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Modelling the impact of immunization on the epidemiology of varicella zoster virus

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SUMMARY

The objective of this study was to develop and apply a dynamic mathematical model of VZV transmission to predict the effect of different vaccination strategies on the age-specific incidence and outcome of infection. To do so a deterministic realistic age-structured model (RAS) was used which takes account of the increased potential for transmission within school aged groups. Various vaccine efficacy scenarios, vaccine coverages and vaccination strategies were investigated and a sensitivity analysis of varicella incidence predictions to important parameters was performed. The model predicts that the overall (natural and breakthrough) incidence and morbidity of varicella would likely be reduced by mass vaccination of 12-month-old children. Furthermore, adding a catch-up campaign in the first year for 1–11 year olds seems to be the most effective strategy to reduce both varicella incidence and morbidity (in the short and long term), though with the possible detrimental effect of increasing the incidence of zoster.

INTRODUCTION

Varicella and zoster

Varicella zoster virus (VZV) is a herpes virus that produces two distinct diseases: varicella or chickenpox in common parlance; and herpes zoster also known as shingles. Varicella results from a first time or primary infection with VZV. As a general rule clinical illness is mild for all immunocompetent hosts although illness severity increases with age. Relative to adolescents and children respectively, adults have a 10–20 fold higher rate of varicella pneumonia and a 3- to 17-fold higher rate of hospitalization for varicella or a related complication [1–4]. The lifetime risk of acquiring varicella is over 95%. Following varicella, VZV becomes latent in the dorsal root ganglia and can reactivate generally after a long period to cause zoster (shingles) [5, 6]. Reactivation occurs in 15–25% of individuals over 70% of which are in adults [7, 8]. Zoster is associated with severe morbidity (hospitalization occurs in 4% of cases) and significant case fatality (0·07% of cases) making it an essential issue to be considered when analyzing the epidemiology of VZV [5].

The precise relationship between varicella and zoster incidence is still unclear. It has been established that zoster is infectious and can transmit varicella [8]. By doing so zoster appears to stabilize the variability in varicella epidemics permitting VZV to persist in small populations [9–11]. Although zoster is thought to be less infectious than varicella, the contribution zoster makes to the overall force of varicella infection remains uncertain. The role of varicella on zoster incidence is more ambiguous primarily because of the lack of understanding of the mechanism of reactivation. It has been suggested that varicella can decrease the risk of zoster by boosting specific immunity to VZV [8]. However, no conclusive

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evidence exists which demonstrates that varicella has any effect on zoster incidence.

Vaccine and vaccination

A live attenuated varicella virus (Oka) vaccine was developed by Takahashi and colleagues at the beginning of the 1970s [12]. Since then, numerous studies have shown the vaccine to be safe, immunogenic and protective against severe varicella in healthy children and adults [13–24]. Based on these studies, live attenuated varicella virus vaccines (Varivax® Merck Research Laboratories, Varilix® SmithKline Beecham) have been licensed for healthy children in many countries and routine childhood immunization was introduced in the United States in 1995 [25].

Some important questions remain which limit the widespread acceptability and implementation of the vaccine in developed countries. The primary concern is that by reducing exposure to infection, vaccination could lead to a shift in the average age at infection from children to adults, where the risk of complications is greater [1, 4]. Hence, by increasing incidence in adults varicella vaccination programmes could lead to an overall reduction in public health. Such a phenomenon has been observed with rubella vaccination in Greece [26]. Furthermore, a high number of breakthrough cases of varicella have been reported in some vaccine efficacy studies [27]. Clinical trials have shown that 0·2–4·5% of vaccines a year develop mild breakthrough varicella (modified varicella) in the first years following vaccination [27]. An additional concern is the unknown impact of immunization on the epidemiology of zoster [10]. Zoster may occur more frequently in adults who have not been boosted by varicella contacts during their adult life [28]. If this is so, reduction of varicella incidence after mass vaccination could reduce the likelihood of such boosting and thus increase the incidence of zoster. Due to the higher severity of zoster, a small increase in zoster incidence could counterbalance the reduction in varicella morbidity compromising the effectiveness of VZV vaccination. Finally, the live attenuated varicella virus vaccine is the first vaccine that can establish latency [28]. The likelihood and severity of reactivation (zoster) in vaccines is thus an additional concern.

Mathematical models

Previous modelling work on the impact of VZV vaccination has focused mainly on the change in incidence and morbidity of varicella due to shifts in the age at infection [30, 31]. These studies used a model developed by Halloran and colleagues, which indicates that vaccination of 12-month-old children would reduce both varicella incidence and hospitalization in the United States. However, within this work a small number of vaccine coverages and policies were investigated, vaccine efficacy parameters were optimistic [32], the age structure of the model did not accurately reflect the epidemiology of varicella and no sensitivity analysis was performed on the Who-Acquires-Infection-From-Whom matrix (WAIFW). In addition, the possible effects of immunization on the epidemiology of zoster were not explored. A number of countries are now relying on Halloran and colleagues mathematical model and vaccine parameters to evaluate the cost-effectiveness of varicella vaccination [31]. Given that varicella vaccination may only be marginally cost-effective the impact of lower vaccine efficacy as well as possible changes in the incidence of herpes zoster on vaccination effectiveness should be investigated.

Garnett and Grenfell [9, 10] were the first to explore the relationship between varicella and zoster using mathematical models. They examined the impact of vaccination on the long-term equilibrium incidence of these diseases, but ignored the possible short to medium-term. Ferguson and colleagues [11], on the other hand, examined the possible influence of zoster on the transmission dynamics of varicella, but did not investigate the impact of vaccination on the incidence of zoster (their model assumes a constant background force of infection from zoster which remains unchanged through time).

In this study we use a mathematical model to simulate transmission of varicella and zoster in developed countries before and after vaccination using Canada as an example. The four main questions addressed are: (1) the effect of vaccination in healthy children on the overall varicella morbidity; (2) the role of vaccine efficacy on varicella incidence and morbidity; (3) the effect of vaccination strategies in minimizing incidence and morbidity; and (4) the possible impact of vaccination on zoster.

METHODS

Population

The Canadian population is assumed to be stable – i.e. birth is set to equal death. Birth rates are assumed

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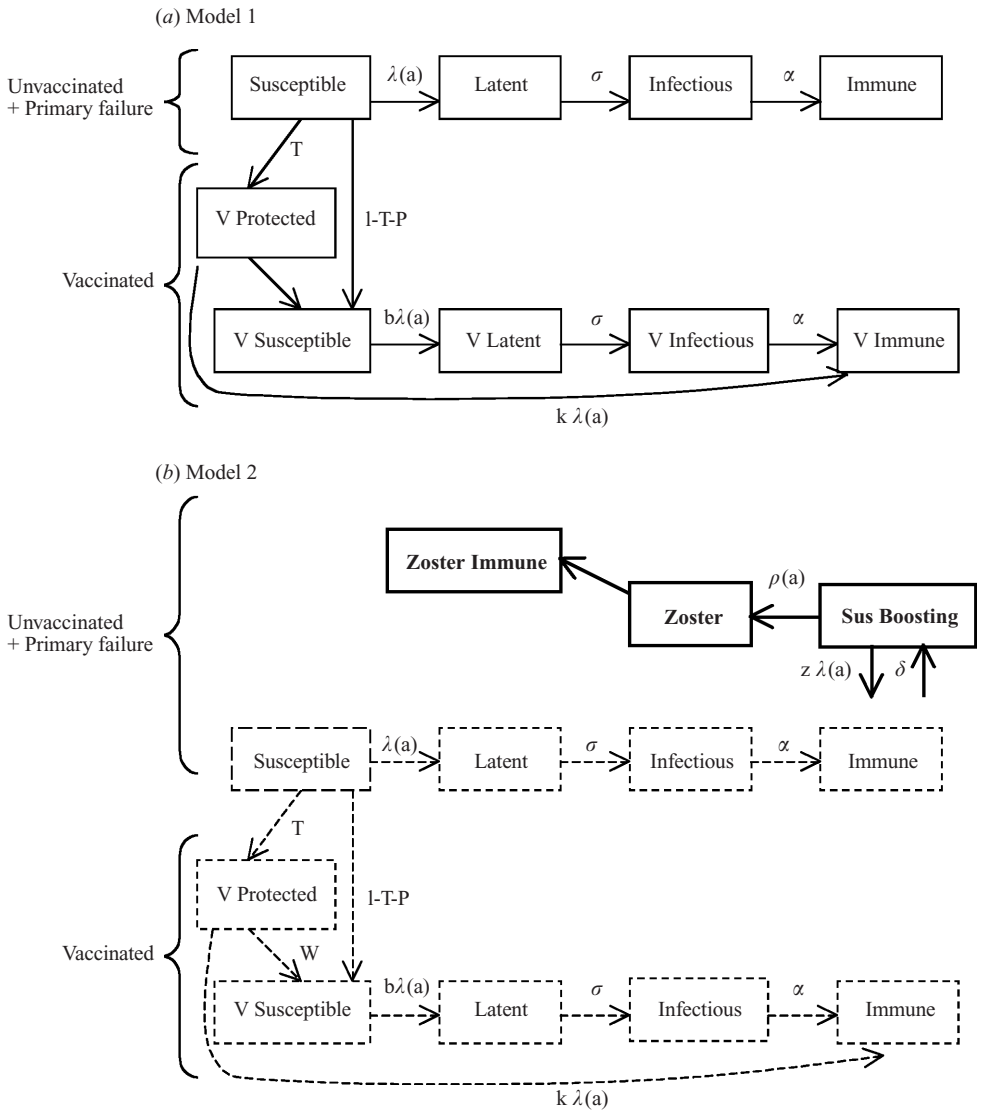

Fig. 1. Flow diagram of varicella and zoster before and after vaccination. The mutually exclusive compartments represent the different varicella and zoster epidemiological states. Arrows represent the flow between these states (*a*) Model 1, represents the transmission dynamics of varicella. (*b*) Model 2, represents the transmission dynamics of both varicella and zoster. See text and Table 1 for details.

constant through each year. Mortality is assumed to be zero until 65 years and constant thereafter producing an average life expectancy of 75 years. The population is stratified into 66 age cohorts (0, 1, 2, 3, … , 65+). This type of simplified age structure is widely used and is a reasonable approximation of the demography of Canada (Statistic Canada).

