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A model-based evaluation of the national immunization programme against rubella infection and congenital rubella syndrome in The Netherlands

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SUMMARY

In order to improve the prevention of cases of congenital rubella syndrome in The Netherlands, in 1987 the selective vaccination strategy against rubella infection in girls was replaced by mass vaccination. This decision was supported by mathematical model analyses carried out by Van Druten and De Boo. In order to compare the predicted impact of the rubella vaccination programme with the current available data in more detail, a similar model was built. Although the model predicts elimination of the rubella virus, data show that virus circulation is still present at a higher level than expected by the model. Simulation studies indicate that import of infection and a lower vaccine effectiveness, related to possible asymptomatic reinfection of vaccinated people, could be sources contributing to the present virus circulation. Even though the number of infections is much higher than the number of reported cases of disease, limited serosurveillance data and case notification data show that females of childbearing age are well protected by immunization.

INTRODUCTION

Symptoms of acquired infections with rubella virus are usually mild. However, severe complications, the so-called congenital rubella syndrome (CRS), can develop in children born to mothers who were infected during pregnancy. Malformations of major organ systems in the developing foetus can lead to deafness, eye defects, cardiac abnormalities and mental retardation. During the prevaccination period most girls became immune by natural infection before childbearing age. In order to prevent cases of CRS among women not infected before childbearing age, vaccination against rubella infection of girls at the age of 11 years was introduced in 1974 in the national immunization programme (NIP). Virus circulation was still maintained by boys and by girls younger than 11 years of age.

In 1984 the Dutch Health Council recommended that selective vaccination should be changed to mass vaccination [1]. This recommendation was supported by mathematical model predictions. Models developed by Van Druten and De Boo [2–5], which were based on the work of Knox [6, 7], Dietz [8], Hethcote [9], and Anderson and May [10], were used to analyse and compare several strategies. With mass vaccination virus circulation was expected to decrease and therefore the average age at infection of non-vaccinated girls would increase as the probability of infection would become smaller. If the average age at infection of cases rises to childbearing age, the CRS incidence might even increase. Whether this situation will occur primarily depends on the vaccination coverage. In The Netherlands the overall vaccination coverage for rubella is high (92–94%), but not all municipalities reach such a high coverage. People who refuse to have their children vaccinated for religious reasons are socially and geographically clustered. Municipalities in that geographic region have a lower

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coverage. With mass vaccination the models predicted a further decrease in incidence of CRS and possibly elimination of the virus, given the high vaccination coverage in The Netherlands. Although small outbreaks might occur in municipalities with a low coverage, possibly leading to a small number of cases of CRS, rubella would no longer be endemic in The Netherlands.

In 1987 the mass vaccination strategy was adopted. Both boys and girls were vaccinated with a combined mumps, measles, and rubella (MMR) vaccine at the age of 14 months. In order to offer a second chance to individuals not immunized at 14 months, a second dose is given at the age of 9 years.

Although more sophisticated models have been developed for the evaluation of vaccination programmes, for instance age-structured models with age dependent heterogeneity in transmission [11–14] and waning immunity [15, 16], or a cohort based age-structured model with a seasonally changing mixing pattern of school attendance [17–19], the aim of this paper is to evaluate the vaccination programme against rubella and CRS by comparison of the former predictions of a less sophisticated model with the current available case-notification data and seroprevalence data. Discrepancies found between predictions and data will be studied by simulation for an explanation. In addition some assumptions in the model will be studied by means of sensitivity analysis.

METHODS

In this section the model will be described first. Then, second, the data sources will be presented. Third, analyses are described that were carried out in order to compare the model outcome with data. However, comparison revealed some discrepancies between model outcome and data. Therefore fourth, analyses are described to examine these discrepancies. Fifth, analyses to determine the sensitivity of simulated incidence and serological profiles to model parameters are described. The selective vaccination strategy followed by the mass vaccination strategy together will be referred to as the combined strategy.

Model description

The models of Van Druten and De Boo were mainly used to compare different strategies [3–5]. In order to be able to compare their former predictions on the impact of the combined strategy, with case-notification data and seroprevalence data in more detail, a model was developed similar to their deterministic model.

The model is conceptually built up of three parts, a demographic model with birth, mortality and ageing, an infection model describing the infection process, and a vaccination strategy model describing the rubella vaccination programme. Apart from vaccination parameters, which are set to the actual values, all parameters and data used in the model are the same as used by Van Druten and De Boo. For a detailed description of the model equations and an overview of the sources of model parameter assignments see Appendix. A schematic representation of the model is shown in Figure 1.

The demographic model consists of a homogeneously mixed population which is stratified by gender and age. The model uses 1-year age classes for convenient implementation of vaccination strategies and for generation of serological profiles in 1-year age classes. Each age class contains an equal number of people. Life expectancy is 75 years. For age 0–74 the mortality rate is 0. For age 75 or older the mortality rate is infinite (type I mortality [20]). Population size is kept constant at 14·58 million people, therefore the number of newborns is equal to the number of deaths. Whether newborns will be maternally immune depends on the fraction of immune women in the female population and their age-dependent fertility (see Appendix). The childbearing age ranges from 15 to 45 years.

The infection model incorporates the states maternally immune, susceptible, latent (infected but not yet infectious), infectious, and immune (by natural infection or vaccination). Immunity is defined as detectable immunity, which means presence of specific antibodies assessed in serological tests. Immunity is assumed to last life-long. The model uses a maternally immune period of 6 months, a latent period of 10 days, and an infectious period of 11 days. The force of infection at a presumed equilibrium before vaccination was introduced, is estimated by Van Druten [2] at 0·12 infections per person per year and represents the *per capita* rate at which susceptibles acquire infection. From this estimate a basic reproduction number of 9, and an effective contact rate per day of 0·82 is derived (see Appendix). This transmission parameter represents the product of the number of contacts per person per day and the probability of transmission per contact and is assumed to be constant over time. Serological data from the prevaccination period, from which the equilibrium force

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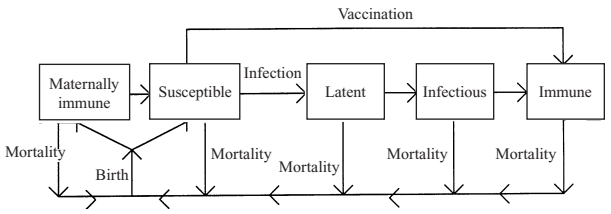

Fig. 1. Schematic representation of the model. Depending on the processes infection, vaccination, birth, and mortality, individuals may move between the states maternally immune, susceptible, latent infected, infectious, and immune. Ageing is not shown in the figure.

Table 1. *Rubella vaccination policy in The Netherlands: time period, age at vaccination, target group and coverage*

Period	Age	Gender	Coverage
1974–88	11 years	Female	92%
1987–91	4 years	Male, female	93%
1987–present	14 months	Male, female	94%
1987–present	9 years	Male, female	91%

of infection was estimated, were limited to one age class only. Therefore transmission in the model is not taken age-dependent. The probability of vertical transmission by an infected pregnant woman, resulting in the viable birth of a baby with CRS, is 10% [2]. This value is an overall estimate for the total duration of pregnancy, taking into account a higher risk of CRS when infected during the first 3–4 months of pregnancy and a lower risk later on. No import of infectious sources from outside the population is applied in the model.

