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Simulations of rubella vaccination strategies in China

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Abstract

Many infants whose mothers have rubella infections during their first trimester of pregnancy have birth defects called congenital rubella syndrome (CRS). China does not routinely vaccinate against rubella in the public sector, but may need to start as its 'one child per couple' policy changes the population age distribution and the dynamics of rubella epidemiology, so that the incidence of rubella in pregnant women increases. Computer simulations with demographic transitions and rubella transmission dynamics predict that, with no or limited rubella vaccination, CRS incidence in China in the 30 years after 2020 will be more than twice the level in 2005. Comparisons of rubella vaccination strategies using computer simulations show that routine vaccination of over 80% of 1-year-old children would be effective in reducing total CRS cases in 2005–2051 and eliminating rubella in China by 2051. Routine immunizations at higher levels and the addition of early mass vaccinations of 2–14-year-old children and women of childbearing ages would further reduce total CRS cases and speed up the elimination of rubella.

Keywords: Rubella; Congenital rubella syndrome; Vaccination; China; Simulations; Non-linear dynamics

1. Introduction

Rubella (also called German measles) is a mild or asymptomatic illness, but infection during the first trimester of pregnancy can lead to fetal death or a constellation of birth defects known as

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congenital rubella syndrome (CRS) [1,2]. The goal of a rubella vaccination program is to prevent rubella infection in pregnant women and the resulting fetal loss or CRS in their children [2]. Currently more than one-fourth of the world's people live in countries/territories that do not routinely vaccinate against rubella [3].

Strategies for the use of rubella vaccine include routine infant immunization to build up high levels of population immunity (interrupting viral transmission) and selective vaccination of adolescent girls (directly protecting them prior to childbearing). Mass vaccinations of age cohorts during National Immunization Days sometimes supplement these routine vaccinations [4,5]. No vaccination against rubella is a reasonable option in highly endemic countries where most females experience rubella infection before childbearing age and the burden of CRS is low [6,7]. In this situation, however, it is recommended that countries periodically reevaluate the susceptibility to rubella and CRS incidence to assess whether rubella vaccination would be beneficial [8,9]. In countries where measles control is already a national priority, the benefits of using the combined measles-rubella (MR) vaccine at a small increase in cost are important to consider [7,8,10].

China with a population of about 1.3 billion and a birth cohort of about 18 million does not currently include rubella vaccination in the national immunization program, but rubella-containing vaccine is available in some areas [11]. Imported measles-mumps-rubella (MMR) vaccine has been available in the private sector of some large cities since at least the mid-1990s. In addition, domestic capacity exists to produce up to 6 million doses of rubella-containing vaccine per year [11]. Thus the annual doses of rubella-containing vaccine in China could be as much as half of the annual birth cohort. It has been shown that this level of private sector rubella vaccination can lead to increases in CRS incidence [12]. Thus rubella vaccination strategies in China should be examined carefully.

Limited data exist on rubella incidence in China. Surveillance at sentinel sites in 1990–1997 showed a large rubella epidemic in 1993–1994 [11]. As of 2000 there were no CRS surveillance data in China [11]. A number of rubella seroprevalence studies in the late 1970s and early 1980s showed high levels of rubella immunity by age 15, providing evidence of high forces of infections [13–24]. Static mathematical modeling based on results of the largest (16658 people) of these seroprevalence surveys [15] estimated an incidence of 3–15 CRS cases per 100000 live births, which is lower than estimates for most developing countries [6]. Because rubella vaccine efficacy is about 95% [5], no-vaccination might have been a reasonable strategy in this period when about 90–95% of women acquired immunity through infection before childbearing age. However, a seroprevalence survey in 1993–1995 of 2610 women aged 16–30 years in five provinces in China found that only 83.6% were immune to rubella [11]. This suggests that rubella immunity among women of childbearing age decreased in the 1990s. Thus new rubella vaccination strategies in China should be considered.

China's national one-child policy [25] since 1979 resulted in dramatic changes in the birth rate and age structure of its population. Demographic changes can affect the transmission patterns of rubella and consequently, can increase the average age of rubella infection and CRS incidence [26]. Here computer simulations of rubella transmission dynamics are used to assess the impact on rubella and CRS incidence in China of the changes in the demographic structure and seroprevalence. The mathematical model used here is similar to those used in studies of other vaccine-preventable diseases [27–31].

2. Methods

Recent Chinese data were used to establish a time dependent demographic model that mirrors the age distribution of the population in China each year from 1966 to 2002 and then projects the age distribution out to 2051. Then the age groups were subdivided into epidemiological classes. Data were used to estimate the epidemiological parameters in the compartmental model. Computer simulations of the model were used to compare the effects of no vaccination and several rubella vaccination policies. The vaccination strategies considered are combinations of routine vaccinations (1-year-old children and/or 12-year-old girls) and mass vaccinations (2–14-year-old children and/or 15–40-year-old women).

