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Predicting and preventing measles epidemics in New Zealand: application of a mathematical model

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SUMMARY

A mathematical model of the dynamics of measles in New Zealand was developed in 1996. The model successfully predicted an epidemic in 1997 and was instrumental in the decision to carry out an intensive MMR (measles–mumps–rubella) immunization campaign in that year. While the epidemic began some months earlier than anticipated, it was rapidly brought under control, and its impact on the population was much reduced. In order to prevent the occurrence of further epidemics in New Zealand, an extended version of the model has since been developed and applied to the critical question of the optimal timing of MMR immunization.

INTRODUCTION

Immunization against measles was introduced in New Zealand in 1969, but coverage was inadequate to alter the pattern of 2- to 3-yearly epidemics until 1980 [1]. In 1978, a 5-year measles epidemic elimination programme was instituted. The level of coverage achieved by that programme is not known, yet it was sufficient to defer the next epidemics after 1980 to 1985 and then 1991. In November 1990, the measles vaccine was replaced by the measles–mumps–rubella vaccine (MMR). A second dose of MMR, scheduled at age 11 years, was added in 1992 in response to the 1991 measles epidemic [2]. In the 1990s, coverage has been only a little above 80% for the first scheduled dose (MMR1) [3, 4]. Coverage for the second dose (MMR2) is likely to be about the same, although there are no national data.

In 1996 a mathematical model for the dynamics of measles in New Zealand was developed. The model included a representation of the vaccination strategies employed from 1969–96, and assumed that the 1996 strategy would be continued until 2000. It successfully predicted the 1997 measles epidemic, and showed that the current levels of vaccine coverage would result in further epidemics at intervals of approx. 6 years [5]. To help guide a decision about the optimal timing of MMR doses, the model was extended (existing age classes subdivided) and used to compare the likely effects of different potential vaccination strategies. In the present paper the initial (1996) model is referred to as the 'prediction' model, and its extension with a further sub-division of age classes is referred to as the 'prevention' model. The results from both models are summarized below.

METHOD

The dynamics of measles were modelled under varying immunization strategies in a population with size and age structure similar to that of New Zealand, using a deterministic *SIR* (susceptible-infective-recovered) model. The boundaries of the age classes were chosen using the assumption that those aged less than

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6 months or more than 25 years take no part in the epidemic, with the other age-class boundaries coinciding with potential ages at vaccination. Hence the 'prediction' model had four active age classes and the 'prevention' model had eight. Vaccination rates were based on the proportion of children vaccinated at each opportunity and the vaccine efficacy. For example, if a proportion q of the population are vaccinated, and the vaccine efficacy is 90%, then the proportion protected is $p = 0{\cdot}9q$. Disease transmission was assumed to be seasonal, with high transmission between 28 February and 1 December, and lower transmission throughout the summer. The overall transmission rate was chosen by fitting the output of the 'prediction' model to the historical timing of measles epidemics. Full details of the models are presented in the Appendix.

Table 1. *Vaccination coverage rates used in the 'prevention' model*

Vaccination		Rate (%)
MMR1	Low	80
MMR1	Medium	85
MMR1	High	90
MMR1	Target	95
MMR2	As second vaccination	90
MMR2	(As first vaccination)	
	Infant schedule	5
	Preschool schedule	50
	School schedule	70
	Current schedule	70
Catch-up at 3 years	Infant schedule	50
	School schedule	50
	Current schedule	50
Catch-up at 5 years	Infant schedule	50
	Preschool schedule	75
	School schedule	50
	Current schedule	50

The prediction model

The model was solved numerically using the Rkadapt function of Mathcad Plus 6.0 [6]. The time period for solution was $1962 < t < 2000$, where $t = 1962$ implies 1 January 1962. Initially the equations were solved with no vaccination to establish a 'no-control' pattern of epidemics. This was used to specify starting values (at 1962) for state variables that gave the correct pre-control epidemic timing, i.e. epidemics in 1963, 1965, 1967 and 1969. The equations were then solved using historical vaccination rates and different values of the parameters that control inter-class contact rate (ϵ), the magnitude of the seasonal fluctuation in transmission (δ), and the basic reproduction ratio (R_0), until a combination was found that gave the correct timing of epidemics for the period 1970–92. The solution was then continued until 2000 to obtain a short-term prediction for future epidemic events. The number of time steps was initially set at 1983 (equivalent to a step size of 1 week), then calculations were repeated with ten times the number of steps leading to the same result, to confirm numerical stability.

