THESIS ARGUMENT MAP: Mathematical models for respiratory syncytial virus (RSV) transmission, by Alexandra Hogan 2017. Adapted by ANU Academic Skills.

Research problem/questions/aims: To understand the seasonal patterns of RSV and develop mathematical models that capture key transmission characteristics. Understanding seasonal patterns and having mathematical models can assist with planning the future rollout of an RSV vaccine.

Argument/key message: I find that both the seasonality and immunity parameters must exceed certain thresholds for the model to produce biennial patterns. I identify a window of birth rate parameters that produces biennial patterns, showing that RSV seasonality may not be only driven by weather and climatic factors as was previously thought. I apply a mathematical time series analysis method, complex demodulation, to assess the validity of using bronchiolitis hospitalisations as a proxy for RSV cases. I find bronchiolitis and RSV are similar in terms of timing, but that epidemic magnitudes differ. I adapt the compartmental model to incorporate a finer age structure, contact patterns and naturally-derived maternal immunity, to assess the potential impact of a maternal vaccination strategy. I find that the introduction of a maternal vaccine is unlikely to alter the regular biennial RSV pattern, but that the vaccine would be effective in reducing hospitalisations due to RSV in children under six months of age.

Introduction	**Chapter 2: Literature review**	**Chapter 3: Data sources and linkage**	**Chapter 4: Age-structured models for RSV**
1.1 Background 1.2 Research motivation: The health care and economic burden of RSV is substantial, yet the transmission characteristics of RSV are not well understood, and little is known about the drivers of the seasonal patterns of incidence. 1.3 Research themes: The goal of this thesis is to obtain a better understanding of the transmission dynamics of RSV by developing mathematical models that capture the RSV infection process. Three research topics form the basis for the grouping of chapters: 1. Age structure and immunity; 2. Seasonality and climate; and 3. Vaccination.	**Broad purpose**: This literature review is in two parts. In the first part, I discuss the known epidemiology of RSV, the available treatment options, the progress towards vaccine development, and the data on RSV detections in different climatic zones. In the second part, I provide a brief summary of the mathematics of infectious disease modelling, before discussing the mathematical modelling of RSV published in the literature to date. **Section**: The clinical nature and epidemiology of RSV I will **argue**: RSV is a significant economic and health care system burden and a current priority for vaccine development. … I reviewed the available literature to identify the dominant RSV seasonal pattern (particularly whether annual or biennial) in a range of countries and regions. This summary, while not exhaustive, indicates how RSV dynamics vary with latitude. **Section**: Mathematical modelling of RSV I will **argue**: Mathematical models are important tools for analysing, understanding and predicting outbreaks of infectious diseases.	Broad **purpose**: This chapter contains a brief description of the data linkage process, and an explanation of the variables used for this thesis. **Section**: Data linkage I will **argue**: Data linkage is the process whereby records from different administrative sources or systems are brought together for each person in a cohort, using a best-practice protocol that protects the privacy of individuals **Section**: West Australian research projects I will **argue**: Western Australia is a world leader in data linkage for health research … which has resulted in a unique set of laboratory-confirmed RSV detections on which this research is based. **Section**: Data used in this thesis I will **argue**: For this thesis, the de-identified linked data were prepared for analysis so as to include only the variables of interest for the present research.	Broad **purpose**: This chapter includes two peer-reviewed papers. The first paper introduces deterministic, ordinary differential equation models for RSV, with both single and multiple age classes. The models are of the compartmental SIR form described in the Literature Review, and I include a preliminary exploration of the dynamics of these models. The main outcome of this paper is to introduce the age-structured differential equation model for RSV transmission, and show that the model produces both annual (one year) and biennial (two-year) dynamics for a range of plausible parameter values. The second paper describes how the multiple age class model was fitted to RSV data for one age class (children younger than 24 months) in Western Australia. In the additional material, I extend the approach from in the second paper to demonstrate how the compartmental model can be successfully fitted to two childhood age classes simultaneously, by modifying the fitting routine and fit statistic. The resulting parameters from fitting to two age classes will be the starting point for the parameter space analysis of the model in later chapters.

