Bulletin of Mathematical Biology (1999) **61**, 1031–1064
Article No. bulm.1999.0126
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Modeling the Effects of Varicella Vaccination Programs on the Incidence of Chickenpox and Shingles

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Two possible dangers of an extensive varicella vaccination program are more varicella (chickenpox) cases in adults, when the complication rates are higher, and an increase in cases of zoster (shingles). Here an age-structured epidemiologic–demographic model with vaccination is developed for varicella and zoster. Parameters are estimated from epidemiological data. This mathematical and computer simulation model is used to evaluate the effects of varicella vaccination programs. Although the age distribution of varicella cases does shift in the simulations, this does not seem to be a danger because many of the adult cases occur after vaccine-induced immunity wanes, so they are mild varicella cases with fewer complications. In the simulations, zoster incidence increases in the first three decades after initiation of a vaccination program, because people who had varicella in childhood age without boosting, but then it decreases. Thus the simulations validate the second danger of more zoster cases.

1. INTRODUCTION

The virus *Herpesvirus varicellae* is the Latin name for the varicella zoster virus (VZV). This virus is the agent for the highly contagious disease varicella, whose common name is chickenpox. Secondary attack rates from a varicella infection are about 90% in susceptible household contacts and day-care centers. Among children, primary varicella (chickenpox) is usually a mild disease that lasts about 4–7 days and is characterized by fever, malaise, and a generalized vesicular rash typically consisting of about 250–500 lesions. VZV is transmitted through respiratory secretions or by direct, droplet, or aerosol contact with vesicular fluid from the skin lesions. Adolescents, adults, and immunocompromised people usually have more severe symptoms and are more likely to have complications. A primary infection results in lifelong immunity, but the levels of humoral and cell-mediated immunity decrease with time unless there is boosting due to re-exposure (Arvin and Gershon, 1996; CDCP, 1997).

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0092-8240/99/061031 + 34 $30.00/0

Since almost all children become infected with VZV, the annual incidence of varicella is approximately equal to the birth rate. At least 90% of adults in the United States are immune to VZV, but rates of immunity to VZV in adults can be as low as 50% in tropical areas (Arvin and Gershon, 1996). The age-specific distribution of cases of varicella in the United States in 1980–90 in a National Health Interview Survey was about 10% in those less than 1 year of age, 33% in 1–4 year old children, 36% in 5–9 year old children, and 11% in 10–14 year old children, and 4% in 15–19 year old persons (CDCP, 1997). The most common complications of varicella, which result in about 9000 hospitalizations in the United States per year, are bacterial infections of the skin lesions, pneumonia, dehydration, encephalitis, and hepatitis. In the United States about 50–100 people die of varicella complications each year (CDCP, 1997). Complication and death rates from varicella are higher in very young children and adults. Adults are 5 to 10 times more likely to have complications and to be hospitalized (Preblud, 1981; Guess *et al*., 1985; Gershon, 1995) and are 10 to 20 times more likely to die from varicella complications (Preblud, 1981; Benenson, 1995). Oral acyclovir can be used for the treatment and prevention of varicella. Congenital varicella syndrome is rare, but it can occur among infants born to mothers infected during the first half of their pregnancy. Newborn infants can also be infected at birth by a mother with varicella (CDCP, 1997).

Following a varicella infection, VZV is established in a latent form in the dorsal root ganglia by an ascending infection along sensory nerves from the skin. This latent herpes virus becomes reactivated during the lifetimes of about 15% of those who had a primary varicella infection, causing zoster (commonly known as shingles), a painful vesicular rash appearing along one or two of the sensory root nerves. Reactivation correlates with diminished VZV cell-mediated immunity, so that zoster develops more frequently among people immunocompromised by age, disease, or therapy. Thus zoster occurs at all ages, but is more common among the elderly. Transmission of VZV from people with zoster can occur, but is much less likely than from people with primary varicella (Hope-Simpson, 1965; Arvin and Gershon, 1996; CDCP, 1997).

A varicella virus vaccine has been produced from the Oka strain of live, attenuated VZV. This varicella vaccine was licensed in several European countries in 1984, in Japan in 1986, in Korea in 1988, and in the United States in March, 1995. It is now recommended for routine vaccination of children aged 12–18 months and for vaccination of susceptible older children, adolescents and adults (Arvin and Gershon, 1996; CDCP, 1997). Varicella vaccinations of adults have also been proposed in order to boost their immunity and decrease the likelihood of reactivation of zoster (Halloran *et al*., 1994; Plotkin, 1994; Gershon *et al*., 1996). This vaccine is safe and has a seroconversion rate of about 97% in children. In adults, approximately 78% seroconverted after one dose, and 99% seroconverted after a second dose given 4–6 weeks later (Krause and Klinman, 1995). Unfortunately, the vaccine-induced immunity wanes, so that vaccinated people eventually become

susceptible again. Wild-type VZV infections in those who have been previously vaccinated are called 'breakthrough cases'. Individuals who become infected with VZV after vaccination have a milder case of varicella with fewer lesions, so that they are generally less infectious than infected individuals who were never vaccinated. Vaccinated healthy children are very unlikely to transmit the vaccine-type varicella virus, but transmission from vaccinees who are immunocompromised can occur and seems to be associated with the occurrence of a rash following vaccination (Arvin and Gershon, 1996). Zoster from the vaccine-type virus can occur, but it is rare and also seems to occur only in the few people who a have rash after vaccination (CDCP, 1997).

There are two major concerns about the varicella vaccination program. First, widespread varicella vaccination might result in more varicella cases in adults, for whom the complication and death rates are higher (Preblud, 1981; Brunell, 1991; Watson *et al.*, 1993; Huse *et al.*, 1994; Krause and Klinman, 1995; Wharton, 1996). This shift in the age distribution of varicella cases could occur for two reasons. A vaccination program often raises the average age at which unvaccinated people are infected. Thus varicella vaccination in a population would decrease the reservoir of infection, so that unvaccinated individuals would be less likely to be infected with VZV as children and more likely to be infected as adults. The vaccine-induced immunity wanes with time and universal vaccination implies that there is less boosting of immunity by wild-type varicella cases. Thus another cause of an age shift is that people vaccinated as children could lose their immunity as adults and could then become infected with VZV.

The second major concern is that universal varicella vaccination might lead to more cases of zoster (Hardy *et al.*, 1991; Krause and Klinman, 1995; Garnett and Ferguson, 1996; Wharton, 1996). Zoster is more likely to occur in people when their cell-mediated immunity declines with age. As the fraction of vaccinated children increases, exposures of the general population to varicella infectives become less frequent. Because fewer people infected in childhood are boosted as they age, more older people will have weaker immunity to VZV, so that zoster may reactivate in more people.

The potential positive and negative effects of the widespread use of the varicella vaccine on the incidence of varicella and zoster are investigated here using a mathematical and computer simulation model described in Section 2. The goal of the computer simulations is to examine the two major concerns expressed above, and thus provide a better understanding of the advantages and disadvantages of the varicella vaccination program in the United States. The demographic part of the model is based on recent birth and death rate data in the United States. The epidemiologic structure consists of 15 classes for individuals who are in various epidemiologic states corresponding to being susceptible, latent, infectious, recovered, vaccinated, reactivated with zoster, etc. The incidence of varicella is higher in winter when children are in school, but we are primarily concerned with the effects of vaccinations, so that seasonal variations in the contact rate are not included in the model

here. Mixing between the age groups is given by a proportionate-mixing contact matrix, which is estimated from the varicella forces of infection on each age group. The model has varicella vaccination of young children and zoster incidence, which increases with age, so that the model includes both time and age as independent variables. The model parameters for varicella and zoster are estimated from data in Section 3. A computer simulation of the vaccination model with the baseline parameter set is used in Section 4 to calculate the fractions in each of the 15 epidemiologic classes in the 30 age groups for a 100 year period after the vaccination program is started.

In the simulations with vaccination of 90% of 1 year old children, there is a shift in the age distribution of varicella (chickenpox) cases towards older ages, but many of these cases are milder cases, since they occur in those who have been previously vaccinated. Thus the vaccination program would not increase the number of complications and deaths due to varicella infections. In the simulations, total zoster cases do increase by about 30% during the first three decades of the varicella vaccination program, but then they decrease significantly. Compared to the prevaccination level, zoster cases are about the same after 70 years, half after one century and one-third after about 150 years. The sensitivities of the simulation results to the choices of the parameter values are estimated in Section 5. The simulation results and limitations of the model are discussed in Section 6.

There are references in a pertussis modeling paper (Hethcote, 1997) to many age-structured mixing models for infectious diseases and to the study of complex vaccination effects such as boosting, waning, and partial protection for diseases such as pertussis, measles, rubella, hepatitis A and B, and HIV/AIDS. Previous authors have used modeling and benefit–cost analyses to study the effects of varicella vaccination programs. In a benefit–cost analysis using the costs of direct vaccination, direct medical care, and lost work time, Preblud *et al*. (1985) concluded that vaccination was cost effective. Using the steady-state age distribution of a mathematical model of varicella and zoster, Garnett and Grenfell (1992a) concluded that the probability of VZV reactivation as zoster must increase with age in order to fit the observed age pattern of zoster cases. Using the same model, Garnett and Grenfell (1992b) found that, under some conditions, zoster incidence could increase after vaccination. Halloran *et al*. (1994) used an age-structured varicella model with vaccination, but without zoster, to study the incidence, age distribution of varicella cases, and the sensitivity to estimated parameter values. Comparing benefits and costs that included medical treatment and work loss from varicella (but ignoring zoster), both Huse *et al*. (1994) and Lieu *et al*. (1994) concluded that varicella vaccination was cost effective. Ferguson *et al*. (1996) and Garnett and Ferguson (1996) used a stochastic simulation model without boosting to study the infectivity of zoster cases compared to varicella cases and their influence on maintaining VZV in a vaccinated population. Allen and Thrasher (1998) used the steady-state age distribution for an age-structured model to study the effects of vaccination on varicella infections, average age of infection, and zoster cases. The

dynamic simulation model used here has some similarities to the model of Halloran *et al*. (1994), but the model here is unique because it includes boosting of immunity by re-exposure and vaccination, and seven new classes for high immunity, low immunity and zoster.

2. THE MODEL FOR VARICELLA AND ZOSTER

The model used here is a system of differential equations that simultaneously describes the aging of the population, the transmission of the varicella zoster virus (VZV), and the incidence of varicella (chickenpox) and zoster (shingles). The demographic part of the model is based on fertility and mortality data in the United States. The epidemiological part of the model consists of a sequence of compartments for the epidemiological states of susceptible, latent, infective, recovered with high or low immunity, having zoster, vaccinated with high or low immunity, etc., as shown in Fig. 1. The computer simulation model is used to compare the effects of different vaccination levels of children at 1 year of age on the age-specific incidence of varicella and zoster. In order to assess the effects on varicella and zoster in adults, simulations are also computed with a supplementary varicella vaccination program, which has boosters given every 10 years starting at 50 years of age.

