Projections of zoster incidence in Australia based on demographic and transmission models of varicella-zoster virus infection

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We developed a dynamic age-structured mathematical model informed with historical Australian birth and death rates to reproduce varicella and HZ incidence over time. Furthermore we analysed how different assumptions on duration of boosting and HZ recurrence affect the HZ incidence trends. The model is calibrated against age-specific varicella seroprevalence data collected between 1997 and 1999 and varicella and HZ hospitalisation data from AIHW collected between 1993 and 2009.

We show that the reduction of varicella incidence follows the overall decline in birth rate. In the period 1950-2000, this reduction in varicella circulation, together with the aging population, produced a 19.1% increase in HZ crude incidence. However, following age-standardisation, HZ trends showed an increase of 3.3% over the same period.

We found that demographic changes may be partially responsible for the rise in HZ incidence observed prior to and at the beginning of the varicella immunisation program. In order to explain and project more realistic disease incidence trends, future mathematical models should account for demographic changes and present age-standardised results.

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ABSTRACT

Varicella Zoster Virus (VZV) firstly manifests as varicella infection early in life, and then it may reactivate in older age causing herpes zoster (HZ). It is believed that re-exposure to varicella infection boosts against reactivation (exogenous boosting dynamic) delaying or suppressing HZ disease. In this study, we examine the effect that demographic changes could have had on boosting, by reducing VZV re-exposure, and consequently on VZV epidemiological trends in Australia over the 20th century.

We developed a dynamic age-structured mathematical model informed with historical Australian birth and death rates to reproduce varicella and HZ incidence over time. Furthermore we analysed how different assumptions on duration of boosting and HZ recurrence affect the HZ incidence trends. The model is calibrated against age-specific varicella seroprevalence data collected between 1997 and 1999 and varicella and HZ hospitalisation data from AIHW collected between 1993 and 2009.

We show that the reduction of varicella incidence follows the overall decline in birth rate. In the period 1950-2000, this reduction in varicella circulation, together with the aging population, produced a 19.1% increase in HZ crude incidence. However, following age-standardisation, HZ trends showed an increase of 3.3% over the same period.

We found that demographic changes may be partially responsible for the rise in HZ incidence observed prior to and at the beginning of the varicella immunisation program. In order to explain and project more realistic disease incidence trends, future mathematical models should account for demographic changes and present age-standardised results.

1 LITERATURE REVIEW

1.1 Varicella-zoster virus and disease

1.1.1 The varicella-zoster virus

Varicella-zoster virus (VZV) is a double-stranded DNA virus and part of the herpesviradae family of viruses. It has a number of similarities to the herpes simplex viruses, with both types of virus establishing latent infection in the dorsal root ganglia[1].

1.1.2 Natural history of disease

Varicella and herpes zoster (HZ) are the two different disease manifestations of VZV infection. Primary VZV infection is called varicella or chickenpox. After primary infection, the virus enters sensory nerves and travels to the sensory dorsal root ganglia, where it remains in a latent state within the body, potentially for many years, until reactivation as herpes zoster (HZ) or shingles.

The symptoms of the two manifestations differ. Varicella is characterised by a rash that turns into itchy, fluid-filled blisters that eventually form scabs. Varicella infection occurs typically in early childhood and is predominantly mild, with complications in only 1% of cases on average [2] . For HZ, early symptoms, before the rash, are numbness, itching, tingling or a burning pain, but usually this affects only a small part of one side of the body [3]. The initial rash forms clear vesicles, which then become pustular and develop a crust later in the episode. The incidence of HZ, estimated using data on hospital admissions, increases

markedly in older age (>60 years) [4,5]. The high burden of morbidity associated with HZ is mostly due to extended and painful sequelae, such as postherpetic neuralgia (PHN), a persistent pain following the resolution of the HZ rash. PHN affects about 12.5% of HZ patients older than 50 years, with the proportion increasing with age, and symptoms can persist for months or even years [6], with substantial impacts on quality of life [7]. Older age and greater acute pain severity are robust predictors for PHN [8].

While HZ recurrence in immunosuppressed people is well known, it is less clear what happens in immunocompetent people. A study in Minnesota [9] found that the rates of HZ recurrence were comparable with the rates of the first HZ episode. However, others studies [10,11] found that recurrent HZ is rare among immunocompetent adults, with a recent study review[12] founding the risk of recurrence ranged from 1% to 6%. Based on this uncertainty, mathematical models for VZV transmission have generally used the conventional assumption of one HZ reactivation in a lifetime.

1.1.3 Transmission, treatment and prevention

Varicella transmission is mainly person-to-person via the respiratory route, but also occurs by direct contact with vesicle fluid of patients with varicella or HZ infection [13]. However, varicella is a much more contagious disease compared to HZ. Regardless of whether a varicella susceptible person is infected by contact with a case of HZ or varicella, they will develop varicella not HZ. The best way to prevent varicella and HZ is by vaccination, but there are also some antiviral medications, such as Acyclovir, prescribed typically for the treatment of HZ[14].

1.2 VZV reactivation

The predominant explanation for why reactivation occurs, postulated by Hope-Simpson in 1965 [15], is that there is a decline in cell-mediated immunity to VZV with age and time since primary infection. This decline provides an opportunity for reactivation of latent VZV infection causing HZ. However, the dynamics of immune response and reactivation with time and age are not well-characterised [16]. Cell-mediated immunity against VZV is believed to be maintained, at least partially, by periodic immunologic boosting. Endogenous boosting might occur in response to subclinical reactivation of latent VZV or to development of HZ itself, while exogenous boosting occurs in response to external exposure to VZV [17]. Rates of exogenous boosting are therefore likely to be lower in the elderly due to less contact with infected children [18]. Increased rates of reactivation are also seen in infants infected with varicella either congenitally or in the first year of life [19,20] and immunocompromised individuals [21]. However, it is not yet clear which immunological parameters predict who will develop HZ in older ages.

1.3 Duration of exogenous boosting

The hypothesis of exogenous boosting is now supported by numerous studies [22–26], but the extent and duration of boosting is less clear. It has been demonstrated that immunisation of the elderly with a live attenuated VZV vaccine increases VZV cell mediated immunity (CMI) supporting an impact of exogenous boosting [11,27,28] on reactivation risk. Vaccination of individuals >60 years of age with a high-dose live attenuated VZV vaccine in the Shingles Prevention Study (SPS)

showed efficacy of 51% against HZ reactivation, 61% against HZ morbidity and 66.5 % against PHN over a mean follow-up period of 3.13 years [29]. However, the efficacy has been shown to decrease with the age of the vaccine recipients [30] and with time since vaccination [31,32]. The vaccine efficacy beyond 7 years is in doubt with results from the SPS long-term follow up study showing non-significant efficacy at 10 years post vaccination (estimated at 14.1%) [33], and a large US-based retrospective cohort study showing vaccine effectiveness of 4.6% at 8 years after vaccination [34]. In a modeling study, Brisson et. al. [35] used UK general practice data stratified into individuals living with and without children (as a proxy for exposure to VZV) to estimate the duration of protection from boosting. The 'best-fit' model suggested a mean protection of 20 years but this estimate had wide confidence intervals (7-41 years) [35].

The literature on boosting effects of exposure to VZV was recently reviewed by Ogunjimi et. al. [36]. The study supported an overall effect of exogenous boosting on protection against HZ reactivation. However, the duration of the immunity boost from re-exposure varied between studies and a boosting effect did not occur for all people or in every situation. The majority of these studies supported a shorter duration of boosting than suggested by Brisson's analysis, with rises in VZV-CMI lasting in the order of 2 years. Other evidence suggests that the proportion experiencing boosting and the duration of subsequent immunity is related to factors such as the intensity and duration of the contact [37] and the age of the exposed person [38].

1.4 Epidemiology of VZV infection in the pre-vaccination era

1.4.1 Varicella

The lifetime risk of varicella infection in the absence of immunisation is close to 100% [39,40], with most infections occurring between 0 and 14 years of age. The average age at varicella infection has been observed to differ between countries, and trends to be higher in the tropical regions. A higher average age at infection implies a lower force of infection and, as a result, infection rates in adults are higher in tropical regions [41]. Besides climatic effects [41], differences have been attributed to country specific factors such as community and household sizes (larger sizes can increase the probability of spread).

In Australia, before the introduction of universal childhood varicella vaccination in 2005, an estimated 83% of the population were immune to varicella by 10-14 years of age [42], with a lower force of infection than estimated in European countries[43]. An average of 3.5 deaths from varicella were registered between 1980 and 1998 [44], with the highest death rate in the age-group 0-4 years.

Prior to the availability of varicella vaccine, the hospitalisation rate was 9.9 per 100000 population from 1999-2000 [45], with the mean age of varicella infection requiring hospitalisation being 15 years old [46].

1.4.2 Herpes zoster

The lifetime risk of HZ following primary VZV infection is estimated to be 20% to 30% [47–49]. Based on a review of 130 studies from 26 different countries using

prospective surveillance and medical record data, the global incidence of HZ was estimated to be about 3-5 cases per 1000 persons each year, with hospitalisation rates higher in countries with larger elderly populations [12]. Another review [50] found that about the 13-26% of people with HZ develop complications, and studies from England found an increased risk in immunocompromised people [51,52].

In Australians aged >50 years, HZ and PHN incidence rates were estimated to be 10 per 1000 persons and 1.4 per 1000 persons respectively per year using general practice data from 2000 to 2006[53]. This compare with hospitalisation rates of 0.67 and 0.38 per 1000 persons for HZ and PHN respectively per year [53], with the mean age of HZ infections requiring hospitalisation being 69 years old[46].

1.5 Varicella vaccination and concerns

Takahashi et al. [54] developed a live attenuated varicella vaccine in Japan in 1974, using the Oka strain of VZV, with initial use in protection of immunocompromised children [55,56]. In 1989 the vaccine was recommended for immunocompetent children in Japan and Korea [57], but the first country to introduce a 1-dose universal varicella vaccine schedule for children was the USA in 1995. Several other countries such as Uruguay (1999) [58], Canada (2000) [59], Taiwan (2004) [60], Qatar, Korea (2005) [61], Australia (2005) and Japan (2014) [62] followed. There are two live-attenuated-virus varicella vaccines available, Varilrix and Varivax, as well as a quadrivalent formulation that also includes mumps, measles and rubella (MMRV).

In 1998, the World Health Organization (WHO) recommended routine childhood varicella vaccination in countries where the disease is a relatively important public health and socioeconomic problem [63]. However, in Europe only a few countries, such as Germany, Greece and Spain, have introduced universal vaccination [64], while the majority of countries, including the UK, Netherlands, and Italy, do not have varicella vaccination programs.

The three main concerns about the introduction of routine childhood varicella vaccination are in relation to:

1) Vaccine effectiveness;
2) Potential to shift the burden of varicella to adults who have a greater risk of complications;
3) Potential to increase HZ incidence in the short to medium term through reduced boosting.

1.5.1 Vaccine effectiveness

One-dose varicella vaccine showed a sufficient impact on severe natural varicella infection, with effectiveness estimated as 80%-85%. However clinical trials [65–68] indicated that varicella infection occurring in vaccinated individuals (breakthrough infection) was quite common following one-dose of varicella vaccine. Generally breakthrough disease is milder, [66,69] although hospitalisation from breakthrough varicella can still occur [70]. Two-doses of varicella vaccine have higher efficacy (>90%) for both, mild and severe disease [71], with the risk of breakthrough disease over 10 years being estimated to be three times lower than among individuals who received one dose[68].

