchiolitis than for RSV. Our results show that bronchiolitis hospitalisations are a reasonable proxy for the timing of RSV detections, but may not fully capture the magnitude of RSV epidemics.

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1. Introduction

Respiratory syncytial virus (RSV) is the most common cause of severe respiratory illness in young children. RSV is associated with bronchiolitis and pneumonia, with up to 70% of bronchiolitis hospital admissions attributable to RSV infection (Mansbach et al., 2012). Like influenza (Thai et al., 2015; Alonso et al., 2015), RSV fluctuates with season (Pitzer et al., 2015), potentially due to climatic drivers. In temperate regions, RSV is highly seasonal, with annual or biennial (two-yearly) epidemics, while the epidemiology of RSV in the tropics is less well understood (Weber et al., 1998; Paynter et al., 2014).

To plan for RSV epidemics, two measures are of interest: the number of cases at the epidemic peak, and the timing of this peak. In this paper, we use complex demodulation, a time series approach that allows us to visualise both the timing and size of RSV epidemics, and to detect shifts in epidemic behaviour over time. Complex demodulation has previously been applied to the

analysis of geomagnetic data (Kingan et al., 1980) and individual-level health data such as cardiovascular rhythms (Hayano et al., 1993; Shin et al., 1989; Kondo et al., 2014; Sasai et al., 2013), but to our knowledge has not yet been applied to population-level epidemiological data, except in the analysis of suicide data (Nader et al., 2011).

Laboratory testing for RSV is not routinely conducted in all jurisdictions and thus some studies have relied on hospitalisation coding for bronchiolitis to indicate the timing, severity and hospital burden of RSV epidemics (Walton et al., 2010; Murray et al., 2014; Polkinghorne et al., 2011). As other pathogens, such as adenoviruses and influenza viruses, also contribute to the burden of bronchiolitis, it is of interest to investigate the extent to which bronchiolitis hospitalisations are representative of RSV detections.

In this study, we examined over a decade of RSV detections and bronchiolitis hospitalisations in children aged up to 17 years from an extensive linked dataset from Western Australia. Geographic information on individuals in this dataset allowed us to compare seasonal patterns of illness across eight geographic regions spanning temperate, sub-tropical and tropical climate zones. We used a time series approach to identify seasonal patterns in RSV and bronchiolitis epidemics, and to detect changes in the timing and severity

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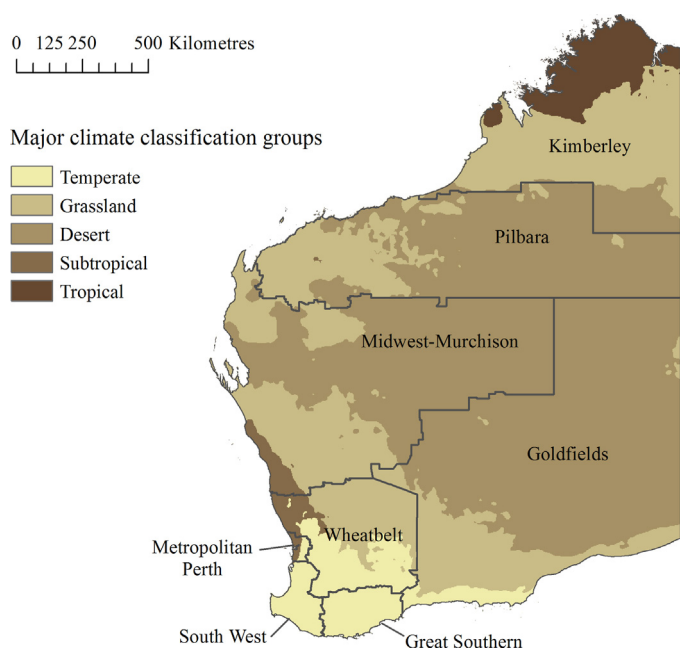


Fig. 1. Geographical map showing the eight administrative health regions in Western Australia and the major climatic zones, based on the Köppen classification system. The data for the climatic zones were sourced from the [Australian Government Bureau of Meteorology \(2016\)](#), and that for the administrative regions from the [Australian Bureau of Statistics \(2011\)](#), using the 2006 Statistical Divisions as a close proxy for the health administrative regions.

of these epidemics over time. By comparing RSV and bronchiolitis data, we assessed the extent to which the characteristics of these outbreaks coincided, and thus the value of bronchiolitis data as a proxy for RSV.