The prevention model

Immunization schedules

Four different immunization schedules each involving two vaccinations were regarded as practical alternatives, and hence were tested in the model. These represent the earliest possible time for both doses (infant schedule: MMR1 at 12 months, MMR2 at 15 months), and retaining MMR1 at 15 months and delivering MMR2 at entry to child care (preschool schedule: MMR2 at 3 years), in the first year of primary school (school schedule: MMR2 at 6 years) or at 11 years (current schedule). As well as the scheduled events, entry to an early childhood centre (at 3 years of age) and to school (at 5 years of age) provide 'catch-up' opportunities. For the preschool schedule, only catch-up at 5 years applies, as there is a scheduled immunization event at 3 years of age.

Immunization coverage

For details of immunization coverage rates see Table 1. For MMR1 four coverage rates (labelled 'low', 'medium', 'high' and 'target') were modelled. For MMR2 coverage was assumed to be dependent on behaviour at MMR1. For those children not immunized at MMR1, coverage at MMR2 was assumed to increase with age until school entry, then stabilize (reflecting the fact that this represents a 'hard to reach' group of children, even when 'captive' at school). Coverage of catch-up vaccinations was assumed to be 50%, with the exception of the preschool schedule. As there is only one catch-up opportunity for the preschool schedule, 75% catch-up at 5 years of age was allowed for this schedule only. Catch-up was considered to apply equally to children

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Table 2. *Scenarios used in the 'prevention' model*

Scenario (symbol)	Conditions
N	No catch-up, low failure
NF	No catch-up, high failure
C3	50% catch-up at three years of age, low failure†
C3F	50% catch-up at three years of age, high failure‡
C5	50% catch-up at five years of age*, low failure†
C5F	50% catch-up at five years of age*, high failure‡

* For the preschool schedule catch-up of 75%.
† Low failure means 10% primary vaccine failure rate and no allowance for secondary failure.
‡ High failure means 20% primary vaccine failure for children who failed to respond to their first dose (10% otherwise), and an allowance for secondary failure (see text).

who had missed one or both scheduled immunizations.

Vaccine failure

The literature on the short-term efficacy of MMR vaccines is conflicting. Variables such as vaccine formulation, cold chain integrity, and injection technique can influence response. Initially a primary vaccine failure rate of 10% was modelled (12% for the infant immunization schedule to allow for interference from residual maternal antibody at age 12 months), as had been used in the earlier 'prediction' model. The question has often been raised as to whether children who fail to respond to their first immunization are more likely to fail again when re-immunized. Although there is little evidence to support this, for these children primary vaccine failure rates of both 10 and 20% at MMR2 were modelled.

A meta-analysis of published data found no evidence for secondary vaccine failure [7]. Our model does not allow for a flux from the removed class into susceptible classes; however, in the high failure scenarios an allowance was made for potential secondary failure by adding 0·5% multiplied by the time to next vaccination to the primary failure rate.

Calculations

For each schedule (infant, preschool, school, and current) and MMR1 coverage rate (low, medium, high, and target), the model was analysed for the six scenarios based on catch-up and vaccine performance summarized in Table 2, giving a total of 96 scenarios. All calculations were performed using Mathcad 7 Professional [8].

Output

Reproduction ratio with immunization (R_V). The basic reproduction ratio (R_0) of an infectious disease is defined as the average number of secondary cases generated by a primary case in a fully susceptible population [9, 10]. R_V is similarly defined as the average number of secondary cases generated by a primary case in a population rendered incompletely susceptible as a result of immunization. If $R_V < 1$, disease elimination occurs. In practice, a safety margin is needed because of seasonal variation in transmissibility and heterogeneities in the population (for example, the geographic clustering of 'pockets' of susceptibles), and R_V needs to be well below one before elimination becomes realistic.