The vaccination strategy model describes the subsequent strategies against rubella infection in The Netherlands (Table 1). The model only includes vaccination through the NIP, not vaccination on a private basis offered to women wishing to become pregnant in the near future. From 1974 until 1988 selective vaccination was applied. From 1987 onwards mass vaccination is adopted. From 1987 until 1991 a catch-up campaign was added, targeting boys and girls aged 4 years. In the model vaccination at the age of 14 months was implemented as vaccination at the age of 1 year. A vaccine effectiveness of 95% is assumed, meaning that 95% of the susceptibles who are vaccinated gain complete protection against both infection and disease. The remaining 5% is not protected at all. Vaccination is assumed to provide the same level and duration of immunity and transferred maternal immunity as natural infection.

The model has been implemented as a set of differential equations for discrete 1-year age classes. A simulation programme has been developed in Borland Pascal 7.0 and runs under MS-DOS. Numerical integration is performed with a time step of 1 day. The number of days per year is set to 360 for convenience. Incidence of rubella and CRS in the model are calculated by summing up daily incidences over one year. Simulation starts in 1973 assuming endemic equilibrium in the prevaccination period.

Data sources

Data used for comparison with model outcome are case-notification data and serosurveillance data. Cases of rubella have been reported since 1952. Cases of CRS are reported since 1976. From 1981 onwards cases of CRS are not reported separately, but together with rubella. Serological data for rubella have been gathered in 1980 and 1985, 1986–7, and 1994. In 1980 and 1985 798 and 679 sera respectively were collected from healthy visitors to sentinel practices distributed all over the country, aged between 10 and 65 years and over [21]. These sera were analysed for antibodies against rubella virus. In 1986–7 a large serosurveillance was carried out by local public health services and blood banks in Utrecht, Nijmegen, Rotterdam and Alkmaar. A total of 11179 sera were analysed for MMR antibody levels. Age of the blood donors varied from 1 to 20 years and over [22]. In 1994 a pilot study was carried out in four municipalities in the province of Utrecht to investigate the feasibility of the establishment of a representative serum bank in order to estimate age-specific immunity against childhood diseases in the NIP. Sera were collected from 814 randomly selected individuals aged between 0 and 79 years and over [23].

Analyses

Comparison of data with model predictions

Dutch notification data do not allow to distinguish clearly between cases of rubella and cases of CRS. Therefore the simulated incidence of rubella infections including cases of CRS will be compared to the number of reported cases of rubella disease including cases of CRS.

Introduction of a new vaccination programme will affect the force of infection and therefore has an impact on serological profiles. To show clearly this impact, profiles in one year age classes for both

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genders are needed. Serological profiles based on field data could not be used for this purpose as either sample size was not large enough to use 1-year age classes (1980, 1985, 1994), or the (published) age range was not wide enough (1980, 1985, 1986–7), or profiles for both gender and age were not presented as needed (1986–7). Therefore simulated serological profiles generated by the model are used to provide insight in the impact of vaccination. Simulated age distributions of seronegative males and females generated by the model at the last day of a year are related to the number of male and female cases according to age that were reported in The Netherlands in the following year.

Serological profiles based on field data can however be used for validation of the model. The female serological profile from 1994 will also be used to indicate how well females of childbearing age are protected against infection.

Average age at infection is not used to indicate the age class at risk of CRS for females during an elimination strategy. Beside a shift in age at infection to the older age classes, which is expected for non-vaccinated girls, a decreased virus circulation may also account for an increased number of newborns without maternal immunity, because non-vaccinated susceptible women have a smaller probability of natural infection. This may result in a relative increase in cases of rubella among 0-year-old children. Effects of waning immunity could account for an increase in cases in the older age classes. Therefore the average age at infection might not represent the age class at risk as the age distribution of cases could be multimodal. Instead the number of reported cases of rubella among women of childbearing age is studied together with the fraction of reported cases of rubella among women of childbearing age relative to the total number of reported cases among women.

In order to verify the expectation that small outbreaks will be limited to municipalities with a lower vaccination coverage, the geographical distribution of cases from 1993–1996 is compared to the geographical distribution of coverage for the MMR vaccine of all municipalities for the birth cohort of 1993. Coverage data will be compared to the critical coverage derived from simulation.

Analysis of discrepancies

Elimination of a virus as a result of mass vaccination means that the virus cannot maintain itself endemically in the population. Introduction of virus from outside the population might lead to a few cases of infection, but will fade out by lack of susceptibles. Despite predictions of the model about elimination of the virus in the general population, case-notification data and the male serological profile from 1994 indicate that virus circulation is still present at a higher level than expected. Therefore possible explanations for virus circulation were studied by simulating their effect on these data. Instead of the incidence of rubella, the incidence of CRS is studied to allow detection of a possible increase in the number of cases of CRS as a result of an upward shift in average age at infection when virus circulation decreases.

A second dose of vaccine at 9 years of age was meant to offer a second chance to children not immunized at 14 months. A source of virus circulation could be a lower effective second chance coverage, reaching more of the children already immunized and less of the children not yet immunized. The second chance vaccination coverage in the model was originally set to 91%. To see whether the coverage of the second dose could be responsible for the discrepancy, the second chance vaccination parameter was varied with values 0, 25, 50 and 75%.

Another explanation could be a lower effectiveness of the vaccine than assumed in the model. Vaccine-effectiveness was originally set to 95%. In order to study effects of a lower effectiveness the effectiveness parameter was varied with values from 0 to 90% with a step-size of 5%.

Also a higher force of infection than estimated for the prevaccination period could raise immunity in the population. The model originally used a pre-vaccination equilibrium force of infection of 0·12 per person per year from which the transmission parameter in the model was derived. The force of infection was varied using values of respectively 0·16, and 0·20 per person per year.

Another reason for continuing virus circulation could be import of infectious cases from outside The Netherlands caused by mobility and migration. To investigate effects of import with the model, each day a constant number of infectives are added. In order to keep population size constant, added infectives were interchanged with susceptibles and immunes either one of which is usually large for every age class (see Appendix for formulas). Values for import used in the model are 0·01, 0·1, 1, 10, 100, and 500 infectives per day. Although values of 100 and 500 infectives per day are unrealistically high, they are used to explore how

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much import is needed to be able to eliminate the discrepancy.

For each explanation studied by simulation only the relevant parameter will be varied. Once assigned, parameter values are kept constant during each simulation.

Sensitivity analysis

In order to simplify the model and to overcome limited availability of data many assumptions are made. But not all assumptions appear to be realistic afterwards. Fertility data and population size used in the model are assumed to be constant over time. However, from 1973 until 1997 the age distribution of pregnant women has shifted to older ages. Sensitivity of the simulated incidence of CRS to fertility data will be studied by using the model with fertility data from respectively 1973, 1983 and 1993.