2. Methods

2.1. Setting

Western Australia is Australia's largest state by land area, spanning approximately 2.6 million square kilometres. Approximately 80% of the population resides in the Metropolitan region surrounding and including Perth, in the state's south-west. Western Australia is characterised by a range of climatic zones, including tropical, sub-tropical, grasslands and temperate. The state is classified into different health administrative regions: Kimberley, Pilbara, Goldfields, Midwest-Murchison, Wheatbelt, Great Southern, South West and Metropolitan. [Fig. 1](#) shows a map of the state created using ArcMap 10.3.1, with administrative health regions and the main climatic zones based on the Köppen classification system. As of June 2014, Western Australia had a population of approximately 2.57 million people, 3.6% of whom identify as Aboriginal and Torres Strait Islander (hereafter referred to as Aboriginal) ([Australian Bureau of Statistics, 2013](#)). Demographic characteristics vary across the state, with the Pilbara and Kimberley regions (in the north of the state) having a much higher proportion of Aboriginal children and a lower population density than the Metropolitan region ([Australian Bureau of Statistics, 2007](#)).

2.2. Linked data

This study forms a part of a larger program of work which aims to investigate the pathogen-specific epidemiology of acute lower respiratory infections in children. For the parent study, using the total population-based Western Australian Data Linkage System (WADLS), data relating to a birth cohort of 469,589 children born

in Western Australia from 1996 to 2012 were extracted from the following datasets: Midwives Notification System (MNS), Birth and Death Registry, Hospital Morbidity Data Collection (HMDC), Emergency Department Data Collection (EDDC), PathWest Laboratory Medicine Database (PathWest) and the Western Australian Notifiable Infectious Diseases Database (WANIDD). For this study, we used information for all live births from the MNS, Birth and Death Registry and their associated hospital (from HMDC) and laboratory data (from PathWest).

PathWest covers approximately 80% of all pathology samples in Western Australia and is the reference virology laboratory for the state. PathWest data for RSV testing for the children in our cohort were extracted for January 2000–December 2013. RSV testing was conducted using immunofluorescence, polymerase chain reaction (PCR), viral culture, or complement fixation protocols. For one part of the analysis, these data were combined with hospitalisation data to calculate the number of hospital admissions for which an RSV test was recorded, but elsewhere all PathWest laboratory confirmed RSV data were used, regardless of whether it was associated with a hospital admission. An RSV test was considered to be associated with a hospital admission if the date of specimen collection was within a four day period of hospital admission (48 h before until 48 h after). Repeat tests recorded for the same child within 14 days after the first test were considered as being from the same infection episode and were combined. The geographical region was determined based on the postcode recorded for the mother at the time of the child's birth. The residential postcode at the time of specimen collection was not recorded.

For the bronchiolitis cases, we extracted only hospital admissions where acute bronchiolitis was the primary diagnosis (ICD-10-AM code J21/ICD-9-CM code 466.1) for January 1996–June 2013. These comprised 92% of all admissions with any diagnosis of bronchiolitis. Admissions that occurred within 14 days of each other with the same principal diagnosis were assumed to be due to the same bronchiolitis episode. The geographical region was determined based on the residential postcode of the child at the time of hospital admission.

Ethical approval for this research was granted by the Department of Health Western Australia Human Research Ethics Committee (Projects 2011/78 and 2012/56) and The Australian National University Human Research Ethics Committee (Protocol 2015/177).

2.3. Data analysis

We performed a descriptive analysis of the seasonal pattern of RSV detections by plotting the total number of cases for each month between January 2000 and December 2013 for each health region.