Inter-epidemic period. The model was solved numerically over 20 years for selected strategies, to determine the timing and scale of predicted epidemics. A relationship exists between R_V and the inter-epidemic period, and visual representation of future epidemics adds no new information.

RESULTS

Prediction

The parameter values that produced the best agreement between the occurrence of model epidemics and the observed historical pattern were consistent with $R_0 = 12{\cdot}8$ and $R_V = 2{\cdot}85$ with current vaccination

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Table 3. *Observed and predicted epidemic years*

Observed	1963	1965	1967	1969	1972	1975	1977	1980	1985	1991	1997
Predicted	1963	1965	1967	1969	1972	1975		1979	1985	1991	1997

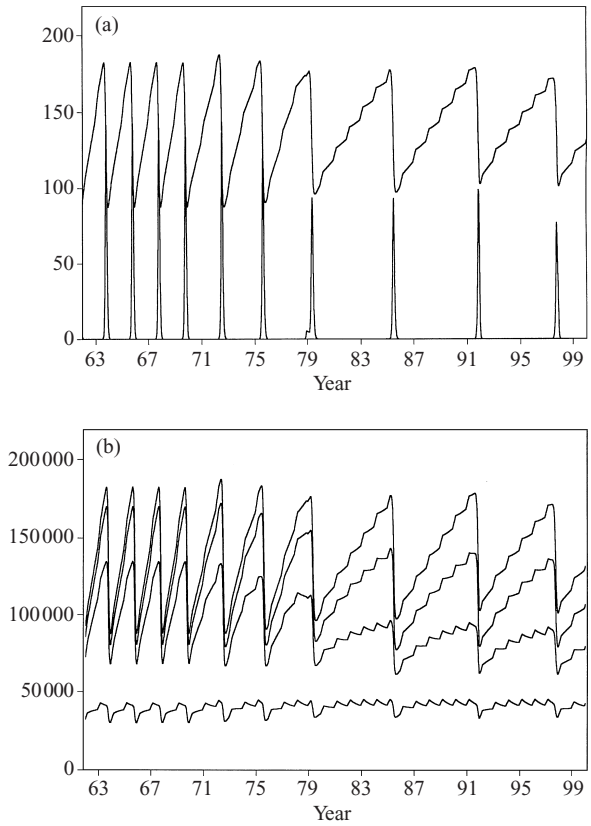

Fig. 1. Results from the prediction mode. (*a*) Predicted number of susceptibles (thousands) and infecteds (hundreds) in ages 0·5–25 years. (*b*) Predicted numbers of susceptibles in age classes (reading from bottom) 0·5–1·25 years, 0·5–5 years, 0·5–11 years and 0·5–25 years.

procedures. These produced the epidemic patterns summarized in Table 3 and Figure 1. Of note is the prediction of an epidemic in 1997 (the calculations were performed in 1996). Figure 1 also shows the age structure of epidemics, as determined by the model. When the epidemic occurred it was contained by a mass-vaccination effort. Figure 2 shows the weekly number of cases reported compared with model predictions, note that the starting date of the model epidemic has been adjusted to coincide with that of the observed epidemic. For further details of the 1997 epidemic in New Zealand, including its age and ethnic structure, hospitalization and reporting rates see [11].

Prevention

The model output is summarized in terms of R_V for different schedules, coverages, and scenarios (see Tables 1 and 2) in Figure 3. The results show that at low MMR1 coverage, no schedule will lead to measles elimination. At intermediate coverage, only the school schedule yields $R_V < 1{\cdot}0$, and then only if catch-up is high and vaccine failure low (scenarios C3 and C5). At high coverage, both the school and preschool schedules are capable of measles elimination ($R_V \ll 1$). At this coverage, the school schedule slightly outperforms the preschool schedule, whereas the opposite is the case at target coverage. Essentially, these schedules are equivalent.