2.1. ***The demographic model.*** The simple demographic model used here assumes that the population is at a demographic steady-state age distribution and that the total population size is constant. This demographic model is deliberately chosen so that it is consistent with the reasonably simple epidemiologic model. This demographic model guarantees that observed features in the model simulations are due to the epidemiologic and vaccination patterns, and not to any complexities in the demographic modeling. The varicella and zoster incidence must be considered for all ages; the 30 age groups chosen are 0–5 months, 6–11 months, years 1, 2, 3, . . . , 18, 19, and 5 or 10 year intervals 20–24, 25–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and over 90.

Age-specific fertility and death rates change slightly from year to year, but these minor variations are negligible in this varicella modeling. With the 1990 fertilities and death rates (U.S. Bureau of the Census, 1994, Table 93), the large time growth rate would be 0.065% per year. In the model, the 1990 death rates are used and the 1990 fertilities are reduced by 1.7% in order to keep a constant population size. Thus the parameters in the demographic model approximate recent age-specific birth and death rates in the United States, but the model does not attempt to describe any demographic trends. For convenience, the sizes P_i of the age groups are chosen so that they are the fractions of the total population (i.e., the total population size is scaled to one). More details about the derivation of the demographic model are given in Appendix A of a pertussis modeling paper (Hethcote, 1997).

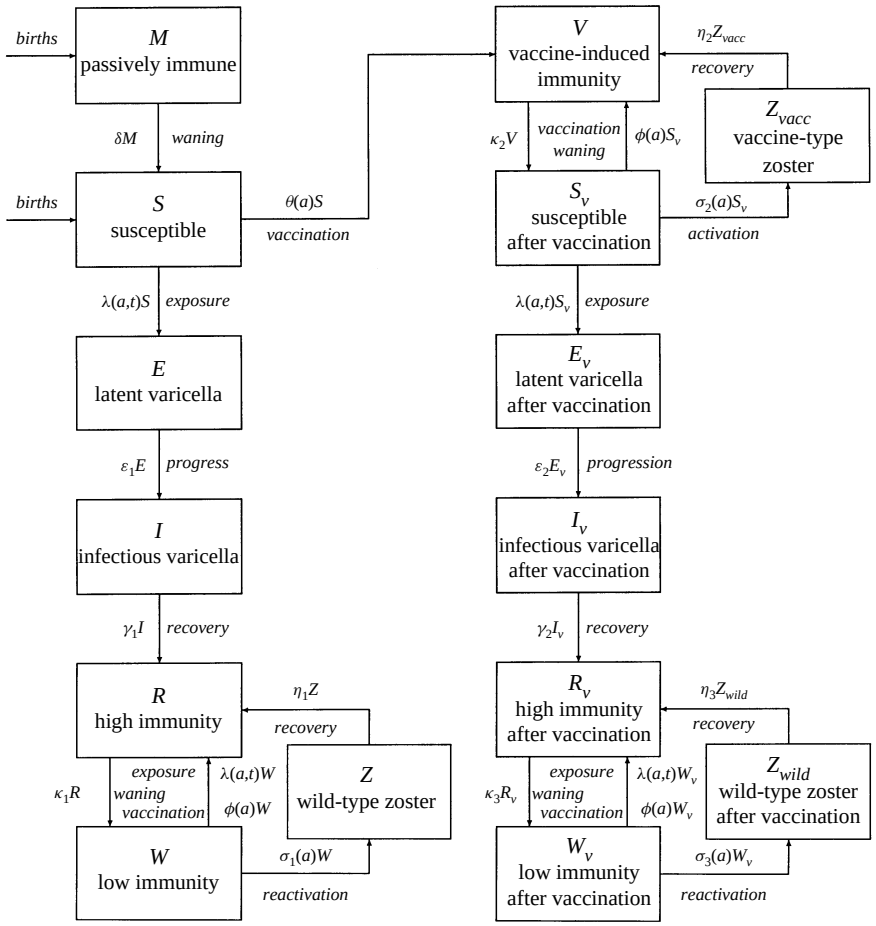

Figure 1. Transfer diagram for the varicella–zoster model with vaccination.

2.2. ***The age-structured epidemiologic model.*** The epidemiologic model developed here is a mathematical description of VZV transmission and the occurrence of varicella and zoster in an age-structured population. The population is divided into 15 distinct epidemiologic classes as shown in Fig. 1. The class M contains those infants who have passive immunity to VZV. If the mother has been infected or recently vaccinated, then her newborn infant will have some passive immunity, but as these maternal antibodies decay, the infant becomes susceptible. Otherwise, her newborn enters directly into the class S of susceptible individuals. When there is a sufficient contact of a susceptible with a person with varicella or zoster so that transmission occurs, then the susceptible enters the E class of exposed people who have a latent (incubating) VZV infection. Upon becoming infectious with VZV, the exposed person enters the class I of infective people who have varicella.

When the infectious period for VZV ends, the individual enters the R class of

recovered people with high immunity. Note that infection-acquired immunity to VZV is permanent, but the cell-mediated immunity of a recovered person decreases to a low level, so that the person eventually enters the class W consisting of weakly immune people. If a weakly immune person is vaccinated or has an adequate contact with a varicella infective or a person with zoster, then the immunity is boosted so that the person returns to the R class of recovered people with high immunity.

Individuals who have had a VZV infection can get zoster. The per capita incidence rate of zoster increases with age (see Fig. 6); this may be due to the general decline of the immune system with age and lower immunity from the lack of boosting by contacts with those with varicella or zoster. In the model, the rate of acquiring zoster is age dependent and zoster only occurs in those in the weakly immune class W. People in the zoster class Z are infectious, but their probability of transmitting VZV is much less than that of a person with varicella. Individuals who recover from zoster move back to the high immunity class R.

When susceptible people are vaccinated, a fraction of them become immune and move into the vaccination class V as shown in Fig. 1. The fraction of vaccinated susceptibles who become immune is called the vaccine efficacy. The vaccine-induced immunity of those in the vaccinated class wanes, so that people eventually move to the S_v class of susceptibles who were previously vaccinated. People in this S_v class have low immunity so that they can become infected with the wild-type varicella zoster virus. Although zoster from the vaccine-type virus is very unlikely, it can occur, so that a small fraction of those in the S_v class could get vaccine-type zoster and move into the Z_{vacc} class. Upon recovery from this vaccine-type zoster, individuals move back into the class V of those with high immunity to the vaccine-type virus.

If a previously vaccinated susceptible in the S_v class has an adequate contact with a person with varicella or zoster, then the exposed susceptible moves into the class E_v of previously vaccinated latent people and then into the class I_v of previously vaccinated infectious people who have the wild-type varicella zoster virus. Individuals in the I_v class usually have fewer lesions, so they are less infectious than those in the I class. Upon recovery the infective moves from I_v into the class R_v of previously vaccinated recovered people with high immunity. The movements of these previously vaccinated people between the recovered class R_v, the weakly immune class W_v, and the wild-type VZV zoster class Z_{wild} are analogous to those for the R, W, and Z classes, except that the likelihood of getting zoster seems to be less for those who have been previously vaccinated.

The age distributions for the 15 classes are given by $M(a,t)$, $S(a,t)$, $E(a,t)$, ..., $Z_{wild}(a,t)$, where a is age and t is time. For example, the number of susceptibles in class S in the age interval $[a_{i-1}, a_i]$ at time t is the integral over this interval of the age distribution $S(a,t)$. The transfers out of many of the classes in Fig. 1 are assumed to be proportional to the age distributions for the classes. These transfers are δM, $\varepsilon_1 E$, $\gamma_1 I$, $\kappa_1 R$, $\eta_1 Z$, $\kappa_2 V$, $\eta_2 Z_{vacc}$, $\varepsilon_2 E_v$, $\gamma_2 I_v$, $\kappa_3 R_v$, and $\eta_3 Z_{wild}$. These

assumptions are equivalent to the assumption that the waiting times due to each term have negative exponential distributions, so that the mean waiting times are the reciprocals of the rate constants (Hethcote *et al.*, 1981). Thus the mean period of passive immunity is $1/\delta$, the mean latent periods are $1/\varepsilon_i$, the mean infectious periods are $1/\gamma_i$, the mean periods of high immunity for those with vaccine-induced or infection-induced immunity are $1/\kappa_i$, and the mean periods for a zoster occurrence are $1/\eta_i$. The force of infection $\lambda(a,t)$ is a function of age and time, and the zoster rate coefficients $\sigma_i(a)$ are functions of age. The childhood and adult vaccination transfer rate coefficients $\theta(a)$ and $\phi(a)$ are also age dependent, since they occur in specific age groups.

The transfers due to infection are assumed to be governed by the principle of mass action, so that the incidence (i.e., the number of new cases per unit time) is proportional to the product of the numbers of susceptibles and infectives. Let the fraction ρ_v and ρ_z be the ratios of the infectiousness, compared to those in the infectious class I, of those in the previously vaccinated infectious class I_v, and those in the zoster classes Z and Z_{wild}. Because the infectivity potential of the few people in the vaccine-type zoster class Z_{vacc} is very small, it is not included in the model (Gershon *et al.*, 1992; CDCP, 1997). A measure of the infectiousness of the population at time t is the sum of the infectious age distribution $I(a,t)$ plus ρ_v times the previously vaccinated infectious age distribution $I_v(a,t)$ plus ρ_z times the combined zoster age distribution $Z(a,t)+Z_{wild}(a,t)$. Let $\omega(a,a')$ be the contact rate between those of age a and those of age a'. For example, the contact rates are higher for elementary school children and much lower for elderly people. The force of infection $\lambda(a,t)$ at age a and time t is the sum (i.e., the integral) over all ages a' of the contact rate $\omega(a,a')$ times the measure given above for the infectiousness divided by the total population size at time t. The division by the total population size makes the contact rate $\lambda(a,t)$ independent of the population size; this assumption is consistent with numerous studies which show that the contact rate is nearly independent of the population size (Hethcote, 1978; Mena-Lorca and Hethcote, 1992; DeJong *et al.*, 1995). Hence at time t, the transfer rate of those at age a out of the susceptible class S is the product of the force of infection $\lambda(a,t)$ times the susceptible age distribution $S(a,t)$. Similarly, the transfer rate out of the susceptible class S_v is $\lambda(a,t)S_v(a,t)$. The transfer rates for boosting out of the low immunity classes W and W_v are the products of the force of infection $\lambda(a,t)$ times the age distributions $W(a,t)$ and $W_v(a,t)$, respectively.

The differential equations for the epidemiologic model are given in Appendix A. There the partial differential equations with age and time as the independent variables are converted by integrating over the age intervals to 450 ordinary differential equations corresponding to the 15 epidemiologic classes within each of the 30 age groups. These 450 equations given in (6) are used in the simulations. The model starts with and maintains the demographic steady-state age distribution. For any set of epidemiological initial conditions and no vaccination, the solutions of the 450 differential equations reach an endemic steady-state distribution within each

age group after about 100–200 years. After this prevaccination epidemiological steady state is established, it and the prevaccination forces of infection are used in another computer program to determine the contact matrix among the age groups (see Section 3.3 and Appendix B). Then the prevaccination initial epidemiological state and the contact matrix are used in the main computer program, in which a vaccination program is simulated in the population for 100 years.