1.5.2 Increase in the average age at infection

Immunisation of children is expected to increase the average age at infection, which may increase the burden of disease as infection at an older age is generally more severe [72]. In order to avoid this problem a study [73] suggested that countries which introduced universal vaccination for varicella should achieve high coverage (>90%) among children and adolescents. Despite some observations to the contrary [74], there has been evidence of an increase in the average age at varicella infection in the 5 years following the introduction of a one-dose varicella vaccine program in the USA [75], as well as in Taiwan [76]. Furthermore a US study [77], based on active surveillance systems between 1995 and 2010, found a shift in average age at infection, after the introduction of a two-dose vaccine schedule.

1.5.3 Fear of HZ incidence increasing

Vaccination is expected to greatly reduce the circulation of VZV and therefore the force of infection. As such, the number of boosting exposures that people experience is expected to substantially decline. If the Hope Simpson hypothesis is correct, this would lead to a reduction in population immunity to HZ and could lead to a rise in HZ incidence at least in the short term. Evidence in support of this link is provided by observational studies, which observed an increase in HZ incidence after the introduction of varicella vaccination. While lack of age-standardisation could explain this trend in ageing populations [78], an increase in age-standardised incidence has also been found in the USA [79,80] and in Australia

[81,82] (using age-standardised HZ GP consultation data). Furthermore, epidemiological studies [25,35,83], have shown that living with children led to increased protection against VZV reactivation in adults.

1.6 Epidemiological trends following varicella vaccination introduction

Universal varicella vaccination has led to a dramatic decline in varicella incidence in all countries that have introduced an immunisation program [84].

1.6.1 The USA experience

In the USA, introduction of varicella vaccination led to a major reduction in varicella incidence and circulation of VZV [85–91]. However, 1-dose [92] effectiveness was only 80-85% [93], which was insufficient to prevent outbreaks, especially in school environments where exposure is intense [94,95], even in settings with high coverage (97%) [96]. Furthermore, 1-dose vaccine protection has been shown to wane over time in some studies [97,98]. However, another study, following-up vaccinated children for 7 years, showed no waning over time [99], and a 14 year follow-up study [100] showed no-waning over time with the exception of the first few years following vaccination, when most breakthrough varicella infections occurred. In order to achieve a higher vaccine effectiveness, in the USA in 2006, a second dose of varicella vaccine was introduced, with a reported effectiveness of over 90%, resulting in a substantial reduction in varicella incidence and transmission in institution-based outbreaks [101–105].

1.6.2 The Australian experience

In 2005, the VZV vaccine was funded in Australia for use in children at 18 months of age, under the National Immunisation Program (NIP). In Australia, high (>90%) vaccination coverage was reached rapidly. A study looking from 1998 to 2010 [78] found the varicella hospitalisation rate in the target age group (18-59 months) fell to one quarter of that in the pre-vaccine period and a reduction in rates amongst (unvaccinated) children less than one year of age, suggesting a herd immunity effect [78]. A study comparing incidence data from national active prospective surveillance conducted between 1995-7 with similar data from 2006-9 showed a reduction of over 85% in varicella cases [106]. Projections from a modeling study in this context, suggest varicella incidence will continue to decline until 2050 under a one-dose schedule [107].

1.6.3 HZ trends post-immunisation

A number of epidemiological studies have been conducted post varicella vaccine introduction to look at potential impacts on HZ trends with either rising or stable trends identified [46,81,108,109]. However, studies have shown a rise in HZ after vaccination compared with the pre vaccination period: in Australia, using either GP data from BEACH [81] or when looking at HZ hospitalisations in Victoria [109]; in the USA based on hospitalisation rates [80]; and another ecological study based on insurance claims data from Taiwan [110].

An increasing trend began prior to vaccination was also found in a recent study from the USA, based on Medicare claims data [108], an Australian based study on

hospitalisation and antiviral prescription data for HZ [46], and other studies from Canada [111] and Taiwan [112] based on insurance claims data.

However, stable trends were found in three studies [78,85,113] conducted in Australia, the USA and Canada, when age-standardised rates were provided.

A review study conducted in 2008 in the USA on HZ trends highlighted the divergent findings and underlined the need to identify and explore different factors associated with the varicella vaccination program which could affect HZ incidence [114].

The differences between studies are in part due to limitations with the available data, especially hospitalisation data, where errors in coding diseases can occur [113]. Furthermore, a rise in HZ incidence can be due to aging in the population and to an increase in the percentage of older immunocompromised people who are more likely to develop HZ. These different results highlight the need to report age-standardised rates to improve comparisons between different time periods and countries. While age-standardisation is fundamental in presenting more precise HZ incidence trends over time, it is only an initial step towards a proper assessment of the effect that the reduced immune boosting from re-exposures has on the incidence of HZ.

1.7 Mathematical models and predictions of vaccine impact on zoster

Mathematical models have long been used in combination with epidemiological data to identify strategies for the control of infectious diseases. Differing

patterns of disease transmission have led to the development of a wide variety of models to describe outbreaks or transmission chains and subsequent dynamics[115]. In the context of vaccine preventable diseases, it is common to consider a continuous population divided between a discrete set of disease states connected through linear and non-linear transition rates. The susceptible (S), infected (I), recovered (R) model is the basic model used for epidemic dynamics and can be adapted to account for details of the specific disease's natural history and differences between population subgroups. Acronyms for epidemiology models are often based on the flow patterns between the different diseases compartments (SIR) [116].

Several studies have used mathematical models to predict the incidence of varicella and HZ after the introduction of varicella vaccination. The first deterministic age-structured compartmental model used to study the impact of immunisation on the epidemiology of VZV was published by Garnett and Grenfell in 1992 [117,118], which suggested an increase in HZ following immunisation. Following this, Halloran in 1994 [119] used a model without HZ compartments to study the impact of immunisation on varicella, suggesting a substantial decrease in varicella cases among children. Five years later, Brisson [120] used a model that included the interaction with HZ, with the model schematic shown in Figure 1. The inclusion of HZ and the effect of boosting from varicella exposure led to the conclusion that immunisation was very likely to increase HZ incidence in the short-medium term.

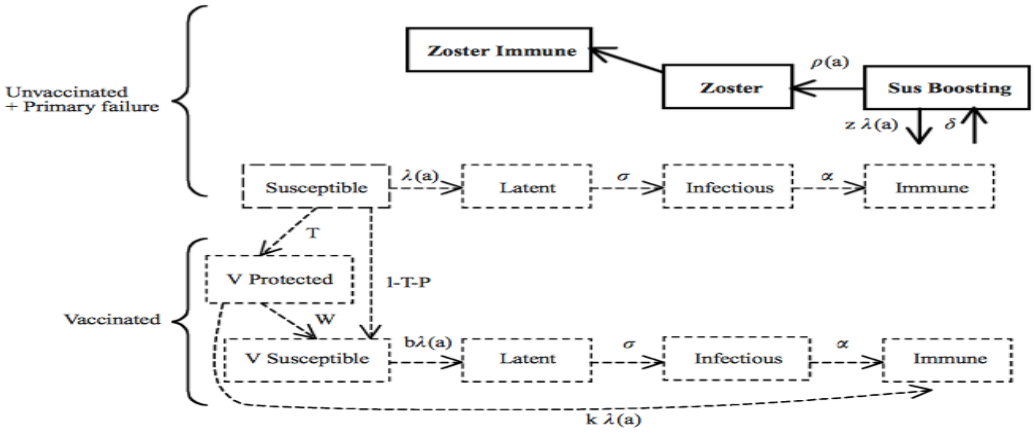


Figure 1: Flow diagram of varicella and zoster before and after vaccination. The mutually exclusive compartments represent the different varicella and zoster epidemiological states. Arrows represent the flow between these states [120]***.***

The effectiveness of varicella vaccination and its effect on HZ incidence are dependent on the assumption in regard to exogenous boosting [121,122]. Modelling studies that assume a boosting effect typically suggest an increase in HZ incidence in people who had previously experienced primary VZV infection [25,117,120,123–125]. However, there is some variation between studies in the duration of the rise of HZ. A modelling study conducted in the Finnish population, using varicella serological data, HZ case-notification data, and new knowledge about contact patterns and infection transmission, suggested that the introduction of a varicella universal vaccination program would increase HZ incidence by more than two thirds in the following 50 years [126]. Another study conducted in Australia predicted that HZ incidence would rise for the first 37 years from the introduction of the infant mass vaccination program [123]. Furthermore a recent modelling study by Ogunjimi et al [127], which uses an individual-based model that integrates within-host data on VZV-CMI and between-host transmission data to simulate HZ incidence, predicted a 75% peak increase in HZ incidence 31

years after vaccination introduction. Finally another recent modelling study from Germany [128] suggested HZ incidence would increase for the first 50 years following introduction of the varicella vaccine, until the vaccinated people reach the age-classes with originally high HZ incidence. The differences in duration of effect are mostly related to the different HZ boosting assumptions and age distributions of varicella and HZ assumed prior to vaccination in these studies. The effect of choice of age distributions for varicella and HZ disease was explored in a model-based evaluation using data from three European countries [129]. This study showed country specific HZ trends in response to vaccine introduction depended on their pre-vaccination force of boosting, and that an increase in HZ was more likely to occur where the pre-vaccine HZ incidence was low.

In summary, these modeling studies, which assume a boosting effect, have suggested that VZV vaccination will increase HZ incidence during the 30-70 year period after vaccine introduction. This fear of an increase in HZ in the initial period after the introduction of the varicella vaccination has been the main reason why many European countries have chosen not to introduce a universal varicella vaccination program [130].

1.8 Demographic changes

The 20th century has seen large increases in life expectancy globally [131]. In industrialised countries such as Australia, increases up to 1950 were primarily driven by declines in infant mortality, while in the latter half of the 20th century

life expectancy increased primarily due to a decline in chronic diseases (Figure 2).

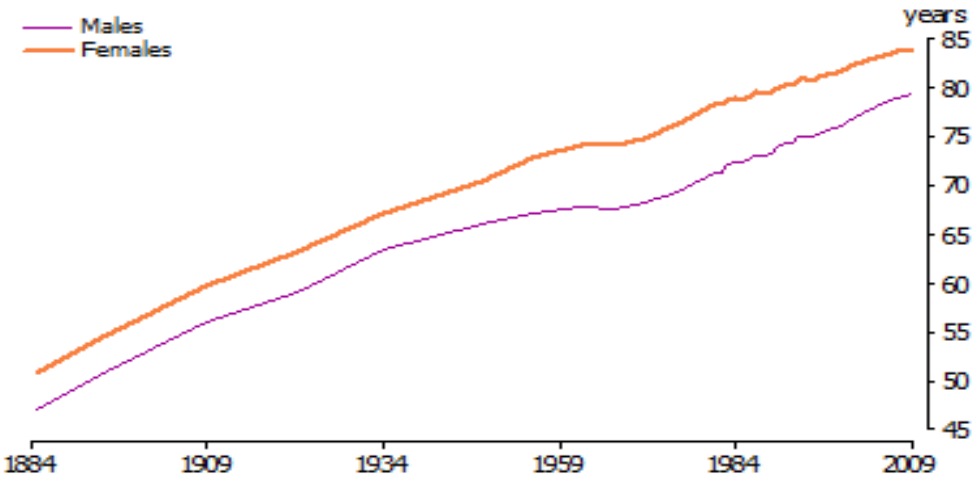


Figure 2: Australian life expectancy at birth, males and females, 1884-2009. *Source: ABS* ***Australian Historical Population Statistics 2008*** *(cat. no. 3105.0.65.001); ABS (cat. no. 3302.0)*

At the same time a large decline in birth rates occurred [132,133], due to lifestyle choices driven by socio-economic changes associated with the growth of urban industrial societies. In Australia over the 20th century the fecundity fell from just under 4 babies per woman in the first decade, to 1.9 babies per woman in 2011, with a post-world war II peak in 1961 of 3.5 [134]. Figure 3 shows the crude Australian birth rate over the century.