2.1. The demographic model

Demographic data such as birth rates, death rates, fertility rates in age groups, death rates in age groups, and population sizes in age groups were obtained for men and women in China [32,33]. The 58 female and 58 male age groups are 1-year age groups from 0 to 49, 5-year age groups from 50 to 84, and final groups for those 85 years or older. We use a standard discrete time demographic model [34] with a 1-year time interval, where the fertility and survival rates in the Leslie matrix change slightly each year.

The age distribution, fertility and death rates in 1965 were estimated by shifting the known 1987 age distribution and rates [32] backward to 1965. Then data on the birth rates and death rates each year were used as scaling factors on the 1992 values to estimate fertilities and age-related death rates each year between 1966 and 1992, so that the size and age distribution of the population matched the data. The fertilities and age-related death rates between 1992 and 2000 were found by interpolation from data [32,33] in 1992 and 2000, and then were held constant after 2000. Thus the age distribution shifts forward 1 year each year of time and the size of the 0-year-old group is determined by the sizes and fertility rates of the age groups of women of child-bearing age. Note that the model provides a simple approximation of the actual situation, since it does not consider pair formation, but the effects of the one-child policy are reflected in the fertility rates of the women in the different age groups.

2.2. The epidemiological model

Compartments M, S, E, I, R, and V are used for the epidemiological classes shown in Fig. 1. If a mother was infected or vaccinated, then some rubella IgG antibodies are transferred across the placenta, so that her newborn infant has temporary passive immunity to rubella infection. The class M contains these infants with passive immunity. After the maternal antibodies disappear, the infant moves to the susceptible class S; that is, those who can become infected. If a mother was never infected or vaccinated, then her infants enter directly into the class S of susceptible individuals.

When there is an adequate contact of a susceptible with an infective so that transmission of the infection occurs, then the susceptible enters the exposed class E of those in the latent period (infected, but not yet infectious). After the latent period ends, the individual enters the class I of infectives, who are capable of transmitting the infection. When the infectious period ends, the individual

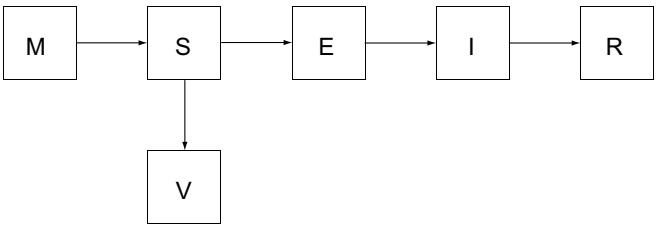

Fig. 1. Transfer diagram for the epidemiological model.

enters the recovered class R consisting of those with permanent infection-acquired immunity. The class V contains those who have permanent vaccine-induced immunity. The flow into V is equal to the product of the number of susceptibles vaccinated per day and the vaccine efficacy.

The simulation model is similar to the age-structured models with discrete age groups used for varicella and pertussis [28–31]. For more details see Appendix B in [29]. The epidemiological model with the infection transmission dynamics is built from the demographic model described in the previous section. The 58 age classes for women and men are subdivided into the six epidemiological classes shown in Fig. 1. Thus the deterministic model consists of 696 ($58 \times 2 \times 6$) simultaneous, non-linear differential equations. The computer simulations make daily transfers between the compartments based on births, aging, deaths, loss of passive immunity, becoming latently infected, becoming infectious, recovery, and vaccination.

Let $[a_{i-1}, a_i]$ be the ith age interval and let the epidemiological, discrete age classes of women be

$$M_{wk}(t) = \int_{a_{k-1}}^{a_k} M_w(a', t)\,\mathrm{d}a', \quad S_{wk}(t) = \int_{a_{k-1}}^{a_k} S_w(a', t)\,\mathrm{d}a', \text{ etc.}$$

Let $w(a, a') = w_{jk}$ for $a \in [a_{j-1}, a_j]$ and $a' \in [a_{k-1}, a_k]$. Let $M_w(a_k) = c_k M_{wk}$, $S_w(a_k) = c_k S_{wk}$, etc. as in [28]. Then the 348 differential equations for the women are

$$\mathrm{d}M_{w1}/\mathrm{d}t = kg \sum_{j=1}^{58} f_j[1 - S_{wj}] - [\delta + c_{w,1} + d_{w,1}]M_{w1},$$

$$\mathrm{d}M_{wk}/\mathrm{d}t = c_{w,k-1}M_{w,k-1} - [\delta + c_{w,k} + d_{w,k}]M_{w,k}, \quad k \geqslant 2,$$

$$\mathrm{d}S_{w1}/\mathrm{d}t = \delta M_{w1} + kg \sum_{j=1}^{58} f_j S_{wj} - [\lambda_1 + c_{w,1} + d_{w,1}]S_{w1},$$