The results show that target MMR1 coverage (95%) is not required for measles elimination, provided the timing of MMR2 is modified (to either school or preschool entry). Yet if the current schedule is continued, measles will not be eliminated at any (realistic) level of coverage, catch-up and vaccine failure. Unless coverage at scheduled opportunities is at target level, a catch-up programme is also required for measles elimination. For example, with the school schedule and high (90%) coverage, $R_V = 0{\cdot}7$ with preschool catch-up (scenario C3), but $R_V = 0{\cdot}9$ without it (scenario N). On the other hand, given high coverage at both scheduled and catch-up ages, vaccine failure is of little consequence.

Figure 4 shows the relationship between R_V and inter-epidemic period for selected scenarios and coverage rates. It clearly shows that as the value of R_V decreases, the inter-epidemic period increases. However, at values of R_V between one and two other details of control strategies are secondary determinants of the inter-epidemic period.

Conclusions

The 'prediction' model successfully predicted the 1997 epidemic of measles in New Zealand, which was then contained by a mass vaccination campaign. It also showed that if no change is made in vaccination policy, the next measles epidemic will occur in 2003 or 2004 and involve approx. 60000–80000 cases.

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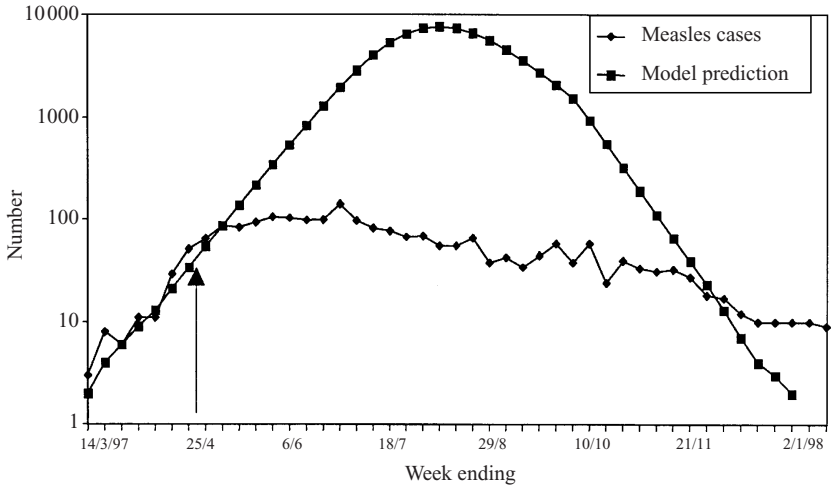

Fig. 2. Reported and predicted weekly measles cases in New Zealand in 1997 shown on a log scale. The vertical arrow is at the beginning of the vaccination campaign. (Adapted from [11].)

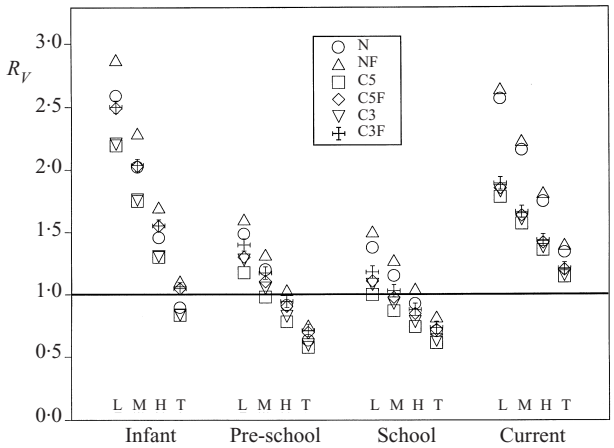

Fig. 3. Calculated values of the basic reproduction ratio under vaccination (R_V) from the prevention model, with different coverage rates (Low, Medium, High, Target; see Table 1) and under different vaccination scenarios (see Table 2).