In the model the vaccination rate coefficient $\theta(a)$ corresponds to vaccination of young children and $\phi(a)$ corresponds to booster vaccinations. Most of the simulations here have only vaccination of children, in which case ϕ is zero. The recommended varicella vaccination of 1 year old children is incorporated by moving, from the susceptible class S to the vaccination class V, the successfully vaccinated fraction of those transferred each day due to aging between the 1 year old group (the third group) and 2 year old age group (the fourth group). The transferred fraction is the product of the fraction vaccinated times the vaccine efficacy (VE). For example, in the S class, the term $(c_3P_3/P_4)s_3$ in the differential equation for ds_4/dt is replaced by $(1-\theta \times VE)(c_3P_3/P_4)s_3$ and the term $(\theta \times VE)(c_3P_3/P_4)s_3$ corresponding to those successfully vaccinated is added to the differential equation for dv_4/dt, corresponding to the V class. Adult booster vaccinations at ages $50, \ldots, 90$ years are simulated by similar transfers.

3. ESTIMATES OF THE PARAMETERS

The baseline set of parameter values chosen here is summarized in Table 1 and is used in the computer simulations in Section 4. The sensitivity of the simulation results to the choices of parameter values is studied in Section 5.

3.1. ***Estimates of the epidemiological parameters.*** Passive immunity to varicella has been estimated (Gershon *et al.*, 1976) to last about 6 months (182.5 days), so that $\delta = 1/182.5$. The mean latent period for varicella is about 14 days (Garnett and Grenfell, 1992a), so that $\varepsilon_1 = \varepsilon_2 = 1/14$. The mean infectious period is estimated to be 7 days for unvaccinated people and 4.5 days for those who have been previously vaccinated (Izurieta *et al.*, 1997), so that $\gamma_1 = 1/7$ and $\gamma_2 = 1/4.5$. These latent and infectious periods are consistent with values given by others (Benenson, 1995; Krause and Klinman, 1995; CDCP, 1997; Redbook, 1977). Although it is known that immunity wanes with time (Hope-Simpson, 1965; Gershon *et al.*, 1992; Krause and Klinman, 1995; Arvin and Gershon, 1996; CDCP, 1997), the distinct classes R and W for high and low immunity are features of our model; there are no data on the average time in the high immunity class R. However, zoster is relatively infrequent in younger people and only those in the low immunity class W can get zoster, so it seems reasonable to use 20 years (7300 days) as the mean period of high immunity after a VZV infection, which implies that $\kappa_1 = \kappa_3 = 1/7300$. The mean period for a zoster occurrence is estimated to be 4

weeks (28 days) (Garnett and Grenfell, 1992a), so that $\eta_1 = \eta_2 = \eta_3 = 1/28$. [t]

Table 1. Baseline parameter values.

Parameter	Explanation	Value
$1/\delta$	Average period of passive immunity	6 months
$1/\varepsilon_1$, $1/\varepsilon_2$	Average latent period	14 days
$1/\gamma_1$	Average infectious period for varicella in never vaccinated people	7 days
$1/\gamma_2$	Average infectious period for varicella in previously vaccinated people	4.5 days
$1/\eta_1$, $1/\eta_2$, $1/\eta_3$	Average length of a zoster case	28 days
$1/\kappa_1$, $1/\kappa_3$	Average period of high immunity after varicella infection	20 years
$1/\kappa_2$	Average period of high immunity after vaccination	20 years
$\lambda(a,t)$	Forces of infection in the age groups	[a]
ρ_v	Relative infectivity of previously vaccinated people with varicella	0.17
ρ_z	Relative infectivity of people with wild-type zoster	0.07
$\sigma_1(a)$	Yearly rate of zoster per 100 000 people	[b]
$\sigma_2(a)$	Yearly rate of vaccine-type zoster in the low immunity class S_v	$0.05\ \sigma_1(a)$
$\sigma_3(a)$	Yearly rate of wild-type zoster in the low immunity class W_v	$0.23\ \sigma_1(a)$
VE	Vaccine efficacy	0.90
$\theta(a)$	Percentage of 1 year olds vaccinated	90%[c]

[a] Values estimated from Halloran *et al*.; see Section 3.2.

[b] $\sigma_1(a)$ is chosen in the simulations to match the per capita zoster data in the age groups. For people under age 50 years, the value used is 600 per 100 000 and in subsequent 10 year age intervals the values used are 1014, 1715, 2900, and 4903, respectively. For people over age 90 years the value used is 8290 per 100 000.

[c] Percentage is increased linearly from 0% to 90% over the first 10 years of the vaccination program and then held constant at 90%.

The varicella vaccine was licensed in the United States in March, 1995. National coverage levels among children aged 19–35 months for varicella vaccine have been estimated to be 19% during July, 1996 to June, 1997 and 25% during April–June, 1997 (CDCP, 1998a). It is not possible to estimate what fractions of 1 year old children will be vaccinated for varicella in the future, but the coverages among children aged 19–35 months for other vaccines including MMR (measles-mumps-rubella), polio, and DTP (diphtheria-tetanus-pertussis) are now about 90% (CDCP, 1998a). Consequently, it is assumed in the simulation modeling that varicella vaccination of 1 year old children increases linearly from 0% up to 90% during the first 10 years and then remains at 90% for the next 90 years. This simple vaccination scenario is not meant to be accurate or predictive, but it is useful in estimating the possible effects of a varicella vaccination program that eventually reaches approximately 90% coverage for 1 year old children.

Varicella booster vaccinations of adults stimulate an immune response and hence provide higher immunity with protection from zoster (Brunell, 1991; Levin *et al*., 1994; Arvin and Gershon, 1996; Gershon *et al*., 1996). The effects on varicella and zoster of varicella booster vaccinations for older adults are estimated in one simulation. The levels of vaccination for people aged 18–64 years and over 65 years

are 56% and 28%, respectively, for tetanus-diphtheria boosters within 10 years in 1994, and less than 30% and 58% for influenza vaccinations in 1995 (CDCP, 1998c,d). Based on these vaccination levels, it is assumed in the simulation with adult boosters that 50% of people over age 50 receive varicella vaccinations every 10 years.

The seroconversion rate (i.e., the fraction for whom their immune system mounts an immune response) for the varicella vaccine has been estimated to be 0.94 and 0.96 by Huse *et al*. (1994) and Gershon *et al*. (1992), and 0.97 for those up to 12 years of age (CDCP, 1997). The vaccine efficacy (VE) is the fraction protected from an infection or from disease by a vaccine. The vaccine efficacy for the varicella vaccine has been estimated to be 0.70 to 0.96 (Krause and Klinman, 1995), 0.86 (Arvin and Gershon, 1996), 0.95 (Gershon *et al*., 1992), and 0.90 by an expert panel (Halloran *et al*., 1994). A publication (CDCP, 1997) on varicella by the Centers for Disease Control and Prevention concludes that the varicella vaccine provides 70–90% protection against infection and 95% protection against severe disease for 7 to 10 years after vaccination. Thus there is some variability in the estimates of the vaccine efficacy. In the simulations, a vaccine efficacy of 0.90 is used. Note that only the product of the fraction vaccinated and the vaccine efficacy is relevant in the simulations, so that a net fraction of 0.45 of an age group moved to the vaccinated class would correspond to vaccinating 0.50 with $VE = 0.9$ and also correspond to vaccinating the fraction 0.5625 with $VE = 0.8$.

It has been observed that varicella cases in previously vaccinated people (often called breakthrough cases) are milder than varicella in unvaccinated individuals (Watson *et al*., 1993; Huse *et al*., 1994; CDCP, 1997). One study found that breakthrough cases had about one-sixth as many total and vesicular lesions as unvaccinated cases (Bernstein *et al*., 1993; Krause and Klinman, 1995). It is reasonable to assume that infectiousness is proportional to the number of lesions, so that the relative infectivity parameter ρ_v is taken to be 0.17. A study of breakthrough varicella in leukemic children found them to be milder cases with less than one-tenth the usual number of skin lesions (Gershon, 1995). Another study (Izurieta *et al*., 1997) found that nine varicella cases in previously vaccinated individuals were all mild cases with less than 50 varicella lesions, but in unvaccinated individuals, 19 varicella cases were mild with less than 50 lesions, 43 were moderate with 50 to 250 lesions, and 10 were severe with over 250 lesions. Weighing the cases by the average number of lesions and again assuming that infectiousness is proportional to the number of lesions, we estimate that previously vaccinated individuals are only one-fifth as infectious as unvaccinated individuals. This value is consistent with the estimate $\rho_v = 0.17$ above.

Transmissions of infection from zoster patients do occur, but they are relatively rare (Benenson, 1995; CDCP, 1997). The relative infectivity parameter from those with zoster has been estimated (Ferguson *et al*., 1996) using a stochastic SIR model to be 0.07, so $\rho_z = 0.07$ is used in our simulations.

Immunity wanes after varicella vaccination (Hammerschlag *et al*., 1989; CDCP, 1997). A clinical trial in the United States of the varicella vaccine found that at least 90% of vaccinated children had detectable antibody after 10 years (Gershon *et al*., 1992). A study in Japan found that immunity after varicella vaccination persisted for 20 years (Asano *et al*., 1994). In the simulation model, the mean period of vaccine-induced immunity is assumed to be 20 years (7300 days), so that $\kappa_2 = 1/7300$. This is roughly consistent with the estimate of an expert panel that no more than 15% of vaccinated people will get varicella in their lifetime, if immunity is not boosted by natural infection (Halloran *et al*., 1994).

There is evidence that zoster can develop when cellular immunity is low (Hope-Simpson, 1965; Hardy *et al*., 1991; CDCP, 1997). In the simulations, the age-dependent values of the zoster rate coefficient $\sigma_1(a)$ for movement from the W class to the Z class are chosen so that the incidence of zoster in the prevaccination era matches the reported age-specific incidence of zoster in the United States (Donahue and Manson, 1995) as shown by asterisks in Fig. 6. These zoster incidence data were 46 cases per 100 000 for both sexes aged 0 to 14 years, 103 for ages 15–24, 192 for ages 25–34, 226 for ages 35–44, 313 for ages 45–54, 571 for ages 55–64, 992 for ages 65–74 and 1425 cases per 100 000 for those over age 75 years. Other estimates of zoster incidence are generally consistent with these estimates. Studies of zoster in those aged 0–19 years found 42 cases (Guess *et al*., 1986) and 77 cases (CDCP, 1997) per 100 000 person/years. A 1947–62 study with 3534 cases in England (Hope-Simpson, 1965) found 74 cases per 100 000 person years for those aged 0–9 years, 138 for ages 10–19, 258 for ages 20–29, 229 for ages 30–39, 292 for ages 40–49, 509 for ages 50–59, 679 for ages 60–69, 642 for ages 70–79, and 1010 cases per 100 000 for ages 80–89 years. Overall rates of zoster have been estimated to be 340 cases (Hope-Simpson, 1965), 400 (Kurtzke, 1982), and 480 cases (Whitley, 1992) per 100 000 person years. The values used in the baseline parameter set for the zoster incidence rate coefficient $\sigma_1(a)$ are 600 per 100 000 people per year for the age intervals between 0 and 49 years, and then geometrically increasing values 1014, 1715, 2900, 4903, and 8290 in the 10 year intervals 50–59, 60–69, 70–79, 80–89 and the last age group over 90 years. Note that these values are consistent with the concept that the cell-mediated immunity of individuals is fully effective until people reach about age 50 years and then it starts to decline with age.