$$\mathrm{d}S_{wk}/\mathrm{d}t = \delta M_{wk} + cw_{k-1}S_{w,k-1} - [\lambda_k + c_{w,k} + d_{w,k}]S_{w,k}, \quad k \geqslant 2,$$

$$\lambda_k(t) = \sum_{j=1}^{58} w_{kj}[I_{wj} + I_{mj}],$$

$$\mathrm{d}E_{w1}/\mathrm{d}t = \lambda_1 S_{w1} - [\varepsilon + c_{w,1} + d_{w,1}]E_{w1},$$

$$\mathrm{d}E_{wk}/\mathrm{d}t = \lambda_k S_{wk} + c_{k-1}E_{w,k-1} - [\varepsilon + c_{w,k} + d_{w,k}]E_{wk}, \quad k \geqslant 2,$$

$$
\begin{aligned}
dI_{w1}/dt &= \varepsilon E_{w1} - [\gamma + c_{w,1} + d_{w,1}]I_{w1},\\
dI_{wk}/dt &= \varepsilon E_{wk} + c_{k-1}I_{w,k-1} - [\gamma + c_{w,k} + d_{w,k}]I_{wk}, \quad k \geqslant 2,\\
dR_{w1}/dt &= \gamma I_{w1} - [c_{w,1} + d_{w,1}]R_{w1},\\
dR_{wk}/dt &= \gamma I_{wk} + cw_{k-1}R_{w,k-1} - [c_{w,k} + d_{w,k}]R_{wk}, \quad k \geqslant 2,\\
dV_{w1}/dt &= -[c_{w,1} + d_{w,1}]V_{w1}\\
dV_{wk}/dt &= -[c_{w,k} + d_{w,k}]V_{wk} \quad k \geqslant 2.
\end{aligned}
$$

The parameter kg is the fraction of newborns who are girls, f_j is the fertility of women in the jth age group, $c_{w,k}$ is the transfer rate constant out of the kth age group due to aging, and $d_{w,k}$ is the death rate constant in the kth age group. The transfer terms out of the M, E, and I classes correspond to distributed delays with negative exponential distributions [35], so that the mean residence times are $1/\delta$ for the passively immunity classes, $1/\varepsilon$ for the exposed (latent) classes, and $1/\gamma$ for the infectious classes. The 348 differential equations for the men are similar. Vaccination is simulated as people are moving from one age group to the next. For example, routine vaccination of 1-year-old children is simulated by transferring a fraction (the fraction vaccinated times the vaccine efficacy) of the susceptible children who are moving from the 0-year-old age class to the 1 year age class into the 1 year vaccinated class.

Mixing patterns and contact behaviors vary with age. For example, school age children mix more with other school age children than they do with adults. An adequate contact is one that is sufficient for transmission from an infective to a susceptible. In the matrix $[w_{kj}]$ of adequate contact rates, each matrix entry depends on the adequate contact rates between individuals in the k and j age groups. Proportionate mixing is assumed, so that the people contacted per day by a person in age group k are distributed among people in the age group j in proportion to the fraction of all contacts per day received by people in age group j. This is equivalent to assuming that each age group has an inherent activity level and the matrix entries w_{kj} are the products of the activity levels in the k and j age groups.

The force of infection $\lambda_k(t)$ on the kth age group in the equations above is the sum over all 58 age groups of the adequate contact rates w_{kj} times the prevalences $[I_{wj}(t) + I_{mj}(t)]$. The incidence of rubella in the kth age group susceptibles at time t is the product of the force of infection $\lambda_k(t)$ and the number $S_{w,k}(t)$ of susceptibles.

2.3. Estimates of the epidemiological parameter values

The average period of passive immunity for rubella is about 6 months, the incubation period from exposure to rash onset is about 16–18 days with a range of 14–23 days, and the period of communicability is about 7 days before rash onset to about 5–7 days after rash onset [36,37]. Hence in the model the average period $1/\delta$ of passive immunity is 6 months, the average latent period $1/\varepsilon$ (i.e. from exposure to infectiousness) is 10 days, and the average infectious period $1/\gamma$ is 12 days.

Table 1 contains the seropositivity to rubella antibody in 16658 people in China in 1979–1980 [15,16]. By using force of infection values λ_k in 1980 of 0.20 per year for less than 1 year, 0.24 for 1–4 years, 0.27 for 5–9 years, 0.15 for 10–14 years, 0.10 for 15–49 years, 0.04 for 50–64 years, and 0.03 for 65 years or older, the computer simulations matched this 1979–1980 data.