Fourier analysis was applied to the RSV and bronchiolitis data for each of the Metropolitan, Pilbara and Kimberley regions. This method identifies dominant seasonal patterns in data, with a strong signal at 12 months indicating an annual epidemic peak. For the Metropolitan region, the analysis was carried out using weekly data, whereas for the other regions, monthly data were used due to smaller numbers. Linear trends in each dataset were removed using linear regression. The de-trended data were padded with zeros in order to increase the frequency resolution and produce smoothed plots ([Bloomfield, 2000](#)). Fourier analysis was performed on the resulting time series data to identify the dominant periodicities (the length of the seasonal cycle), using MATLAB's periodogram analysis algorithm ([Bloomfield, 2000](#)).

Complex demodulation was applied to weekly RSV and bronchiolitis data (separately) for January 2000–June 2013 for the Metropolitan region using MATLAB. There were insufficient data to perform complex demodulation for the other regions. An introduction to complex demodulation is provided in the Supplementary

Table 1

The total number of RSV and bronchiolitis cases for each region. The RSV data are for January 2000–December 2013, whereas the bronchiolitis data are for January 1996–June 2013.

Region	Number of RSV cases	% under 2 years	Number of bronchiolitis cases	% under 2 years
Kimberley	348	80.5%	1,852	95.8%
Pilbara	306	82.0%	1,140	95.7%
Midwest–Murchison	381	81.4%	1,164	94.9%
Goldfields	663	82.5%	1,217	96.0%
Wheatbelt	362	77.1%	929	92.0%
Metropolitan	8,969	81.8%	14,681	98.0%
Great Southern	313	72.8%	920	91.3%
South West	498	81.3%	1,338	94.0%

material. Briefly, with respect to an underlying annual seasonality, complex demodulation extracts the size of the epidemics (the ‘amplitude’) and the timing of the epidemics (the ‘phase’).

The method is as follows. Using the notation of Bloomfield (2000), we constructed the demodulated series y_t from the given time series data x_t , as:

$$y_t = x_t e^{-2\pi i f_0 t} = R_t e^{2\pi i \phi_t},$$

where the amplitude is represented by R_t , the phase is represented by ϕ_t , and we assumed a 52 week period ($f_0 = 1/52$). A 52-week moving average filter was then applied to smooth the demodulated time series, and we then extracted the amplitude R_t , and the phase ϕ_t , from the smoothed data (see Supplementary material for more detail).

As an addition to a visual representation of the complex demodulation results, we calculated correlation coefficients for the complex demodulation amplitudes and phases for the RSV and bronchiolitis data. This provided a statistical measure of the alignment between the RSV and bronchiolitis data.

In order to perform a preliminary investigation of the relationships between weather variables and RSV and bronchiolitis epidemics, we obtained daily records of minimum and maximum temperatures, and monthly records of total precipitation, from the Australian Government Bureau of Meteorology (2016). We applied complex demodulation to each of these time series, and extracted the filtered amplitudes and phases.

2.4. Sensitivity analysis

While the majority of RSV infections are detected in children less than two years of age, older children may still be diagnosed (Borchers et al., 2013). In the hospital setting, bronchiolitis is generally diagnosed only in children less than two years old. Further, as our analysis was conducted on birth cohort data, not all ages are represented at the start and end of the time windows. To test for any bias resulting from these factors, we repeated the analysis for hospitalisation data for children less than two years of age. There were insufficient data to analyse children two years and older. We also repeated the Fourier analysis of the bronchiolitis data for 2000–2013 in order to perform a direct comparison with the Fourier analysis of the RSV data for the same time period.

3. Results

The descriptive analysis showed that nearly all bronchiolitis hospitalisations were in children less than two years of age, while 73–83% of RSV diagnoses were in children aged less than two years. Table 1 summarises the number of RSV and bronchiolitis cases for each health region. Between 2000 and 2012, of 18,710 hospitalisations with a principal diagnosis of bronchiolitis, 54.6% ($n = 10,219$)

were tested for RSV within 48 h of presenting to hospital. Of these, 58.3% ($n = 5966$) were found positive for RSV.

Most regions of Western Australia had a seasonal peak in RSV detections in July or August (Fig. 2). However, in the Pilbara region the seasonal peak was less well defined, and no pronounced seasonal peak was visible for the Kimberley region. A corresponding figure for the bronchiolitis data is provided in the Supplementary material (Fig. S2). The subsequent analysis focuses only on the three regions with distinctly different seasonal patterns: the Metropolitan, Pilbara and Kimberley regions.