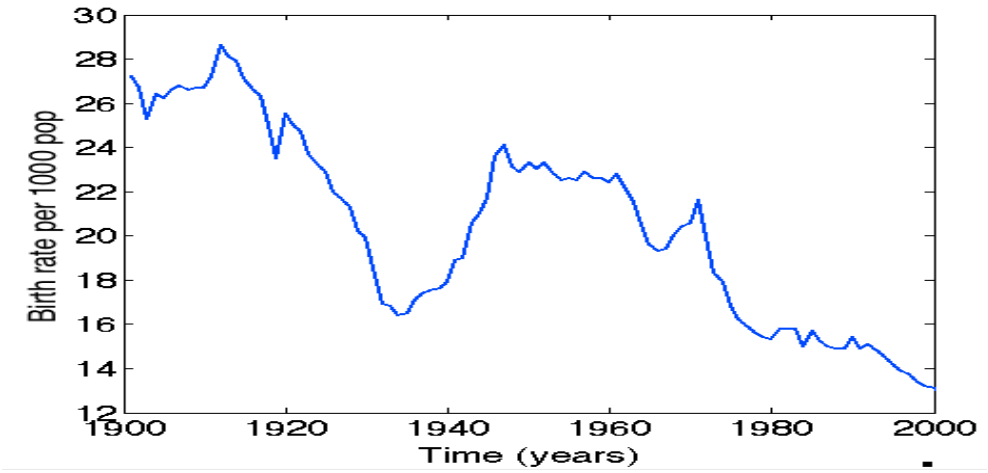


Figure 3: Australian birth rates, 1901-2000, Source: ABS historical crude birth rate [135]

These demographic changes affect the population structure and consequently the mixing patterns for the spread of infectious disease [43,136,137]. In particular, as the population ages, contact with adults increases for all age groups; and decreasing fertility produces smaller household sizes and an overall decreasing contact rate.

A reduction in the birth rate will reduce the proportion of new susceptibles and, together with changes in age-specific contact patterns, can have a substantial influence on both the force of infection and the reproduction number (R_0). R_0 depends on the duration of the infectious period, the probability of transmission from a contact and the number of new susceptible individuals contacted per unit time.

When a constant birth rate is assumed, the potential for demographic change to influence disease dynamics is missed. The effects of changing birth rates were explored for measles in New York city over the 20th century[138] and shown to influence both the incidence and epidemic spacing[139].

Adapting these ideas, a recent modelling study applied to Italian measles incidence data showed a good match between model predictions and declining incidence prior to introduction of immunisation, with the declining birth rate directly leading to a three-fold drop in the force of infection [140]. Another modeling study in Thailand showed that a demographic transition toward lower birth and death rates can explain the reduced dengue transmission rates and the observed shift in age at infection [141].

What are the implications of these ideas for VZV dynamics and disease? Firstly, one would expect a corresponding fall in varicella incidence, in line with the measles results, as birth rates decline. Secondly, assuming that exogenous boosting contributes to HZ immunity, a reduction in birth rates would lead to a decrease in HZ immunity and a subsequent increase in the rate of HZ reactivation. Finally, the reduction in the force of infection is expected to cause a potential shift to older ages for varicella infection and to younger ages for HZ reactivation.

The increases in life expectancy may also play a role. The number and relative proportion of people over 65 (or 85) years is increasing in countries such as Australia. Age is a key risk factor for HZ and PHN, with a considerable increase in rates in people aged more than 60 years [142]. A higher proportion of elderly people in the population is likely to increase the crude incidence for HZ, particularly if multiple reactivations are possible.

These ideas were applied to historical Spanish data by Marziano et. al. [143], with the study finding that incorporation of a demographic model (in this case through an agent-based approach) reproduced the increase in HZ incidence observed between 1997 and 2004.

Similar effects on varicella incidence might be expected in Australia as a result of the declining birth rates during the 20th century. In addition, declining birth rates (Figure 4) might also affect zoster trends, given the likely decline in levels of boosting and the increasing proportion of elderly (Figure 2).

With this study we aim to answer the following two questions:

1. How demographic changes in the Australian population have influenced the epidemiology of varicella infection over the 20th century and
2. How these changes could impact on HZ epidemiology.

Furthermore we aim to underline the importance of using mathematical models informed with demographic changes to predict the spread of infectious diseases.

2 METHODS

2.1 Data sources

2.1.1 Demographic Data

The key demographic parameters used in this analysis are age-specific mortality and birth rates and the population distribution by age, as derived from historical demographic data held by the Australian Bureau of Statistics (ABS). As the age-distribution of the Australian population was not available prior to 1901, our analysis focuses on the period 1901-2050 using both observed and projected values for birth and death rates.

Annual birth rates (Figure 4a) were available between 1901 and 2011 [135], while age and gender-specific death rates (Figure 4b) were only published at intervals between these dates Single-year of age death rates are provided as averages for the periods 1901-1910, 1920-1922, 1932-1934, 1946-1948, 1953-1955, 1960-1962, 1965-1967, 1970-1972, 1975-1977, 1980-1982, 1985-1987, 1990-1992, 1993-1995 and then for each calendar year until 2011. After averaging over gender we arrived at estimates stratified by single year of age, with linear interpolation used to provide values in each calendar year between 1901 to 2011, assuming that the recorded data applied to the mid-point of each time interval described above.

Projections used the medium ABS estimates for the birth rate between 2012 and 2026 before being held fixed, while death rates used the projected annual values from 2012 to 2050 [144].

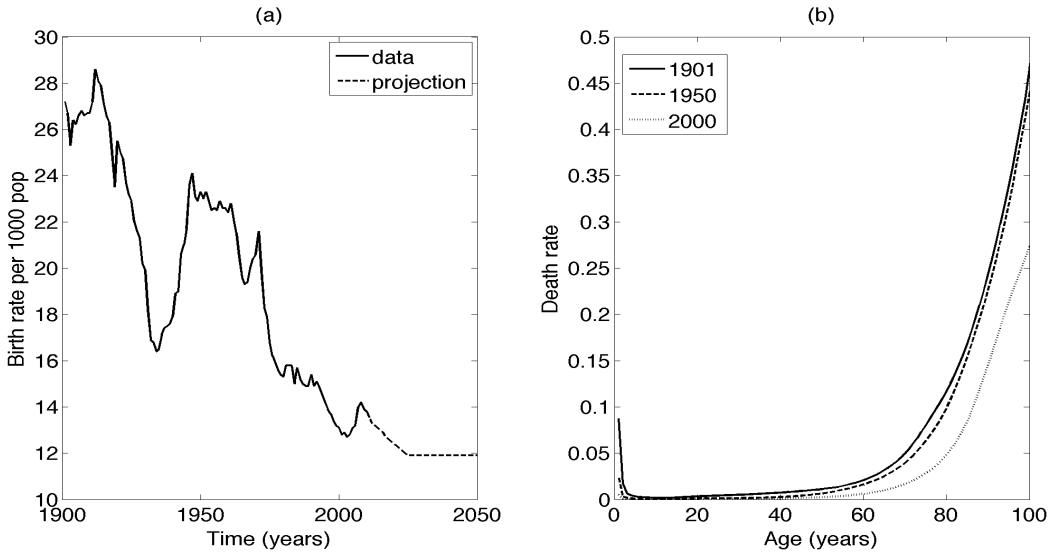


Figure 4: (a) Historical birth rate per 1000 population from 1901 to 2011 [135] ***and projected birth rate from 2012 to 2100*** [145]***. (b) Age specific death rate in 1901, 1950 and 2000*** [146]***.***

After an initial increase, the birth rate (Figure 4a) dropped from 1910 to 1935, followed by the "baby boom", where the rate peaked at 24 births per 1000 population in 1945, with sustained high rates until the 1970s before a rapid decline up to the year 2000. In 2011 the rate was around 13 births per 1000 population.

Age specific mortality rates (Figure 4b) generally decreased between 1901 and 1950 for all ages, but in particular for the first year of life, while for the year 2000 the age specific death rate is shifted downwards by almost 10 years compared with 1950.

The age-distribution of the population was initialised in 1901 by interpolating from ABS data given in 5-year age groups from 0 to 84 years old and for 85+ years [147], as shown in Figure 5 below. Simple linear interpolation was used for ages between 2 and 84 years, while in children <2 years we assumed the same population as for 2 years of age. For the last age group, 85+ years, we calibrated

the distribution by single year of age using the age specific death rates described above from the same year.

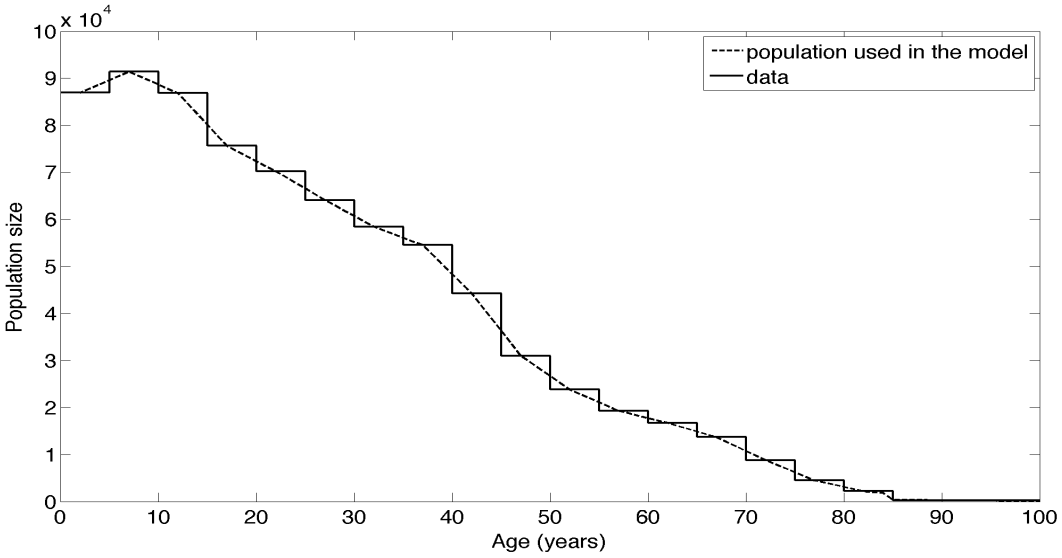


Figure 5: Average population in 1901 within age groups (data) compared with interpolated population as used in the model.

2.1.2 Hospitalisation data

We used national age-stratified hospitalisation data for admissions with a primary diagnosis of varicella and HZ obtained from the Australian Institute of Health and Welfare (AIHW). These data are collected by financial year, and data for the period 1993/1994 to 2009/2010 were available for this study. Different coding practices were used during this period with ICD-9-CM codes used from 1993 to 1997 (052 for varicella and 053 for HZ) and ICD-10-AM codes from 1998 to 2009 (B01 for varicella and B02 for HZ).

This data was then converted to age-specific hospitalisation rates, by dividing by annual ABS age-specific population estimates [147]. These rates were then used for model calibration (see 'Model calibration' section).