Table 1
Seropositivity to rubella antibody in China in 1979–1980 [15,16]

Age range	Seropositivity (%)
0–1 years	34.5
2 years	41.9
3 years	56.9
4 years	63.5
5 years	73.6
6–10 years	88.5
11–15 years	96.0
16–20 years	96.2
21–25 years	95.2
26–30 years	94.6
31–40 years	96.8

Because of the proportionate mixing assumption, the 58 simultaneous equations for the forces of infection λ_k in 1980 involve only 58 unknown activity levels, since the 1980 prevalences $I_{wj} + I_{mj}$ are known from the simulations. These 58 simultaneous equations can be solved to estimate the mixing activity levels and the corresponding entries in the 58×58 mixing matrix (see Appendix C in [29]). It is assumed that mixing patterns between individuals in the age groups do not change, so that the mixing matrix between people of different ages remains constant. As the population age-structure changes over time and vaccination starts in 2005, the prevalences, the forces of infection, the sizes of the age groups, and the seropositivities change, but it is assumed that the contact rates between individuals in different age groups remain constant. Since the forces of infection in the previous paragraph are defined on seven age intervals, the 58×58 mixing matrix is actually the block 7×7 matrix given below

$$[w_{kj}] = \begin{bmatrix} 0.530 & 0.635 & 0.715 & 0.397 & 0.265 & 0.106 & 0.0794 \\ 0.635 & 0.763 & 0.858 & 0.477 & 0.318 & 0.127 & 0.0953 \\ 0.715 & 0.858 & 0.965 & 0.536 & 0.357 & 0.143 & 0.107 \\ 0.397 & 0.477 & 0.536 & 0.298 & 0.199 & 0.0794 & 0.0596 \\ 0.265 & 0.318 & 0.357 & 0.199 & 0.132 & 0.0530 & 0.0397 \\ 0.106 & 0.127 & 0.143 & 0.0794 & 0.0530 & 0.0212 & 0.0159 \\ 0.0794 & 0.0953 & 0.107 & 0.0596 & 0.0397 & 0.0159 & 0.0119 \end{bmatrix}.$$

2.4. Possible vaccination strategies

In simulating routine vaccinations for 1-year-old children or 12-year-old girls, we assume a linear increase in vaccination coverage of 0.2, 0.4, 0.6, 0.8, 1 times the specified coverage during the years 2005 to 2009 and that the coverage remains at the specified level after 2009. Mass vaccination campaigns in 2005 focus on 2–14-year-old children, 2–14-year-old girls, and/or 15–40-year-old women. The vaccine efficacy is 0.95 in the model [5]. Combinations of routine and mass vaccination strategies are also considered in the computer simulations.

3. Results

3.1. Demographic model fit to data and projections

The demographic model age distributions correspond well to the 1990 and 2000 data [33]. As shown in Fig. 2 for the year 2000, the proportions of the population between ages 8 and 15 years and between 25 and 38 years are larger due to high birth rates during previous time periods. The dip in population size at about age 40 years is expected, given the famine in 1959–1961. In Fig. 3 the total population size and the percentage growth in the simulations match the data from the same time period [33]. The growth rate is now about 0.5% and is projected to reach 0% in the 2020s. The size of the 0–9-year-old age group in Fig. 4 is generally decreasing from 1970 to 2051 with peaks in the early 1970s, the 1990s, and the late 2010s. The size of the 20–29-year-old age group has a peak in the early 1990s and then decreases with a lower peak in the early 2010s.

3.2. Simulations of rubella and CRS without vaccination

Rubella incidence without vaccination in Fig. 5 oscillates with peaks in 1974, 1990, and 2017. These peaks correspond roughly to the peaks in Fig. 4 in the size of the 0–9-year-old age group where most rubella cases occur. The decreases in rubella after 1990 are due to the decreasing number of children available to become infected with rubella.

The large peaks in CRS in about 1974 and 1990 in Fig. 6 are consistent with large peaks in rubella cases in those years in Fig. 5. The large 1990 CRS peak occurred when there were simultaneous peaks in Fig. 4 in 0–9-year-olds (where most rubella infections occur) and 20–29-year-olds (where rubella infections during pregnancy can lead to CRS cases). Despite smaller peaks in

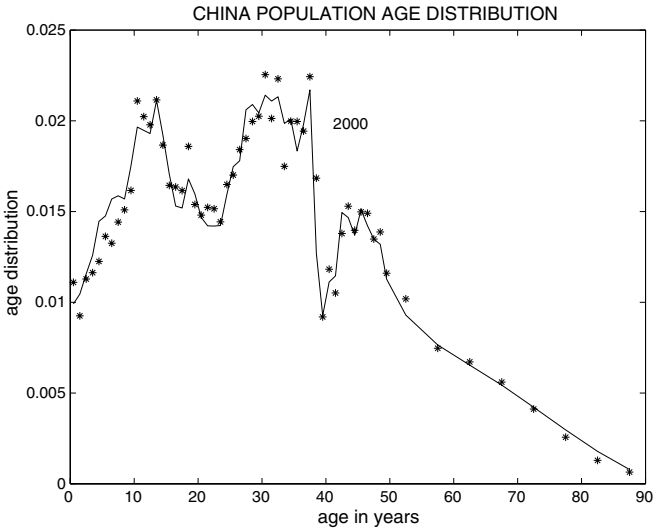

Fig. 2. The solid curve is the 2000 age distribution in the computer simulations of the demographic model. The asterisks are the values from the 2000 census in China [29].