Model structure

Two models were used in this study. Model 1 (Fig. 1 *a*) was built to assess the impact of varicella transmission before and after vaccination in Canada whereas Model 2 (Fig. 1 *b*) was built to investigate the potential impact of varicella vaccination on zoster. Both transmission models are realistic age-structured deterministic models (RAS) based on a set of ordinary differential equations. Similar types of models have been used in other work to study childhood infections such as measles and varicella [30, 33–35]. Models 1 and 2 possess 8 age groups (0–1, 2–4, 5–11, 12–18, 19–24, 25–44, 45–64 and 65+ years). The younger age groups represent the Canadian school structure (i.e. infant, pre-school, primary school, high school, college and university) while older age groups are stratified to better capture differences in varicella and zoster incidence and morbidity with age. The models start at the mean varicella epidemic cycle.

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Model 1 is illustrated by the flow diagram in Figure 1*a*, which characterizes the natural history of varicella with and without vaccination (the mathematical structure is presented in Appendix 1). The mutually exclusive compartments represent the different epidemiological states of the disease and the arrows represent the flow of individuals between them. At 6 months of age, once maternal antibodies to varicella have waned, children enter the susceptible class (*Susceptible*) and if infected pass through the latent (*Latent* – i.e. infected but not infectious) and infectious (*Infectious*) periods before acquiring lifelong immunity (*Immune*). Following vaccination, individuals either remain in the fully susceptible class (*Susceptible*) because of complete vaccine failure (primary failure) or pass into one of two mutually exclusive classes: (1) a temporary protection class (*V Protected*) in which individuals are immune from infection but may lose protection over time; and (2) a modified susceptible class (*V Susceptible*) in which individuals retain some degree of partial protection (1-*b*) and if infected are likely to experience a less severe infection [36]. Vaccinated protected individuals can also become permanently immune (*V Immune*) by having an effective contact with an infectious individual (contact which would otherwise lead to infection).

The age-specific varicella force of infection $\lambda(a, t)$ (the per susceptible rate of infection) is composed of the force of infection caused by varicella ($\lambda_v(a, t)$) and by zoster (λ_z) (see Appendix 1). The force of infection caused by varicella ($\lambda_v(a, t)$) is a function of the age-specific number of infectious individuals and the effective contact rate between age groups. It adopts different values in each of 8 age groups (< 2, 2–4, 5–11, 12–18, 19–24, 25–44, 45–64 and > 64 years). In model 1, the force of infection due to zoster is constant through time (λ_z) – i.e. independent of the prevalence of zoster.

Model 2, illustrated by Figure 1*b*, adds a complexity to Model 1 by attempting to incorporate the natural history of zoster (solid bold boxes and lines) (see Appendix 2 for mathematical structure). Following varicella infection individuals acquire lifelong immunity to varicella and a temporary immunity to zoster (*Immune*). Once immunity to zoster has waned individuals become susceptible to zoster (*Sus Boosting*). Unless they die in the meantime, two events can then occur: (1) individuals have a reactivation episode (*Zoster*) and then become permanently immune (*Zoster Immune*); or (2) individuals are boosted by contacts with varicella and return to the temporarily immune class (*Immune*). Repeat cases of zoster were not modelled since reoccurrence is low (close to 1%); [28]. Furthermore, zoster was assumed not to occur in vaccines even though studies in immunocompromised children have shown VZV to reactivate after vaccination. However, after vaccination zoster is reduced by sixfold and cases are less severe [7].

In Model 2 the force of varicella infection caused by zoster ($\lambda_z(t)$) is a function of the overall number of zoster infectives (see Appendix 2). The rate of VZV reactivation ($\rho(a)$) is assumed to be dependant on age (see Appendix 2).

Mixing patterns – The Who-Acquired-Infection-From-Whom matrix

The standard technique to take account of age-dependant mixing patterns of the population is to use a Who-Acquired-Infection-From-Whom (WAIFW) matrix [37]. The WAIFW matrix represents the effective contact rate between age groups – i.e. the rate at which an infective of age X will infect a susceptible of age Y. Since the elements of the matrix cannot be observed directly in populations they must be estimated from the pre-vaccination force of infection. With such a technique a large number of possible matrix structures can be assumed from the same observed data. It is therefore necessary to perform a sensitivity analysis to assess how changes in the matrix structures influence results. In this study we explore the effect of five WAIFW matrices on the results. The chosen matrix structures are; our base matrix (*base matrix*); two variations on the base matrix matrices (*matrix 1* and *matrix 2*); a purely proportional (*proportional matrix*); and a highly assortative mixing matrix (*assortative matrix*) (see Appendix 3 for the matrix structures).

The structure of the *base matrix* was chosen to reflect the importance of school transmission of varicella. Contact rates within pre-school (2–4 years old), primary school (5–11 years), high school (12–18 years), university (19–24 years) are allowed to be large. The highest contact rates are observed within the 19–24 age group, which may reflect higher contact patterns amongst university students [38]. Infants (0 and 1) are assumed to come into contact with all other children at a similar rate and with adults at different rates (the highest estimated rates were with the 24–44 year group, which probably represents parent–infant

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contacts). Adults (25–44, 45–64 and 65+) are assumed to mix with themselves and with children at similar rates. School-aged children (2–4, 5–11 and 12–18) mix with other children not of their own age at a unique rate.

Matrix 1 has an identical structure as the *base matrix* but with contact rates in the 19–24 age group set to be 2/3 of the *base matrix*. *Matrix 2* is different to the *base matrix* in that specific rates are added for parent–child contact (0–1, 2–4, 5–11 with 25–44) and work related contacts (19–24, 25–44 and 45–64), creating a more assortative matrix structure (like-with-like) than the *base matrix*. The purely *proportional matrix* assumes that each age group has a unique contact rate and the rate of effective contact between two age groups is dependent on the product of their respective contact rates. This matrix structure puts the least emphasis on mixing within age groups. Finally, the *assortative matrix* (like-with-like) implies a strong amount of within age group mixing. The *assortative matrix* has unique coefficients along the leading diagonal for all but the 65+ age group. It is important to note that this structure is not purely like-with-like since it allows a low contact rate between different age groups.

Model output

Following mass immunization, varicella cases are classified into two groups characterized by their degree of severity; (1) Natural (NV) and (2) Breakthrough varicella (BV). Natural or full-blown varicella occurs in unvaccinated individuals and primary failures. Breakthrough varicella, which occurs in seroconverted vaccinated individuals, is clinically modified and significantly less severe than natural varicella [36]. Since breakthrough cases are very mild and are assumed to require no medical care we primarily investigate the influence of vaccination on natural varicella cases.

Varicella morbidity is represented by the total number of inpatient days due to varicella. The frequency of hospitalization for varicella and length of stay per admission were determined using the Manitoba population-based hospital separation data from 1979–97 [39]. We applied the age-specific length of stay per varicella case (Table 1) to the predicted number of natural cases of varicella. Breakthrough cases were assumed not to require hospitalization. Using the hospital separation data might overestimate the severity of illness among older individuals since the validity of diagnostic codes for varicella decreases markedly after age 50 years [40]. Furthermore, the incidence of co-morbid disease increases with age making it difficult to be sure that all days in hospital are attributable to varicella. On the other hand, our results assume that breakthrough varicella never requires hospital admission, which might be an underestimation of morbidity among older adults.

Biological parameters

The parameter definitions and values are described in Table 1. The average duration of latency ($1/\sigma$) and infectiousness ($1/\alpha$) for varicella is respectively 14 and 7 days [6]. Natural immunity to varicella is assumed to be life-long. Duration of immunity to zoster after boosting (Model 2) is set at 2 and 20 years to represent the plausible range of values for this parameter. The average length of zoster infectiousness ($1/\alpha_z$) is 7 days [6].