The model uses a constant population size of 14·58 million people corresponding to 194400 births per year. The actual Dutch population size has been increasing from 13·49 million people in 1973, to 14·09 million people in 1980, to 15·01 million people in 1990. In the model the number of births per year directly depends on the population size. If the population size is constant, then the number of births per year is constant. Birth can be seen as a supply of new susceptibles in the population and therefore is an important factor. The actual number of live births per year changes from 194993 in 1973 to 170246 in 1983 and to 195748 in 1993 after a rise to 250914 in 1964 (effect of the birth wave after World War II). The population size used in the model is close to the actual maximum population size over the period 1973–97. To study the influence of population size and birth on the CRS incidence a model population size of 12·75 million people, which is close to the actual minimum population size over the period of 1973–97, is used corresponding to 170000 births per year.

Sensitivity analysis of the CRS incidence to fertility and population size were only applied to the model without import varying only the relevant parameter for each. Once assigned, parameter values were kept constant during each simulation.

RESULTS

Comparison of data with model predictions

In the prevaccination equilibrium period an incidence of 116 cases of CRS per year is predicted by the model. With a continuation of the selective vaccination strategy the model shows an incidence of 19 cases of CRS (10–20 cases of CRS according to Van Druten [3]), a reduction of 84% (Fig. 2*a*). Changing from a selective to a mass vaccination strategy the model predicts elimination of rubella and CRS. The quantitative difference between the number of reported cases and the simulated number of cases is high. Before introduction of mass vaccination the model overestimates the number of reported cases, while after introduction the model underestimates the incidence. The model predicts elimination, but notification data show that virus circulation is still present at a higher level than expected by the model (Fig. 2*b*).

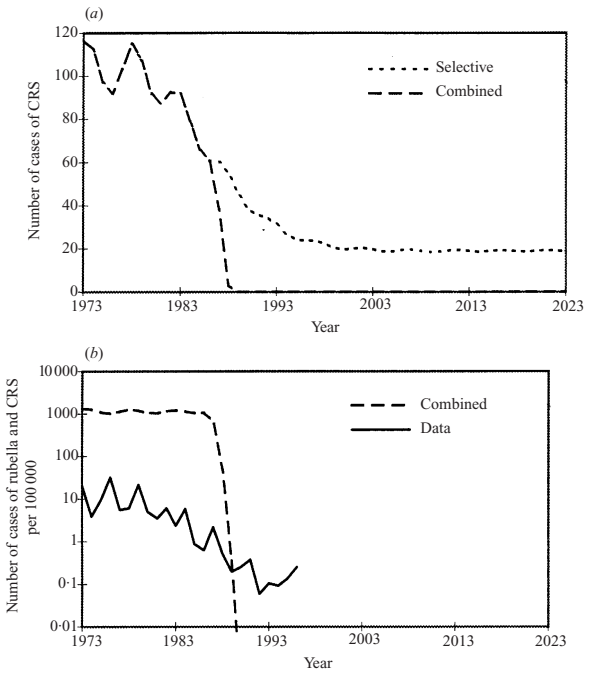

Fig. 2. Incidence of rubella and CRS. Simulated incidences of CRS for both continuation of the selective vaccination strategy and the combined vaccination strategy (*a*), and simulated incidence per 100000 of rubella infections including cases of CRS compared to the reported incidence per 100000 of rubella disease including cases of CRS plotted on a log-scale (*b*). Note that after introduction of mass vaccination there seems to be more virus circulation than predicted by the model.

Serological profiles in 1-year age classes generated by simulation of the combined vaccination strategy were used to illustrate the impact of the vaccination programme. In Figure 3 simulated serological profiles for both males and females in 1973, 1974, 1981, 1987, 1991 and 2003 are shown. In 1973, before introduction of the selective vaccination strategy, the simulated profiles for males and females are

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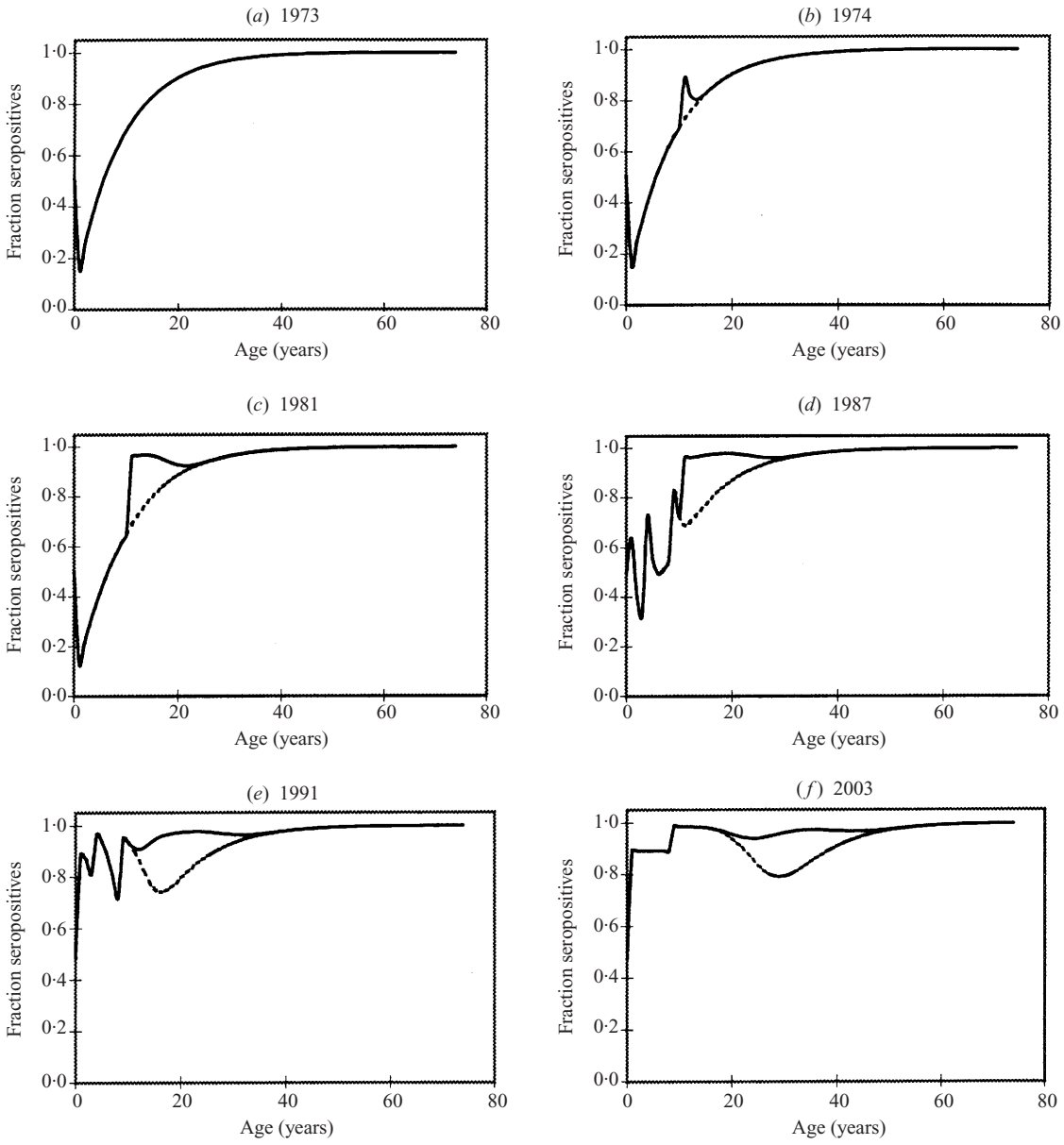