2.1.3 Serosurvey data

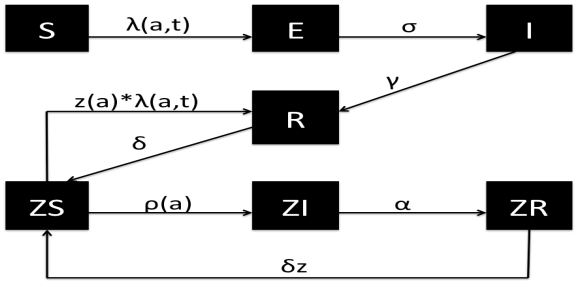
Varicella immunity was estimated in the pre-vaccine era in Australia via a national serosurvey performed using residual sera submitted during 1997-1999 to diagnostic laboratories across Australia [148]. The Enzygnost enzyme immunoassay (EIA) was used to measure anti-VZV IgG in a nationally representative sample of 2027 sera, with sample sizes chosen to obtain consistent precision of +/-5% for estimates in the following age groups 1-2, 3-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-39, and 40-49 years old (with approximately equal gender distribution). Results were classified into positive, negative and equivocal, with equivocal sera retested and then excluded from further analysis if the result remained equivocal (0.7% of all samples).

As described later in section 2.4.4, we used these data to calibrate the per-unit time infectiousness of varicella in our model by matching the modelled prevalence of immunity by age to the seroprevalence data.

2.2 Basic model structure

We used a deterministic, age-structured model of VZV transmission and varicella and zoster disease. The transmission model was adapted from previous models by Wood, Gao and Gidding [149,150] which were in turn adapted from Brisson et al. [120]. The main difference here is the incorporation of detailed changes in population size and structure over time, similar to the approach taken by Merler et al. and Marziano et al. [43,140].

The model used ordinary differential equations with the population divided into epidemiological states relating to their varicella/HZ infection status (Figure 6). Individuals are born susceptible to varicella infection (S) and they can be infected (E) with varicella disease according to the age specific force of infection ($\lambda(a)$). After a period of latency ($1/\sigma$ days) they become infectious (I). We assumed that after an infectious period ($1/\gamma$ days) people will recover (R). After recovering we assumed lifelong immunity to varicella disease and an immunity period ($1/\delta$ years) to HZ reactivation. All durations described in this section are assumed to be exponentially distributed. We assumed that exposure to varicella cases boosts immunity to HZ (exogenous boosting), and the probability of boosting from contact with the virus ($z(a)$) is age-dependent [151]. The population of individuals susceptible to zoster (ZS) develop zoster at the age specific reactivation rate ($\rho(a)$), and recover after the period $1/\alpha$ days. Based on some evidence for recurrent HZ episodes (as explained in section 1.1.2 of the 'literature review'), in the base case model we allowed more than one episode of HZ, so after recovery from the first reactivation, and an immune period, people will return to the ZS compartment. Parameter values for the model are shown in Table 1 below.



VARICELLA STATES:
- S = susceptible
- E = infected
- I = infectious
- R = recovered

HERPES ZOSTER STATES:
- ZS = susceptible
- ZI = infected
- ZR = recovered

Figure 6: flow chart of varicella and HZ infection states

Within each year people are moved between states following the model differential equations, with $\delta_z = \delta$ in our base case:

$dS(a,t)/dt = -\lambda(a,t)*S(a,t)$,

$dE(a,t)/dt = \lambda(a,t)*S(a,t) - \sigma*E(a,t)$,

$dI(a,t)/dt = \sigma*E(a,t) - \gamma*I(a,t)$,

$dR(a,t)/dt = \gamma*I(a,t) - \delta*R(a,t) + z*\lambda(a,t)*ZS(a,t)$,

$dZS(a,t)/dt = \delta*R(a,t) - z*\lambda(a,t)*ZS(a,t) - \rho(a)*ZS(a,t) + \delta_z*ZR$,

$dZI(a,t)/dt = \rho(a)*ZS(a,t) - \alpha*ZI(a,t)$,

$dZR(a,t)/dt = \alpha*ZI(a,t) - \delta_z*ZR$

Here a represents the 100 age cohorts (0,1,2,...,100) and t represents time [0,200] in years. The change in the population distribution within each year is described in section 2.4.1 below.

2.3 Biological parameters

Table 1: *Model parameters*

Symbol	Meaning	Value	Source
$1/\sigma$	Duration of latency	14 days	[120,126,149,150,152–154]
$1/\gamma$	Duration of infectiousness	7 days	[120,126,149,150,152–154]
$1/\delta$	Years immune to HZ after V exposure	24.4 years	[150,151]
$1/\delta_z$	Years immune to HZ after HZ episode	24.4 years	(see section 2.7)
$1/\alpha$	Duration of zoster infection	7 days	[126,153,154]
ρ(a)	Reactivation rate for zoster (age dependent)	$\rho(a)=0.0957 * e^{-0.1865*a} + \frac{10.7648}{100000} * a^{1.1435}$	Adapted from [151,153] (see section 2.4.2)
z(a)	Percentage of effective varicella infection contacts that boosts against zoster reactivation	$z(a)=-0.000541 * a^2 + 0.054243 * a - 0.612759$	[150,151,153]
β	Transmission parameter for varicella infection	0.5707 per day	Estimated (see section 3.2.1)

When fitting to UK data stratified by exposure to children, Brisson et. al. estimated protection against HZ reactivation to be on average 20 years (95%CI 7-41 years) [151]. Following the Shingles prevention study [31], Brisson et. al. [152] repeated the analysis assuming that the probability of being boosted is equal to the estimated age-specific zoster vaccine efficacy in this trial. In that study, a duration of 24.4 years was used and for consistency we chose this value for $1/\delta$ in our base case model. In our sensitivity analysis we used a shorter duration of 2 years (used by Brisson et al as a lower bound in [120] and suggested as the duration of immunologic boosting by Ogunjimi et. al. in their recent paper [127]).

Due to the lack of detailed age-specific data on HZ incidence in Australia, we used a reactivation rate by age (Figure 8) adapted from estimates by Brisson et al [120,152] which were based on fitting to Canadian age-specific HZ incidence rates [155]. They assumed the age specific rate of reactivation ρ(a) to have the form:

$$\rho(\mathrm{a})=\omega * e^{-\varphi a}+a^{\eta} * \frac{\pi}{100000}$$

where a=age and ω, φ, η, π are free parameters determined from fitting their mathematical model to the observations. We used Brisson's parameters in the scenario where zoster occurred only once but refit this function in our base case and in the other scenarios used here (described in more detail in the 'Calibration' section below).

Several modelling studies [120,149] have made the assumption that the probability of being boosted after exposure is the same for all ages. However the Shingles Prevention Study [29] showed that the live attenuated VZV vaccine efficacy against HZ is age dependent, which suggests that the effect of exogenous boosting due to VZV exposure might also be age dependent. We follow the assumption of Brisson et. al. [150,151,153] that the proportion of individuals boosted is age-dependent (see Figure 7 below). Note that as trial data was not available below the age of 50 years or for subgroups above 80 years, we assumed a fixed response equal to the closest observed response for values outside of the observed age range.

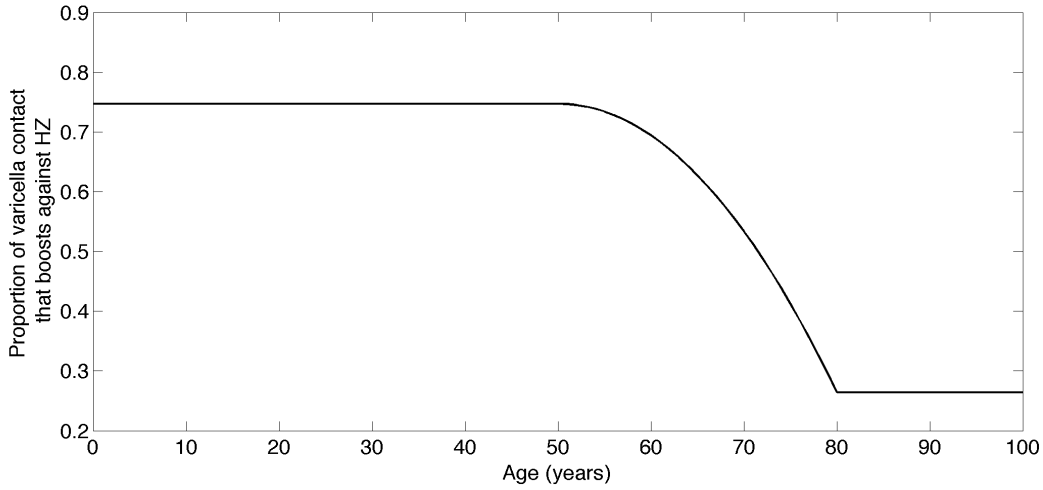


Figure 7: Age specific proportion of varicella contacts that boost against HZ reactivation used in the model (based on [150,151,153]***)***

2.4 Model calibration

2.4.1 Incorporation of age and demographic changes

In order to initialise the proportions of the population in each disease state by age, the model was run to equilibrium from a single infected case (<1 years old) in an otherwise susceptible population (a period of 300 years) assuming birth and age-specific mortality rates as in 1901. We scaled these equilibrium proportions by the single-year of age population sizes in 1901 (obtained as described above and shown in Figure 5) to initialise the population for simulating varicella and HZ disease incidence over the period 1901-2050.

We used Matlab R2013b and the ode45 solver to simulate the model demographic changes in each year and within epidemiological states.

The demographic and transmission dynamics are decoupled. For instance, at the end of each year people were shifted, in each state, from one age to the next

following the age specific death rate (Figure 4b), while for the susceptible state the first age group was updated each year to contain newborn children, according to the annual birth rate (Figure 4a). More specifically, for disease state X, where $X \in S, E, I, R, ZS, ZI, ZR$

$$X_a(t+1) = X_{a-1}(t) * (1 - \mu_{a-1}(t)) \qquad a = 1, \dots, 99$$

$$X_{100}(t+1) = X_{99}(t) * (1 - \mu_{99}(t)) + [(1 - \mu_{100}(t)) * X_{100}(t)]$$

In the first age group, the equations appear as

$$X_0(t+1) = 0 \qquad \text{for } X \in E, I, R, ZS, ZI, ZR$$

$$X_0(t+1) = b(t+1) * N(t) \qquad \text{for } X = S$$

where the $\mu_a(t)$ are the age-specific death rates and b(t) the birth rates derived from ABS data and population projections as described in section 2.1.1 above.

This discrete age-evolution is typically referred to as a realistic age structured (RAS) model. The main rationale for such models, as described by Schenzle[156] and others[157,158] is that in schools, it is the integer school grade, rather than the exact age that primarily determines contact pattern[159]. For convenience we adopt this structure for all age groups but note this is a departure from true discretisations of the underlying partial differential equations that govern population dynamics. Perhaps the most obvious artefact of this discretisation is that it creates an annual forcing and seasonal fluctuations in incidence that resembles reality but may not reflect the underlying process governing seasonality.

2.4.2 The HZ age-specific reactivation rate

It was necessary to adapt the HZ age-specific reactivation rate from Brisson et. al. [151,153] to our base case model, in which multiple reactivations were possible as opposed to a single reactivation used by Brisson. In order to arrive at HZ incidence profiles that are of similar magnitude, we constrained all scenarios (described below) to produce the same zoster incidence by age as when faithfully applying Brisson's assumptions (1 HZ episode only) in the year 1998. This year was chosen because it also reflects when the serosurvey data was available. The four parameters describing reactivation were estimated by minimising the least squares difference between the base-case model output (and additional scenarios) and the age-specific HZ incidence as generated in 1998 using Brisson's assumption of 1 HZ episode only (Figure 8).