Vaccine efficacy parameters and estimates

The waning rate (W), proportion of individuals who become temporarily protected after vaccination (T), residual susceptibility (b) and boosting (k) were estimated concurrently to take into account dependencies (inter-relationships) between parameters (see Brisson and colleagues [32] for more details). Estimation involved comparing the results of a simple model to data from clinical trials. Previously unpublished data from Merck Research Laboratories were chosen to represent the *base vaccine* scenario since the study vaccine is nearly identical to the currently licensed product. The Oka/Merck vaccine clinical trials producing the lowest and highest breakthrough rates were chosen to represent the *best* and *worst vaccine* scenario in order to represent the plausible range of vaccine efficacy [27, 32]. The rate of primary vaccine failure (P) observed in clinical trials has ranged from 0–6% [15, 19, 21]. For the model P was set to 1% for the *best vaccine*, 4% for the *base vaccine* and 6% for the *worst vaccine* scenario. Relative residual infectiousness (m) is defined as the relative rate of varicella transmission to susceptible non-vaccinated contacts (NV) from infected vaccinees (i.e. those with breakthrough infection) versus that from infected non-vaccinees. M can be estimated epidemiologically by dividing the household second-

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Table 1. *Model parameters*

Model parameters		Mean value	
Demographic parameters			
Canadian population (Statistics Canada)		30000000	
Birth rate (births/year)		400000	
Mortality rates by age group (1/year):			
0–64		0·0	
> 65		0·1	
Biologic parameters			
Proportion of the population contracting varicella in absence of vaccination [5]		99 %	
Force of varicella infection by age group ($\lambda_v(a, t)$) (1/year) (Appendix 2):			
0–1		0·05	
2–4		0·16	
5–11		0·20	
12–19		0·10	
20–24		0·09	
25–44		0·08	
45–64		0·05	
> 65		0·04	
Force of varicella infection due to zoster (λ_z) (1/year):			
Model 1 (Appendix 1)		0·001	
Model 2 (Appendix 2)		$5{\cdot}4^{e-7}$*Zoster Prevalence	
Duration of varicella (days) [6]:			
Duration of latent period ($1/\sigma$)		14	
Duration of infectious period ($1/\alpha$)		7	
Duration of immunity to zoster after varicella infection (years) ($1/\delta$)		2 and 20	
Proportion of effective varicella contacts that boost against zoster (z)		100 %	
	Z = 0 %	Z = 100 %	Z = 100 %
Rate of reactivation by age group ($\rho(a)$) (1/year) with and without boosting (z) for different durations of immunity ($1/\delta$) (Appendix 2):	$1/\delta = 2$	$1/\delta = 2$	$1/\delta = 20$
0–1	2·0*e*–01	2·0*e*–01	2·0
2–4	9·3*e*–03	9·9*e*–03	7·9*e*–02
5–11	3·1*e*–03	3·9*e*–03	2·0*e*–02
12–19	2·5*e*–03	3·1*e*–03	1·1*e*–02
20–24	2·0*e*–03	2·0*e*–03	6·0*e*–03
25–44	2·9*e*–03	3·4*e*–03	8·3*e*–03
45–64	3·8*e*–03	4·3*e*–03	8·9*e*–03
> 65	1·1*e*–02	1·2*e*–02	2·3*e*–02
Mean inpatient days per case of varicella by age group (days) [39]:			
0–1		0·11	
2–4		0·02	
5–11		0·01	
12–19		0·02	
20–24		0·02	
25–44		0·12	
45–64		0·21	
> 65		1·25	
Vaccine efficacy parameters [32]	Best	Base	Worst
Rate at which temporarily protected individuals become partially susceptible to varicella (1/year) (W)	0·021	0·031	0·085
Percent of individuals who become temporarily protected after vaccination (T)	95 %	93 %	83 %
Percent of individuals for which vaccine fails completely (P)	1 %	4 %	6 %
Rate of varicella acquisition of vaccinees compared to non vaccinees (b)	50 %	73 %	100 %
Proportion of temporarily protected individuals who become immune due to contact with varicella (k)	100 %	91 %	50 %
Rate of varicella infectiousness of vaccinees compared to non-vaccinees (m)	20 %	50 %	100 %

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ary attack rate (SAR) from vaccinated to unvaccinated individuals (SAR_{V-NV}) with the secondary attack rate from unvaccinated to unvaccinated individuals (SAR_{NV-NV}) [41]. The observed rate for SAR_{NV-NV} is 86% [42]. There are no published estimates for SAR_{V-NV} however the rate can be estimated from SAR_{V-V}, which has been reported as 5% [16], 8·6% [22] and 12% [43] in three different vaccine trials. If we set SAR_{V-V} to equal 8·6% and we suppose that 10% of vaccinees are susceptible to varicella infection then the relative residual infectiousness is close to 100% ($m = [SAR_{V-NV}/SAR_{NV-NV}] = [(8{\cdot}6\%/10\%)/86\%] = 100\%$). A second method of estimating relative residual infectiousness is through the ratio of lesion numbers observed in vaccinees with breakthrough varicella compared to unvaccinated individuals with natural varicella. Published reports suggest this ratio is 17% [36]. Taking both methods into account, relative residual infectiousness (m) is varied between 20% and 100% (i.e. 20% best vaccine, 50% base vaccine and 100% worst vaccine).

The force of varicella infection due to zoster was assumed to be 1% of the total force of varicella infection. This assumption was based on data collected by the Immunization Monitoring Program–Active (IMPACT), a Canadian paediatric hospital-based surveillance network. Of 1119 children admitted for chickenpox or a related complication, a source of infection was identified for 576 and of these only 5 followed exposure to herpes zoster whereas the rest followed exposure to varicella (unpublished data from Dr Barbara Law).

Vaccination policies

The different vaccination strategies investigated were:

Strategy 1: routine vaccination at 1 year of age.
Strategy 2: strategy 1 + vaccination at 11 years of age for the first 11 years of the program.
Strategy 3: strategy 1 + vaccination of 1–11 year old children in first year of program.
Strategy 4: routine vaccination at 12 years.

RESULTS

Incidence of varicella

Model 1 produces a yearly epidemic of varicella before vaccination (see Fig. 2) with an average predicted incidence rate of 13505 cases/1000000 population-year and 89% of cases occurring in children under 15. Considering reporting rates (< 50% in children and > 90% in adults), these results are consistent with sentinel surveillance and medical billings data from Canada (5110 per 1000000 year; and 85% in under 15s respectively) [39, 44], England (5475 per 1000000 year; and 80%) [39], France (9855 per 1000000 year; and 92%) [45] and Scotland (6205 per 1000000 year; and 79%) [46].

Age distribution and coverage (Strategy 1; base matrix; base vaccine)

At 30% coverage (Fig. 2*a*), the number of annual cases is rapidly reduced then oscillates between high and low epidemic years before reaching a new equilibrium. A slight shift in the age distribution is predicted but the bulk (81% compared to 86%) of infection remains in children under 12 years of age. Such dynamic patterns are observed with the base-case model for levels of coverage under 60%. As coverage increases (between 30 and 60%) oscillations in the number of cases before equilibrium become more pronounced, the number of cases at equilibrium decrease and a greater shift in the age at infection occurs (results not shown).

If high coverage is achieved, as should be expected in Canada (and other developed countries), more complex dynamics are produced. As shown in Figure 2*b*, 90% vaccine coverage produces an immediate decline in cases. A first large epidemic is then expected within the first 5 years of vaccination followed by a 10-year period of low incidence (honeymoon period). During this time fully susceptibles (unvaccinated and primary failures) slowly accumulate. Once a threshold of fully susceptibles is surpassed a large epidemic occurs (post-honeymoon epidemic). Thereafter, the infection settles into a new epidemic cycle and equilibrium. Both epidemics would occur primarily in individuals who were in age groups immediately above those who were vaccinated when vaccination began. The first epidemic occurs in the 5–18 year cohorts (88% of cases in 5–11 year olds) since a lower threshold of susceptibles is needed to induce an epidemic due to the high contact rate within this age group. When individuals still susceptible after this first epidemic reach 19–24 years a second and greater epidemic is produced. Again this is due to the high contact rate in this age group. Finally, at equilibrium proportionately there are more cases in adults (51%