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Chapter5: Analysis of the seasonally forced, age structured model	**Chapter 6: Seasonality in the different climatic zones of WA**	**Chapter 7: Interventions for RSV outbreaks**	**Discussion and conclusion**
Broad **purpose**: This chapter includes two publications. In the first paper I explore different age structures in the compartmental ordinary differential equation model, and show that for the RSV transmission model, the inclusion of an age structure with continuous ageing does not change the overall qualitative dynamics produced by the model. This finding validates using a model with only two age classes for the subsequent numerical analyses. The second paper presents sensitivity, parameter space and bifurcation analyses of the two age class model for RSV transmission. The main outcome of this paper is to explore the ranges of parameters that produce different types of solution dynamics - annual, biennial, delayed biennial and tropical - and to quantify the sensitivity of variation in the model output to the parameters. The results in this paper help to explain the different patterns in RSV detections observed globally. In particular, both the immunity and seasonality parameters must exceed certain thresholds for the model to produce biennial and delayed biennial patterns, which aligns with immunity estimates from clinical studies, and RSV epidemic patterns observed at different latitudes. Further, a central region of birth rate parameters produces biennial patterns, outside which regular annual patterns occur. This shows that RSV seasonality may not be only driven by weather and climatic factors, but that demography seems to also play a key role. Finally, the supplementary material to this paper outlines the calculation of the basic reproduction number R0 in the absence of seasonality, which has implications for RSV control measures.	Broad **purpose**: This chapter includes two publications. The first paper is published in The ANZIAM Journal, and introduces the application of a time series analysis method called complex demodulation to seasonal infectious disease data. This paper outlines the mathematics of complex demodulation, and shows the utility of using synthetic data to inform the interpretation of complex demodulation applied to real data. Complex demodulation is also illustrated in the context of national influenza notifications. The second paper is published in Epidemics, and investigates the seasonal patterns of RSV and bronchiolitis in the different climatic regions of Western Australia, to show the difference in seasonality between the temperate and tropical regions. I apply complex demodulation to RSV and bronchiolitis data for the Metropolitan region to investigate how the size of the seasonal peak and epidemic timing change over time, and compare these outputs for RSV and bronchiolitis.	Broad **purpose**: This chapter includes one manuscript, which is currently being reviewed by Vaccine. In this paper, I extend the compartmental, ordinary differential equation models presented in the earlier chapters to include a more realistic age structure. I then incorporate a maternal vaccine for RSV into the model, as well as a mechanism for naturally-derived protective maternal antibodies. I consider a range of vaccine coverage, effectiveness and duration scenarios to evaluate the likely public health benefit of a maternal RSV vaccine in Western Australia. An example of the MATLAB code used to implement the vaccination model is provided in Appendix B.	The objective of this research was to use mathematical models to investigate the seasonal patterns of respiratory syncytial virus (RSV) in Western Australia. In the first stages of this project, I developed simple age-structured compartmental models and fitted these models to data (Chapter 4). I performed numerical analyses to quantify and visualise the broad range of model dynamics, and related these outputs to observed patterns in different regions (Chapter 5). I then conducted a time series analysis of data for Western Australia to identify seasonal patterns in tropical and temperate regions. I also captured changes in the yearly epidemics of respiratory illness in children from year to year in terms of the timing and magnitude of the epidemic peak (Chapter 6). Finally, I extended these models to incorporate a finer age structure and maternally-derived immunity, to evaluate the possible impact of a maternal RSV vaccine program on the number of hospitalised RSV cases in young children (Chapter 7). In this chapter I first provide an overview of the key findings relating to each of the three research themes, and discuss the implications of these findings and their relationship to the existing literature. I then address the strengths and limitations of this research, and suggest directions for future work.