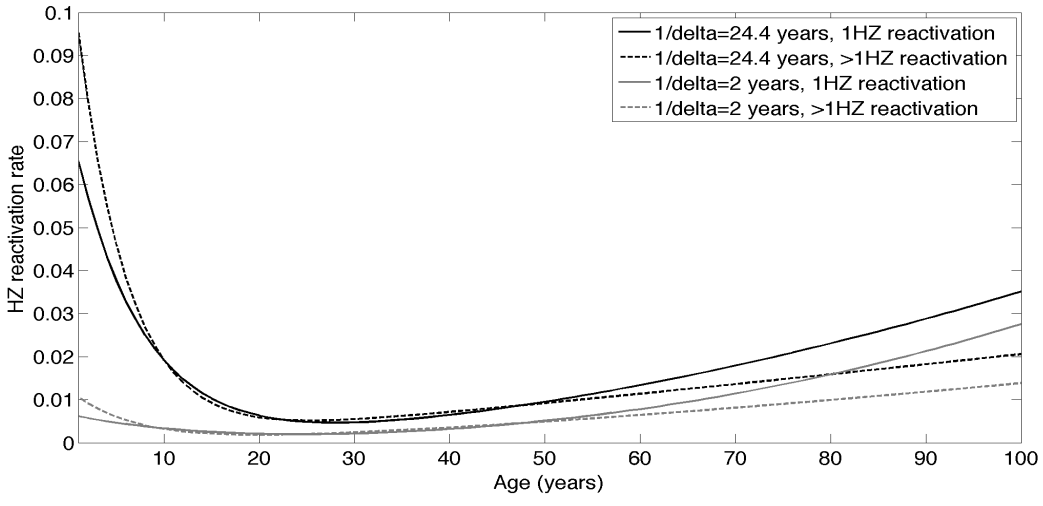


Figure 8: Age-specific HZ reactivation rate per year, Brisson's original (black solid line) and the estimated rates for each different scenario.

2.4.3 Calibration to Australian data

Due to the hospitalisation data only being available in 5-year groups up to 84 years, with an additional 85+ age group, we aggregated the modelled yearly incidence (obtained as explained in section 2.6.1) within these age groups first before calibrating to the hospitalisation data.

In order to calibrate the model to Australian data, we matched the modelled varicella and zoster incidence (for the same age-groups) to varicella (Hv_i) and HZ (Hhz_i) hospitalisation rates using an age-group-specific hospitalisation-ratio that we fixed in time. Annual hospitalisation data from 1993-9 were used to estimate one ratio per age group by minimising the least squares difference over time.

$$Hv_i = x_i * \overline{v}_i + \varepsilon_i \qquad i = 1, \dots, 18$$

$$Hhz_i = y_i * \overline{hz}_i + \eta_i$$

Where *i=1…18* represents 5 years age-groups from 0 to 84 years old and the additional 85+ years old, $\overline{v}_i$ is the annual varicella incidence and $\overline{hz}_i$ the annual HZ incidence for those age-groups, x_i and y_i are the age-group-specific hospitalisation-ratio estimated, finally ε_i and η_i are the errors terms respectively for varicella and HZ.

2.4.4 Transmission parameter for varicella infection

In order to estimate the transmission parameter β, we calibrated the modelled age-specific prevalence of varicella immunity for age 0 to 49 years old to the Australian serosurvey data for 1997-9 (for the mid year 1998).

Calibration to serosurvey data with just one parameter was possible due to the social contact hypothesis[160], the assumption that transmission rates are linearly related to estimated human contact patterns.

2.5 Mixing patterns

The force of infection $\lambda(a,t)$ describes the probability of a susceptible individual of age a being infected at time t:

$$\lambda(a,t) = \int_0^\infty \frac{\beta(a,a',t) * I(a',t)da'}{N(t)}$$

where $I(a,t)$ is the number of infected individuals at age a and time t and $N(t)$ the total population at time t.

This approach (often called 'true mass action' approach), is characterised from the transmission parameter β scaled to the population size[137]. A different approach would have been a density dependent contact rate (often called 'pseudo mass action'), which would have lead to a growing force of infection with increasing the population size[161], and consequently higher rates for varicella infection over time and lower rates for HZ (due to the boosting assumptions). In a modelling study[139]for measles, observed incidence data in varying population sizes was shown to be consistent with frequency-dependent rather than density-dependent transmission of infection. Based on the similarity of transmissions and force of infection between varicella and measles, we chose to use a frequency dependent force of infection. Our assumption allows the

changing age distribution to affect the overall contact patterns leading to a decrease in the force of infection following the aging of the population[137].

In order to obtain age specific transmission parameters, this integral expression was discretised using Euler's approximation, with contact rates assumed proportional (social contacts hypothesis) to patterns observed in the European mixing patterns study, POLYMOD [162]:

$$\lambda_a(t) = \sum_{a'=0}^{100} \frac{\beta_{a,a'}(t) * I_{a'}(t)}{N(t)}$$

Where $\beta_{a,a'} = \beta * c_{a,a'}$, and $c_{a,a'}$ is the contact rate between people in a age group and a' age group. In order to estimate $c_{a,a'}$ we chose to use the matrix of all reported contacts (which account for all contacts that are at least as close as a two-way conversation of several seconds without raised voices) between age groups from Great Britain in 2006 [163] based on the idea that it is the most appropriate to reproduce the Australian mixing patterns and for consistency with other Australian modelling studies [149,150]. No Australian population-based study has been completed, although comparisons between subpopulations in Melbourne are available [164]. The POLYMOD data consists of the average number of persons contacted per day per survey participant, stratified by the age of contactor and contactee (5-year groups between 0 and 69 and then 70+). These contact numbers (m_{ij}) were converted to age-specific rate of contact between age groups a and a' per year ($c_{a,a'}$) by dividing through by the age specific

population of the UK in 2006 (N_{GB_a}) and multiplying by 365 to get an annual contact rate:

$$c_{a,a\prime} = \frac{m_{ij}}{N_{GB_a}} * 365$$

Under the assumption of reciprocal contact ($c_{a,a\prime} = c_{a\prime,a}$), we symmetrised this matrix

$$c_{a,a\prime} \equiv (c_{a,a\prime} + c_{a\prime,a}) / 2$$

If we assume that these rates are fixed in time, then the contact matrix takes the form

$$\beta_{a,a\prime} = \beta * c_{a,a\prime} = \beta * c_{a\prime,a} = \beta_{a\prime,a}$$

2.6 Modelled incidence output

2.6.1 Annual varicella and HZ incidence

By decoupling demographic and infection-related transitions, we introduce a forcing effect commonly observed in RAS-type models that leads to large fluctuations in incidence within in each year. As the focus of this thesis is longer-term change, we convert this time-series to an annual incidence series for varicella ($\overline{v_a}$) and HZ ($\overline{hz_a}$).

For varicella, this average incidence $\overline{v_a}(t)$ was calculated as the difference between the age specific numbers of susceptibles at the start and end of each year, divided by the annual age specific population. For HZ, competing transitions meant another method was required, in this case $\overline{hz_a}(t)$ was calculated by multiplying the mean annual ZS population by age ($\overline{ZS}_a(t)$) by the age-specific reactivation rates and dividing by the average annual age specific population.

$$\overline{v_a}(t) = \frac{S_a(t'') - S_a(t')}{N_a(t)} \qquad t = 1, \dots, 150$$

$$\overline{hz_a}(t) = \frac{\rho(a) * \overline{ZS}_a(t)}{N_a(t)} \qquad t' = first\ time\ step\ within\ the\ year$$

$$t'' = last\ time\ step\ within\ the\ year$$

2.6.2 Average age at varicella infection

The reduction in varicella incidence is expected to increase the average age at varicella infection. In order to demonstrate this effect, we calculate the average age at varicella infection ($\bar{a}$) by multiplying, for each year *t=1901…2100* years, the annual varicella incidence as explained above and used the following formula to get the average age at varicella infection:

$$\bar{a} = \frac{\sum_a \overline{v}(t) * a}{\sum_a \overline{v}(t)}$$

2.6.3 Age-standardisation of varicella and HZ incidence

To calculate the age-adjusted incidence for varicella and HZ, we age-standardised to the Australian single-year of age population for 2001, in the following steps:

1) In order to calculate the expected number of varicella ($\overline{V_s}$) and HZ ($\overline{HZ_s}$) cases for each age and year, we multiplied the single year age specific rates for varicella and HZ in each year (*t)* by the Australian age specific population in 2001:

$$\overline{V_s}(a,t) = \overline{v}(a,t) * N(a,2001) \qquad t = 0,\dots,150$$

$$\overline{HZ_s}(a,t) = \overline{hz}(a,t) * N(a,2001)$$

2) Finally we obtained the total age-standardised varicella ($\overline{v_s}(t)$) and HZ ($\overline{hz_s}(t)$) incidence for each year by summing the expected number of cases found for each age and dividing it by the total population in 2001.

$$\overline{v_s}(t) = \frac{\sum_a \left(\overline{V_s}\,(a,t) * N(a,2001)\right)}{\sum_a N(a,2001)}$$

$$\overline{hz_s}(t) = \frac{\sum_a (\overline{HZ_s}(a,t) * N(a,2001))}{\sum_a N(a,2001)}$$

2.7 Sensitivity analysis

HZ incidence is related to varicella incidence by the combination the duration of immunity to HZ reactivation following primary infection and boosting and the HZ reactivation rate. The modelled trends in HZ incidence over time are sensitive to the duration of immunity to HZ reactivation following varicella infection and recovery, as well as the assumption of only one HZ reactivation per lifetime.

We tested three scenarios in addition to the base case, which explored alternative boosting and reactivation assumptions (summarised in Table 2). These were used to examine how boosting and reactivation assumptions can influence HZ incidence over time. We compared the modelled HZ incidence by age group over time between scenarios.

Table 2: Model scenarios and the respective estimation of the 4 parameters in the reactivation rate equation, coming from the scenario which Brisson used as his base case in [151,153]***.***

Scenario		**Estimated reactivation rate**
Boosting duration (years)	Number of HZ episode in lifetime	
$\frac{1}{\delta} = 24.4$	Unlimited (base case)	$\rho(a) = 0.0957 * e^{-0.1865*a} + \frac{10.7648}{100000} * a^{1.1435}$
$\frac{1}{\delta} = 24.4$	1	$\rho(a) = 0.0655 * e^{-0.1389*a} + \frac{0.6707}{100000} * a^{1.8635}$ (from Brisson et al.)
$\frac{1}{\delta} = 2$	Unlimited	$\rho(a) = 0.0106 * e^{-0.1480*a} + \frac{1.5733}{100000} * a^{1.4758}$
$\frac{1}{\delta} = 2$	1	$\rho(a) = 0.0062 * e^{-0.0707*a} + \frac{0.0349}{100000} * a^{2.4542}$

3 RESULTS

3.1 Demographic changes

In 1901, the Australian population decreased almost linearly with age (Figure 5) but the structure has flattened with time, with declines occurring from about 40 years and 60 years of age respectively in 1950 and 2000 (Figure 9a). In Figure 9a, we show that the model faithfully reproduces this distribution over time, while in Figure 9b we show the modelled ageing of the Australian population contrasted against a declining proportion of young children. The relative increases are 133.3%, 454.5% and 1428.6% for the 65-74, 75-84 and 85+ year age groups respectively compared with a decline of almost 50% for children 0-4 between 1901 and 2000.