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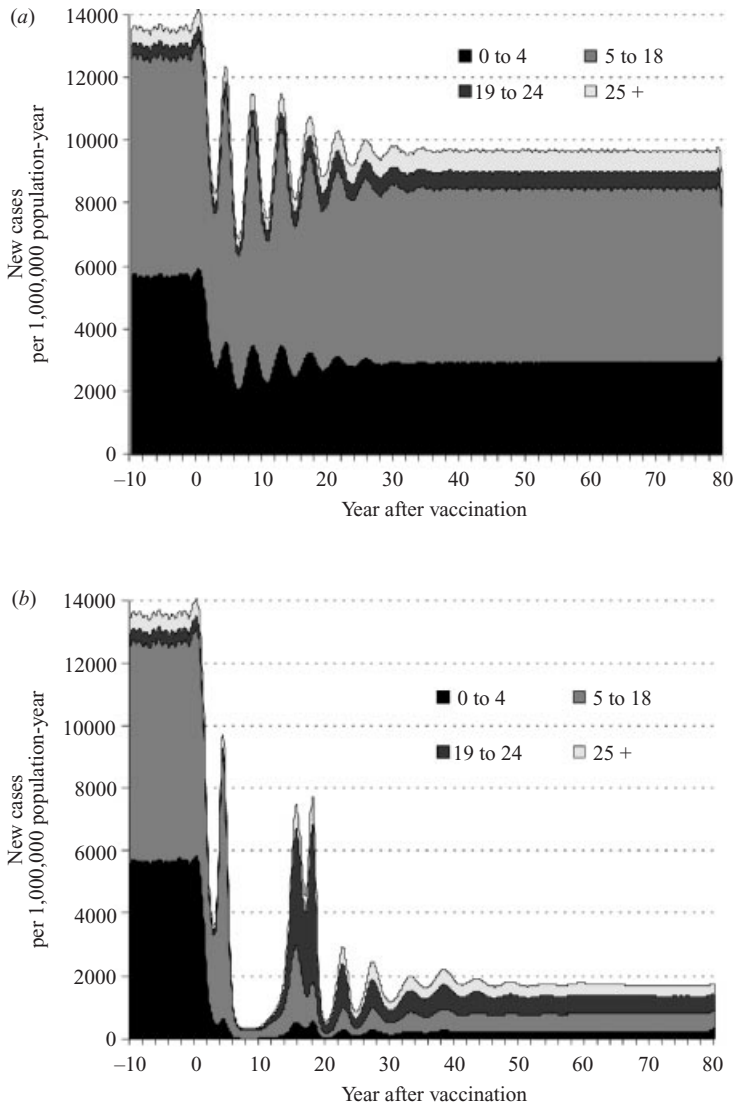

Fig. 2. Age distribution and coverage. (*a*) Age-specific number of natural varicella cases for low vaccine coverage (30%) coverage, *base vaccine*), (*b*) Age-specific number of natural varicella cases for high vaccine coverage (90% coverage, *base vaccine*). The width of each colour band represents the age-specific varicella incidence rate.

occur in those over 18 years of age), but the absolute number remains virtually the same as in the pre-vaccination state. The transmission dynamics shown in Figure 2*b* are similar for vaccine coverage between about 70% and 95%. As coverage increases the honeymoon period is longer, the post-honeymoon epidemic is shorter but more intense and the shift in the age at infection more pronounced (results not shown).

WAIFW matrices (*Strategy 1; 90% coverage*)

The transmission dynamics shown in Figure 2 are dependant on the age-specific mixing patterns. Figure 3 shows the age-specific number of natural varicella cases for the different WAIFW matrices.

The *proportional matrix* (Fig. 3*a*) does not produce a post-honeymoon epidemic. On the other hand, it induces a larger shift in the age at infection due to a higher degree of contact between children and adults (Fig. 3*e*). The remaining WAIFW structures (*Matrix 1*, *2* and the *assortative matrix*) produce an initial epidemic in the 5–18 age group and a second greater post-honeymoon epidemic (Fig. 3*b–d*). *Matrix 1* (Fig. 3*b*) produces a shorter post-honeymoon epidemic than the base-case due to reduced effective contact rates in the 19–24 age group (compare Fig. 2*b* with

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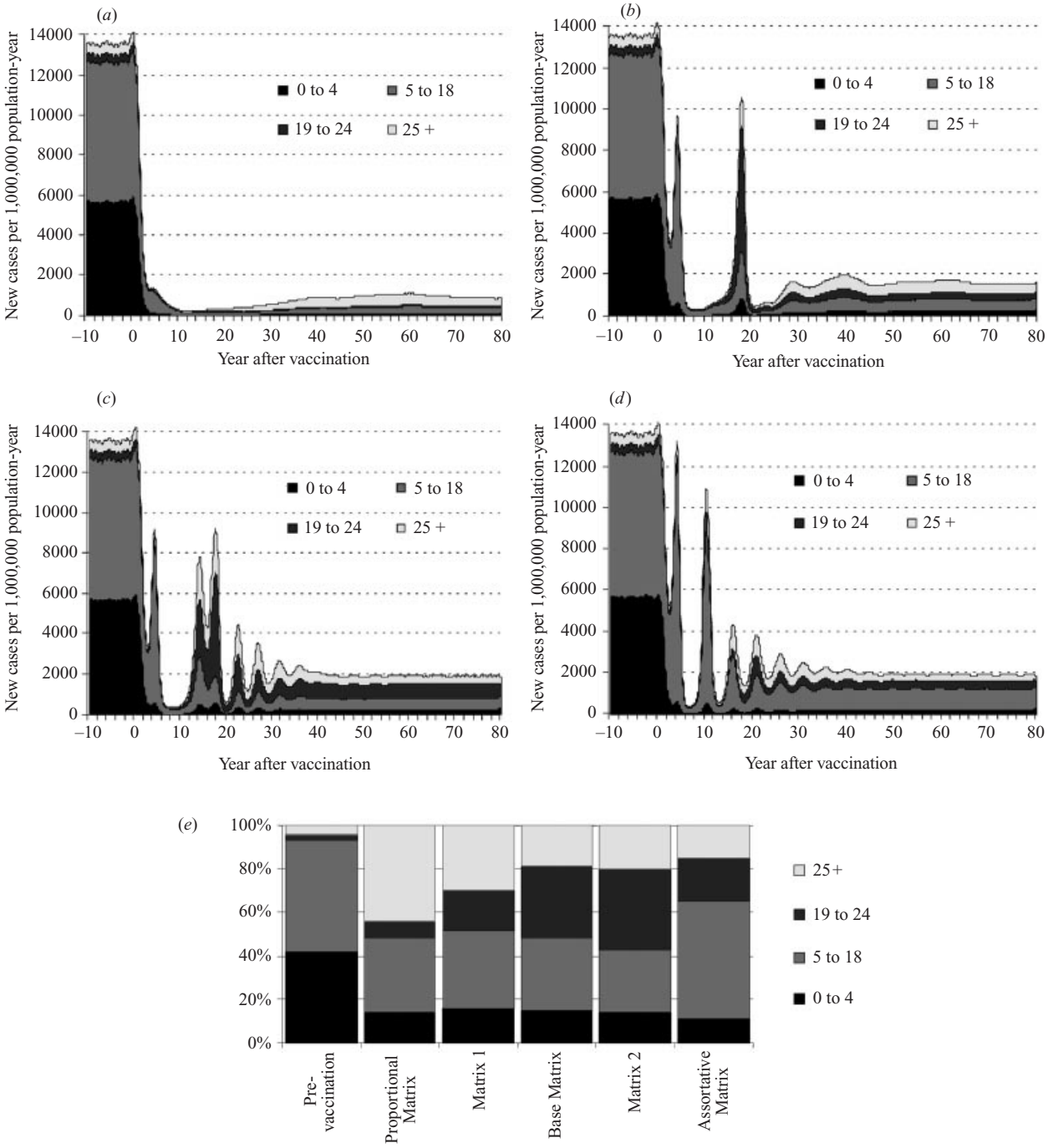

Fig. 3. WAIFW Matrix. Estimated incidence of natural varicella cases for (*a*) *proportional mixing* (*b*) *Matrix 1*, (*c*) *Matrix 2*, (*d*) *assortative mixing*, and (*e*) the age distribution of infection at equilibrium by WAIFW matrix structure. All simulations assume the *base vaccine* and 90% coverage.

3*b*), though the shift in the average age at infection is greater than the *base matrix* (Fig. 3*e*). *Matrix 2* (Fig. 3*c*) produces almost identical short-term dynamics as the *base matrix* and a similar shift in the age at infection (Fig. 3*e*). Finally, the *assortative matrix* (Fig. 3*d*) produces a post-honeymoon epidemic in children (5–18 years) and a small shift in the average age of infection (Fig. 3*e*). Results indicate that unless contacts are proportional, which is highly unlikely, and contact rates are low within the 12–18 and 19–24 age groups the short-term dynamics of varicella after vaccination at high levels of coverage should approximate those of our base case model (*base matrix*, *base vaccine*, *90% coverage*).