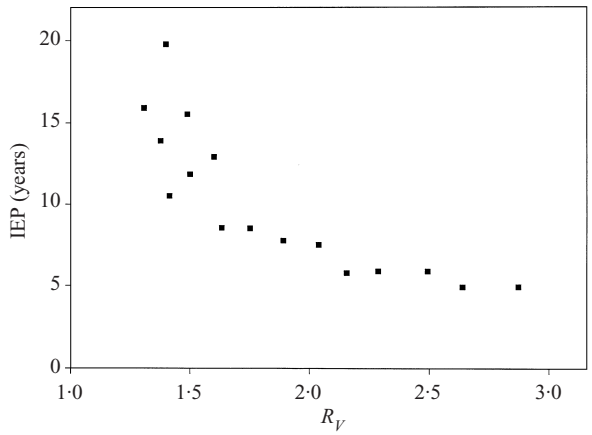

Fig. 4. Calculated values of the basic reproduction ratio under vaccination (R_V) and inter-epidemic period for selected coverage rates and vaccination scenarios.

The 'prevention' model showed that as long as the current MMR schedule (15 months and 11 years) remains in place, measles epidemics will continue to occur. Bringing forward the second dose of vaccine (MMR2) to approx. 3 or 6 years of age is necessary to prevent the further occurrence of measles epidemics in New Zealand. A change in the immunization schedule alone will probably be insufficient by itself to eliminate measles from New Zealand. Coverage at 15 months of age needs to increase to 90% (or more), and effective opportunities for catch-up immunization are also required to be certain of success. The timing of the second dose is not critical from an epidemiological perspective, provided this dose is administered between the ages of approx. 3 and 6 years. Immunization at or around school entry may offer logistic advantages.

DISCUSSION

For our study of the dynamics and control of measles in New Zealand we chose to employ a model with compartments for the numbers susceptible and infectious within different age groups. This format, combined with assigning the boundaries between age groups to vaccination opportunities, provides a model amenable to analysis. The success of the model in reproducing the historical pattern of epidemics is encouraging. Other authors have used models with more detailed age structure to investigate the epidemiology and dynamics of measles control strategies [9, 12–14] and obtained similar results. Although it has been shown that the dynamics of measles models can be qualitatively sensitive to the way in which age

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structure is incorporated, the major difference is that more complex models suppress chaos, which is not a feature in our results [15, 16]. In addition, we have restricted our model population to those under 25 years of age, as those older play a negligible part in the epidemiology of measles. Other authors have included older age groups, but set the force of infection they experience to a much lower level [9, 12–14]. If measles were eliminated from the population for a considerable time it would no longer be true that most adults were immune, and this older age-group could then potentially play a part in any future epidemic.

The set of parameters that led to the best fit of model output to the historical timing of epidemics was consistent with a basic reproduction ratio (R_0) equal to 12·8 (ignoring seasonality). The value of R_0 depends on the biological characteristics of the disease, and the social conditions under which it is transmitted. Hence, for measles R_0 seems to vary from an estimated 11 in the Faroe Islands [17] up to 18 in Africa [18], and is generally in the range 12–18 [9, 16]. Our estimate is consistent with values of R_0 between 12 and 13 quoted for measles in the United Kingdom and United States of America [19].

There is only limited evidence on the impact of different strategies for controlling measles. The consensus is that the most important factor is high coverage with one dose. The second dose counters vaccine failure (increasing vaccine efficacy) and failure to vaccinate (increasing coverage). The model shows that of these two effects, it is the latter (increasing coverage) that is more important until coverage with the first dose exceeds 95%. Similar results have been found by others [20].

Until recently, the World Health Organization (WHO) has not actively promoted two-dose schedules, as it has considered achieving high coverage with one dose to be the priority [21]. The WHO is now promoting delivery of a second dose through mass campaigns as a means of reaching children who would not normally access primary health care services. The effectiveness of this approach has been demonstrated in the Americas [22]. The other approach with demonstrated effectiveness is high coverage with two scheduled doses, which led to the elimination of indigenous measles in Finland [23, 24]. In Finland, MMR has been scheduled at 14–18 months of age and again at 6 years (prior to school entry) since 1982. The vaccine used in Finland has been MMRII (MSD) vaccine, the same vaccine as that now used in New Zealand. The coverage achieved in Finland exceeds 95% for both doses.