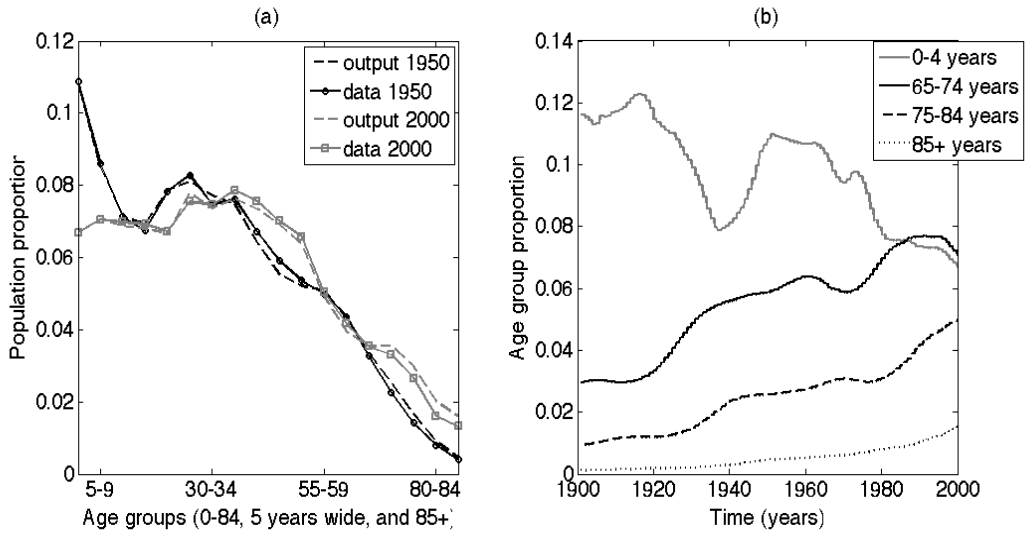


Figure 9: (a) Comparing the proportional age distribution (18 age groups 5 years wide from 0 to 84 and 85+ age group) in 1950 and 2000 from ABS data [147] ***and model output; (b) Modelled proportional distribution of the age-groups 0-4, 65-74, 75-84 and 85+ years over time***

3.2 Model calibration

3.2.1 Transmission

Figure 10a shows the fit of the modelled annualised varicella prevalence of immunity (model year 1998) to age specific varicella seropositivity in Australia measured over the period 1997-1999. We note that as the population structure is changing with time, this is not a conventional equilibrium fit to population seroprevalence. Seropositivity increased rapidly between 0 and 10 years of age, by which time 80% of people had evidence of prior infection with VZV, with a more gradual increase to around 98% by age 49 years. The best fitting estimate was $\beta=0.5707$ infectious contacts per infectious person per day. When demographic change over time is combined with this estimate we observe a reduction in the basic reproduction number over time, from 5.6 to 4.0 between 1901 and 2000 (Figure 10b).

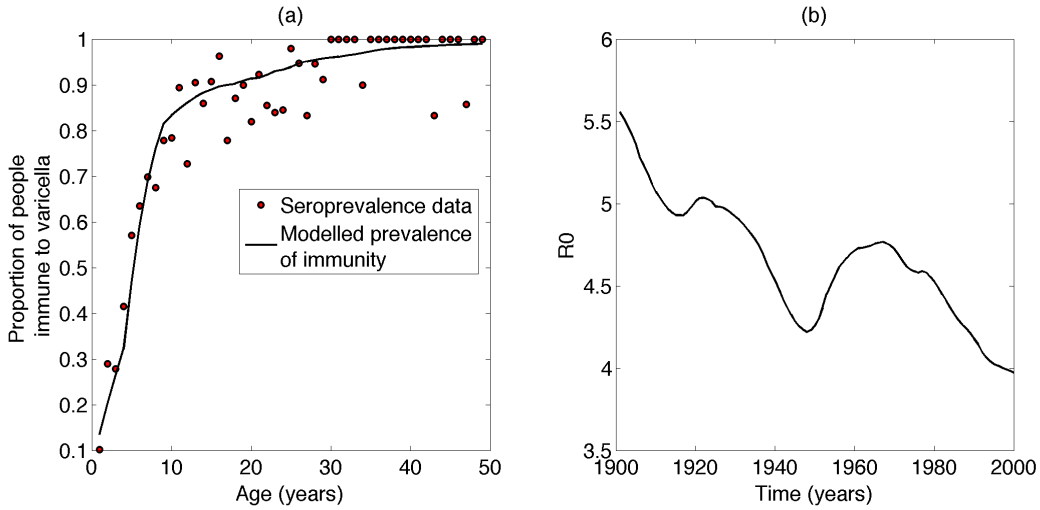


Figure 10: (a) Estimated and observed proportions of sera positive for varicella IgG antibody by age from 1 to 49 years old; (b) Modelled reproduction number for varicella infection between 1901 and 2000.

3.2.2 Proportion of hospitalised cases

The simulated rate of hospitalization is shown in Figure 11 for varicella (a) and HZ (b) for selected age groups alongside empirical data. Predicted trends are similar to the data trends up to 2005 for the 5-9 and 10-14 year groups in respect to varicella and the 85+ years group for HZ. Some deviation is observed for the 65-74 and 75-84 year groups in relation to HZ and the 0-4 year varicella hospitalisation rate is more varied with an apparent epidemic period observed between 1995 and 2002. In 2005, varicella vaccination was introduced into the national immunisation program (NIP) in Australia, with large declines in varicella hospitalisations observed between 2005 and 2009. Vaccination is not included in our model, hence the divergence between varicella outputs and data over this period. No particular trend after vaccination can be seen in the elderly HZ hospitalization data.

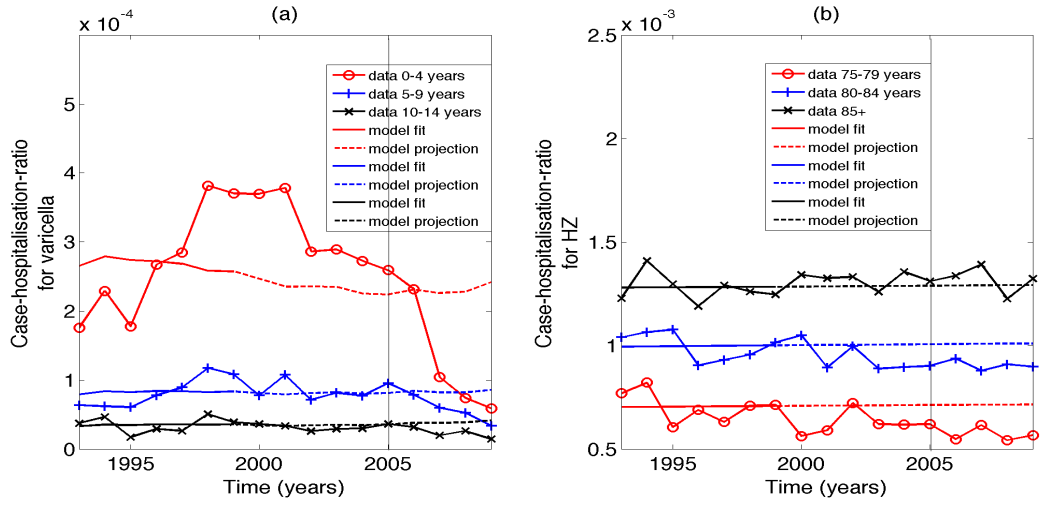


Figure 11: Observed and modelled rates of hospitalised cases for varicella (a) and HZ (b) for the age groups 0-4, 5-9 and 10-14 years old for varicella and 75-79, 80-84 and 85+ years old for HZ. The graphs compare model fit (1993-1999) and model projection (1999-2009) to data. The year 2005 corresponds to the start of the varicella immunisation program in Australia

3.3 Varicella incidence

The generally decreasing crude birth rate observed since 1901 has led to an overall reduction in the rate of entry of new VZV susceptibles to the Australian population. Model simulations showed a decrease of almost 50% in the crude rate of varicella incidence (Figure 12a) between the early 1950s and 2000, while the age standardised varicella incidence was more stable over time. This decrease in VZV circulation and crude varicella incidence, produced a simulated increase (Figure 12b) in the predicted mean age at varicella infection, increasing from 5 years of age in 1950 to 8 years of age in 2000, and almost 10 years of age in 2050 (based on population projections).

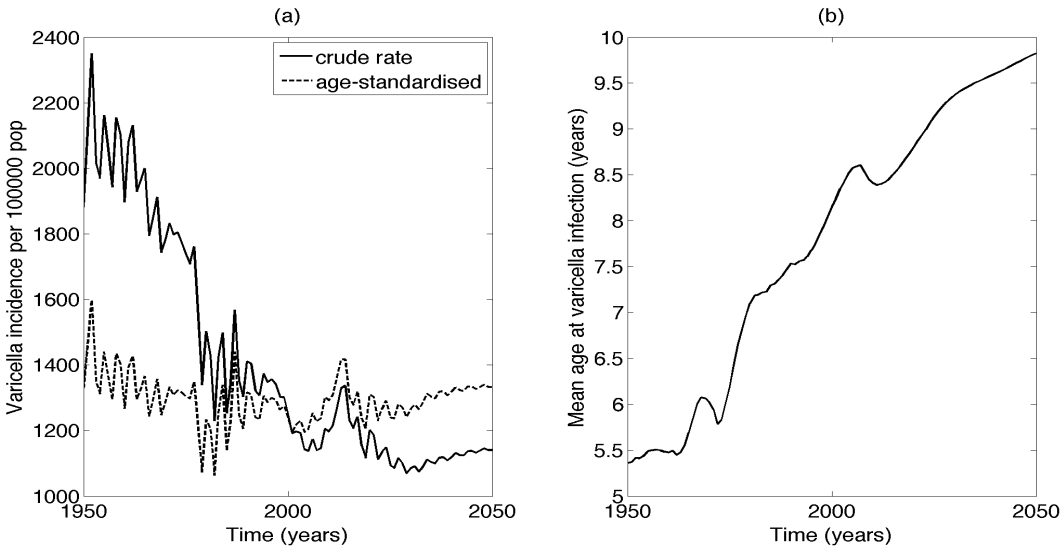


Figure 12: (a) Crude and age-standardised modelled varicella incidence per 100,000 population over time; (b) modelled average age at varicella infection over time

Figure 13 shows the age-distribution, between age 0 and 20 years, of varicella incidence at the start, middle and at the end of the 20th century. While the

varicella incidence decreased over time in the age group 0-4, the graph shows an increase for all other ages. The peak at 5 years is due to the contact matrix used, which has a much higher average number of contact in this age compare to the 0-4 years old age group.