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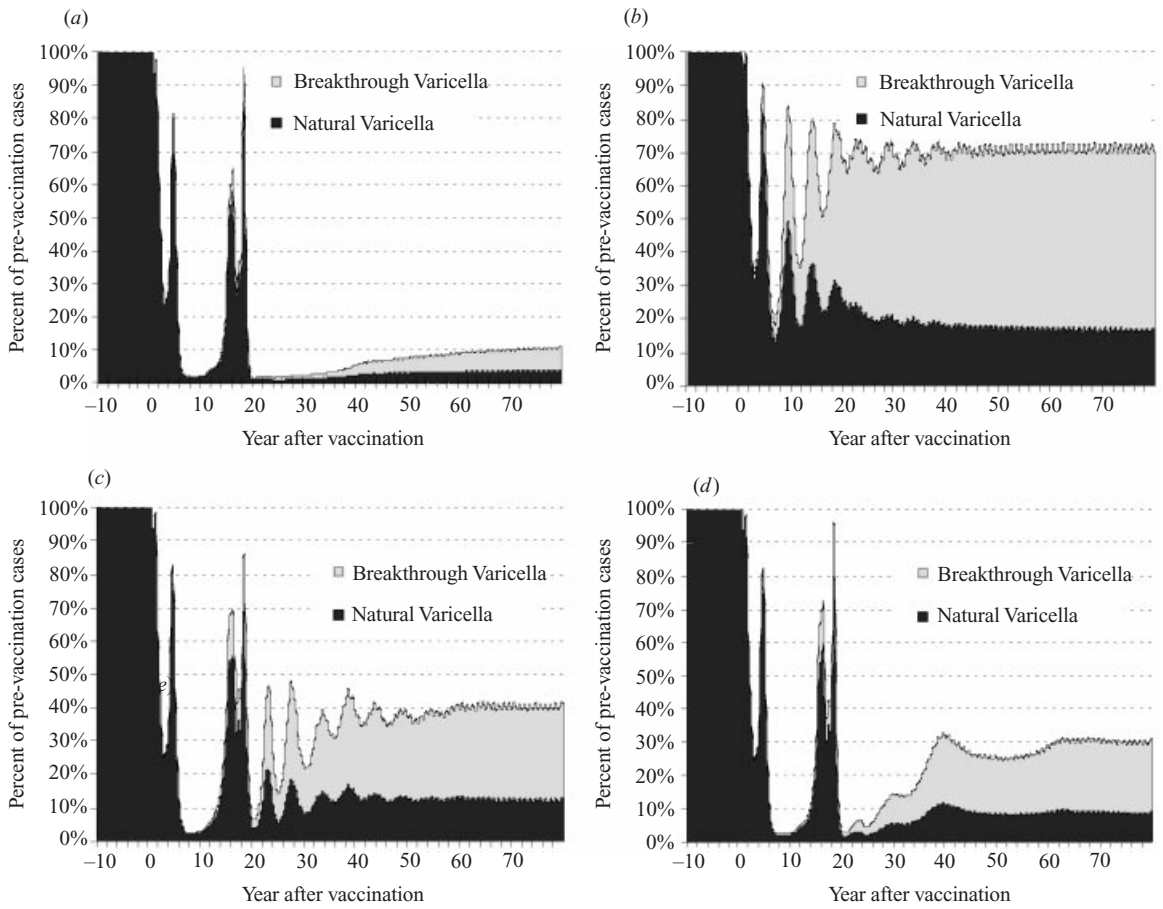

Fig. 4. Vaccine efficacy. Predicted incidence of natural and breakthrough varicella cases over time (90% infant coverage) with (*a*) best case vaccine, (*b*) worst case vaccine, (*c*) base case vaccine and (*d*) base case vaccine and $m = 0{\cdot}20$.

Vaccine efficacy (*Strategy 1; 90% coverage; base matrix*)

Figure 4 shows the predicted impact of the various vaccine efficacy scenarios on the number of natural and breakthrough cases of varicella for high vaccine coverage. Before attaining post-immunization equilibrium, the *worst vaccine* (Fig. 4*b*) produces several epidemic peaks whereas the *best* and *base vaccines* produce two larger epidemics (Fig. 4*a*, *c*). The continuing transmission of varicella following vaccination with the *worst vaccine* is thus expected to prevent the post-honeymoon epidemic.

At equilibrium the *base* and *worst vaccines* are expected to produce similar numbers of natural varicella cases (12 and 17% of pre-vaccination state respectively). If, under the *base vaccine* scenario, residual infectiousness (*m*) is reduced from 0·50 to 0·20, the number of natural varicella cases is expected to decrease to 9% of the pre-vaccination state (Fig. 4*d*). Although the *worst*, *base + low infectiousness* (m = 0·2) and *base vaccine* scenarios are expected to be similar, they are predicted to cause very different numbers of breakthrough infections. The *worst vaccine* scenario results in roughly twice as many breakthrough cases at equilibrium as the *base vaccine*. If breakthrough cases are taken into account, the *worst vaccine* is expected to reduce the number of total cases of varicella by only 30% in contrast to 60 and 70% for the *base vaccine* and the *base + low infectiousness vaccine*. Moreover, the expected lifelong risk of varicella in individuals who received the vaccine is predicted to be 54% (53% breakthrough (BV), 1% natural (NV)) for the worst vaccine which compares with 29% (28% BV, 1% NV), 22% (21% BV, 1% NV) and 7% (almost all BV) for the *base*, *base + low infectiousness* (m = 0·2) and *best vaccines* respectively.

Vaccination strategies (*Strategies 1 to 4; 90% coverage; base matrix; base vaccine*)

Strategy 1. As already presented above vaccination at 12 months of age with no-catch-up campaign is

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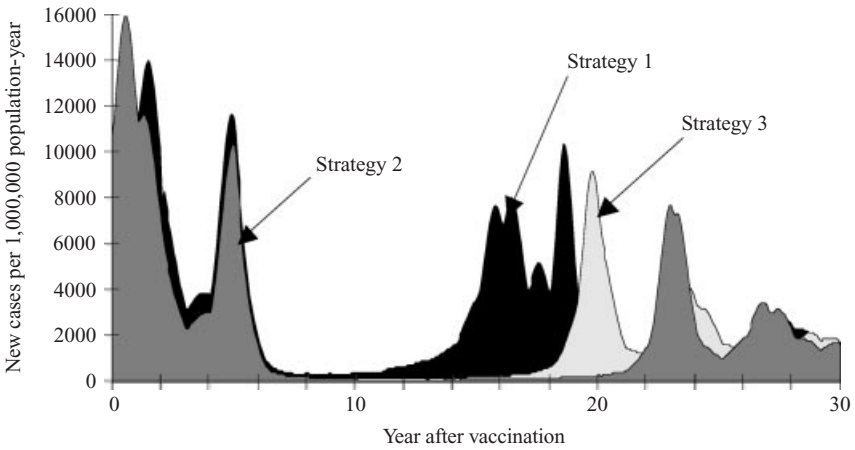

Fig. 5. Vaccine strategy. Estimated incidence of natural varicella cases over time by vaccine strategy (90% coverage, *base vaccine*). Strategy 1 is continuous infant only vaccination. Strategy 2, is continuous infant vaccination with vaccination of 11 year olds (90 % coverage) for the first 11 years of the programme. Strategy 3 is continuous infant vaccination with a campaign of vaccination of 1–11 year olds in the first year of the programme.

expected to produce two large epidemics among individuals who were 1–11 years old when the immunization programme began (Figs 2, 3, 4, 5).

Strategy 2. Model results suggest including a yearly catch-up programme aimed at 11 years olds for the first 11 years of the immunization programme would not prevent the first epidemic (in children aged 5–18) but would eliminate the post-honeymoon epidemic (in 19–24 year olds). See Figure 5.

Strategy 3. In contrast to *strategies 1* and *2*, an initial intensive catch-up campaign for all children between 1 and 11 years would be expected to have a greater immediate impact on varicella transmission. Following the first year of vaccination the bulk of susceptibles in the population (over 90%) would be immunized. This practically eliminates transmission. Accumulation of susceptibles is slower creating a longer honeymoon period (20 years). Furthermore, the post-honeymoon epidemic is expected to be smaller than *strategy 1* due to fewer and a more homogeneous distribution of susceptibles within the age groups. Within the strategies examined, *strategy 3* minimizes the number of cases of varicella under our *base case* assumptions (*90% coverage*; *base matrix*; *base vaccine*).

For *strategies 1*, *2* and *3* the number of cases of varicella at equilibrium would be identical. Coverage and vaccine efficacy influences the number of cases at equilibrium whereas catch-up programmes do not.

Strategy 4. Vaccination at 12 years of age is the least effective strategy producing only a slight decrease in the annual number of natural cases (results not shown). Vaccinating 12-year-old children with the *base vaccine* and 90% coverage is predicted to reduce the total number of natural varicella by only 13% at post-immunization equilibrium. This is because by age 12 more than 85% of children have developed varicella. However, this strategy is expected to prevent 93% of adult cases of natural varicella at equilibrium.

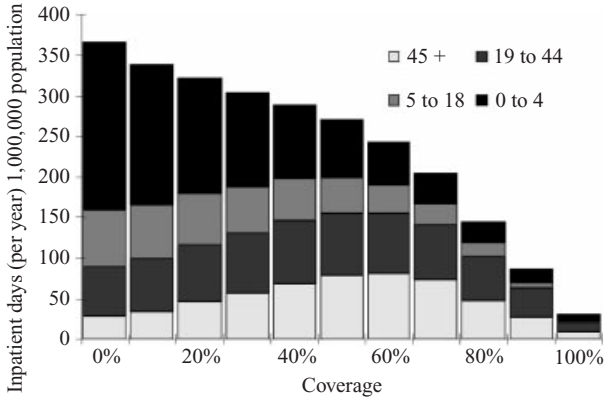

Fig. 6. Age distribution and coverage. Predicted age distribution of varicella associated inpatient days (morbidity measure) at equilibrium by vaccine coverage (*base case* vaccine used).