Fig. 3. Simulated impact of the combined vaccination strategy on age-specific serological profiles. The impact on the serological profile for males (dotted line) and females (solid line) in 1973 before vaccination was introduced (*a*), at the end of 1974 after selective vaccination was introduced (*b*), in 1981 halfway between the start of selective vaccination and the change to mass vaccination (*c*), at the end of 1987 after changing to mass vaccination (*d*), in 1991 after 5 years of mass vaccination (*e*), and prediction of the impact in 2003 (*f*). Simulation shows that, after introduction of mass vaccination, the gap in immunity in the male serological profile is no longer reduced by natural infection.

the same as males and females have experienced the same force of infection in the past (Fig. 3*a*). In 1974 selective vaccination causes a peak in the simulated female age serological profile at the vaccination age of 11 years (Fig. 3*b*). The level of immunity for females in the age range 12–20 in 1974 is still raised by natural infection (Fig. 3*c*, *d*). At the end of 1987 peaks in seropositivity from vaccination can be seen at the vaccination ages 1 year, 4 years and 9 years for both males and females as a result of mass vaccination and for 11 to 24-year-old females who have been vaccinated by the selective strategy. Males older than 9 will neither be immunized by vaccination nor by natural infection as virus circulation is close to elimination. They stay at the prevaccination level of immunity according to their age in 1987. In the male serological profile this low level of immunity looks like a gap (Fig. 3*d*). This gap, corresponding to a peak

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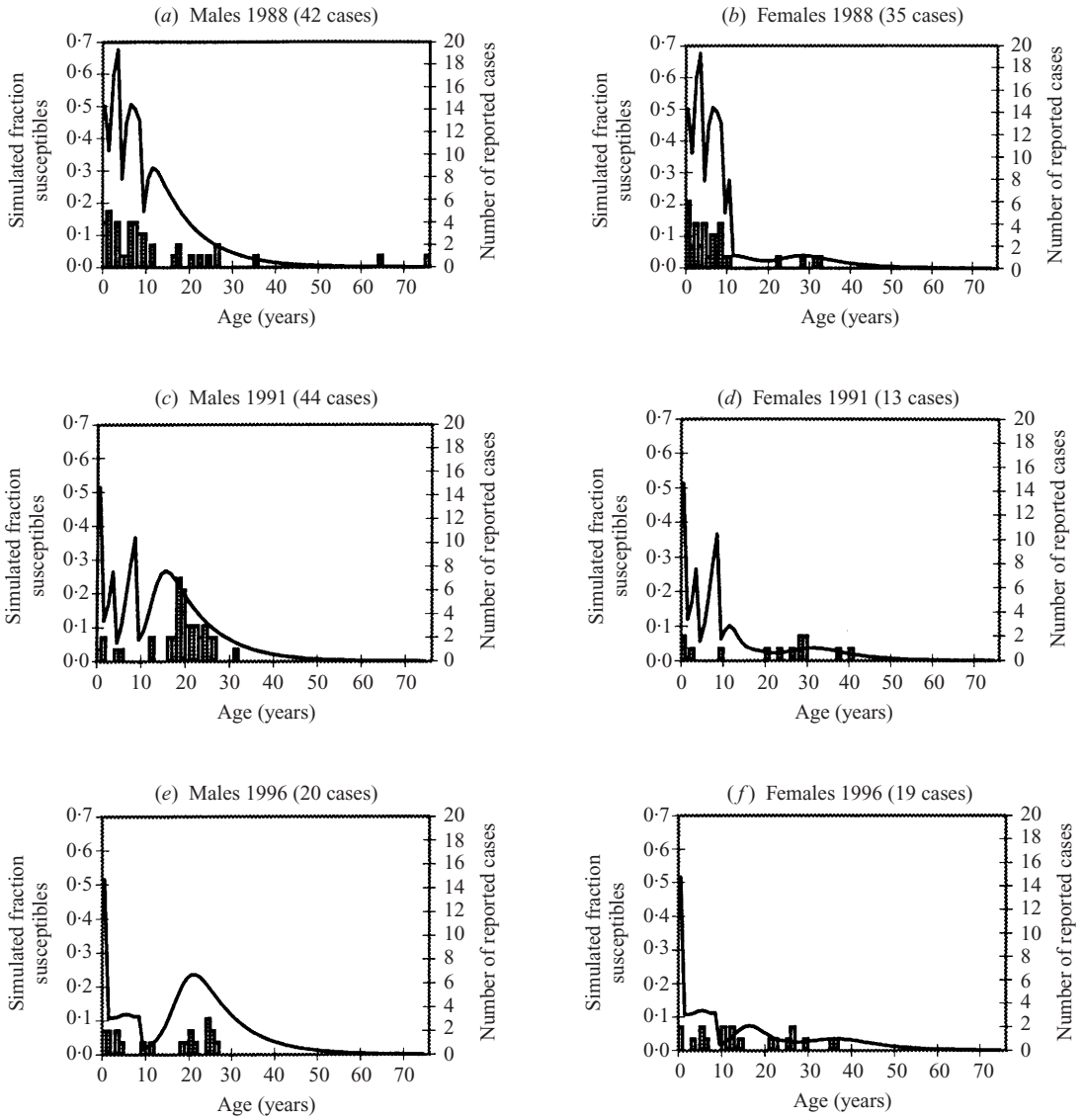

Fig. 4. Comparison of notification data with simulated age distribution of susceptibles. Number of reported cases of rubella and CRS (bars) and simulated fraction susceptibles at the last day of the preceding year (solid line) for males and females in 1988 (*a*, *b*), 1991 (*c*, *d*) and 1996 (*e*, *f*). Simulation reveals the age distribution of susceptibles indicating at which ages cases of infection can be expected.

of male susceptibles, will shift to older ages in time (Fig. 3*e*, *f*). This gap does not show up in the female profile as selective vaccination of females in preceding years reduced this deficit of immunes. The gaps in immunity for both males and females in 1987 between vaccination ages 1, 4 and 9 years are reduced by vaccination during the next 3–5 years.