In the model in Fig. 1, those in the S_v class, whose immunity after vaccination has become very low, can get zoster from the vaccine-type virus. Zoster from the vaccine-type varicella virus is uncommon, but it can occur (Hammerschlag *et al*., 1989; Plotkin *et al*., 1989). It seems that the vaccine-type varicella virus does not reach the dorsal root ganglia where it could lead to zoster unless there is some skin involvement such as a rash or a few lesions after vaccination (Hardy *et al*., 1991; Gershon *et al*., 1992). The fraction of those vaccinated who have a rash has been estimated to be 0.04 or 0.05 (Gershon *et al*., 1992; Huse *et al*., 1994). Consequently, in the baseline simulations it is assumed that the age-dependent values of

the rate coefficient $\sigma_2(a)$ for vaccine-type zoster are 0.05 times the corresponding values of the rate coefficient $\sigma_1(a)$ for zoster in unvaccinated people.

In the model, previously vaccinated people who are in the low immunity class S_v can become infected with the wild-type varicella zoster virus and have a mild case of varicella, so that some wild-type varicella zoster virus travels to the dorsal root ganglia. After recovery, they enter the class R_v of those with high immunity to the wild-type virus, but eventually they move to the class W_v when the immunity to the wild-type varicella virus wanes. Weakly immune individuals in the W or W_v classes can have their immunity boosted (Gershon *et al.*, 1996) back up to the higher level by re-exposure (modeled by λW and λW_v). Indirect evidence of this raising of weak immunity is that a high level of varicella transmission in a community at a given time seems to suppress the reactivation of VZV as zoster (Garnett and Grenfell, 1992b). The immunity can also be boosted (Gershon *et al.*, 1996) back to the higher level by vaccination (modeled by ϕW and ϕW_v), but adult booster vaccinations are considered in only one of the simulations here.

These people in the class W_v with low immunity can get zoster from the latent wild-type varicella zoster virus in their nerve ganglia. The incidence of zoster seems to be lower in those who have been vaccinated. The incidence of zoster of unspecified type after varicella vaccination among otherwise healthy people was estimated by the vaccine producer in some limited time studies to be 18 cases in children and 12.8 cases in adults per 100 000 person years. The former is lower by a factor of 0.23 than the rate of 77 per 100 000 person years for healthy children (CDCP, 1997). In a study of leukemic children, the incidence of zoster was 2% in vaccinees and 15% in controls (Arvin and Gershon, 1996). A review of the literature in Garnett and Grenfell (1992b) did not find any decrease in zoster cases among vaccinated people. In the baseline parameter set, the rate coefficient $\sigma_3(a)$ values for wild-type zoster in previously vaccinated people are 0.23 times the corresponding values of the rate coefficient $\sigma_1(a)$ for zoster in unvaccinated people with low immunity. The sensitivity analysis in Section 5 considers $\sigma_3/\sigma_1 = 1$, in which case the relative frequency of zoster in those with low immunity does not depend on whether the person has ever been vaccinated.

3.2. ***Estimates of the forces of infection.*** When the population is divided into n age groups, there are n forces of infection λ_i to be estimated from the data. The force of infection λ_i in the ith age group is the total contact rate with infectives in all age groups. Hence the incidence in the ith age group with susceptible fraction S_i is $\lambda_i S_i$. The forces of infection λ_i for the age groups can be estimated using maximum likelihood methods from data on the incidence in the age groups or the seropositivity as a function of age (Grenfell and Anderson, 1985). Note that it is assumed that the population is unvaccinated and that the endemic disease has reached an equilibrium state, so that the forces of infection λ_i and the age distributions in the epidemiological classes are independent of time.

Halloran *et al*. (1994) used this method to estimate the forces of infection for chickenpox in the United States. For the five age groups 0–4, 5–9, 10–14, 15–19, and $\geq$20 years, they obtained 0.096539, 0.198778, 0.191471, 0.135138, and 0.102531. In the model, these values are used for those over age 5 years, but for younger children, an increasing sequence of 1-year forces of infection is used, so that the average is the value 0.096539 above. In order to obtain this average, the values used are 0.096539 times $1/3$ for those less than 1 year, $2/3$ for age 1 year, 1 for age 2 years, $4/3$ for age 3 years, and $5/3$ for age 4 years. Garnett and Grenfell (1992a) use serological survey data from various countries to estimate the forces of infection for varicella in age groups. Their pattern is similar to that above, with the highest force of infection in the 5–14 year old age group. Age-specific forces of infection have been estimated for other diseases including measles and pertussis (Anderson and May, 1985a,b; Grenfell and Anderson, 1989; Anderson and May, 1991, Chap. 8). Measles and pertussis are both more easily spread than varicella; estimates in the prevaccination era of the average ages of attack are about 5 years for both pertussis and measles as compared to 7 years for chickenpox (Anderson and May, 1991, p. 51).

3.3. ***Estimates of the contact matrix.*** People in some age groups have more encounters with those in certain age groups and fewer with those in other age groups. In general, retired people may have fewer daily contacts than those who are still working. Children in school usually have many contacts with other school children, but fewer contacts with adults. In the simulation model, it is assumed that mixing between two given age groups is related to the mixing activity levels of the groups and occurs between randomly chosen members of these groups. The simulation model uses parameter values based on averages of all interactions that occur in families, in schools, at workplaces, in public places, in small cities, in big cities, etc. This simplification works reasonably well for childhood diseases such as pertussis, measles, rubella, mumps, and chickenpox, because the school and community structures in which mixing occurs are somewhat similar throughout the United States.

From the forces of infection λ_i for the n age groups, it is possible to estimate the $n \times n$ contact matrix $[w_{ij}]$ between the susceptibles in the ith group and the infectives in the jth group. Since only n parameters can be estimated from the n values of the forces of infection, the contact matrix form can have only n unknown parameters. A simple choice for the contact matrix is a proportionate-mixing matrix, in which the entries depend on n activity levels for the n age groups. This proportionate-mixing method assumes that the number of contacts between members of two age groups is proportional to the activity levels and sizes of the two groups. Proportionate mixing has been used for both multigroup models and continuous age-structured models (Hethcote, 1978; Hethcote and Van Ark, 1987; Allen and Thrasher, 1998). This approach is given by the algorithm in Appendix B, which is related to the method developed in Hethcote (1996), Rouderfer

et al. (1993), and Hethcote (1997). Some of the 30 original age intervals are combined to obtain 10 aggregated age intervals. Using the 10 forces of infection, the multiplying factors $l_j/D^{\frac{1}{2}}$ for the 10 aggregated age groups of 0–11 months, 1, 2, 3 and 4 years, 5–9 years, 10–14 years, 15–39 years, 40–59 years, and over 60 years are found to be 0.261, 0.523, 0.784, 1.046, 1.308, 1.615, 1.556, 1.098, 0.833, and 0.406. Here the activity level is highest for the 5–9 year old age group.

Other mixing matrices are discussed in Hethcote (1997). One example is the preferred mixing matrix, that is, a convex combination of proportionate mixing and internal mixing. The preferred mixing matrix has been used for sexually transmitted diseases, where the convex combination parameter is related to the correlation between the sexual activity level of the susceptible person and the sexual activity level of the person contacted (Hethcote and Yorke, 1984). Anderson and May (1991, pp. 176–177) present several different mixing matrices which they label WAIFW (who acquires infection from whom); these are based on assumptions about which groups would have the most contacts with each other. WAIFW matrices have been used in several previous varicella models (Garnett and Grenfell, 1992a,b; Halloran *et al*., 1994; Ferguson *et al*., 1996).

4. COMPUTER SIMULATIONS WITH THE BASELINE PARAMETER SET

A computer simulation of the transmission and vaccination model for varicella and zoster with the baseline parameter set estimated in the previous section has been used to approximate the effects of a varicella vaccination program for 1 year old children. Figure 2 shows the varicella (chickenpox) incidences per year when the vaccination coverage of 1 year old children is increased over 10 years from zero up to 90% and then maintained at that level. The incidence in the never vaccinated (or unsuccessfully vaccinated) susceptibles in class S under 20 years of age decreases rapidly and then decreases slowly. The incidence in the never vaccinated susceptibles over 20 years of age decreases slightly and then returns to about the prevaccination level. The incidences in the previously vaccinated (i.e., those successfully vaccinated, but now susceptible again) susceptibles in class S_v increases first for those under 20 years of age and later for those over 20 years of age. Because the incidence in the previously vaccinated susceptibles increases, the total incidence decreases and then rebounds slightly between 30 and 70 years, after which it decreases very slightly to a near equilibrium. However, once the 90% vaccination level is achieved in 10 years, the incidence is always at least 62% lower than in the prevaccine era.

Figure 3 shows the varicella incidence per year of age for various age groups. As expected, the varicella incidence decreases in the younger age groups, since many children are protected from an infection by their varicella vaccination. The varicella incidence in people over age 20 years starts increasing about 20–30 years into the vaccination program, because these older people are getting varicella after

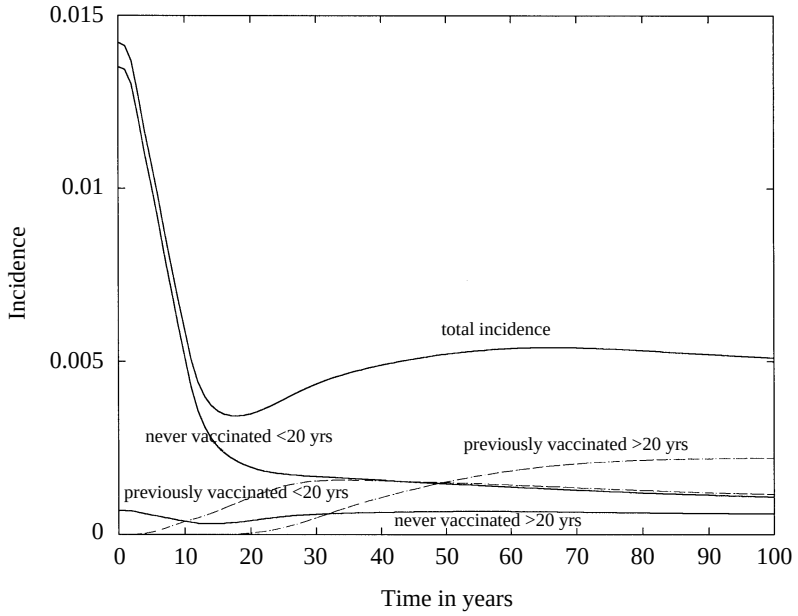

Figure 2. Simulated total varicella incidence as a function of time with separate graphs for subpopulations based on age and previous vaccination status.

the immunity from their vaccination at age 1 year fades away and they become susceptible as adults. It is this increase in varicella cases in previously vaccinated adults that causes the rebound in the total varicella incidence seen in Fig. 2.