Varicella morbidity

Age distribution and coverage (*Strategy 1; base matrix; base vaccine*)

Figure 6 represents the estimated yearly age-specific number of inpatient days expected in a population of 1 000 000 at equilibrium after mass vaccination, for the *base case*. Mass vaccination seems to reduce the

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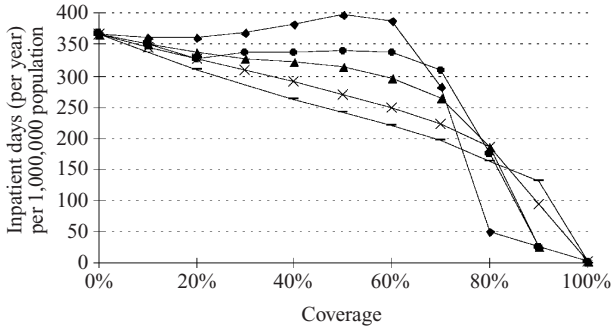

Fig. 7. WAIFW matrix. Estimated morbidity (annual inpatient days) at equilibrium for the *base matrix* (▲), *Matrix 1* (●), *Matrix 2* (×), *assortative* (−) and *proportional matrix* (◆).

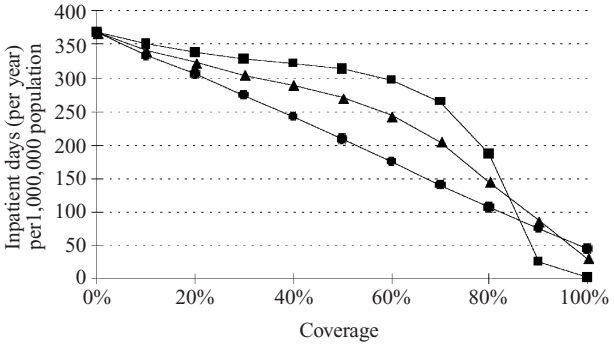

Fig. 8. Vaccine efficacy and coverage. Estimated morbidity (annual inpatient days) at equilibrium for the *base* (▲), *worst* (●), and *perfect vaccine* (■). *Base case* matrix used.

overall morbidity as coverage increases despite a shift in the average age at infection and an increase in morbidity with age. The overall number of inpatient days decreases less than proportionately with an increase in coverage for levels of coverage below about 60%. This is because the sharp decrease in morbidity in children (at 60% coverage an estimated decrease of from 260 prior to vaccination to 73 inpatient days) is offset by the increase in adult morbidity (108 to 171 inpatient days). Only when coverage exceeds 80% does vaccination seem to reduce varicella transmission sufficiently to reduce both adult and child morbidity. Thus, small increases in coverage between 70% and 90% are expected to significantly reduce the overall morbidity.

WAIFW matrices (*Strategy 1; base vaccine*)

As shown by Figure 2*b* and 3, mixing patterns influence the nature and scale of the shift in the age distribution of infection after immunization. Since severity of varicella changes with age (Table 1), it is essential to assess the impact different WAIFW matrices can have on morbidity. In doing so we can quantify the uncertainty of our *base matrix* results.

The shift in the average age at infection is smaller as mixing becomes more assortative (like-with-like). The more contact across age groups the higher the potential for adverse effects of vaccination on varicella morbidity. For *proportional* mixing vaccination with the *base vaccine* is predicted to lead to a long-term increase in morbidity between 40% and 60% coverage (Fig. 7). The *base matrix* and *matrix 1* only slightly reduce morbidity until 60–70% coverage (Fig. 7). On the other hand, the more assortative matrices (*matrix 3* and *assortative*) have a virtually linear relationship between coverage and morbidity at equilibrium (for levels of coverage below 80–90%). For all mixing patterns overall morbidity is expected to be reduced over 70% coverage. As mentioned above, this is because above 70% coverage vaccination reduces transmission enough to offset the effect of the age shift of varicella infection.

Vaccine efficacy (*Strategy 1; base matrix*)

Figure 8 represents the estimated yearly number of inpatient days at equilibrium after routine mass immunization with different levels of coverage and vaccine efficacy. Paradoxically, the *worst vaccine* results in fewer inpatient days than the *perfect vaccine* ($P = 0\%$, $T = 100\%$, $W = 0\%$) under about 85% coverage. This happens because a perfect vaccine reduces the transmission of varicella more than a leaky vaccine producing greater shifts in the average age at infection.

It should be stressed that the results shown in Figures 6, 7 and 8 are at equilibrium and will not be seen for at least 50 years after the start of vaccination.

Zoster incidence (*Strategy 1; 90% coverage; base matrix; base vaccine*)

All previous figures showed results with a constant number of cases of varicella due to zoster contacts (Model 1). In this section, we add a complexity by modelling the possible relationships between zoster and varicella – i.e. varicella boosting zoster immunity and varicella infection acquired by zoster (Model 2). Since little is known of these relationships, results produced by Model 2 are speculative and meant only to present the potential impact of vaccination on zoster.

The model produces similar annual zoster incidence rates (3176 new cases/1 000 000 population-year *with-*

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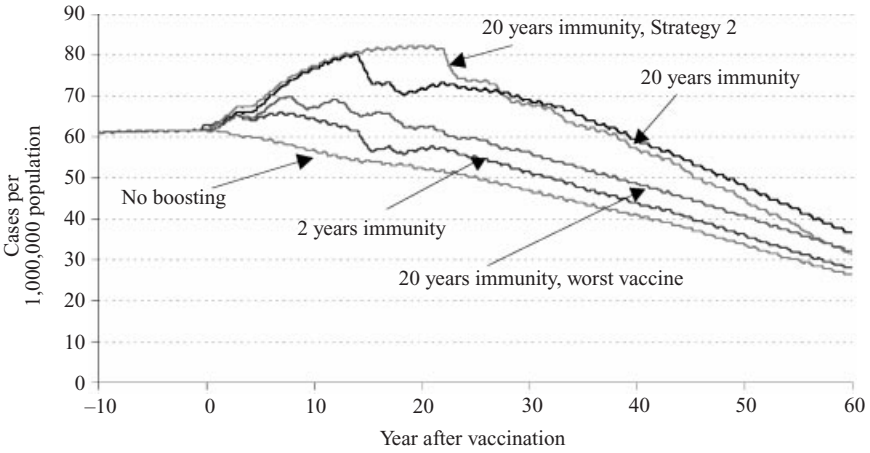

Fig. 9. Boosting. Estimated prevalence of zoster cases over time following the introduction of vaccination (at year 0) assuming different mean lengths of time exposure to varicella protects against zoster. All simulations use 90% infant only coverage with the *base vaccine*, except '20 years immunity, Strategy 2' which assumes that 90% of 11 year olds are also vaccinated for the first 11 years of the programme, and '20 years immunity, worst vaccine' which uses worst-case vaccine efficacy parameter values.

out repeat cases) to observed data from Canada (3212 new cases/1000000 population-year *without repeat cases*) and England (3431 new cases/1000000 population-year *with repeat cases*) [39, 44]. The age distribution of cases is also similar to observed data from industrialized countries [39, 44]. The pre-vaccination and post-vaccination varicella dynamics produced by Model 2 are nearly identical to Model 1.

Figure 9 illustrates the potential danger of an increase in zoster cases following reduction in varicella cases due to vaccination. If incidence of varicella has no influence on zoster (no boosting) and seroconverted vaccinated individuals do not acquire zoster, cases of zoster will decrease slowly as the proportion of vaccinated individuals in the population increases. This is because we assume that vaccinated individuals do not develop zoster. Hence as cohorts are vaccinated the overall incidence declines. When the vaccinated cohorts pass into the age groups with a high risk of zoster (the elderly) the decline in incidence becomes more marked. On the other hand, if contact with varicella can boost immunity against zoster, cases of zoster could significantly increase in the short to medium term following vaccination. For a given vaccine coverage, efficacy and strategy the number of cases of zoster seems to depend on the time for which an individual remains immune to zoster after boosting (1δ in Fig. 1). The longer the period of immunity after boosting the greater the increase in incidence of zoster would be expected following vaccination, and the longer the period of increased incidence (Fig. 8).

If contact with varicella can boost zoster immunity very effective programmes in terms of varicella reduction could be harmful to public health in terms of zoster morbidity – i.e. the gain in reduction of varicella morbidity could be offset in the short-term by the increases in zoster morbidity. For example, when catch-up (*strategy 2*) is introduced the dip in zoster cases corresponding to the post-honeymoon epidemic is eliminated (Fig. 9). Furthermore, other things being equal (and assuming that exposure to varicella can boost immunity to zoster) then the number of cases of zoster after vaccination is lower for the worst vaccine than more efficacious ones (Fig. 9).

In the long-term, once individuals from every cohort in the population have been vaccinated, zoster incidence will decrease with or without boosting unless vaccine recipients are as likely to develop zoster as naturally infected individuals.

DISCUSSION

The model suggests that the overall *varicella* incidence of infection (natural and breakthrough) and morbidity (measured by inpatient days) will likely be reduced by mass vaccination of 12-month-old children in Canada. However, the overall level of effectiveness of routine immunization depends highly on the level of coverage, the type of vaccination strategy, the efficacy of the vaccine and the relationship between varicella and zoster. Importantly, the most effective programmes at reducing the incidence of varicella result in the biggest

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increase in zoster cases, if exposure to varicella prevents, or delays, the development of zoster.