Simulated seronegative profiles for males and females at the last day of the preceding year were related to the number of male and female cases that were reported in the following year (Fig. 4*a–f*). From 1988 onwards reported cases were stored in a database per 1-year age class (registration notifiable diseases). Those data are used for this purpose. In order to minimize the relative contribution of stochastic variation due to small numbers the years 1988, 1991, and 1996 were taken, because those years showed peaks in the incidence of rubella and CRS. In 1988 the peak in the age distribution of the female cases clearly falls into the age range with the simulated peak of female susceptibles (Fig. 4*b*). In 1991 the peak in the age distribution of the male cases clearly falls into the age range with the peak of male susceptibles (Fig. 4*c*). In 1996 the peak in the age distribution of male cases is not very clear anymore (Fig. 4*e*). No peaks in the childbearing age range are found in the simulated

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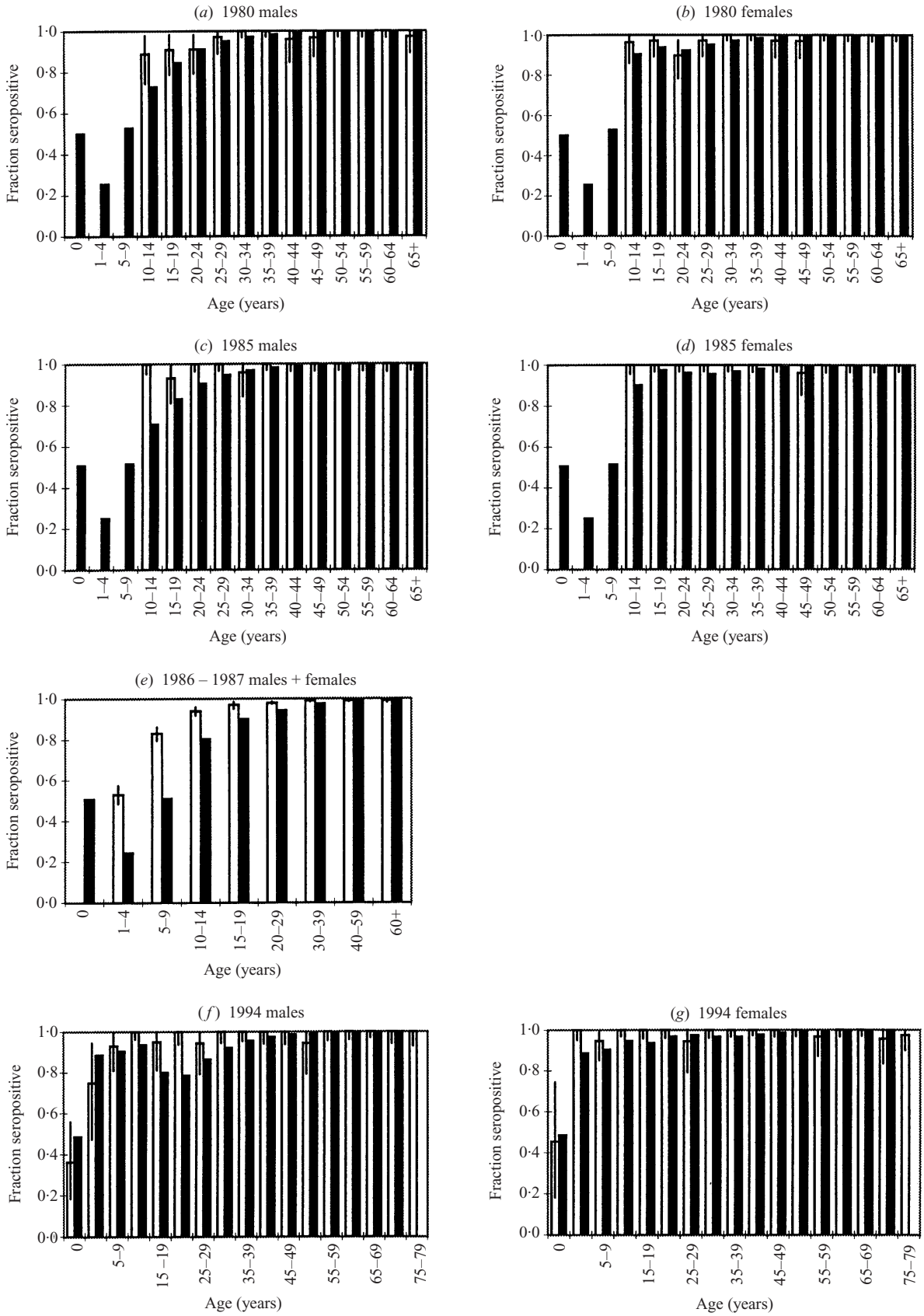

Fig. 5. Serological profiles based on data compared to simulated serological profiles. Simulated serological profiles (black bars) and profiles based on data (white bars with 95% confidence interval) from sentinel studies in 1980 [21] for males (*a*) and females (*b*), sentinel studies in 1985 [21] for males (*c*) and females (*d*), a study in 1986–7 [22] regardless of gender (*e*),

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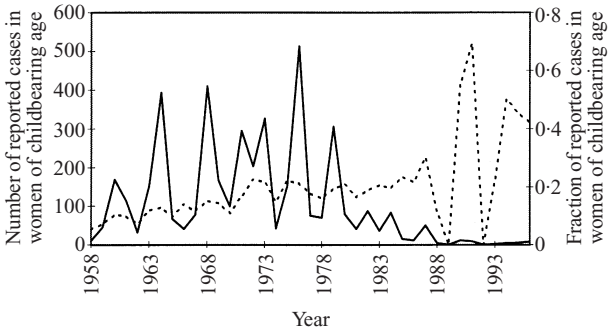

Fig. 6. Reported cases among females of childbearing age. The number of reported cases among females of childbearing age relative to the number of reported cases among females has increased (dashed line). However, the absolute number of reported cases among females of childbearing age has decreased (solid line).

age distribution of seronegative females in 1996 (Fig. 4*f*).

Validation of the model with serological profiles based on data from 1980, 1985, and 1986–7, shows that immunity is rising faster over age in the data profiles than in the simulated profiles (Fig. 5*a–g*). Comparison of the male profile based on data from 1994 with the simulated profile shows that the predicted gap in immunity in the simulated profile for males (Fig. 5*f*) is not found in the data. Therefore, virus circulation must be still present. The serological profile for females based on data from 1994 shows that females are well protected against CRS, as the fraction of immune females at childbearing ages is high (Fig. 5*g*).

Notification data from 1958 onwards show that the number of reported cases among females of childbearing age relative to the number of reported cases among females has increased. In the period before vaccination was introduced this relative increase was the result of increasing hygiene causing a decrease in virus circulation. From 1987 onwards the effect of mass vaccination, a decreased virus circulation causing an upwards shift in age at infection among non-vaccinated people, is seen (Fig. 6). However, the absolute number of reported cases of rubella among females of childbearing age has become very small by vaccination. The small number of cases causes large variation in those fractions over time. Because of difference in partitioning into age classes over the years, childbearing age is taken as 15–49 years for the period 1958–72 and 15–44 years from 1973 onwards.