Both RSV and bronchiolitis exhibited strongly annual seasonal epidemics in the Metropolitan region. This became less pronounced in the Pilbara region, and there was no clear seasonal cycle evident from analysis of the Kimberley data. Figs. 3 and 4 demonstrate this using a Fourier analysis of the RSV and bronchiolitis data. Each graph shows the different seasonal cycles on the horizontal axis, with the strength of this cycle on the vertical axis. A comparison of Figs. 3 and 4 indicates that the periodicities of RSV and bronchiolitis are very similar in all three regions. Results were similar when this analysis was repeated with the dataset restricted to children less than two years of age (see Supplementary Figs. S6 and S7), and when the bronchiolitis dataset was restricted to 2000–2013 (see Supplementary Fig. S5), although in both cases the signal was weaker.

The complex demodulation results are plotted in Fig. 5. The weekly RSV and bronchiolitis cases for Metropolitan Western Australia between January 2000 and June 2013 show a clear seasonal pattern, although there is greater variability in peak heights in the RSV data (Fig. 5, top two panels). With the exception of 2010–2011, there is visible evidence of an alternating pattern of bigger and smaller annual peaks (a biennial pattern) in the RSV data that is less apparent in the bronchiolitis data. The average weekly RSV cases are noticeably higher in even years while there is less change in average weekly bronchiolitis cases. The third ‘amplitude’ panel also captures the change in the RSV pattern in the years 2010–2012, where the cycle appears to shift from biennial to annual.

In terms of the complex demodulation phase, the peak RSV and bronchiolitis cases are observed in mid-July through to early August throughout 2000–2006 (Fig. 5, fourth panel). Apart from 2007, the timing of the epidemic peaks of RSV and bronchiolitis are very similar, with later epidemic peaks typically coinciding with smaller outbreaks. The correlation coefficient for the complex demodulation phases is $\rho = 0.963$, compared to the amplitude correlation coefficient of $\rho = 0.667$. In 2007 however, there is a clear ‘dip’ in the phase that indicates a shift in epidemic peak timing in that year, with RSV peaking in September and bronchiolitis peaking in August. We repeated the complex demodulation analysis for children less than two years of age, and found similar results, with correlation coefficients of $\rho = 0.757$ and $\rho = 0.964$ for the complex demodulation amplitudes and phases, respectively (see Supplementary Fig. S8). The complex demodulation results for weather variables in Perth, Western Australia, are shown in Supplementary Figs. S9–S11.

4. Discussion

Our study enabled us to characterise the seasonal patterns of RSV and bronchiolitis in the different climatic zones of Western Australia. The data analysis (Figs. 2–4) showed that both RSV detections and bronchiolitis hospitalisations exhibit clearly defined epidemic peaks in July or August in the southern Western Australia regions. There is a less identifiable seasonal pattern in the Pilbara region in the state’s north, and no seasonal peak evident in the Kimberley region. We used complex demodulation (Fig. 5) to show that the timing of RSV and bronchiolitis epidemics over 13 years