It seems unlikely that infant vaccination will shift the average age at infection to such an extent that the net outcome (in terms of inpatient days due to chickenpox) is worse than the pre-vaccination state. Using our *base case* assumptions regarding vaccine efficacy then, of the scenarios tested, only the unlikely situation of proportional mixing and coverage between 40 and 70% resulted in a long-term increase in varicella morbidity. Whilst not predicted to cause harm to public health, there are many (more likely) scenarios in which vaccination at intermediate levels of coverage results in only marginal long-term benefits. Indeed, the more efficacious the vaccine (higher degree of individual protection), and the more contact that occurs between adults and children the more likely that infant vaccination at intermediate levels of coverage will result in few health benefits at the population level. On the other hand, varicella morbidity is eventually expected to decrease significantly for all scenarios if coverage is high (greater than approximately 70%, see Figs 7, 8). To limit the risk of adverse effects and significantly increase the effectiveness of varicella vaccination (at preventing varicella), programmes should aim at achieving a higher coverage than 70%.

Such levels of coverage might be difficult to achieve in some countries. Only 60–70% of mothers say they would definitely, or probably have their children vaccinated against chickenpox in England [47]. Furthermore, varicella vaccine coverage is currently only about 50% in the USA [48]. Higher vaccine coverage is likely to be ensured once a combined varicella–MMR vaccine is available [49].

If high levels of coverage (over 70%) are attained post-honeymoon epidemics are expected to occur, unless there is very little within-group mixing, or the vaccine has very low efficacy. Such epidemics have been observed after measles (1989–90) and mumps (1970–80) vaccination campaigns in the United States [50, 51] and elsewhere [52]. The use of catch-up campaigns can reduce these epidemics as well as minimize the overall number of varicella cases after vaccination.

Vaccination of children at 12 months with a catch up programme in the first year for 1–11 year olds (*strategy 3*) seems to minimize the number of natural varicella cases in the short-term. On the other hand, routine vaccination at 12 months with an annual catch-up of 11 year olds for the first 11 years (*strategy 2*) delays and minimizes the post-honeymoon epidemic after 15–25 years (Fig. 5). Which of these strategies is preferable depends, to an extent on decision makers' attitudes regarding future versus current health benefits. Other strategies do exist. For example, vaccination at 1, 5 and 11 years of age of age for 6 years would eliminate the first epidemic after 5 years and minimize the second large post-honeymoon epidemic (results not shown). Although catch-up programmes have a major impact on the short-term dynamics of infection, they do not influence the long-term effectiveness of vaccination.

As expected, the higher the vaccine efficacy the more mass vaccination reduces the incidence of varicella *infection*. On the other hand, lower vaccine efficacy reduces the shift in the average age at natural infection by allowing a certain number of cases to occur every year. Thus, paradoxically, for intermediate levels of coverage, lower efficacy vaccines could be more effective in reducing morbidity than better vaccines, particularly if exposure to varicella does boost the immune response to zoster. However, less efficacious vaccines are expected to result in a significant number of breakthrough cases even at high levels of coverage. Although breakthrough cases are mild and are assumed, here, to require no medical care, such a high number of cases in vaccinees may have an impact on vaccine acceptance.

Since the number of breakthrough cases of varicella might be significant even at high levels of coverage, elimination is unlikely to be a goal of routine immunization. Given the mild nature of breakthrough varicella, reduction of morbidity of chickenpox is a more realistic target. If morbidity reduction is the goal of vaccination then using a vaccine with lower efficacy could actually be more effective than the use of higher efficacy vaccines. These results might provide some reassurance to concerns that, in the field, the vaccine would lose potency because it requires freezing.

Understanding of the exact relationship between zoster and varicella is remarkably poor. A short to medium term increase in zoster may occur after vaccination if exposure to varicella is an important mechanism for preventing reactivation, particularly if a vaccination programme is very successful in reducing the number of varicella cases. If zoster does increase after vaccination this would have a major impact on the effectiveness and cost-effectiveness of VZV vaccination. Especially, since varicella is unlikely to be cost saving without including zoster morbidity [31, 53].

Although a short to medium-term increase in the incidence of zoster is a possibility following infant vaccination, in the long-term a reduction of zoster cases would be expected to occur provided vaccine recipients are less likely to develop zoster than individuals who acquire natural infection. However, if zoster can occur in a high proportion of vaccinees and varicella can boost immunity against zoster there is a risk that incidence of zoster could increase in the long-term [10]. This scenario is unlikely. Studies in immunocompromised children have shown a sixfold reduction in zoster after vaccination [7]. Thus it seems likely that in the long-term the incidence of zoster will decrease following the introduction of childhood vaccination, though a short to medium term increase in incidence of the possible size shown in Figure 9 could have a negative effect on public health and confidence in immunization.

The model presented here differs and extends that of Halloran and colleagues [30] in several ways. First, we used improved vaccine parameter estimates, based on up-to-date data from clinical trials [32]. Second, we used a more sensitive morbidity measure than hospitalization rates, namely inpatient days, since both hospitalization rates and average length of stay tend to increase with age at infection (although correct classification of chickenpox and shingles cases in the elderly is difficult – see earlier). Third, the age-structure of the model more accurately reflects school aged mixing patterns. Fourth, we assessed the sensitivity of our results to different age-dependent mixing patterns and discussed which of the patterns are more likely given available evidence on observed mixing patterns. Finally, we attempted to assess the possible effect of VZV vaccination on the incidence of herpes zoster.

The limitations of the model rest heavily on the largely unknown relationship between varicella and zoster incidence; in particular on whether exposure to varicella may boost the immune response offering a degree of protection from zoster. This possibility was explored in Model 2. It should be stressed, however, that since the mechanisms that lead to zoster are poorly understood the model structure and parameter estimates are speculative, and probably over-simplified. For instance repeat zoster episodes were ignored, and vaccinated sero-converters were assumed to not develop zoster. However, to ignore the potential impact of vaccination on zoster is to ignore many of the more serious consequences of infection with VZV – thus devaluing conclusions regarding the effectiveness and cost-effectiveness of vaccination. Clearly, more work is needed in this area. The clinical trials currently underway to determine whether varicella vaccination can protect against zoster in the elderly [54] may provide valuable information on this issue. Ironically, if the results are favourable (i.e. exposure to the vaccine offers protection against zoster) then this may decrease the usefulness of the vaccine in childhood programmes, since exposure to the wild virus is likely to perform the same function. In the mean time, in those countries in which immunization is planned or underway, sensitive surveillance of zoster incidence should be a priority.

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APPENDIX 1 – MODEL 1

Mathematical structure

Model 1 represents the transmission dynamics of varicella. The model possesses 66 age cohorts (0, 1, 2, …, 64 and 65+). Children enter continuously throughout the year into the first age cohort (at 6 months of age). Thereafter, individuals change age cohorts at the beginning of each school year thus taking into account the importance of school transmission on the dynamics of varicella [33]. Vaccination is performed at the end of the year as individuals move up an age class. Within each cohort, the differential equations for this deterministic RAS model are as follows:

$$\mathrm{d}S(a,t)/\mathrm{d}t = B(a) - [\lambda(a,t) + (c(a)\,(1-P)) + \mu(a)]\,S(a,t), \quad (1)$$

$$\mathrm{d}E(a,t)/\mathrm{d}t = \lambda(a,t)\,S(a,t) - (\sigma+\mu(a))\,E(a,t), \quad (2)$$

$$\mathrm{d}I(a,t)/\mathrm{d}t = \sigma\,E(a,t) - (\alpha+\mu(a))\,I(a,t), \quad (3)$$

$$\mathrm{d}R(a,t)/\mathrm{d}t = \alpha\,I(a,t) - \mu(a)\,R(a,t), \quad (4)$$

$$\mathrm{d}VP(a,t)/\mathrm{d}t$$

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$$= c(a)\ T\ S(a,t) - (W + K\,\lambda(a,t) + \mu(a))\ VP(a,t), \quad (5)$$

$$\mathrm{d}VS(a,t)/\mathrm{d}t = c(a)\ [1 - T - P]\ S(a,t) + W\ VP(a,t) - (b\ \lambda(a,t) + \mu(a))\ VS(a,t), \quad (6)$$

$$\mathrm{d}VE(a,t)/\mathrm{d}t = b\ \lambda(a,t)\ VS(a,t) - (\sigma + \mu(a))\ VE(a,t), \quad (7)$$

$$\mathrm{d}VI(a,t)/\mathrm{d}t = \sigma\ VE(a,t) - (\alpha + \mu(a))\ VI(a,t), \quad (8)$$

$$\mathrm{d}VR(a,t)/\mathrm{d}t = K\,\lambda(a,t)\ VP(a,t) + \alpha\ VI(a,t) - \mu(a)\ VR(a,t). \quad (9)$$

The number of individuals of age a at time t who are varicella susceptible, naturally infected but not infectious, infectious, immune, temporary protected, modified susceptible, vaccinated infected but not infectious, vaccinated infectious, vaccinated immune are defined by the state variables $S(a,t)$, $E(a,t)$, $I(a,t)$, $R(a,t)$, $VP(a,t)$, $VS(a,t)$, $VE(a,t)$, $VI(a,t)$ and $VR(a,t)$ respectively. The different parameters determining the rates of flow between disease states for natural varicella are: $B(a)$, rate of entry into the first age cohort; $\mu(a)$, mortality rate; $c(a)$, vaccine coverage; $\lambda(a,t)$, force of varicella infection by age group; σ and α, rates of flow from latent to infectious and infectious to immune.