By contrast, in 1982 Sweden introduced a two-dose MMR schedule at 18 months of age and 12 years. Initial experience showed declining incidence of measles from 1982 to 1986, with achievement of over 90% coverage for both doses [25]. More recent experience has not been fully reported, although a 1994 paper describing serological response reports continuing success with the Swedish schedule [26]. The WHO database shows a declining number of cases in Sweden from 1986 to 1996, although no data were reported for 1994 and 1995. Since 1995, coverage in Sweden at 12 years of age has been 99% for one dose and 90% for two doses (J. M. Olive, WHO, personal communication). The very high coverage, relative homogeneity of the population, and low population density may be factors contributing to the success of measles control in Sweden despite an apparently suboptimal schedule.

Mathematical modelling in France has replicated the findings of this New Zealand study, and has led to the recommendation that MMR2 be brought forward to the time of school entry (or earlier) to enable elimination of measles [27]. A serological study of Canadian children supports delivery of the second dose before school entry [28]. Some provinces in Canada administer the second dose at 18 months of age while others currently deliver it around school entry [29]. The United Kingdom and United States schedule MMR2 at school entry. Australia is currently considering a change in the timing from the current 10–16 years to around school entry [30].

The 1997 measles epidemic in New Zealand, modelling results presented in this report, limited serological data, and international practice, all support bringing forward the timing of MMR2. The only evidence against such a change appears to be the success of Sweden in eliminating measles with a similar schedule to that currently used in New Zealand. However, this assumes firstly that Sweden will not in fact experience another measles epidemic over the next decade, and secondly that New Zealand is capable of achieving and sustaining MMR immunization coverage rates of similar magnitude to those achieved in Sweden. In deciding whether to bring the second dose of MMR forward, the impact of such a change in the childhood immunization schedule on diseases other than measles must also be considered. There are also logistic aspects to consider. The results of epidemiological modelling reported here represent only one input into the decision-making process. However, New Zealand is currently considering a shift in the timing of the second

Table 4. *Age classes used in the models*

Prediction	Ages	Prevention	Ages
Class number 1	6 months to 15 months	Class number 1	6 months to 1 year
		Class number 2	1 year to 15 months
Class number 2	15 months to 5 years	Class number 3	15 months to 18 months
		Class number 4	18 months to 3 years
		Class number 5	3 years to 5 years
Class number 3	5 years to 11 years	Class number 6	5 years to 6 years
		Class number 7	6 years to 11 years
Class number 4	11 years to 25 years	Class number 8	11 years to 25 years

Table 5. *Parameter values assumed in the models*

Parameter	Definition	Value
a_1	Activity level	1
a_2	Activity level	2
a_3	Activity level	6
a_4	Activity level	3
δ	Magnitude of seasonal variation	0·2
ϵ	Factor reducing inter-class activity	0·4
β	Disease transmission coefficient	$2{\cdot}005 \times 10^{-4}$/year
γ	1/(mean time infectious)	52/year

scheduled dose of MMR to 5 or 6 years of age (i.e. around the time of school entry).

APPENDIX

The models used for the 'prediction' and 'prevention' investigations were similar, but whereas the former had 4 active age classes, these were subdivided to obtain 8 classes for the latter. The annual birth rate was assumed constant at $B = 57435$ births/year [31]. The size of each age class (see Table 4) was fixed at class width $\times$ B, and the transition rate to the next class at (class width)$^{-1}$. For example, Class 5 in the 'prevention' model covers ages 3–6 years, $N_5 = 172305$ and $\mu_5 = \frac{1}{3}$. Hence, model class sizes remain constant and deaths are neglected up to age 25.