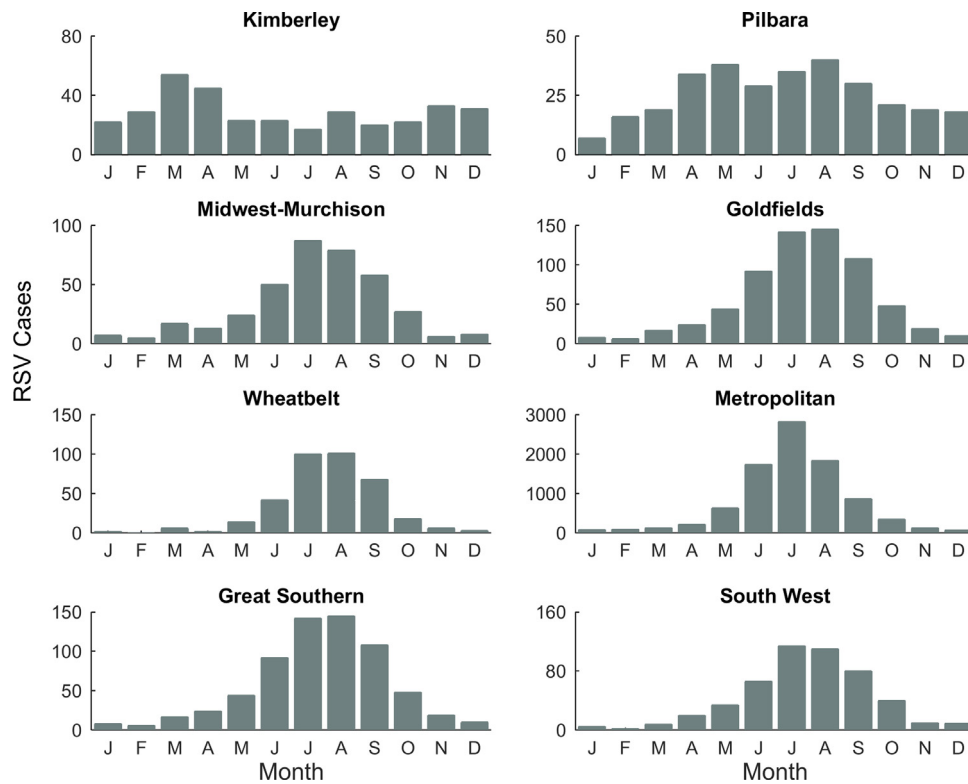


Fig. 2. Total number of positive RSV detections by month between 2000 and 2013 inclusive for each health region in Western Australia. Note that the vertical axis differs by region. See Fig. 1 for a map of these eight regions.

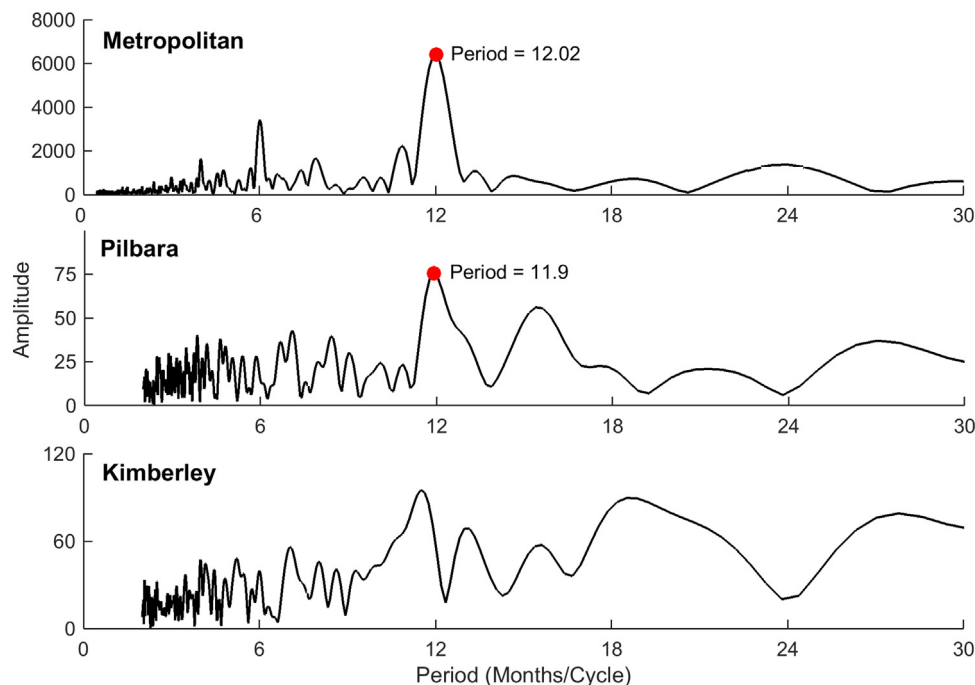


Fig. 3. Monthly periodicity of RSV detections in three health regions in Western Australia: Metropolitan, Pilbara and Kimberley, generated using Fourier analysis. Where a clear dominant period is present (as it is for the Pilbara and Metropolitan regions), the period is marked, but as the periodicity is not clear for the Kimberley, it is not marked.

generally coincided. However, the sizes of the epidemics differed, with a more marked change in the size of RSV epidemics from year to year.