In order to determine whether small outbreaks are restricted to municipalities with lower vaccination coverage the geographical distribution of cases is compared to the geographical distribution of coverage. MMR vaccination coverage data of all 625 municipalities for the birth cohort of 1993 show that 3 municipalities (0·48%) have a coverage between 60 and 70%, 21 municipalities (3·36%) have a coverage between 70 and 80%, 46 municipalities (7·36%) between 80 and 90%, 145 municipalities (23·2%) between 90 and 95%, and 410 municipalities (65·6%) between 95 and 100% (Fig. 7*a*). The critical coverage in the simulation of the combined strategy was determined at 76% assuming an effectiveness of 95%. Below this coverage elimination of the rubella virus could not be achieved. Twelve municipalities have a coverage below 76%. Notification data from 1993–6 show that reported cases of rubella are spread all over the country (Fig. 7*b*). Cases are not restricted to municipalities with a lower vaccination coverage.

Analysis of discrepancies

Varying the coverage of the second dose at 9 years of age hardly influences the incidence of both rubella and CRS (Fig. 8*a*). Despite a lower coverage the virus is eliminated. Increased virus circulation as a result of a lower second dose vaccination coverage cannot reduce the gap in immunity in the profile for males from 1994 (Fig. 8*b*).

Lowering vaccine effectiveness shows that virus circulation can be maintained (Fig. 9*a*), but the gap in immunity shown in the profile for males from 1994 cannot be reduced (Fig. 9*b*).

A higher estimated prevaccination equilibrium force of infection cannot prevent the virus from being eliminated (Fig. 10*a*). However, the gap in the serological profile for males from 1994 can be reduced (Fig. 10*b*).

Import of infectious cases can maintain virus circulation (Fig. 11*a*). A lower level of import causes a lower incidence of rubella, but can cause a higher incidence of CRS. Import can reduce the gap in the serological profile for males from 1994 (Fig. 11*b*). However, unrealistically high levels of import are needed to reduce this gap.

and a study in 1994 [23] for males (*f*) and females (*g*). Age class ranges are shown as originally published. Data show a higher level of immunity in the younger age classes than the simulation results. The predicted gap in the male profile of 1994 is not revealed in the data.

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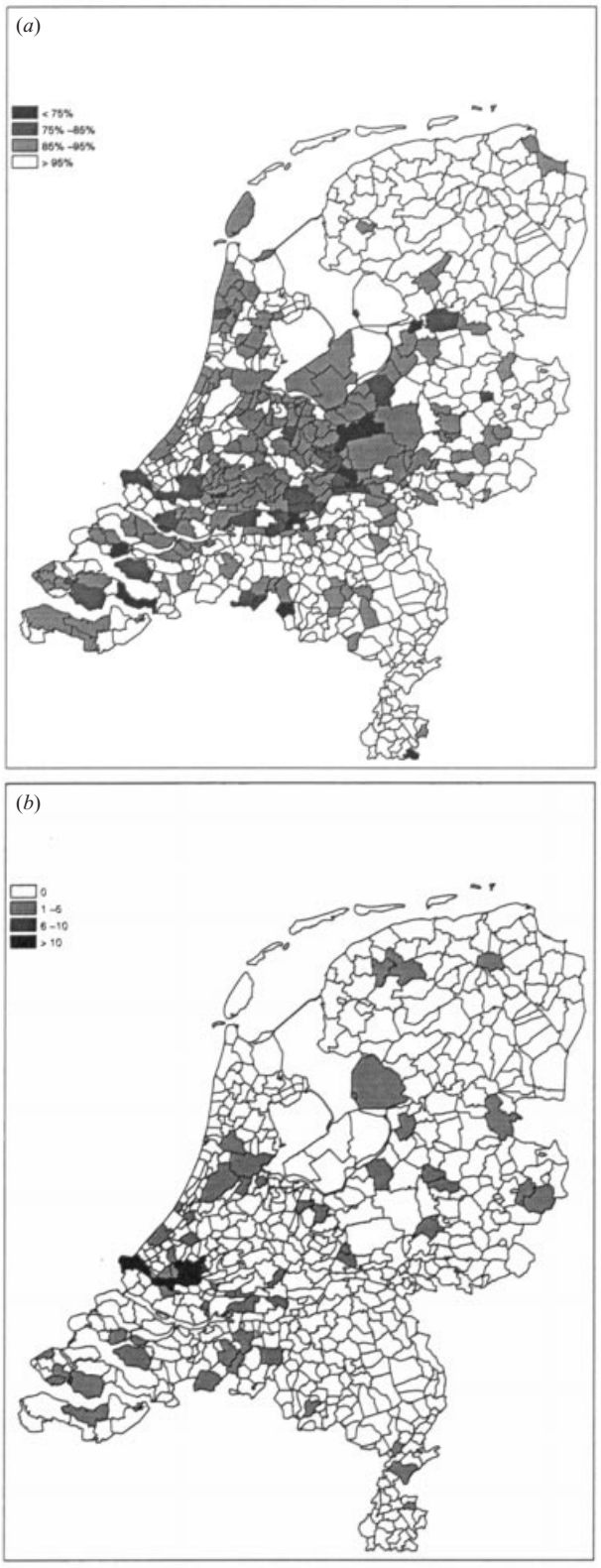

Fig. 7. Comparison of the geographical distribution of coverage for the birth cohort of 1993 (source: Medical Inspectorate of Health) (*a*) and the geographical distribution of reported cases in the period 1993–6 (source: Registration Notifiable Diseases) (*b*). Comparison shows that reported cases of rubella are not restricted to municipalities with a lower vaccination coverage.

Sensitivity analysis

Sensitivity analysis was performed to assess the effect on the CRS incidence of varying fertility and population size. From 1973 to 1993 the average age of pregnant women has shifted to older ages (Fig. 12*a*). This upward shift in age at pregnancy should slow down an increase in number of cases of CRS by an upward shift in age at infection caused by a decreased virus circulation. The simulated incidence of CRS in the prevaccination equilibrium is lowered by a factor 2 (Fig. 12*b*). The simulated incidence of CRS appears to be very sensitive to the age distribution of pregnant women in a quantitative way. The simulated incidence of rubella is hardly influenced by the fertility distribution.

Increasing population size, in this model directly resulting in an increase in birth rate, increases the incidence of CRS only in a quantitative way. Changing the number of births (or population size) by a certain factor changes the prevaccination incidence of both rubella and CRS by the same factor.