The disease transmission model was constructed as follows. Consider first the situation with a single age class. If the number of contacts that an individual makes with another per unit time is C, then the number of contacts with an infectious individual is CI. If the number of new infectives formed per infectious contact is β, then the rate at which susceptibles become infected (force of infection) is βCI. Where contact rates vary throughout the year we introduce a periodic function $\varpi(t)$ as a multiplier, hence with n age classes the force of infection in class i is

$$\lambda_i(t) = \varpi(t)\beta \sum_{j=1}^{n} C_{ij} I_j,$$

where C_{ij} is the rate of contact between individuals in age class i and those in age class j. It is convenient to estimate contact rates relative to those in one selected class, for example age-class one. The parameter β then has dimension (year)$^{-1}$.

Suppose that an individual in age class i has an activity level measured by a_i. Under the proportionate mixing assumption the number of contacts per unit time between individuals in age class i and individuals in age class j is proportional to $\sqrt{(a_i a_j)}$; and under the preferred mixing assumption this is true for within-class contacts, but between-class contacts are assumed to be zero. We have combined the two assumptions by choosing a parameter $\epsilon < 1$ to weight between-class contacts [32]. The 'prediction' model had four age classes, hence we constructed the contact matrix

$$\begin{pmatrix} C_{11} & C_{12} & C_{13} & C_{14} \\ C_{21} & C_{22} & C_{23} & C_{24} \\ C_{31} & C_{32} & C_{33} & C_{34} \\ C_{41} & C_{42} & C_{43} & C_{44} \end{pmatrix} = \begin{pmatrix} 1 & \epsilon\sqrt{(a_2)} & \epsilon\sqrt{(a_3)} & \epsilon\sqrt{(a_4)} \\ \epsilon\sqrt{(a_2)} & a_2 & \epsilon\sqrt{(a_2 a_3)} & \epsilon\sqrt{(a_2 a_4)} \\ \epsilon\sqrt{(a_3)} & \epsilon\sqrt{(a_2 a_3)} & a_3 & \epsilon\sqrt{(a_3 a_4)} \\ \epsilon\sqrt{(a_4)} & \epsilon\sqrt{(a_2 a_4)} & \epsilon\sqrt{(a_3 a_4)} & a_4 \end{pmatrix}.$$

This plays a similar role to the familiar *WAIFW* matrix [9, 33]. The 'prevention' model had 8 age classes. In order to keep contact rates within and between classes compatible in both models we used the contact rate matrix C equal to

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$$\begin{pmatrix} a_1 & a_1 & \epsilon\surd(a_1a_2) & \epsilon\surd(a_1a_2) & \epsilon\surd(a_1a_2) & \epsilon\surd(a_1a_3) & \epsilon\surd(a_1a_3) & \epsilon\surd(a_1a_4) \\ a_1 & a_1 & \epsilon\surd(a_1a_2) & \epsilon\surd(a_1a_2) & \epsilon\surd(a_1a_2) & \epsilon\surd(a_1a_3) & \epsilon\surd(a_1a_3) & \epsilon\surd(a_1a_4) \\ \epsilon\surd(a_1a_2) & \epsilon\surd(a_1a_2) & a_2 & a_2 & a_2 & \epsilon\surd(a_2a_3) & \epsilon\surd(a_2a_3) & \epsilon\surd(a_2a_4) \\ \epsilon\surd(a_1a_2) & \epsilon\surd(a_1a_2) & a_2 & a_2 & a_2 & \epsilon\surd(a_2a_3) & \epsilon\surd(a_2a_3) & \epsilon\surd(a_2a_4) \\ \epsilon\surd(a_1a_2) & \epsilon\surd(a_1a_2) & a_2 & a_2 & a_2 & \epsilon\surd(a_2a_3) & \epsilon\surd(a_2a_3) & \epsilon\surd(a_2a_4) \\ \epsilon\surd(a_1a_3) & \epsilon\surd(a_1a_3) & \epsilon\surd(a_2a_3) & \epsilon\surd(a_2a_3) & \epsilon\surd(a_2a_3) & a_3 & a_3 & \epsilon\surd(a_3a_4) \\ \epsilon\surd(a_1a_3) & \epsilon\surd(a_1a_3) & \epsilon\surd(a_2a_3) & \epsilon\surd(a_2a_3) & \epsilon\surd(a_2a_3) & a_3 & a_3 & \epsilon\surd(a_3a_4) \\ \epsilon\surd(a_1a_4) & \epsilon\surd(a_1a_4) & \epsilon\surd(a_2a_4) & \epsilon\surd(a_2a_4) & \epsilon\surd(a_2a_4) & \epsilon\surd(a_3a_4) & \epsilon\surd(a_3a_4) & a_4 \end{pmatrix}$$

to represent within and between class contacts.