Our findings indicate that there is a clear shift in the seasonality of both RSV and bronchiolitis from temperate to subtropical climatic zones in Western Australia. In the Metropolitan region, there

is a dominant annual seasonal pattern that is stronger for RSV than for bronchiolitis, even though there were more bronchiolitis cases in our dataset. This may be because bronchiolitis can be caused by other pathogens (such as rhinovirus and influenza), which have different, or less regular, seasonal patterns. Also in the Metropolitan region, there was a change in dynamics within the time window

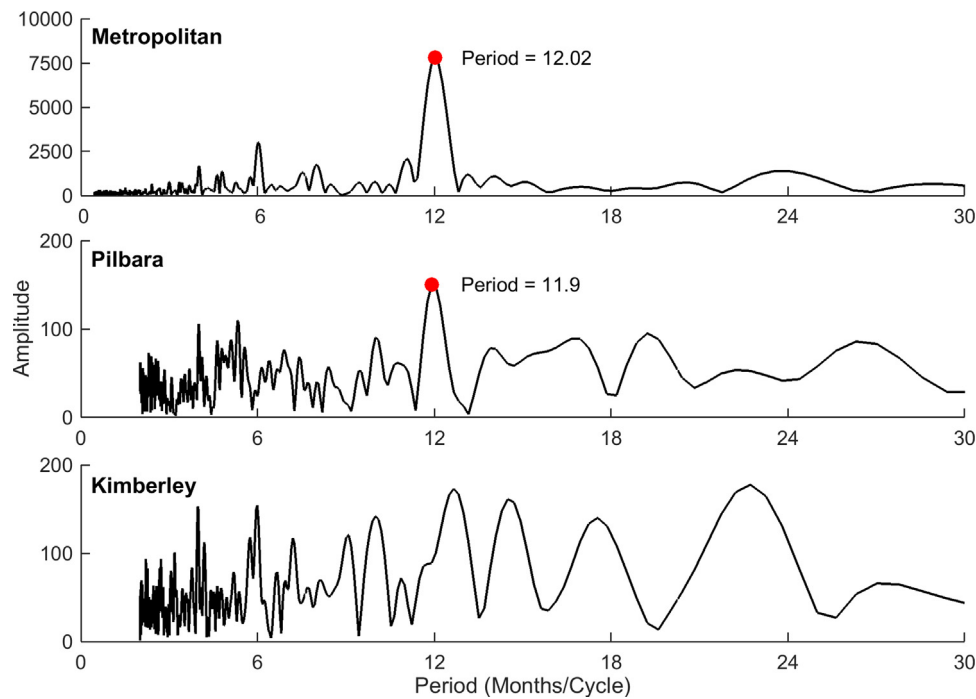


Fig. 4. Monthly periodicity of bronchiolitis hospital admissions in three health regions in Western Australia: Metropolitan, Pilbara and Kimberley generated using Fourier analysis. Where a clear dominant period is present (as it is for the Pilbara and Metropolitan regions), the period is marked, but as the periodicity is not clear for the Kimberley, it is not marked. Here the data analysed was for March 1996–June 2013.