DISCUSSION

Model predictions on the incidence of rubella and CRS are compared to Dutch case-notification data (Fig. 2). However, case-notification data cannot clearly be quantitatively compared to the simulated incidence of rubella and CRS. Case-notification data reflect the number of cases of symptomatic disease, while the model generates cases of infections. Up to 50% of the rubella infections occur without symptoms [24]. Given that in the prevaccination period nearly every child would acquire the infection, an average incidence of rubella infections is expected which almost equals the number of births per year. However, in the prevaccination period the number of reported cases of rubella on average equals 1% of the number of births. In a study it is shown that 50% of the cases that are diagnosed clinically as acute rubella infection are actually caused by the rubella virus [25]. An age-specific bias in reporting and alteration in efficiency of reporting after the introduction of mass vaccination can be expected, and makes adjusting for under-reporting not appropriate. In The Netherlands no case-definition is used for notification, and serological confirmation is not required. Therefore the number of reported cases of disease may only give an impression of probable patterns in the incidence of rubella infection. In order to monitor the impact of rubella

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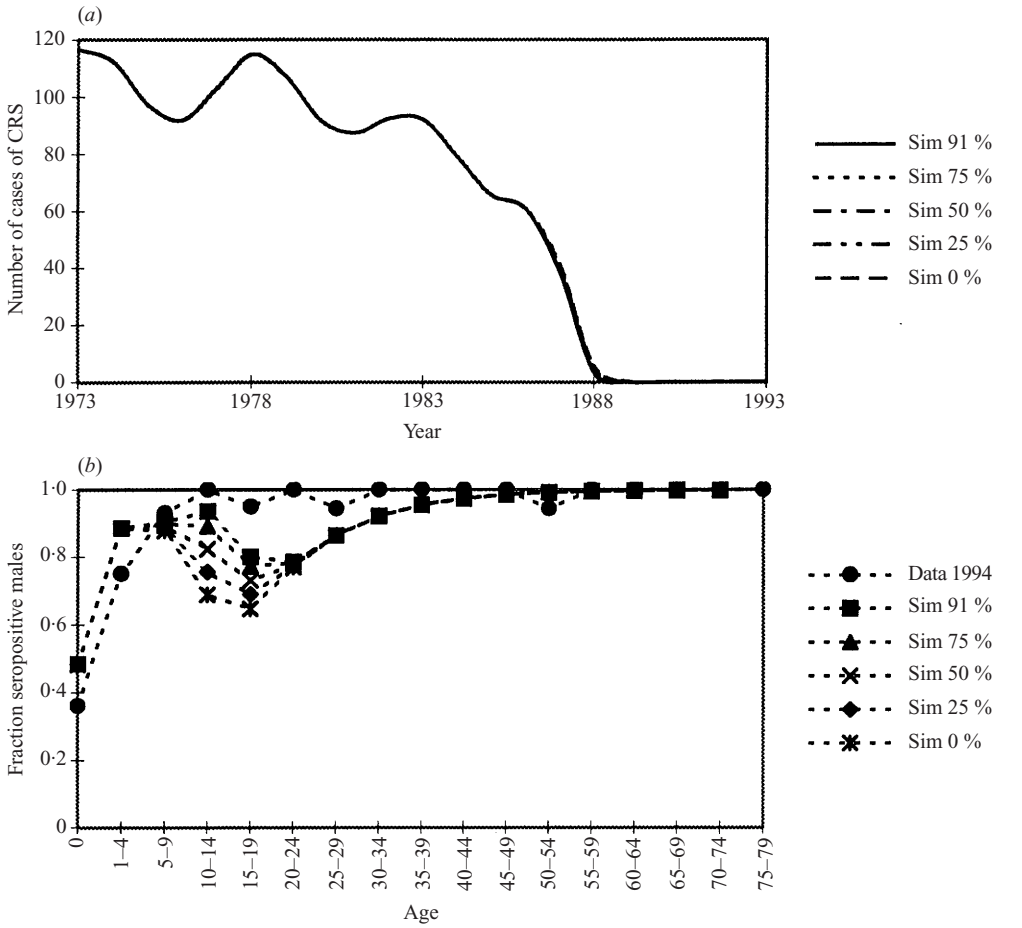

Fig. 8. Simulated effect of variation of the coverage (%) of the second dose MMR vaccination at 9 years of age on the incidence of CRS (*a*), and on the male serological profile from 1994 compared to data (*b*). Despite a lower coverage the virus is eliminated (*a*) and the gap in the male profile cannot be reduced (*b*).

vaccination by the case-notification system more clearly, reported cases of rubella infection and CRS should be reported separately and be serologically confirmed.

The serological profile in 1994 is derived from a small pilot study. The serological profile for males is based on a class size of 14–33 males per 5-year age class. With these small class sizes stochastic variation could be responsible for the reduction of the gap in the serological profile for males. In 1995–6 the large serosurveillance following the pilot study was carried out. Almost 10000 sera were collected from inhabitants of 48 of the 625 municipalities aged between 0 and 79 years and over. The sera are currently being tested for antibodies against rubella and may reveal the true presence or absence of this gap more clearly.

In the model the process of transmission of the virus during contacts between people is derived from one estimated value for the prevaccination equilibrium force of infection based on seroprevalence data of 10 to 12-year-old children in 1970–4. Comparison of simulated profiles with profiles from data from 1980, 1985, and 1986–7 (Fig. 5) shows that immunity is rising faster over age in the field data profiles than predicted by the model. This could be caused by an actual higher force of infection than assumed in the model or by a change to a higher force of infection in the past. However, the estimated value of the prevaccination equilibrium force of infection for The Netherlands was already high in comparison with Germany [8], the United Kingdom [6, 7], and the United States [9]. An explanation for this high force of infection could be the birth wave after World War II, being responsible for an extra number of susceptible newborns in the population.

The model assumes homogeneous transmission between age groups, but age-related transmission is more realistic because of frequent contacts between children of specific agegroups within schools. The estimated value of the prevaccination force of in-