Figure 4 shows that the average age of varicella infection increases from about 8 years in the prevaccination area up to the twenties as the vaccination program expands into the population. It is typical that the average age of infection increases when a vaccination program is introduced, since people have less exposure to infectives in the community. But the effect here is particularly dramatic, because the adults become susceptible again after the vaccine-induced immunity wanes and can then be infected as adults. Figure 5 is a three-dimensional plot of the incidence as a function of both age and time. This plot shows the shift of the age distribution of varicella incidence with time from young ages to older ages as the vaccination program expands through the population.

Recall that the first major concern about a varicella vaccination program is that there could be more varicella cases in adults, for whom the complication and death rates are higher. Although the total varicella incidence decreases, Figs 2–5 do show that the age distribution does shift towards older ages. In order to address the concern about a possible increase in complications (including deaths) in varicella cases, the total complications are now estimated from the simulated incidences. Complications (including deaths) seem to be about 5 to 20 times more frequent for adults (Preblud, 1981; Guess *et al.*, 1985; Benenson, 1995; Gershon, 1995).

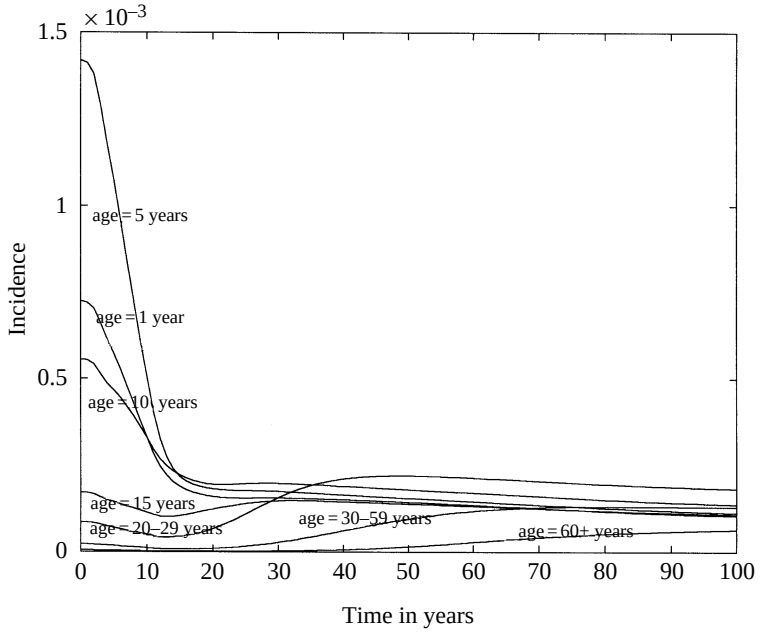

Figure 3. Simulated varicella incidence in age groups as a function of time.

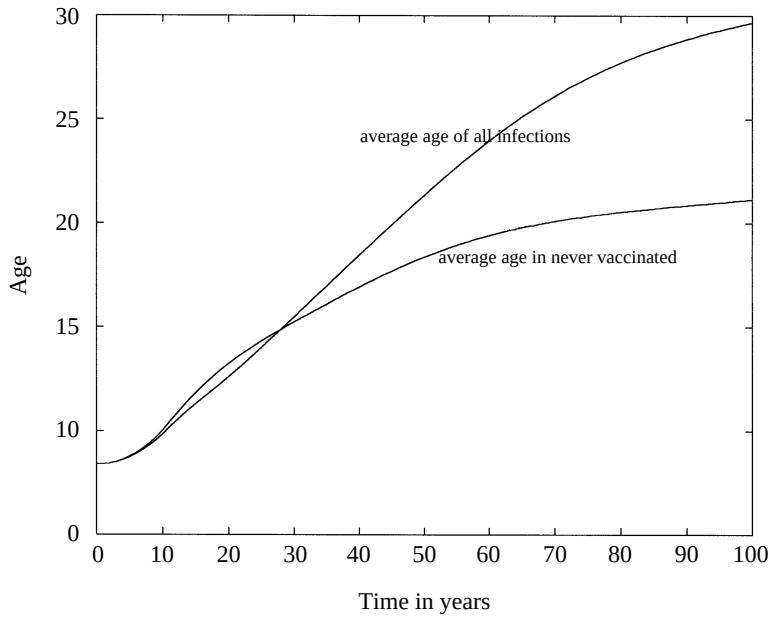

Figure 4. Average ages of varicella infection in the simulations as a function of time.

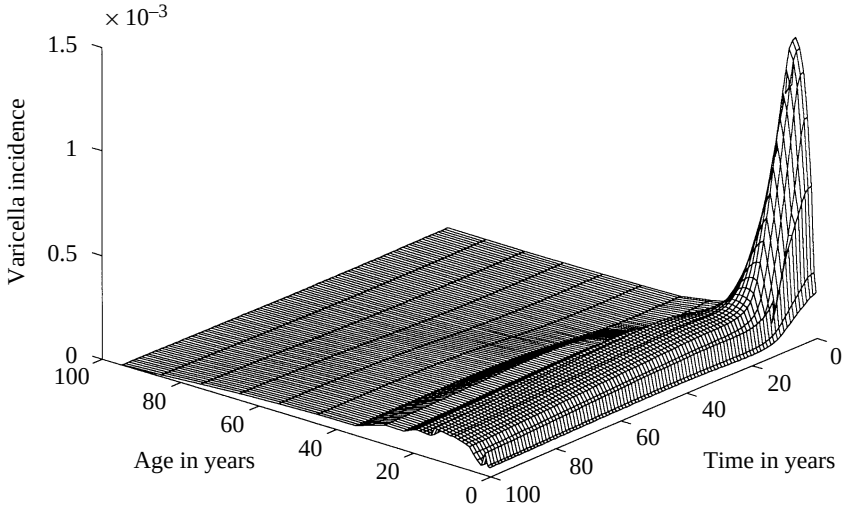

Figure 5. Simulated varicella incidence as a function of age and time.

In the first calculation, the complication rate is c per case for a person under age 20 years and is $20c$ for a person over age 20 years. Because previously vaccinated people who have a varicella infection have a milder case with an average of $1/6$ as many lesions, the first calculation assumes that these people also have $1/6$ as many complications. Thus the total complications would be the sum of the products of the incidences of the four separate categories shown in Fig. 2 and their relative complication rates (c, $20c$, $c/6$, and $20c/6$). Using these values, the total varicella complications after the 90% vaccination level is reached in 10 years are always at least 22% lower than in the prevaccine era. The second calculation uses a lower complication rate of $5c$ for an infected person over age 20 years. An expert panel estimated that previously vaccinated people, who have varicella, are only one per cent as likely to have complications as infected unvaccinated people (Lieu *et al.*, 1994). Using these lower values, the total varicella complications are reduced by at least 58% after the first 10 years. Both estimates show that there are fewer complications under the vaccination program, so that the shift in the age distribution does not lead to more complications.

Figure 6 shows the per capita zoster incidence at the beginning of the vaccination program, after 50 years, and after 100 years. Note that the per capita or relative zoster incidence is the incidence per person in each age group, and the * data points clearly show that this relative zoster incidence increases with age. As described in the parameter estimation section, the zoster incidence rate coefficient $\sigma_1(a)$ has been chosen so that the relative zoster incidence in the simulations matches the relative zoster * data points. Figure 6 shows that after 50 years of the vaccination program, the relative incidence is lower for those under age 40 and higher for those over age 40. After 100 years of the vaccination program, the relative incidence is

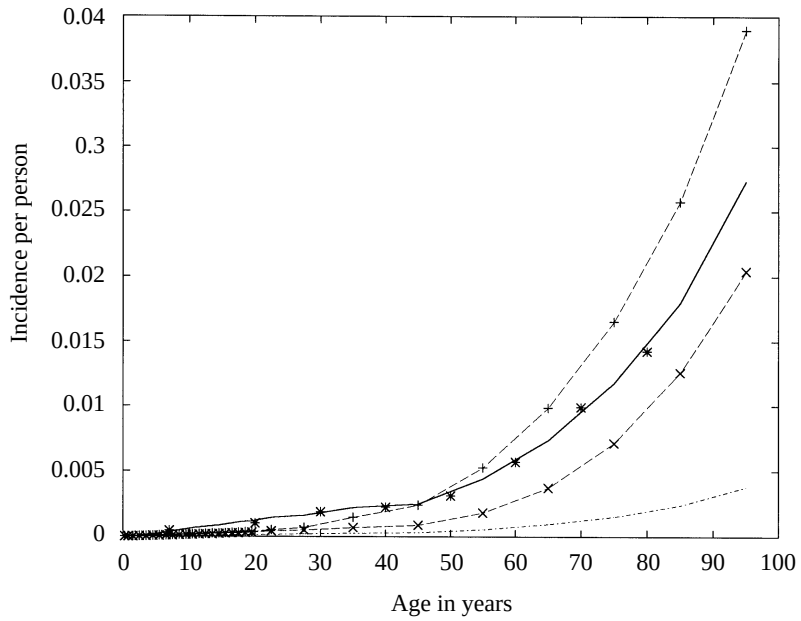

Figure 6. Reported zoster incidence per person in each age group, and the simulated zoster incidence in the prevaccine era, after 50 years and after 100 years of a vaccination program. In the figure $*$ is the zoster incidence data points in time year 0 (prevaccine); the solid line is the simulated total zoster incidence in time year 0; dashed line with $+$ is the simulated total zoster incidence in time year 50; dashed line with $\times$ is the simulated total zoster incidence in time year 100; and the dash-dotted line is the simulated zoster incidence in previously vaccinated people in time year 100.

significantly lower for people of ages less than 50 and somewhat lower for people with older ages. After 100 years the incidence of zoster in previously vaccinated (i.e., successfully vaccinated) people (shown by the dash-dotted curve) is low, so that most of the zoster incidence is still occurring in those who were never vaccinated or did not acquire immunity from a vaccination.

Figure 7 shows that as the vaccination program covers more people in the population, the simulated total zoster incidence increases by about 30% during the first 30 years and then decreases. When compared to the prevaccination level, total zoster cases are about the same after 70 years, half after 100 years and level off at one-third after about 150 years. In the first 100 years, most zoster cases occur in unvaccinated (or unsuccessfully vaccinated) people and very little is vaccine-type or wild-type zoster in previously vaccinated (i.e., successfully vaccinated) people. However, the vaccine-type and wild-type zoster in previously vaccinated people increase slightly beyond 100 years until eventually, these two components together are about equal to the wild-type zoster in unvaccinated people. Of course, projec-

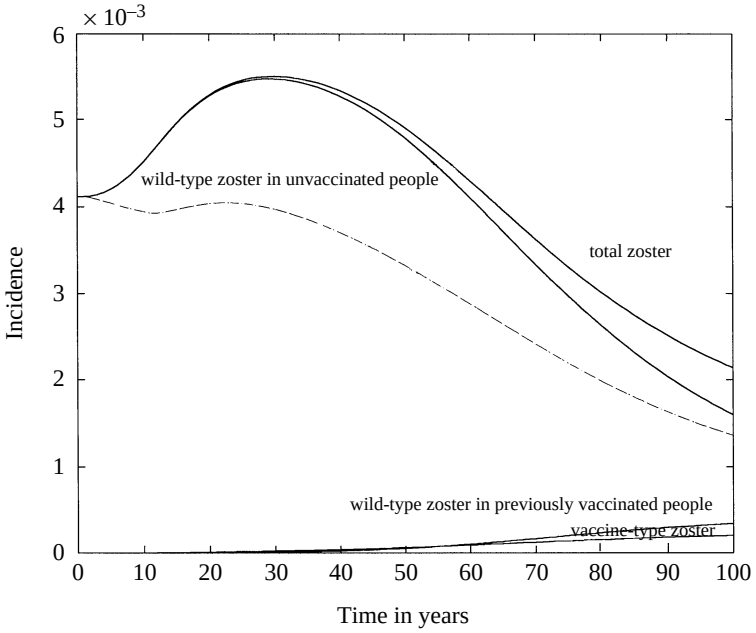

Figure 7. Simulated total zoster incidence (without and with a supplementary adult booster program) as a function of time with separate graphs for the three zoster classes. The solid curves correspond to 90% vaccination at age 1 year and the dashed curve is total zoster when 50% are boosted at ages 50, 60 70, 80 and 90 years.

tions many years after initiation of a vaccination program are questionable, since vaccination levels and conditions would undoubtedly change. Nevertheless, the simulations show the general trends caused by the varicella vaccination program.