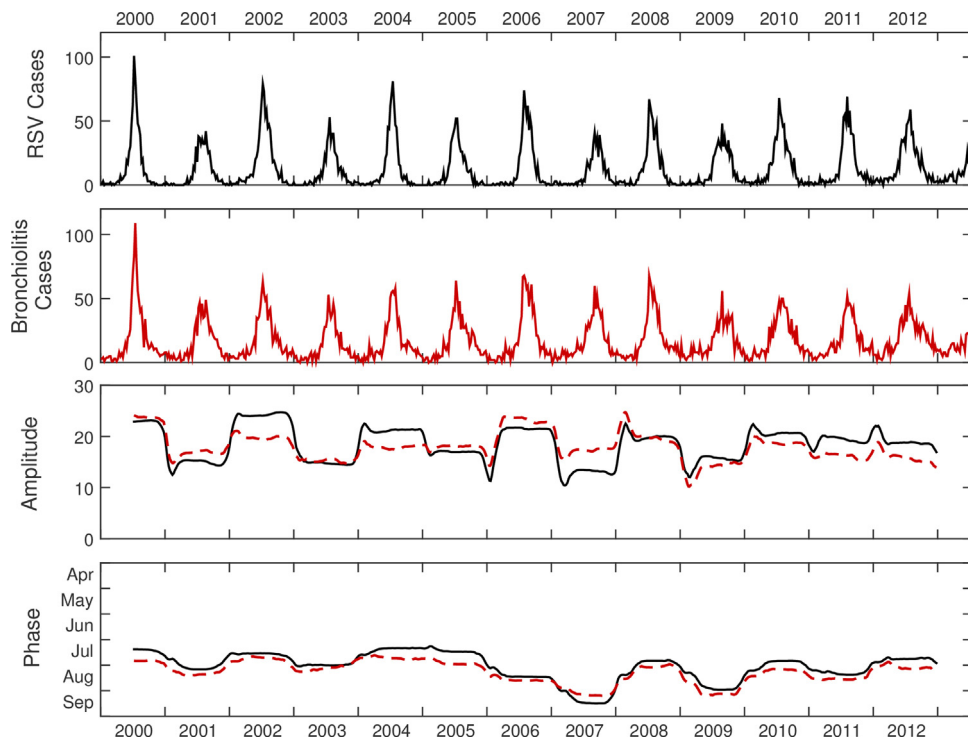


Fig. 5. Results of the complex demodulation analysis applied to RSV and bronchiolitis time series data for Metropolitan Western Australia, for all age groups. The top two panels show weekly RSV and bronchiolitis cases for January 2000–June 2013, while the lower two panels show the amplitude (the yearly moving average of weekly cases for the underlying seasonal pattern), and phase (the timing of the epidemic peak) for RSV (black) and bronchiolitis (red dashed). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of our dataset, with the RSV dynamics shifting from a biennial pattern to an annual pattern, something that has also been observed in California (Pitzer et al., 2015).

The complex demodulation analysis showed a change in epidemic timing for both RSV and bronchiolitis cases in 2007, where

the epidemic peak occurred later than in other years. In another study, we considered factors including demography that could be driving the change in the timing of epidemic peaks in consecutive years (Hogan et al., 2016). As such, we looked at the annual birth rate for Western Australia, but there was no marked change

in either 2006 or 2007 to indicate any demographic shift (Australian Bureau of Statistics, 2009).

Weather has been suggested as a driver of change in RSV's seasonal patterns, and has been investigated in a number of settings (Noyola and Mandeville, 2008; Haynes et al., 2013; Pitzer et al., 2015; Vandini et al., 2013). However, no single driver has yet been identified, and it is likely that a range of factors contribute to the observed seasonal patterns of RSV. Applying complex demodulation to weather records from the Bureau of Meteorology (Supplementary Figs. S9–S11) showed no obvious link between RSV and bronchiolitis dynamics and weather patterns in Western Australia's Metropolitan region, in terms of monthly precipitation and daily maximum temperature. The complex demodulation results for the daily minimum temperature showed dips in amplitude in 2007 and 2009, which corresponded with the dips in phase for RSV and bronchiolitis in the same years. However, further statistical analysis would be required to confirm a link between smaller fluctuations in minimum temperature and delayed RSV epidemics. Another possibility is pathogen interference, such as the circulation of the H3N2 influenza strain in 2007, which resulted in above average influenza circulation (Kelly et al., 2011) and may have competed with RSV.

While RSV outbreaks in temperate climates typically occur in the winter months, seasonal patterns in tropical regions have not been widely studied (Weber et al., 1998). Paynter et al. (2015) investigated the seasonality of RSV in Cairns and Townsville in tropical eastern Australia, and showed that the peak of RSV infections occurs in March in Cairns, and March/April in Townsville. The study indicated that RSV epidemics may be driven by seasonal rainfall in the tropics. Chew et al. (1998) identified a clear seasonal trend in RSV infections in Singapore, with epidemics occurring between March and August, while Chan et al. (2002) documented seasonal variations in RSV infections in Malaysia, with epidemics occurring between November and January. Our data analysis (Figs. 2–4) demonstrated a weak seasonal peak in the Pilbara region, and no clear seasonal pattern in the Kimberley region in Western Australia's north, adding to the existing evidence that RSV dynamics shift between temperate and tropical regions.