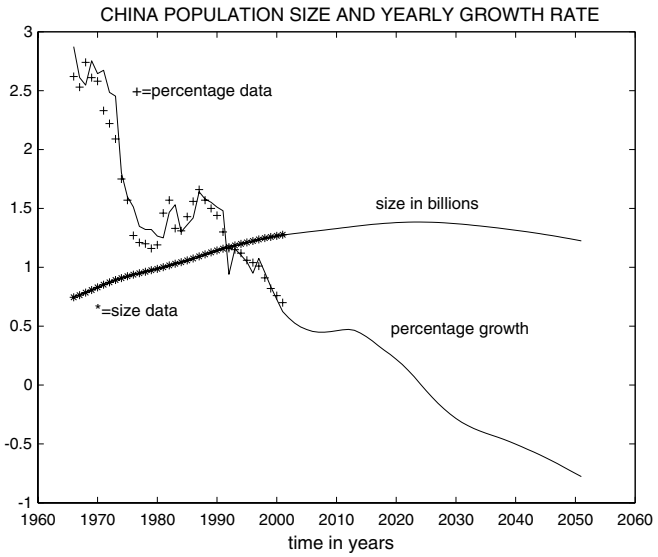

Fig. 3. The solid curves are the computer simulation population sizes and percentage growths. The + and * correspond to data from Chinese Statistical Yearbooks [28].

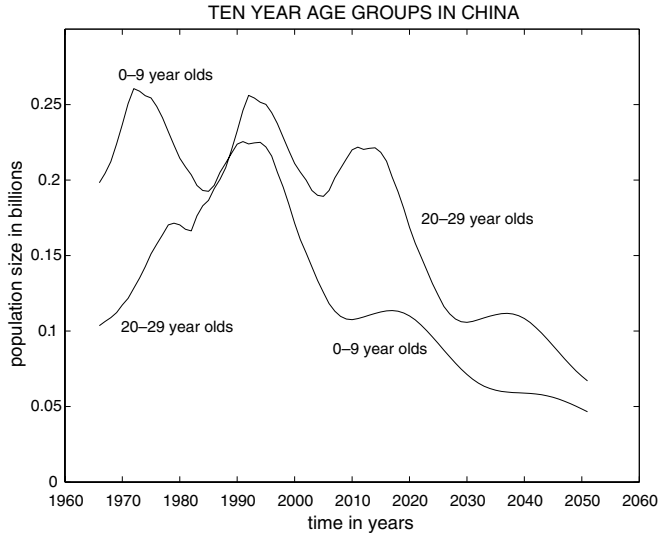

Fig. 4. Computer simulation sizes of the 0–9 and 20–29-year-old age groups in China.

rubella incidence in 2017 and 2045 in the simulations, there were large peaks of CRS cases in these years. This occurs because the average age of rubella infection increases from about 4 years in 1965 to about 8 years in 2051, so that more women of childbearing age are susceptible. It is important to notice that with no vaccination, the simulated CRS incidence increases dramatically between 2005 and 2020, so that the average predicted CRS incidence in the 30 years after 2020 is at least twice the CRS incidence in 2005.

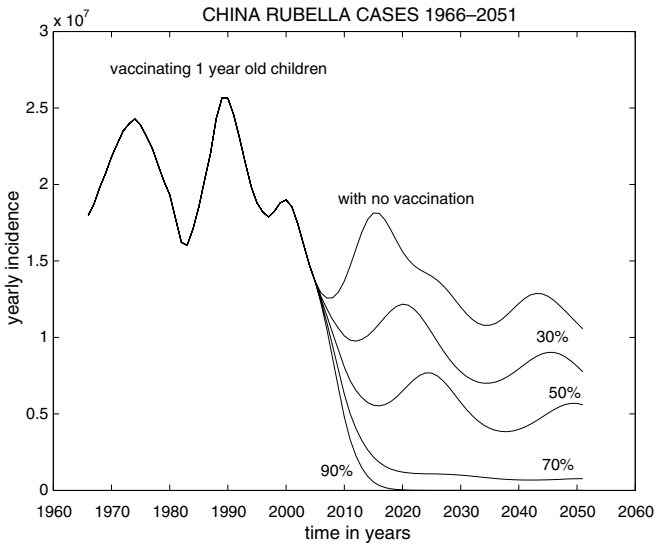

Fig. 5. Simulation values of the rubella incidence with various routine vaccination percentages of 1-year-old children.