It is reasonable to consider a vaccination program for older adults that would reduce or eliminate the increase in total zoster incidence. Figure 7 shows the zoster incidence when the 90% vaccination program for 1 year old children is supplemented by a program in which 50% of adults are given varicella booster vaccinations at ages 50, 60, 70, 80, and 90 years (both vaccination programs are phased in linearly over the first 10 years). This supplementary varicella booster vaccination program reduces total zoster incidence and eliminates the peak at 30 years.

Figure 8 shows the zoster incidence per year of age in the age groups as a function of time since initiation of the vaccination program. For those people under age 20 years, the direct protection of the vaccinations causes the zoster incidence to decrease. For those age groups over 20 years, the zoster incidences increase to a peak and then decrease. The peaks of these zoster incidences range up to 40% higher than the corresponding prevaccination zoster incidences and occur between 30 and 50 years after the initiation of the vaccination program. Figure 9 is a three-dimensional plot of the zoster incidence as a function of time and age. This

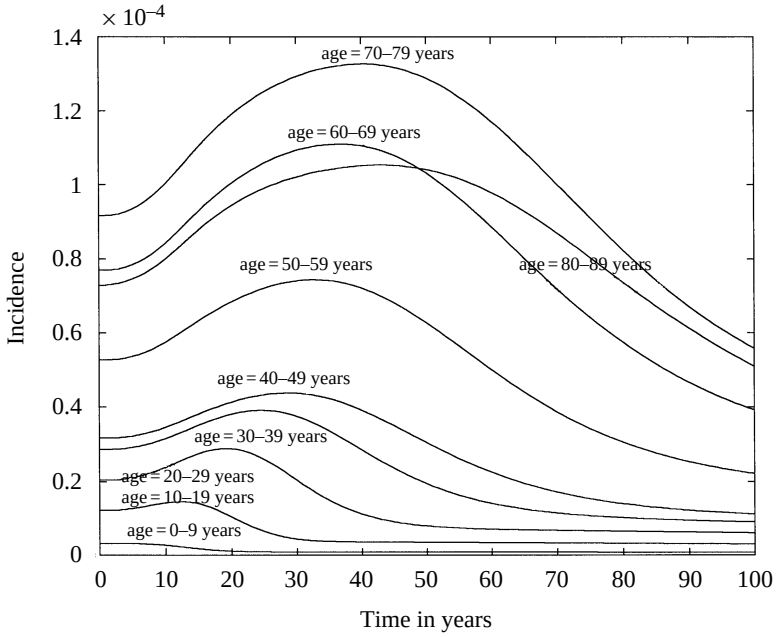

Figure 8. Simulated zoster incidence in age groups as a function of time.

plot shows the low ridge of zoster as people in succeeding age groups lose their high immunity and the high ridge at 70 years of age.

5. SENSITIVITY ANALYSIS

The sensitivity to changes in parameter values is estimated by comparing the simulations in which one parameter value at a time is changed with the simulation for the baseline parameter set. More complicated sensitivity analyses use Latin square designs (Blower and Dowlatabadi, 1994), but the straightforward approach used here is adequate and easier to understand. The simulation results are relatively insensitive to changes in most parameter values, but they are sensitive to changes in the final vaccination level, the relative likelihood of zoster for unvaccinated and previously vaccinated people, and the relative infectivity of varicella cases in previously vaccinated people. Even when the simulation details are sensitive to parameter changes, the general patterns are similar for a wide range of parameter values.

If the final vaccination level of 1 year old children after 10 years is 70% instead of 90%, then the varicella incidences shown in Fig. 10 are higher, and the average ages of vaccination are lower. The pattern of the per capita zoster is similar to that in Fig. 6, but it increases less at year 50 and decreases less at year 100. The pattern of total zoster is similar to that in Fig. 7, but it only increases about 20% instead

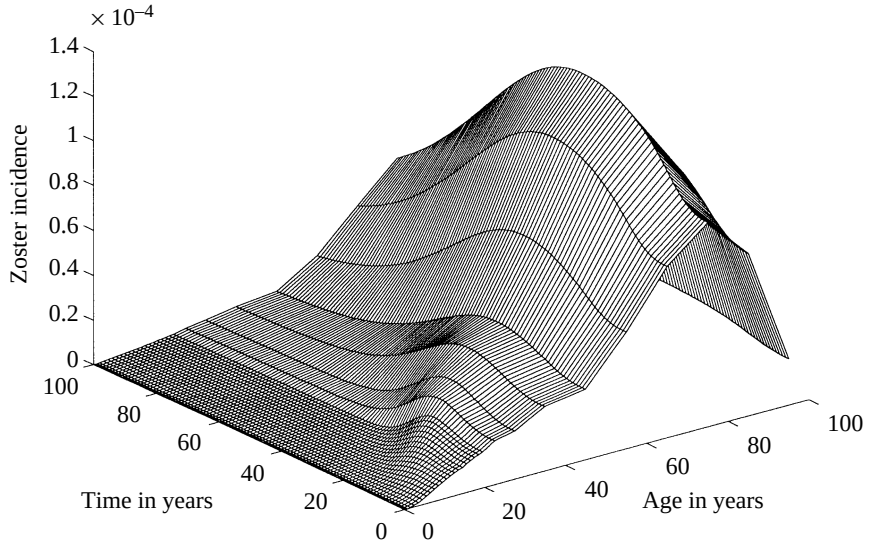

Figure 9. Simulated total zoster incidence as a function of age and time.

of 30% after 30 years, and at 100 years it is only two-thirds of the prevaccination level instead of one-half. Thus a lower final vaccination level in the simulations implies that the patterns are similar to those for the baseline parameter values, but the effects are muted and less dramatic.

The simulation patterns of the varicella and zoster incidences are relatively insensitive to changes in the rate constants δ, ε_1, ε_2, γ_1, γ_2, κ_1, κ_2, κ_3, η_1, η_2, and η_3. Doubling or halving the mean period of passive immunity $1/\delta$ or the mean latent periods $1/\varepsilon_1$ and $1/\varepsilon_2$ causes minor time shifts, but has almost no effect on the incidences. Doubling or halving both mean infectious periods $1/\gamma_1$ and $1/\gamma_2$ has no effect on the simulations, because, as seen from the equations in Appendix B, there is an opposite change in the contact matrix in order to match the fixed forces of infection.

If the mean periods $1/\kappa_1$ and $1/\kappa_3$ of infection-induced high immunity are not changed from 20 years, but the mean period $1/\kappa_2$ of vaccine-induced high immunity is decreased to 10 years, then the varicella incidence is almost unchanged in never vaccinated people and increases in previously vaccinated people, so that the total varicella incidence is about 30% higher than shown in Fig. 2. However, the zoster incidences are nearly identical to those shown in Figs 7–9, because very little of the zoster occurs in those who are previously vaccinated. When $1/\kappa_1 = 40$ years, $1/\kappa_3 = 20$ years, and $1/\kappa_2 = 10$ years, then the total varicella incidence is increased by about 30%, and there is more zoster in previously vaccinated people, but the zoster incidences are still very similar to those in Figs 7–9.

If the three mean periods $1/\kappa_i$ of high immunity are all reduced from 20 years to 10 years, then people are more likely to be in the low immunity class W. Thus the

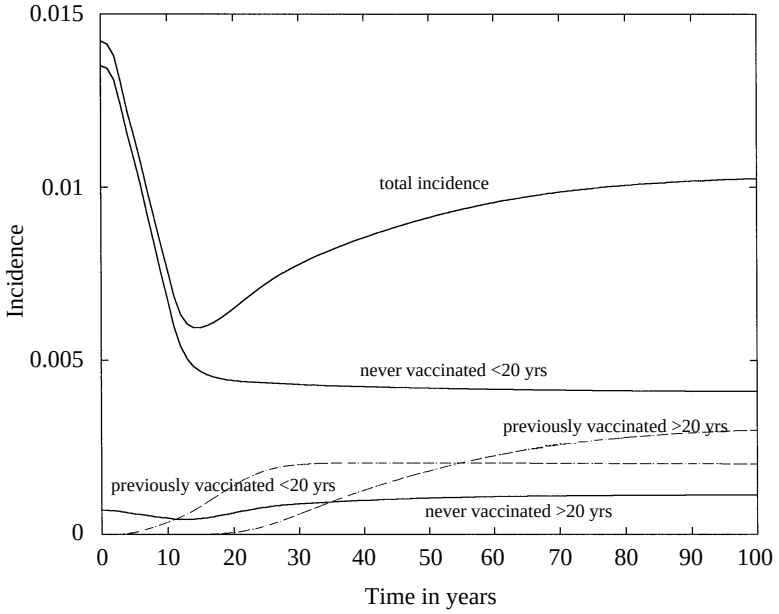

Figure 10. Simulated varicella incidence as a function of time when only 70% of 1 year old children are vaccinated.

zoster rate coefficient $\sigma_1(a)$ for movement from the W class to the Z class must be decreased, so that the simulated incidence of zoster in the prevaccination era again matches the reported age-specific incidence of zoster shown by asterisks in Fig. 6. In simulations with these new lower $\sigma_1(a)$ values, the varicella incidence is nearly unchanged in never vaccinated people and increases in previously vaccinated people, so that the total incidence increases no more than 30%. The per capita zoster incidences are slightly lower at 50 years and 100 years when compared to those in Fig. 7, and the total zoster incidence peaks at about 20% above the prevaccine level instead of the 30% higher peak in Fig. 8. Thus the details are slightly different, but the patterns are very similar. This result may seem surprising, because one might expect that less durable immunity would increase the incidence of zoster. However, the changes in the κ_i are balanced by the changes in the $\sigma_i(a)$, so there is very little net change in zoster incidence.