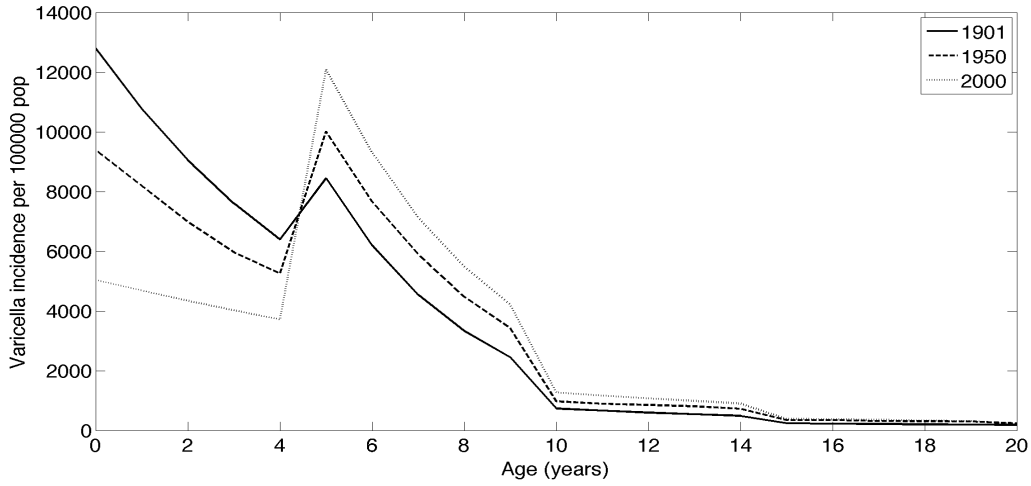


Figure13: Varicella incidence by age (0-20 years old) per 100000 population in 1901, 1950 and 2000

3.4 HZ incidence

Modelled HZ incidence was unstable for the first few decades due to the initial mismatch between the population structure used to inform the model in 1901 (section 3.1.1 Figure 5) and the structure used to reach the disease states equilibrium proportions. Modelled HZ trends over the 20th century showed an increase of 40.2% in crude rate (Figure 14a), while the age-standardised incidence increase by 6.3% between 1920 and 2000 (Figure 14b). The age distribution of HZ incidence remained similar across the time period (Figure

14c), with the exception for the age group 0-25, which showed a progressive decline in incidence over time.

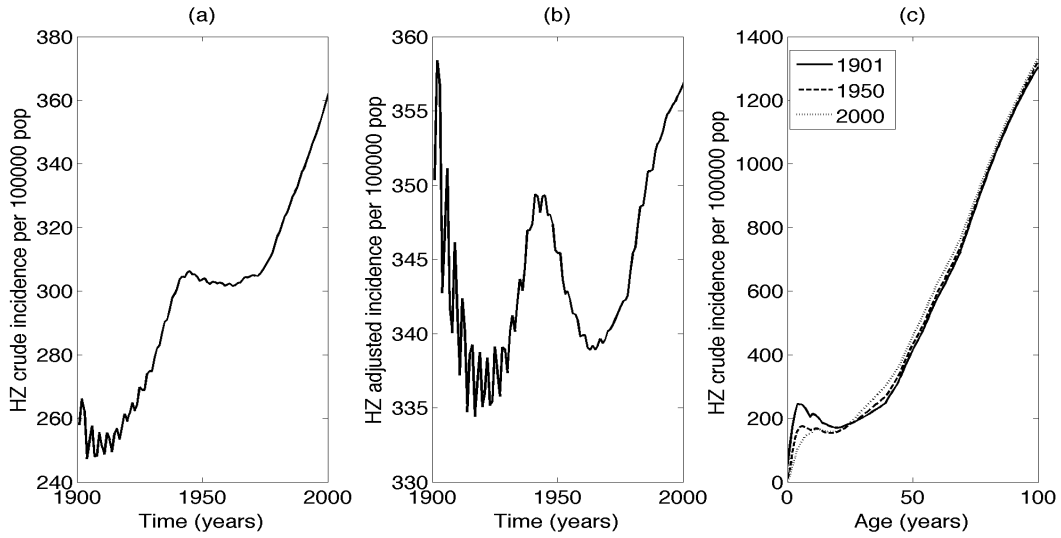


Figure 14: Modelled (a) HZ crude incidence and (b) HZ age-standardised incidence per 100000 population between 1901 and 2000; (c) age-specific HZ crude incidence per 100000 population in 1901, 1950 and 2000

Regarding crude HZ incidence (Figure 15), the trends over time inversely followed trends in the crude birth rate, with about a decade delay. Indeed HZ gradually increased over time in the periods 1920-1944 and from 1972, which corresponds to the decrease in births in the periods 1912-1934 and from 1961; with the relatively constant period 1959-1972 for HZ relating to the period 1947-1961 for births. Over the second half of the century, the incidence rose from 303.6 cases per 100,000 in 1950 to 361.5 cases per 100,000 in 2000, a 19.1% increase, which closely mirrors the 14.1% increase in the mean age of the population from 32 to almost 37 years over the same time (Figure 15).

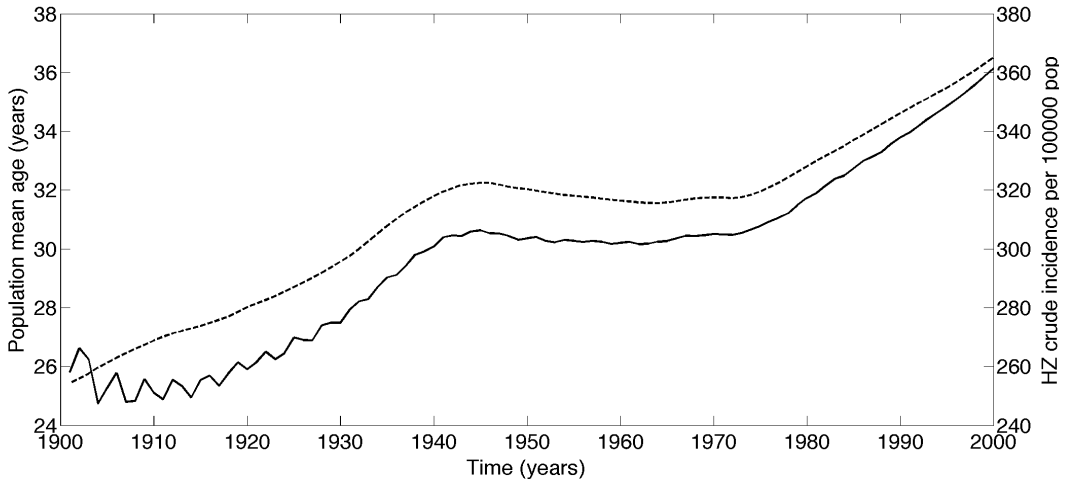


Figure 15: HZ crude incidence per 100,000 population over time (solid line) on the right y axis, compared with the mean age of the population over time (dashed line) on the left y axis

However, after age-standardisation (Figure 16), HZ incidence decreased from 1945 to 1965 before increasing steadily between 1966 and 2000. While the HZ trends still inversely followed the birth rate at about a 10 year delay (Figure 16), the increase in incidence was much reduced when age-standardised. In the first half of the century the birth rate decreased by 42.7% between 1912 and 1934 and about 10 years later the age standardised HZ increased by 4.2% between 1920 and 1945. In the second half of the century a 31.2% decreases in births in 1960-1990, corresponded to an increase in age standardised HZ incidence of 5.1% in 1968-2000. A contributing factor to the higher HZ increase in the second half of the century can be the growing proportion of elderly population (Figure 9b), combined with allowance for multiple HZ episode in lifetime.

The different trends between crude and age-standardised incidence for VZV infections reflect the changes in the age-distribution of the population over time.

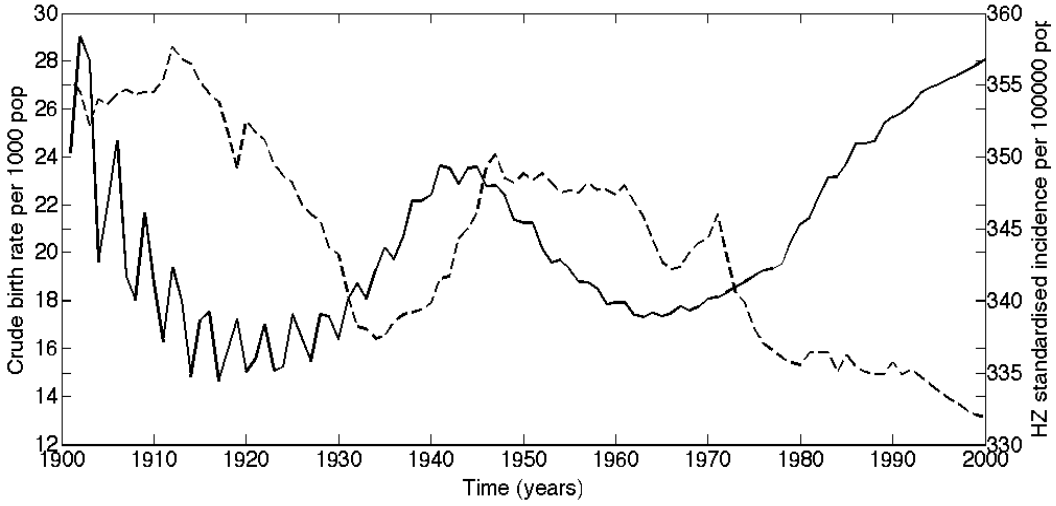


Figure 16: HZ incidence per 100,000 population age-standardised to the Australian population in 2001 (solid line) on the right y axis, compared with crude birth rate per 1000 population (dashed line) on the left y axis, from 1901 to 2000.

3.5 Sensitivity analyses

In sensitivity analysis, we explored the effects of boosting duration and the number of HZ episodes that can be experienced. As noted previously, these assumptions do not affect incidence of varicella and as such we focus only on trends in HZ incidence in what follows. In Figure 17a we show the age-specific incidence of zoster as calibrated to Brisson's assumptions in 1998. Note that differences in the incidence distribution arise as it is not possible for the models with recurrent reactivations to closely match incidence from models with a single reactivation in the 85+ years age group, while also matching the distribution in younger ages.

The trend in crude HZ incidence (Figure 17b) differs primarily by the assumed duration of immunity to HZ following primary infection and HZ recurrence. This difference was projected to decrease with time, with the curves converging just after the year 2000.

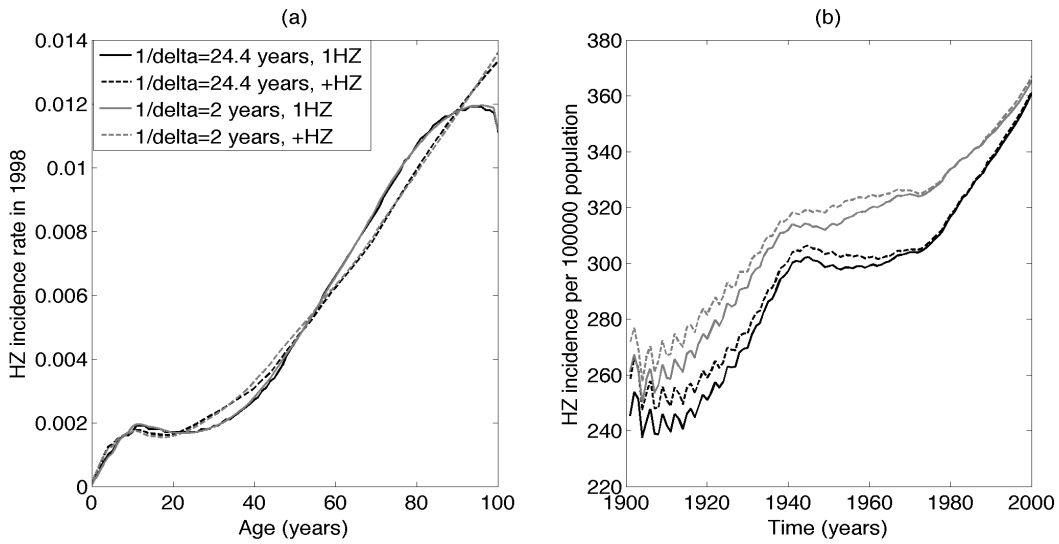


Figure 17: (a) Age-specific modelled HZ incidence rate from each scenario as calibrated in 1998; (b) modelled HZ incidence per 100000 population over time in the 4 different scenarios, using different estimated reactivation rates.