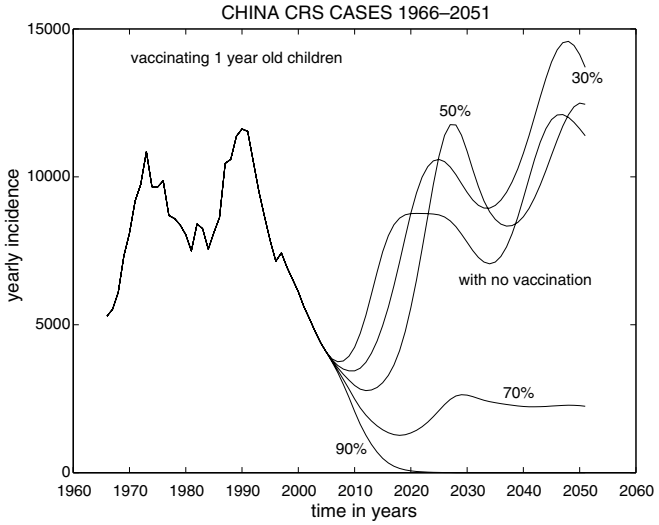

Fig. 6. Simulation values of the CRS incidence with various routine vaccination percentages of 1-year-old children.

3.3. Simulations with routine vaccination of 1-year-old children

Rubella cases and CRS cases corresponding to simulations of vaccination of 1-year-old children at the 30%, 50%, 70%, and 90% levels are shown in Figs. 5 and 6. As the vaccination coverage increases, rubella cases decrease. However, in Table 2 vaccination of 1-year-old children at less than 50% coverage leads to slightly more total CRS cases in 2005–2051 than without vaccination. Thus lower levels of vaccination do not have much impact on CRS cases, because some

Table 2
Comparison of rubella vaccination strategies in China in 2005–2051

Mass: 2–14 girls (%)	Mass: 2–14 boys (%)	Mass: 15–40 women (%)	Routine: 1-year-old children (%)	Routine: 12-year-old girls (%)	Total CRS in 2005–2051	CRS in 2051	# of routine vaccinations	# of mass vaccinations	Total # of vaccinations	Vaccinations per CRS case prevented
90	90	60	90		2578	0	596 350 829	395 198 054	991 548 883	2622
90		60	90		5515	0	596 350 830	277 610 095	873 960 925	2329
90	90		90		5923	0	596 350 828	227 438 932	823 789 760	2198
80		60	90		6022	0	596 350 832	265 404 431	861 755 263	2300
		70	90		8173	0	596 350 828	195 718 976	792 069 804	2126
90			90		12 613	0	596 350 830	109 850 973	706 201 803	1918
80			90		13 545	0	596 350 830	97 645 309	693 996 139	1890
			90		20 757	0	596 350 830	0	596 350 830	1657
			80		27 308	1	530 089 627	0	530 089 627	1500
90				90	87 952	1652	306 150 736	109 850 973	416 001 709	1421
			70		100 970	2247	463 828 423	0	463 828 423	1658
				90	117 601	1722	308 049 970	0	308 049 970	1171
				80	147 426	2837	273 822 196	0	273 822 196	1174
				70	177 105	3941	239 594 421	0	239 594 430	1177
				50	236 027	6120	171 138 872	0	171 138 872	1183
			60		276 978	8139	397 567 219	0	397 567 219	3831
				30	294 358	8258	102 683 323	0	102 683 323	1189
90					302 672	11 015	0	109 850 973	109 850 973	1407
80					312 867	11 058	0	97 645 309	97 645 309	1439
90	90				327 554	10 656	0	227 438 932	227 438 932	4276
80	80				335 555	10 715	0	202 167 940	202 167 940	4474
		80			345 807	11 386	0	223 678 829	223 678 829	6403
		70			350 162	11 386	0	195 718 976	195 718 976	6400
		60			354 520	11 387	0	167 759 122	167 759 122	6398
		50			358 881	11 387	0	139 799 268	139 799 268	6395
			50		362 752	12 453	331 306 016	0	331 306 016	18 417
		40			363 246	11 387	0	111 839 415	111 839 415	6393
		30			367 615	11 388	0	83 879 561	83 879 561	6390
		20			371 986	11 388	0	55 919 707	55 919 707	6388
		10			376 362	11 389	0	27 959 854	27 959 854	6385
			0		380 741	11 389	0	0	0	
			10		399 712	12 307	66 261 203	0	66 261 203	
			40		406 976	13 910	265 044 813	0	265 044 813	
			20		413 971	13 143	132 522 406	0	132 522 406	
			30		419 181	13 701	198 783 609	0	198 783 609	

childbearing women have immunity due to vaccination, but more unvaccinated women are susceptible, so they have more rubella cases. In the simulations the average ages of infection in 2051 are about 8, 11, 14, and 18 years with 0%, 30%, 50%, and 70% vaccination, respectively.