If the three mean periods $1/\kappa_i$ of high immunity for those with infection-induced or vaccine-induced immunity are all increased from 20 years to 40 years, then the zoster rate coefficient $\sigma_1(a)$ for movement from the W class to the Z class must be increased, so that the simulated incidence of zoster in the prevaccination era matches the reported age-specific incidence of zoster. Simulations with these new higher $\sigma_1(a)$ values have one-third less varicella in previously vaccinated adults, because people stay in the vaccinated class V twice as long. However, the pattern of zoster incidence is almost identical to that in Figs 7–9, so that the zoster incidences are insensitive to changes in the mean periods of infection-induced and vaccine-

induced immunity.

Recall from the parameter estimation section that one study found that zoster was less likely in those who had been vaccinated by a 0.23 factor, but another study found no difference. If the ratio σ_3/σ_1 of the zoster rate coefficients for the unvaccinated and previously vaccinated people is changed to 1 from the 0.23 value in the baseline parameter set, then the total varicella incidence pattern is similar to that in Fig. 2, but it is slightly (5% to 14%) higher in the last 50 years. The per capita zoster incidence is almost the same as in Fig. 6 at time year 50. However, the zoster in the previously vaccinated people is over twice as large, so that the per capita zoster at year 100 is just under the per capita zoster incidence at year 0. The total zoster pattern is similar to that in Fig. 7 with the same peak at year 30, but the zoster incidence at year 100 is only about three-fourths of the prevaccination level instead of one-half as in Fig. 7. Thus the simulation results are sensitive to the relative likelihood of zoster for unvaccinated and previously vaccinated people.

Doubling or halving the three mean periods $1/\eta_i$ for a zoster occurrence does not change the zoster incidence. But it does change the incidence of varicella slightly, because the changed period of zoster implies that there is slightly increased or decreased transmission from those with zoster (recall that ρ_z is only 0.07). Doubling or halving ρ_z causes only small increases or decreases, respectively, in the varicella incidences. Thus the simulations are relatively insensitive to changes in the parameter values for η_i and ρ_z.

The baseline estimate $\rho_v = 0.17$ for the relative infectivity of varicella cases in previously vaccinated people is based on their decreased number of lesions. If the relative infectivity is changed to $\rho_v = 0.5$, then varicella incidences are similar to those in Fig. 2, but they are about 60% higher by the time year 100. However, the per capita zoster incidences in all time years are almost identical to those in Fig. 6 and the zoster incidences are almost the same as those in Fig. 7. Thus when there is a change in the relative infectivity in previously vaccinated people, the varicella incidences are higher in the simulations, but the zoster incidences are the same.

6. DISCUSSION

The two main concerns expressed in Section 1 about a varicella vaccination program are the possible shift in the age distribution of varicella (chickenpox) cases towards older ages with more frequent complications and the potential increase in zoster (shingles) incidence. The simulations here of varicella vaccination programs are used to examine these two issues. The purpose is not to obtain accurate predictions, but rather to obtain general patterns and concepts about the effects of vaccination on varicella and zoster incidence. The simulations are designed as an idealized scenario that approximates the varicella epidemiology in the United States. Their simplicity is both a strength because parameter estimation and computer simulations are possible, and a limitation because they only approximate

reality. The results seem robust, since no changes in parameter values led to major changes in the general patterns of the incidences and age distributions.

The decrease in varicella cases and the shift in the age distribution of varicella cases towards older people as the vaccination program progresses with time are clearly seen in Figs 2–5 for the simulation with the baseline parameter set. After 10 years when the 90% vaccination level is reached, varicella cases are at least 62% lower than in the prevaccine era. The age shift may seem alarming, because the rates of complications and deaths from a typical varicella infection are higher for older people. However, after 33 time years in the simulations, the varicella incidence for those over age 20 years in Fig. 2 is higher for previously vaccinated people than for unvaccinated people. Thus more of the older people with a varicella infection have been previously vaccinated, so that their symptoms are milder with fewer lesions. Because complications and deaths are less likely in milder cases, the complication and death rates of varicella in previously vaccinated adults are low. Thus even though the number of adults with a varicella infection increases under the varicella vaccination program, most have milder symptoms with fewer complications and deaths. Calculations in Section 4 show that, after the first 10 years, the total complications (including deaths) are 22% to 58% lower than in the prevaccine era. Thus the first concern about more complications and deaths under the vaccination program does not seem to be a legitimate concern.

In the simulation with the baseline parameter set, the total zoster incidence shown in Fig. 7 increases by about 30% over the first 30 years and then decreases. Figures 8 and 9 show that zoster incidence increases in each age group over 20 years of age and then decreases. Moreover, nearly all of the zoster cases are still the usual wild-type zoster occurring in unvaccinated (or unsuccessfully vaccinated) people, so there would probably be no decrease in the severity of these zoster cases. This increase in zoster cases in the simulations suggests that an increase in zoster incidence could be a problem during the first decades of a new varicella vaccination program. This means that the second concern about more zoster cases during a varicella vaccination program is a legitimate concern. Although the simulations show that there could be more zoster cases during the first five or six decades of a varicella vaccination program, the incidence after that time decreases rapidly, so that there fewer zoster cases after a century. Thus a beneficial long-range effect of a varicella vaccination program for 1 year old children is a reduction in total zoster cases. As shown in Fig. 7, a supplementary varicella booster vaccination program for older adults with 50% participation would decrease zoster incidence immediately and would avoid this problem of a peak after 30 years. However, in view of the compliance rates for the yearly influenza vaccination and the recommended tetanus-diphtheria booster every 10 years (CDCP, 1998c,d) , it might be difficult to convince even half of the adult population to have varicella vaccinations every 10 years after age 50 years to reduce the likelihood that they would get zoster.

In order to match zoster incidence data in age groups in the simulation modeling, the probability of VZV reactivation as zoster was constant out to age 50 years and

then increased geometrically with age. Thus the only two parameters needed in the fit to the asterisk data in Fig. 6 were the value of the zoster rate coefficient $\sigma_1(a)$ below age 50 years and the geometric ratio for 10 year intervals after age 50 years. This simple pattern suggests that cell-mediated immunity functions well up to about age 50 years and then it becomes progressively less effective as people become older.

The demographic model here assumes that the population has constant size and is at a demographic steady-state age distribution. The actual population in the United States is growing slightly and there is an aging cohort of 'baby boomers' between ages 20 and 50 years old, who will soon enter the age groups where the incidence of zoster is higher. Thus it seems that the total zoster incidence could be even larger than the 30% increase in 30 years shown in Fig. 7.

ACKNOWLEDGEMENTS

The authors thank John Glasser at the National Immunization Program Centers for Disease Control and Prevention for discussions about varicella and zoster. We also thank John Randell and Kent Saniga for preliminary varicella modeling in their undergraduate Honors Projects at the University of Iowa.

APPENDIX A. THE EPIDEMIOLOGIC MODEL

Before the age groups are separated, the model described in Section 2 and summarized in Fig. 1 is an initial-boundary value problem for the system of 15 partial differential equations given below.

$$\partial M/\partial a + \partial M/\partial t = -\delta M - d(a)M$$

$$\partial S/\partial a + \partial S/\partial t = \delta M - \lambda(a,t)S - d(a)S$$

$$\lambda(a,t) = \int_0^\infty \omega(a,a')[I(a',t) + \rho_v I_v(a',t) + \rho_z[Z(a',t) + Z_{wild}(a',t)]da' \Big/ \int_0^\infty u(a,t)da$$

$$\partial E/\partial a + \partial E/\partial t = \lambda(a,t)S - \varepsilon_1 E - d(a)E$$

$$\partial I/\partial a + \partial I/\partial t = \varepsilon_1 E - \gamma_1 I - d(a)I$$

$$\partial R/\partial a + \partial R/\partial t = \gamma_1 I + \lambda(a,t)W + \eta_1 Z - \kappa_1 R - d(a)R$$

$$\partial W/\partial a + \partial W/\partial t = \kappa_1 R - \lambda(a,t)W - \sigma_1(a)W - d(a)W$$

$$
\begin{aligned}
\partial Z/\partial a + \partial Z/\partial t &= \sigma_1(a)W - \eta_1 Z - d(a)Z \\
\partial V/\partial a + \partial V/\partial t &= \eta_2 Z_{vacc} - \kappa_2 V - d(a)V \\
\partial S_v/\partial a + \partial S_v/\partial t &= \kappa_2 V - \lambda(a,t)S_v - \sigma_2(a)S_v - d(a)S_v \\
\partial Z_{vacc}/\partial a + \partial Z_{vacc}/\partial t &= \sigma_2(a)S_v - \eta_2 Z_{vacc} - d(a)Z_{vacc} \\
\partial E_v/\partial a + \partial E_v/\partial t &= \lambda(a,t)S_v - \varepsilon_2 E_v - d(a)E_v \\
\partial I_v/\partial a + \partial I_v/\partial t &= \varepsilon_2 E_v - \gamma_2 I_v - d(a)I_v \\
\partial R_v/\partial a + R_v/\partial t &= \gamma_2 I_v + \eta_3 Z_{wild} + \lambda(a,t)W_v - \kappa_3 R_v - d(a)R_v \\
\partial W_v/\partial a + \partial W_v/\partial t &= \kappa_3 R_v - \lambda(a,t)W_v - \sigma_3(a)W_v - d(a)W_v \\
\partial Z_v/\partial a + \partial Z_v/\partial t &= \sigma_3(a)W_v - \eta_3 Z_{wild} - d(a)Z_{wild}. \qquad (1)
\end{aligned}
$$

All of the boundary values at age zero are zero except that the births are given by

$$
\begin{aligned}
M(0,t) &= \int_0^\infty f(a')[u(a',t) - M(a',t) - S(a',t) - S_v(a',t)]da', \\
S(0,t) &= \int_0^\infty f(a')[M(a',t) + S(a',t) + S_v(a',t)]da'. \qquad (2)
\end{aligned}
$$

The initial conditions are the values of the 15 age distributions at time zero. The age distribution $u(a,t)$ for the total population, which is the sum of the age distributions for the 15 classes, satisfies the partial differential equation

$$
\frac{\partial u}{\partial a} + \frac{\partial u}{\partial t} = -d(a)u, \qquad (3)
$$

where $d(a)$ is the age-specific death rate. The initial age distribution is given by $u(a,0) = u_0(a)$. The births at time t are given by

$$
u(0,t) = \int_0^\infty f(a)u(a,t)da, \qquad (4)
$$

where $f(a)$ is the fertility per person of age a. This model is the standard continuous demographic model (Hethcote, 1997).

The population is partitioned into 30 age groups by integrating the age distributions over the age intervals defined by $0 = a_0 < a_1 < a_2 < \cdots < a_{29} < a_{30} = \infty$. For example,

$$
M_k = \int_{a_{k-1}}^{a_k} M(a',t)da', \qquad S_k = \int_{a_{k-1}}^{a_k} S(a',t)da', \text{ etc.} \qquad (5)
$$

The subscripts k denote the parts of the epidemiologic classes in the kth age interval $[a_{k-1}, a_k]$. The contact rate is constant for the interactions between age groups, so that $w(a, a') = w_{jk}$ for $a \in [a_{j-1}, a_j]$ and $a' \in [a_{k-1}, a_k]$. Also let the zoster transfer rate coefficients be constant on the age intervals; for example, $\sigma_1(a) = \sigma_{1,k}$ for $a \in [a_{k-1}, a_k]$. Integrating the partial differential equations (1) on the age intervals $[a_{k-1}, a_k]$, using $M(a_k) = c_k M_k$, $S(a_k) = c_k S_k$, etc., and using the boundary conditions (2) leads to an initial value problem for a set of 450 ordinary differential equations for the sizes of the 15 epidemiological classes in the 30 age groups. The sum at time t of the 15 epidemiologic classes for the kth age group is the size P_k of the kth group. Vaccination is incorporated for the 1 year old age group as explained in Section 2.