Wavelet analysis is another time series method that has been successfully applied to the analysis of epidemiological data (Cazelles et al., 2014, 2007), as well as in other contexts. Wavelet analysis is useful for analysing localised variations in the underlying pattern in the time series data over time. Therefore, wavelet analysis is appropriate when the data is non-stationary (that is, when the dominant frequency changes over time), particularly when the location of some isolated event needs to be identified (Priestley, 1996). In cases where the data is stationary, such as for the present bronchiolitis and RSV data, complex demodulation offers distinct advantages in that it allows us to extract and visualise variations in the data from the underlying dominant seasonal pattern, and it is especially useful for comparing the variation in epidemic size and timing for different datasets. There is potential to apply complex demodulation to other epidemiological datasets, and it could be used to investigate the potential interference patterns between RSV and other respiratory pathogens such as influenza.

A key strength of our study is the breadth of our dataset. Population-based linked epidemiological data for Western Australia provides a valuable opportunity to explore RSV and bronchiolitis dynamics in different climatic regions. While Western Australia spans several climatic zones, data collecting methodologies and health systems are consistent across the state. It should be noted that the dataset is limited to children hospitalised for bronchiolitis or tested for RSV, and not all children with respiratory illness would be hospitalised or tested. However, laboratory testing to detect possible pathogens from respiratory infection-related hospitalisations is routine practice across Western Australia.

As our data is likely only accounting for the severe end of the respiratory illness spectrum, we know little about RSV infection in the community. However, we expect patterns observed in the severe cases to be representative of community patterns.

A limitation is that the postcodes in the health regions in northern Western Australia cover large geographic regions, but in practice, spatial distributions of the resident populations in these areas are uneven. In addition, the case numbers for both RSV and bronchiolitis are small in the northern regions, making seasonal patterns in the data more difficult to detect. Furthermore, there was a shift away from viral culture towards more sensitive PCR testing for RSV from 2008 onwards (data not shown) that was not accounted for in the present analysis, but is unlikely to affect seasonal patterns.

Our findings have public health implications for RSV in terms of health care system planning. Immunoprophylaxis with the monoclonal antibody, palivizumab, has been found to be effective in reducing the severity of RSV-related disease, but requires an understanding of the RSV epidemic timing for implementation (The IMPact-RSV Study Group, 1998). Moore et al. (2009), in a study using bronchiolitis hospitalisations as a proxy for RSV-related illness, recommended that immunoprophylaxis schedules to be broadened in non-metropolitan areas in Western Australia. While there is no licensed vaccine for RSV, there are several candidates undergoing clinical trials (Broadbent et al., 2015). Understanding the dynamics of RSV epidemics in different regions will be important for planning optimal vaccine allocation.

Researchers often use bronchiolitis data for analysis of respiratory viruses in young children, as it is more readily available than laboratory data (Murray et al., 2014). While the connection between RSV and bronchiolitis is widely accepted, with the majority of bronchiolitis cases caused by RSV infection, there is a lack of understanding about how this link varies both within and between RSV seasons. Our findings help to justify the value in using bronchiolitis hospitalisation data as a proxy for RSV cases where testing data is less available, particularly in rural and remote areas.

Acknowledgements

The authors acknowledge and thank the Linkage and Client Services Teams at the Western Australian Data Linkage Branch, in particular Alexandra Godfrey, as well as the custodians of all datasets used. We would also like to thank Charmaine Tonkin and Brett Cawley, from PathWest Laboratory Medicine, particularly for their assistance and support in collating the data. This work was supported by National Health and Medical Research Council Project Grant APP1045668. HC Moore is supported by the National Health and Medical Research Council Early Career Fellowship APP1034254. FJ Lim is supported by a University Postgraduate Award from the University of Western Australia.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.epidem.2016.05.001>.

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