The model equations for the susceptible (S_i) and infectious (I_i) populations are

$$\frac{dS_1}{dt} = \mu_0 N_0 - \left(\mu_1 + \omega(t)\beta \sum_{j=1}^{n} C_{1j} I_j\right) S_1$$

$$\frac{dI_1}{dt} = \omega(t)\beta S_1 \sum_{j=1}^{n} C_{1j} I_j - (\mu_1 + \gamma)\, I_1$$

and for $i = 2, \ldots, n$

$$\frac{dS_i}{dt} = \nu_{i-1} S_{i-1} - \left(\mu_i + \omega(t)\beta \sum_{j=1}^{n} C_{ij} I_j\right) S_i$$

$$\frac{dI_i}{dt} = \mu_{i-1} I_{i-1} + \omega(t)\beta S_i \sum_{j=1}^{n} C_{ij} I_j - (\mu_i + \gamma)\, I_i.$$

The effect of vaccination is to reduce the incoming transition rate to class $i+1$ from μ_i to ν_i. The seasonality function was defined by

$$\varpi(t) = \begin{cases} \kappa(1+\delta) & \text{for } \tau_1 < \tau < \tau_2 \\ \kappa(1-\delta) & \text{for otherwise,} \end{cases}$$

where τ is the decimal part of t, $\kappa = 1/(2\delta(\tau_2 - \tau_1) + 1 - \delta)$ and $\delta < 1$. Note that the mean value of ϖ is 1. We set $\tau_1 = 0{\cdot}1615$ (28 February) and $\tau_2 = 0{\cdot}9151$ (1 December).

Next generation matrices [10] were calculated with $\omega \equiv 1$. The matrix M_0 for the 'prediction' model is equal to

$$\begin{pmatrix} \dfrac{\beta C_{11}N_1}{\mu_1+\gamma} & \dfrac{\beta C_{12}N_1}{\mu_1+\gamma} & \dfrac{\beta C_{13}N_1}{\mu_1+\gamma} & \dfrac{\beta C_{14}N_1}{\mu_1+\gamma} \\ \dfrac{\beta C_{21}N_2+\mu_1}{\mu_2+\gamma} & \dfrac{\beta C_{22}N_2}{\mu_2+\gamma} & \dfrac{\beta C_{23}N_2}{\mu_2+\gamma} & \dfrac{\beta C_{24}N_2}{\mu_2+\gamma} \\ \dfrac{\beta C_{31}N_3}{\mu_3+\gamma} & \dfrac{\beta C_{32}N_3+\mu_2}{\mu_3+\gamma} & \dfrac{\beta C_{33}N_3}{\mu_3+\gamma} & \dfrac{\beta C_{34}N_3}{\mu_3+\gamma} \\ \dfrac{\beta C_{41}N_4}{\mu_4+\gamma} & \dfrac{\beta C_{42}N_4}{\mu_4+\gamma} & \dfrac{\beta C_{43}N_4+\mu_3}{\mu_4+\gamma} & \dfrac{\beta C_{44}N_4}{\mu_4+\gamma} \end{pmatrix}$$

with a similar but larger matrix for the 'prevention' model. For both models the matrix M_V is equal to the same matrix, but with N_i replaced with S_i^*, the steady state value of $S_i(t)$. The basic reproduction ratio R_0 and the basic reproduction ratio under vaccination R_V are the spectral radii of matrices M_0 and M_V respectively. Parameter values assumed for the model are given in Table 5. With these parameter values we obtain $R_0 = 12{\cdot}8$.

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