Note that the fractions of the kth group in the epidemiologic classes are of more interest than the numbers in these epidemiologic classes. At any given time the fractions in the epidemiologic classes for each age group show how the disease has progressed and what the age distributions are for those who are in the epidemiologic classes. These fractions are given by $m_k(t) = M_k(t)/P_k$, $s_k(t) = S_k(t)/P_k$, etc. The age distribution $P_1, P_2, \ldots, P_n$ remains at equilibrium and $\sum_{k=1}^{30} P_k = 1$. Within each age group with size P_k, the fractions $m_k, s_k, e_k, i_k, \ldots, z_{vk}$ in that age group add up to one. The 450 differential equations for these fractions are:

$$
\begin{aligned}
dm_1/dt &= \sum_{j=1}^{30} f_j[1 - m_j - s_j - s_{v,j}]P_j/P_1 - [\delta + c_1 + d_1]m_1, \\
dm_k/dt &= (c_{k-1}P_{k-1}/P_k)m_{k-1} - [\delta + c_k + d_k]m_k, \qquad k \geq 2, \\
ds_1/dt &= \delta m_1 + \sum_{j=1}^{30} f_j[m_j + s_j + s_{v,j}]P_j/P_1 - [\lambda_1 + c_1 + d_1]s_1, \\
ds_k/dt &= \delta m_k + (c_{k-1}P_{k-1}/P_k)s_{k-1} - [\lambda_k + c_k + d_k]s_k, \qquad k \geq 2, \\
\lambda_k(t) &= \sum_{j=1}^{n} w_{kj}[i_j + \rho_v i_{v,j} + \rho_z(z_j + z_{v,j})]P_j, \\
de_1/dt &= \lambda_1 s_1 - [\varepsilon_1 + c_1 + d_1]e_1, \\
de_k/dt &= \lambda_k s_k + (c_{k-1}P_{k-1}/P_k)e_{k-1} - [\varepsilon_1 + c_k + d_k]e_k, \qquad k \geq 2, \\
di_1/dt &= \varepsilon_1 e_1 - [\gamma_1 + c_1 + d_1]i_1, \\
di_k/dt &= \varepsilon_1 e_k + (c_{k-1}P_{k-1}/P_k)i_{k-1} - [\gamma_1 + c_k + d_k]i_k, \qquad k \geq 2, \\
dr_1/dt &= \gamma_1 i_1 + \lambda_1 w_1 + \eta_1 z_1 - [\kappa_1 + c_1 + d_1]r_1, \\
dr_k/dt &= \gamma_1 i_k + \lambda_k w_k + \eta_1 z_k + (c_{k-1}P_{k-1}/P_k)r_{k-1} \\
&\qquad -[\kappa_1 + c_k + d_k]r_k, \qquad k \geq 2,
\end{aligned}
$$

$$
\begin{aligned}
dw_1/dt &= \kappa_1 r_1 - [\lambda_1 + \sigma_{1,1} + c_1 + d_1]w_1,\\
dw_k/dt &= \kappa_1 r_k + (c_{k-1}P_{k-1}/P_k)w_{k-1}\\
&\quad -[\lambda_k + \sigma_{1,k} + c_k + d_k]w_k, \qquad k \geq 2,\\
dz_1/dt &= \sigma_{1,1} w_1 - [\eta_1 + c_1 + d_1]z_1,\\
dz_k/dt &= \sigma_{1,k} w_k + (c_{k-1}P_{k-1}/P_k)z_{k-1}\\
&\quad -[\eta_1 + c_k + d_k]z_k, \qquad k \geq 2,\\
dv_1/dt &= \eta_2 z_{vacc,1} - [\kappa_2 + c_1 + d_1]v_1,\\
dv_k/dt &= \eta_2 z_{vacc,k} + (c_{k-1}P_{k-1}/P_k)v_{k-1}\\
&\quad -[\kappa_2 + c_k + d_k]v_k, \qquad k \geq 2,\\
ds_{v,1}/dt &= \kappa_2 v_1 - [\lambda_1 + \sigma_{2,1} + c_1 + d_1]s_{v,1},\\
ds_{v,k}/dt &= \kappa_2 v_k + (c_{k-1}P_{k-1}/P_k)s_{v,k-1}\\
&\quad -[\lambda_k + \sigma_{2,k} + c_k + d_k]s_{v,k}, \qquad k \geq 2,\\
dz_{vacc,1}/dt &= \sigma_{2,1} s_{v,1} - [\eta_2 + c_1 + d_1]z_{vacc,1},\\
dz_{vacc,k}/dt &= \sigma_{2,k} s_{v,k} + (c_{k-1}P_{k-1}/P_k)z_{vacc,k-1}\\
&\quad -[\eta_2 + c_k + d_k]z_{vacc,k}, \qquad k \geq 2;\\
de_{v,1}/dt &= \lambda_1 s_{v,1} - [\varepsilon_2 + c_1 + d_1]e_{v,1},\\
de_{v,k}/dt &= \lambda_k s_{v,k} + (c_{k-1}P_{k-1}/P_k)e_{v,k-1} - [\varepsilon_2 + c_k + d_k]e_{v,k}, \qquad k \geq 2,\\
di_{v,1}/dt &= \varepsilon_2 e_{v,1} - [\gamma_2 + c_1 + d_1]i_{v,1},\\
di_{v,k}/dt &= \varepsilon_2 e_{v,k} + (c_{k-1}P_{k-1}/P_k)i_{v,k-1} - [\gamma_2 + c_k + d_k]i_{v,k}, \qquad k \geq 2,\\
dr_{v,1}/dt &= \gamma_2 i_{v,1} + \lambda_1 w_{v,1} + \eta_3 z_{wild,1} - [\kappa_3 + c_1 + d_1]r_{v,1},\\
dr_{v,k}/dt &= \gamma_2 i_{v,k} + \lambda_i w_{v,k} + \eta_3 z_{wild,k} + (c_{k-1}P_{k-1}/P_k)r_{v,k-1},\\
&\quad -[\kappa_3 + c_k + d_k]r_{v,k}, \qquad k \geq 2,\\
dw_{v,1}/dt &= \kappa_3 r_{v,1} - [\lambda_1 + \sigma_{3,1} + c_1 + d_1]w_{v,1},\\
dw_{v,k}/dt &= \kappa_3 r_{v,k} + (c_{k-1}P_{k-1}/P_k)w_{v,k-1},\\
&\quad -[\lambda_k + \sigma_{3,k} + c_k + d_k]w_{v,k}, \qquad k \geq 2,
\end{aligned}
\tag{6}
$$

$$dz_{wild,1}/dt = \sigma_{3,1} w_{v,1} - [\eta_3 + c_1 + d_1] z_{wild,1},$$

$$dz_{wild,k}/dt = \sigma_{3,k} w_{v,k} + (c_{k-1} P_{k-1}/P_k) z_{v,k-1},$$
$$-[\eta_3 + c_k + d_k] z_{wild,k}, \qquad k \geq 2.$$

APPENDIX B. ALGORITHM FOR ESTIMATING THE CONTACT MATRIX

The force of infection λ_k given in (6) for group k can be written as

$$\lambda_k = \sum_{j=1}^{n} w_{kj}(I_j + \rho_v I_{v,j} + \rho_z(Z_j + Z_{v,j})). \tag{7}$$

Let l_j be the average number of people contacted by a person in age group j per unit time, so that $D = \sum_{j=1}^{n} l_j P_j$ is the total number of people contacted per unit time. Only contacts which are adequate for transmission of VZV are considered. Because D is also the total number of contacts per unit time received by all people, l_k/D is the fraction of all contacts which are received by a person in age group k. The proportionate-mixing assumption is that the l_j people contacted per unit time by a person in age group j are distributed among people in the age group k in proportion to the fractions l_k/D of all contacts per unit time received by people in the age group k. Hence the mixing matrix is given by

$$w_{kj} = l_j l_k / D = (l_k / D^{\frac{1}{2}})(l_j / D^{\frac{1}{2}}). \tag{8}$$

Because the units of l_k and D are contacts per unit time, w_{jk} also has units of contacts per unit time. Now $\sum_{j=1}^{n} l_j(I_j +_z (Z_j + Z_{v,j}))$ is the number of infectious contacts by people in age group j per unit time and l_k/D is the fraction of contacts received by people in age group k per unit time, so the force of infection λ_k given by (7) is the number of infectious contacts received by people in age group k per unit time.

At an endemic steady state, the equilibrium forces of infection λ_k and epidemiologic class distributions are independent of time. Equations (7) and (8) can be combined to obtain

$$l_k = D\lambda_k \Big/ \sum_{j=1}^{n} l_j(I_j + \rho_v I_{v,j} + \rho_z(Z_j + Z_{v,j})). \tag{9}$$

Multiplying both sides of the equation above by $(I_k + \rho_v I_{v,k} + \rho_z(Z_k + Z_{v,k}))$ and summing yields an expression for $\sum_{j=1}^{n} l_j(I_j + \rho_v I_{v,j} + \rho_z(Z_j + Z_{v,j}))$. Substitution of this expression into the denominator of (9) yields

$$l_k = D^{\frac{1}{2}}\lambda_k \Big/ \left[\sum_{j=1}^{n} \lambda_j(I_j + \rho_v I_{v,j} + \rho_z(Z_j + Z_{v,j}))\right]^{\frac{1}{2}}. \tag{10}$$

Multiplication of both sides of the equation above by the age group sizes P_k and summing yields the expression

$$D^{\frac{1}{2}} = \sum_{j=1}^{n} \lambda_j P_j \Bigg/ \left[\sum_{j=1}^{n} \lambda_j (I_j + \rho_v I_{v,j} + \rho_z (Z_j + Z_{v,j})) \right]^{\frac{1}{2}}. \tag{11}$$

Substitution of this expression into (10) yields

$$l_k = \lambda_k \sum_{j=1}^{n} \lambda_j P_j \Bigg/ \sum_{j=1}^{n} \lambda_j (I_j + \rho_v I_{v,j} + \rho_z (Z_j + Z_{v,j})). \tag{12}$$

Thus the mixing activity function l_k can be estimated from the forces of infection λ_k, the values of I_j, $I_{v,j}$, Z_j, and $Z_{v,j}$ for the number of infectives and zoster cases, and the values P_j for the age group sizes. Note that the mixing matrix entries w_{kj} given by (8) can be found from the values of $l_k / D^{\frac{1}{2}}$, which can be estimated using (10) from the forces of infection, the numbers of infectives, and the numbers with zoster.

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Received 10 January 1999 and accepted 15 June 1999