In Fig. 6 with routine vaccination of 1-year-old children with coverage of 0%, 30%, and 50%, the average predicted CRS incidence in the 30 years after 2020 is more than twice the CRS incidence in 2005. The computer simulations of the model show that vaccination of 1-year-old children only becomes effective in reducing CRS cases at about 70% coverage, and rubella dies out by 2051 when the coverage is over 80%.

3.4. Simulations with routine vaccination of 12-year-old girls

Although vaccinations of 12-year-old girls at various percentages have almost no effect on total rubella cases in Fig. 7, they do decrease the CRS cases in Fig. 8. In Table 2 routine vaccination of 80–90% of 12-year-old girls reduces CRS cases in 2051 by 75–85% and only 1171–1174 vaccinations are needed to prevent one CRS case.

3.5. Simulations with mass vaccinations

In Table 2 mass vaccinations in 2005 cause short-term decreases in rubella and CRS cases, but the benefits soon fade away, so that the CRS cases in 2051 are back to normal levels. The mass vaccination of 90% of 2–14-year-old girls is the most effective with only 1407 vaccinations per CRS case prevented. Mass vaccinations of 2–14-year-old boys and girls, or of women of ages 15–40 are relatively ineffective. Mass vaccinations in 2005 of intermediate levels of 2–14-year-old children creates large oscillations in rubella incidence and only slightly lower cumulative CRS incidence and CRS incidence in 2051 than without vaccination.

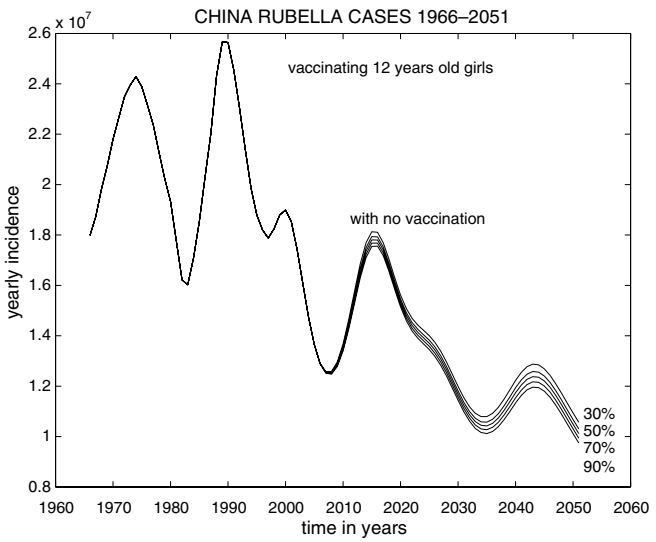

Fig. 7. Simulation values of the rubella incidence with various routine vaccination percentages of 12-year-old girls.

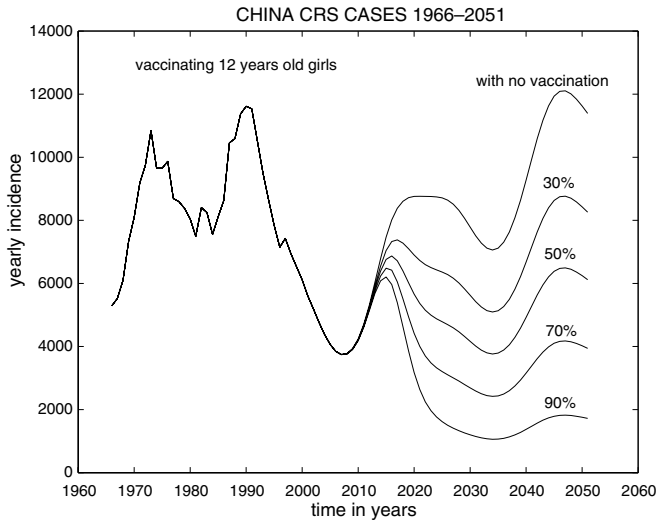

Fig. 8. Simulation values of the CRS incidence with various routine vaccination percentages of 12-year-old girls.

3.6. Simulations with combinations of routine and mass vaccinations

Mass vaccinations can be useful when combined with routine vaccinations in order to accelerate the disappearance of rubella. In Table 2 adding a mass vaccination in 2005 of 90% of 2–14-year-old children to routine vaccination of 90% of 1-year-olds reduces the total CRS cases in 2005–2051 by 71%. Adding mass vaccination in 2005 of 70% of 15–40-year-old women to the same routine vaccination reduces total CRS by 61%. Combining mass vaccinations of both 2–14-year-old children and 15–40-year-old women with routine vaccination of 90% of 1-year-olds reduces total CRS cases even more, while still achieving reasonably low numbers of vaccinations to prevent one CRS case.