The flow between vaccinee disease states are: $c(a)\ T$, the percent of vaccines who become temporarily protected after vaccination; $c(a)P$, the percent of vaccinees for which vaccine fails completely after vaccination; W, waning rate; $b\ \lambda(a,t)$, rate of infection among vaccine susceptible vaccinees; $k\ \lambda(a,t)$, rate of boosting (see Table 1 for values).

Force of varicella infection

The pre-vaccination force of varicella infection in Canada was estimated from Manitoba billings and Canadian antibody prevalence data [39] using methodology described by Farrington and colleagues [55]. Parameter estimates were derived using maximum likelihood. More detailed methods are described in Brisson and colleagues [39].

In Model 1, the age and time dependant force of varicella infection is defined as:

$$\lambda(a,t) = \lambda_v(a,t) + \lambda_z = \sum_{a'=0}^{L} \beta(a',a)(I(a',t) + m\ VI(a',t)) + \lambda_z. \quad (10)$$

Where, $\lambda_v(a,t)$ is the force of infection due to varicella, λ_z is the force of infection due to zoster, $\beta(a',a)$ is the rate at which an infective of age a′ will infect a susceptible of age a, L is life expectancy and m is the rate of varicella infectiousness of vaccinees compared to non-vaccinees.

APPENDIX 2 – MODEL 2

Mathematical structure

Model 2 represents the transmission dynamics of both varicella and zoster. Differential equations 1, 2, 3, 5, 6, 7, 8 and 9 are identical for Model 1 and 2. The remaining differential equations for Model 2 are as follows:

$$\mathrm{d}R(a,t)/\mathrm{d}t = \alpha\ I(a,t) + z\ \lambda(a,t)\ ZS(a,t) - (\delta + \mu(a))\ R(a,t), \quad (11)$$

$$\mathrm{d}ZS(a,t)/\mathrm{d}t = \delta\ R(a,t) - (\rho(a) + z\lambda(a,t) + \mu(a))\ ZS(a,t), \quad (12)$$

$$\mathrm{d}ZI(a,t)/\mathrm{d}t = \rho(a)\ ZS(a,t) - (\alpha_z + \mu(a))\ ZI(a,t), \quad (13)$$

$$\mathrm{d}ZR(a,t)/\mathrm{d}t = \alpha_z\ ZI(a,t) - \mu(a)\ ZR(a,t). \quad (14)$$

The zoster disease states are: lifelong immunity to varicella and temporary immunity to zoster ($R(a,t)$), susceptible to zoster ($ZS(a,t)$), reactivation episode ($ZI(a,t)$) and permanently immune to zoster ($ZR(a,t)$). The rates are determined by: δ, rate of loss of immunity to zoster; $z\lambda(a,t)$, rate of boosting against zoster; and $\rho(a)$, the age-dependent rate of reactivation of VZV in those who are susceptible to zoster.

Force of varicella infection

The age- and time-specific force of varicella infection is defined as:

$$\lambda(a,t) = \lambda_v(a,t) + \lambda_z(t) = \sum_{a'=0}^{L} \beta(a',a)\ (I(a',t) + m\ VI(a',t)) + \omega \sum_{a'=0}^{L} ZI(a',t). \quad (15)$$

Where, $\omega = 5{\cdot}4^{e-7}$.

Rate of reactivation

The age-specific rate of reactivation ($\rho(a)$) was estimated by comparing the expected age-specific prevalence of zoster from Model 2 with that observed in Manitoba (Manitoba billings database (1980–97)). The parameter values, which minimized the least square, were chosen. The parameter values of the force of reactivation were estimated for three scen-

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arios: (1) varicella does not boost against zoster ($z = 0\%$) and average duration of immunity to zoster after varicella infection is 2 years ($1/\delta = 2$); (2) boosting ($z = 100\%$) and a 2 year duration of immunity to zoster ($1/\delta = 2$); (3) boosting ($z = 100\%$) and a 20 year duration of immunity to zoster ($1/\delta = 20$) (Table 1).

Computer details

Numerical results were generated by a Model *Maker* version 3.0 program. The system was solved using Runge–Kutta integration of ordinary differential equations with adaptable time steps. Simulations were performed on a PC.

APPENDIX 3 – WAIFW MATRIX ESTIMATION AND STRUCTURE

The standard technique developed by Anderson and May was used to describe the age-dependant mixing patterns of the population (Who-Acquired-Infection-From-Whom (WAIFW) matrix) [37]. The elements of the WAIFW matrix, $\beta(a', a)$, were estimated from the pre-vaccination force of infection ($\lambda(a, 0)$) using equation 10. Five different matrix structures were used, yielding the following values for the WAIFW matrices:

Base matrix (*β units are effective contact per* 100 *days*):

	0–1	2–4	5–11	12–18	19–24	25–44	45–64	65+
0–1	0·70	0·70	0·70	0·70	0·85	1·15	0·72	0·57
2–4	0·70	4·42	1·20	1·20	0·85	1·15	0·72	0·57
5–11	0·70	1·20	5·16	1·20	0·85	1·15	0·72	0·57
12–18	0·70	1·20	1·20	5·16	0·85	1·15	0·72	0·57
19–24	0·85	0·85	0·85	0·85	15·47	1·15	0·72	0·57
25–44	1·15	1·15	1·15	1·15	1·15	1·15	0·72	0·57
45–64	0·72	0·72	0·72	0·72	0·72	0·72	0·72	0·57
65+	0·57	0·57	0·57	0·57	0·57	0·57	0·57	0·57

Matrix 1:

	0–1	2–4	5–11	12–18	19–24	25–44	45–64	65+
0–1	0·69	0·69	0·69	0·69	1·01	1·15	0·72	0·57
2–4	0·69	4·42	1·20	1·20	1·01	1·15	0·72	0·57
5–11	0·69	1·20	5·15	1·20	1·01	1·15	0·72	0·57
12–18	0·69	1·20	1·20	5·15	1·01	1·15	0·72	0·57
19–24	1·01	1·01	1·01	1·01	10·30	1·15	0·72	0·57
25–44	1·15	1·15	1·15	1·15	1·15	1·15	0·72	0·57
45–64	0·72	0·72	0·72	0·72	0·72	0·72	0·72	0·57
65+	0·57	0·57	0·57	0·57	0·57	0·57	0·57	0·57

Matrix 2:

	0–1	2–4	5–11	12–18	19–24	25–44	45–64	65+
0–1	0·72	0·72	0·72	0·72	0·71	0·74	0·74	0·57
2–4	0·72	4·33	1·30	1·30	0·71	0·74	0·74	0·57
5–11	0·72	1·30	5·10	1·30	0·71	0·74	0·74	0·57
12–18	0·72	1·30	1·30	4·33	0·71	0·71	0·57	0·57
19–24	0·71	0·71	0·71	0·71	12·98	7·32	0·57	0·57
25–44	0·74	0·74	0·74	0·71	7·32	7·32	0·57	0·57
45–64	0·74	0·74	0·74	0·57	0·57	0·57	0·57	0·57
65+	0·57	0·57	0·57	0·57	0·57	0·57	0·57	0·57

Assortative:

	0–1	2–4	5–11	12–18	19–24	25–44	45–64	65+
0–1	2·55	0·57	0·57	0·57	0·57	0·57	0·57	0·57
2–4	0·57	5·42	0·57	0·57	0·57	0·57	0·57	0·57
5–11	0·57	0·57	5·86	0·57	0·57	0·57	0·57	0·57
12–18	0·57	0·57	0·57	12·60	0·57	0·57	0·57	0·57
19–24	0·57	0·57	0·57	0·57	24·92	0·57	0·57	0·57
25–44	0·57	0·57	0·57	0·57	0·57	18·05	0·57	0·57
45–64	0·57	0·57	0·57	0·57	0·57	0·57	27·90	0·57
65+	0·57	0·57	0·57	0·57	0·57	0·57	0·57	0·57

Proportional:

	0–1	2–4	5–11	12–18	19–24	25–44	45–64	65+
0–1	0·22	0·72	0·90	0·45	0·40	0·36	0·22	0·18
2–4	0·72	2·29	2·87	1·43	1·29	1·15	0·72	0·57
5–11	0·90	2·87	3·59	1·79	1·61	1·43	0·90	0·72
12–18	0·45	1·43	1·79	0·90	0·81	0·72	0·45	0·36
19–24	0·40	1·29	1·61	0·81	0·73	0·65	0·40	0·32
25–44	0·36	1·15	1·43	0·72	0·65	0·57	0·36	0·29
45–64	0·22	0·72	0·90	0·45	0·40	0·36	0·22	0·18
65+	0·18	0·57	0·72	0·36	0·32	0·29	0·18	0·14

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