The age-specific HZ incidence rates for the age groups 65-74, 75-84 and 85+ years old over time (Figure 18) show different trends between scenarios. The models with multiple HZ reactivations have lower rates of HZ incidence, consistent with the higher reactivation rate for people aged 55+ years (see Figure 8), while the duration of boosting has more of an effect on the rate of increase over time. Indeed the case scenarios with a long duration of immunity (24.4 years) show consistent increases in incidence over time in all three age groups examined.

In Table 3 are shown relative changes in demography and VZV epidemiology in two time periods.

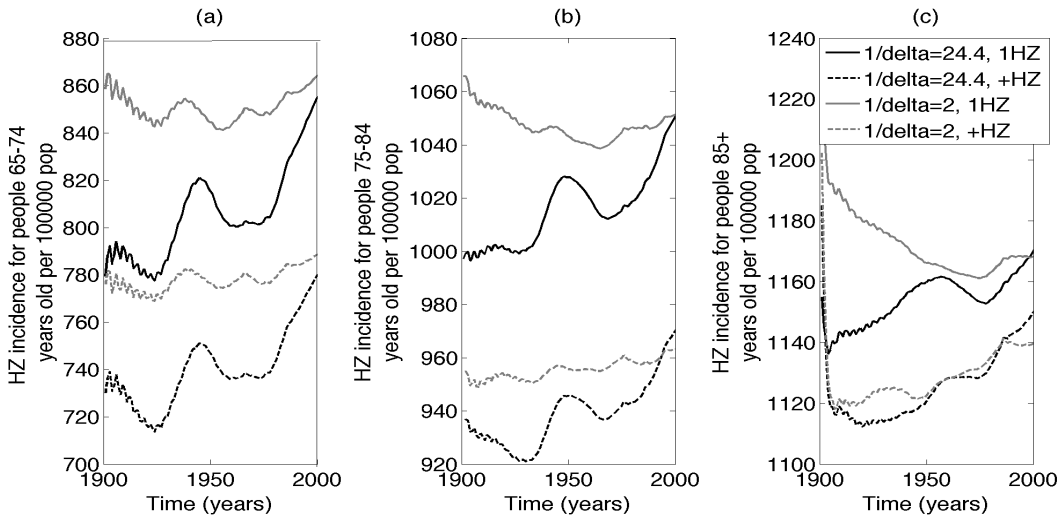


Figure 18: Modelled HZ incidence over time for the 4 different scenarios for people 65-74 years old (a), 75-84 years old (b) and 85+ (c).

Table 3: Relative changes in demography and modelled VZV epidemiology in two time periods, 1901-2000 and 1950-2000

	PERIOD	
	1901-2000	1950-2000
Birth rates	51.8% decrease	43.9% decrease
Population proportion of elderly (65+)	250.0% increase	55.5% increase
Population mean age	11.1 years increase	4.5 years increase
Average age at varicella infection	2.7 years increase	2.8 years increase
HZ crude incidence (base case)	40.2% increase	19.1% increase
HZ age-standardised incidence	1.8% increase	3.3% increase
HZ crude incidence (δ=24.4 years, 1HZ)	47.4% increase	21.0% increase
HZ crude incidence (δ=2 years, 1HZ)	40.5% increase	17.1% increase
HZ crude incidence (δ=2 years, >1HZ)	35.2% increase	14.7% increase

4 DISCUSSION

With this study we aimed to understand how demographic changes in the Australian population have influenced the incidence of varicella and HZ in the 20th century. In particular, we aimed to quantify the potential impact of demographic factors, such as reduction in birth rates, longevity and changes in age distribution, on VZV circulation and the incidence of varicella and zoster.

Our results indicate that demographic changes can contribute to the explanation of observed varicella and HZ trends.

In the 20th century, the Australian population went through a 51.8% decrease in birth rate and a progressive ageing of the population with a 250.0% increase in the proportion of elderly (65+) while the mean age of the population rose from 25 years in 1901 to 36 years in 2000.

Using an age-structured mathematical model for VZV transmission with integrated demographic changes, we found that varicella incidence in Australia followed the birth rate trends, decreasing by about 50.0% in the second half of the century. Indeed, this fall in the birth rate directly reduced the rate at which varicella susceptibles enter the population, producing a progressive decrease in the varicella force of infection. This decrease is responsible for the observed decrease in varicella incidence, which led to a shift in the mean age at infection from 5 years of age in 1901 to 8 years of age in 2000. Of more importance, based on the assumption of exogenous boosting, our model produced a 40.2% increase in HZ incidence over the century, which mirrors the increase in the mean age of the population over time.

However, following age standardisation, we found that the increase in HZ incidence is mostly due to the aging of the population with the exception of a small residual rise, of 1.8% throughout the century with higher increases (3.3%) from 1950 to 2000. This higher increase occurred during a period of progressively lower fertility rates, starting in1947. Indeed, the trend in the age standardised HZ incidence inversely followed the trend in birth rate with a delay of about 10 years (Figure 16). Hence the modelled rise in age-standardised HZ incidence likely reflects the reduced rate of varicella exposure. The two big drops in birth rate are followed by different magnitudes of increases in HZ age standardised incidence. Due to the assumption of multiple HZ reactivations in a lifetime, a possible explanation for this discrepancy is the increased proportion of elderly (from 9% to 14%), which increased the number of HZ susceptibles over time.

Our reproduction of varicella epidemiologic trends are similar to those from a recent study on the Spanish population [43]. Using a mathematical model informed with demographic changes, and calibrated against age-specific VZV seroprevalence data in 1996 for Spain and age-specific data on HZ incidence from 2005 to 2006, Marziano et al [43] qualitatively reproduced the growth of HZ incidence observed in Spain between 1997 and 2004. During the second half of the 20th century, their model produced, with about a 50% decrease in birth rates, a 3-year shift in the average age at varicella infection. However, the authors found an increase in HZ crude incidence of about 133% (from1.5 to 3.5 per 1000 individuals), while our model produced a 19.1% increase in the crude rate of HZ. Due to the lack of age-standardisation, it is difficult to separate the aging population effect from the transmission results. However, certainly the

decline in birth rate was steeper in the context of Spain, as well as apparent differences in the HZ distribution used in the calibration from that observed in Australia. Finally, their model used an agent-based approach that allowed for individual-level infection and boosting histories to be computed.

Our study showed some similarities and differences in comparison to a study by MacIntyre at al [165] analysing different HZ surveillance Australian data. Indeed, we found a much smaller increase in the crude incidence of HZ (1.2%) for the age group 60+ years old, compared to the increase in general practice encounters [165] (29.4%) found between 1998 and 2013. However, our figures are similar to the trend in hospitalisation rates published in the same study with our model and their figures and producing an increase of 3.2% and 4.2% respectively. Divergent findings appear to relate to differences in trends between data sources. We viewed hospitalisation data more reliable in our setting, hence our use of it in model calibration.

Despite a similar birth rate trends between USA and Australia in the period 1950-2000, our HZ age-standardised incidence between 1992 and 2010 shows a much smaller increase (2%) than Hales et al [108] found in the USA over the same period (39% increase) when examining Medicare claims. However, the Hales et al retrospective study is based on a population of beneficiaries older than 65 years, which, as a study on a specific population, may not be representative of the entire population. Also, the data sources used are characterised by an uncertain level and consistency of health-seeking behavior and access to health care, as well as an uncertain accuracy of disease coding [108]. Furthermore, our model does not incorporate the effect of varicella immunisation programs,

which may have led to the larger increases in HZ incidence observed in these recent studies from Australia and the USA.

In the sensitivity analyses we observed how different HZ recurrence assumptions and boosting durations affect HZ incidence trends over time. For consistency, we constrained all scenarios to produce the same HZ incidence by age as when applying Brisson's assumptions (1 HZ episode only) in the year 1998 (Figure 17a). We found that a shorter duration of immunity to HZ produced higher incidence rates with a smaller increase over time, while the assumption of only one HZ episode produced lower incidence rates (Figure 17b). These relatively small differences in predictions despite major changes in key assumptions indicate some of the difficulties in developing more accurate models of HZ disease from epidemiological data.

In terms of limitations, we note that we lacked Australian age-specific HZ incidence data to calibrate our model in periods during the decreasing birth rate. We chose to compare incidence against the Canadian sources in Brisson et al [152,155] to estimate the age-specific reactivation rate, as the comparable Australian data (from the BEACH survey), was less detailed, particularly when considered over age and time. Another limitation of our model is the contact patterns for the transmission of VZV. Due to the lack of historical contact data and the difficulty estimating historical changes in mixing patterns with different approaches, we used a time-independent contact matrix. However the actual mixing pattern may have changed substantially over time due to demographic change and other processes that influence contact [166,167]. Furthermore, Australian data on mixing patterns [168] are not available at national level so we used an age-specific contact matrix based on data observed in UK [163], which may not be representative of

Australia. Regarding the force of infection, in contrast to Brisson's study [120], in our base case we chose to assume HZ disease was not infectious. Due to the very low rate of infectivity, in the case where HZ was assumed to be infectious, not significant changes were observed in varicella and HZ modelled incidence trends, apart a slightly lower varicella mean age at infection over time (data not shown). We note, however, that if varicella immunization was added to this model the force of infection due to HZ might become more influential.

While the dynamics of exogenous boosting from re-exposure to varicella infection is largely supported [11,22,24–28,35,169], it is still far from being completely understood and quantified. Indeed, a further limitation of this study is the co-dependence between the duration of immunity and the reactivation rate, as estimated by Brisson et al from the HZ vaccine effectiveness found in the Shingles Prevention Study.

Due to the absence of detailed Australia-specific data on the incidence of varicella and HZ disease and social contacts, we used data from Canada and the UK to inform key parameters such as the rate of reactivation, contact patterns. As there may be differences between these settings in terms of population evolution, the transmissibility of varicella and patterns of contact, this potentially introduces unknown biases in the results that may influence key outcomes. This was somewhat unavoidable in the circumstances given the timeframe of the project but it would be desirable in future work to consider fitting the models to data from each of the source countries to assess external validity. Regarding demographic changes, the model accounts only for a subset of such changes that are easily incorporated into a deterministic modelling framework. However, taking in consideration differences in population density

[170], patterns of human mobility [171–173] and household size [136,174,175] could help to explain regional differences in diseases incidence and average age at infection. While some of this data is available, there remains the challenge of integration and calibration against infection data.

In order to improve the predictions of VZV models in Australia, the collection of higher quality age-specific incidence data would have been helpful as well as population data on age-specific mixing patterns, including over time. In addition better models of the reactivation process, such as the agent-based approach to modelling CMI, used by Ogunjimi et al [127], may help in refining the connection between varicella and HZ incidence.

We showed that demographic changes have at least the potential to explain HZ trends observed before or at the beginning of vaccination programs, as seen in epidemiological studies, such as in Australia [78,176,177], USA [108] and Canada-UK [111,155]. Furthermore, we showed that the drop in birth rates could explain the decreasing varicella incidence trends, observed in the 20th century, and so taking demographic changes into account could help to better evaluate the effectiveness of the current vaccination program in Australia and its potential impacts on zoster disease.

The use of models accounting for demographic changes may have substantial potential for other infectious diseases, as shown in recent modelling studies for hepatitis B and seasonal influenza [178] and hepatitis A [179]. As a final note, the large differences in trends between crude and age-standardised HZ incidence indicates the importance of modelling studies presenting both classes of results when including demographic change processes.

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