4. Discussion

Public health policy makers must understand the dynamics of rubella epidemiology over time under various scenarios of vaccination or non-vaccination. Although mathematical modeling and computer simulations have been used to estimate the impact of different rubella vaccination strategies in developed countries [27,38,39], these modeling results are not applicable in China, which has a rapidly changing age distribution. Thus a demographic model was constructed as the basis for an epidemiological model for rubella transmission dynamics in China. With vaccination of 1-year-old children at less than 50% coverage (this approximates the current situation in China), the computer simulations predict total CRS incidence in China in 2020–2051 that is more than twice the current level. Under the current one-child policy, the simulations show that CRS could be eliminated by 2051 with 1500 to 2622 vaccinations per CRS case prevented using routine vaccination of at least 80% of 1-year-old infants combined with some initial mass vaccination of 2–14-year-old children and 15–40-year-old women to provide good short-term protection.

The model simulations are consistent with previous observations. Using historical demographic and serological data, the model simulations in Fig. 5 predict a marked increase in rubella incidence around 1990, which is consistent with documented rubella outbreaks in regions of China between 1987 and 1994 [11,13,22]. Our simulations show large oscillations in rubella incidence; however, they are similar to the rubella epidemics observed every 1–10 years in the USA and the UK prior to vaccine licensure [27,39]. It has been shown that observed oscillations in measles incidence in United Kingdom from 1944 to 1964 could be explained by changes in birth rates during this period [40]. We found similar demographic explanations, since the peaks in rubella and CRS incidence in China are related to the peaks in the numbers of 0–9-year-old children and 20–29-year-old women.

Computer simulations were used to compare rubella vaccination strategies in China. With vaccination of 0–50% of 1-year-old children, the average CRS incidence between 2020 and 2051 in Fig. 6 is over two times the current CRS incidence. Rubella cases in pregnant women increase because, as the size of the 0–9 year age group goes down, both the average age of infection and the susceptible fraction of women of childbearing age increase. If parents in China are more likely to pay for MR or MMR vaccination for sons than for daughters [12], then there would be even more CRS cases at each coverage level than predicted in Table 2 and Fig. 6.

Routine vaccination of more than 80% of 1-year-olds causes rubella to disappear by 2051 and the number of vaccinations needed to prevent one CRS case is only about 1500. Supplementary mass vaccinations in 2005 of 2–14-year-old girls and/or 15–40-year-old women would accelerate the disappearance of rubella and lead to fewer total CRS cases in 2005–2051. Moreover, Table 2 shows that many combinations of routine and mass vaccination have numbers of vaccinations needed to prevent one CRS case that are within 50% of the 1500 value above.

Routine vaccinations of 12-year-old girls are effective per dose in reducing CRS. But this strategy has the disadvantage that it never leads to the elimination of rubella, because rubella still circulates in a large pool including all girls under age 12 years, girls over age 12 years who were not vaccinated, and the completely unvaccinated boys and men [27]. However, this strategy seems wasteful, since many of the girls vaccinated at 12 years of age would already be immune from an earlier rubella infection. The simulations of rubella in China are consistent with the epidemiological concept that direct protection of women by vaccinating 12-year-old girls is better if the achievable vaccination coverage is not high. But when coverage is high, vaccination of 1-year-old children is better, because it can lead to herd immunity and elimination of rubella. The threshold for changing strategies seems to be about 80% in China, which is similar to the switching value in developed countries [27,38,39].

Estimates in Table 2 could be used in a cost-benefit analysis in China. For example, if the number of vaccinations needed to prevent one CRS case using a strategy is 2622, then vaccination is advantageous if 2622 vaccinations cost less than the lifetime cost of one CRS case. We do not know the costs of the rubella component in MR or MMR vaccine or the lifetime cost of a CRS case in China, but the cost of rubella vaccine is usually low, so that rubella vaccination is often very cost effective [10]. For example, the Pan American Health Organization rubella component in 2004 cost was only US$0.35 and the benefit-cost ratio was estimated to be 13.3:1 for the interruption of rubella and CRS in the entire English-speaking Caribbean [4,41].

This computer simulation modeling analysis is subject to some limitations. There are uncertainties in the model assumptions, the parameter estimates, and future population planning policies in

China. For example, it may not be a reasonable assumption that the mixing matrix of contact rates between individuals in different age groups does not change over time. Also the routine vaccination ages of 1 and 12 years used here may not match the actual target ages for rubella vaccination in China. However, our sensitivity analyses (details are not included) showed that the results here are not very sensitive to these choices and uncertainties. Thus the computer simulations here yield useful predictions about the risks of vaccinating at suboptimal levels and the effects of various rubella vaccination strategies.

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