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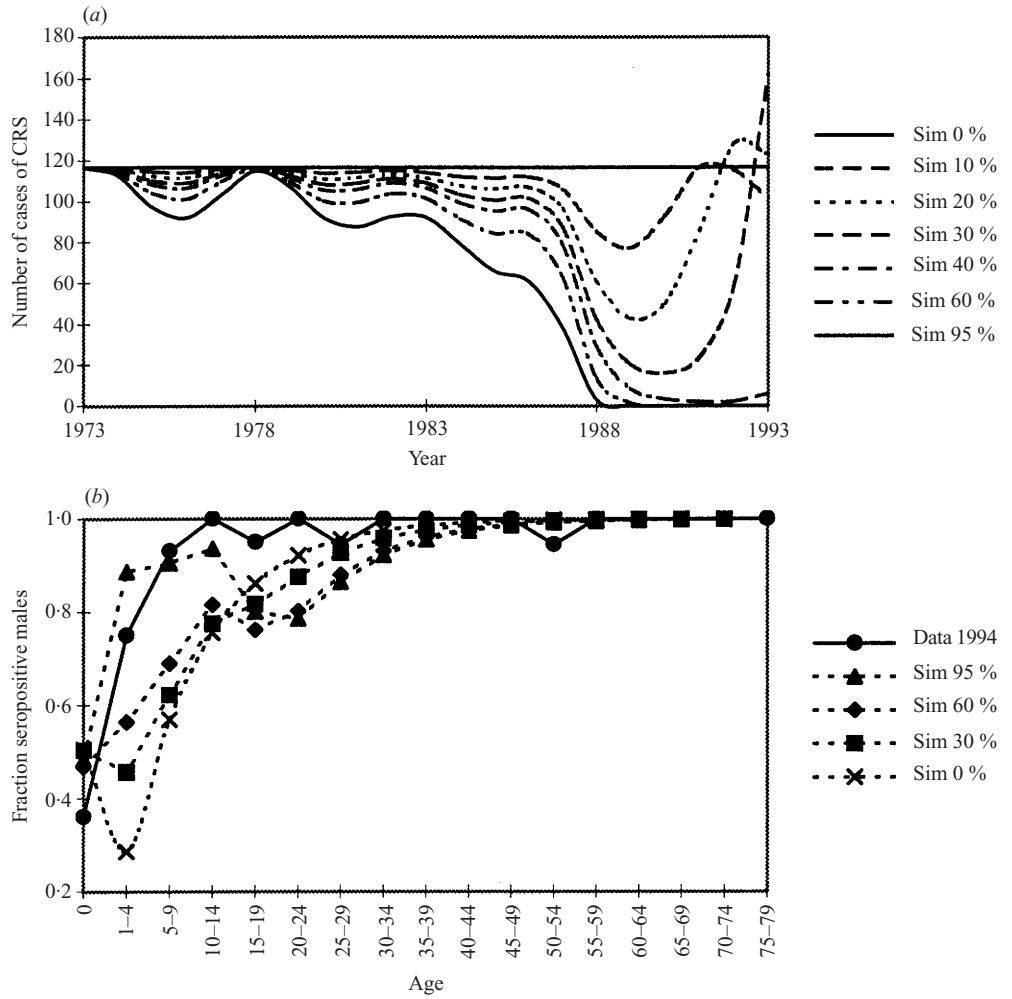

Fig. 9. Simulated effect of variation in vaccine-effectiveness (%) on the incidence of CRS (*a*), and on the male serological profile from 1994 compared to data (*b*). With a lower effectiveness virus circulation can be maintained (*a*), but the gap in the male profile cannot be reduced (*b*).

fection of 0·12 for The Netherlands was based on a seroprevalence of 75% among 11-year-old children in the prevaccination period [2]. Seroprevalence data for rubella from England from 1986–7 show that during selective vaccination, which hardly influences the seroprevalence for boys, 74% of the boys of age 10–12 years were seropositive [26]. This value can be used as an estimate for the seroprevalence in the pre-vaccination period and is in accordance with the Dutch value. Therefore a higher age-related transmission in younger children is expected. Compared to the English data the fraction seropositives for The Netherlands is higher in younger age classes. This could be either a time effect of an increased force of infection or an age effect of a higher age dependent transmission in those younger age classes.

Moderate levels of import can be ignored compared to the large endemic level of virus circulation during the prevaccination period and during the period of selective vaccination, as import hardly influences the dynamics of the transmission of infection. However, with mass vaccination import does influence the dynamics. Therefore comparison of long term effects of different vaccination strategies in terms of CRS ratios should include effects of import.

Modelling shows that unrealistically high levels of import of infectious sources are needed to eliminate the discrepancy between the serological profile for males from 1994 and the simulated profile (Fig. 11). Although not included in the report that supported the recommendation of the Dutch Health Council [1, 3], De Boo and Van Druten [5] studied the effects of a constant import of infectious cases on the incidence of rubella. They estimated an import of 14 cases of infection per day based on data on the number of registered nights spent in The Netherlands

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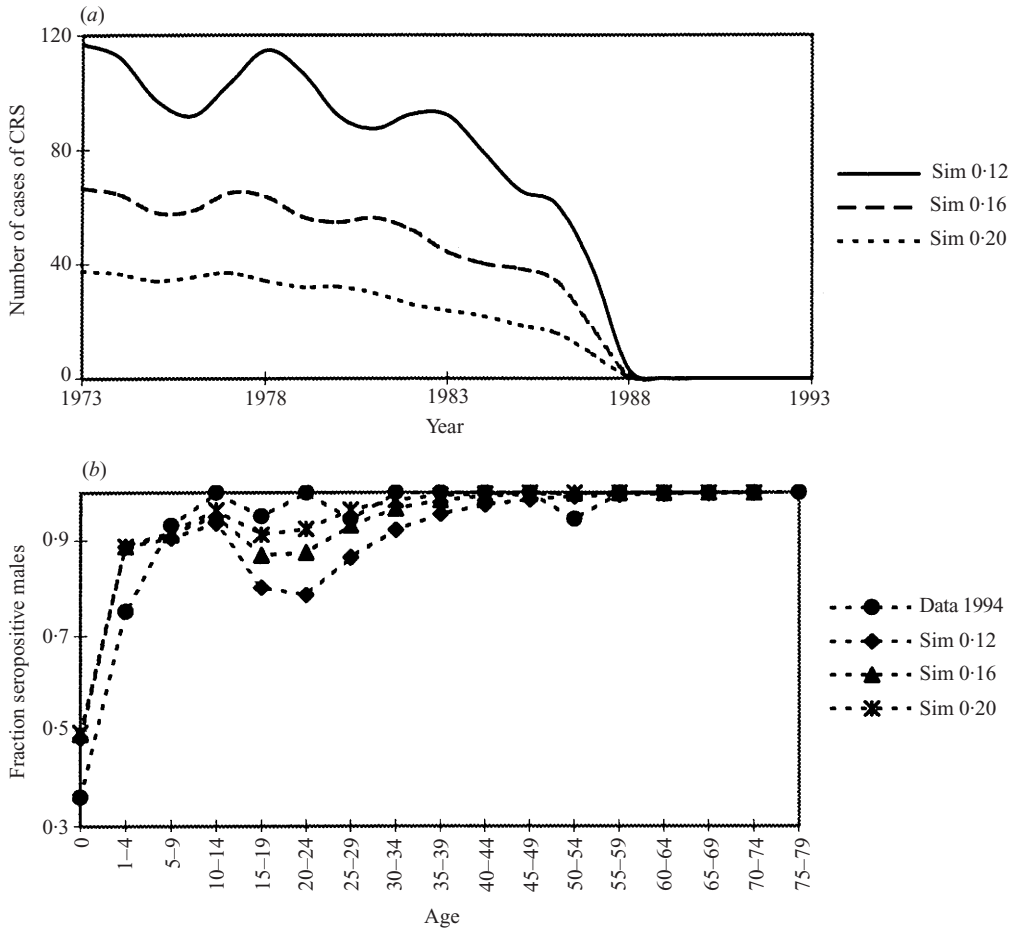

Fig. 10. Simulated effect of variation of the force of infection at prevaccination equilibrium, from which the probability of transmission is estimated, on incidence of CRS (*a*), and on the male serological profile from 1994 compared to data (*b*). A higher force of infection cannot maintain virus circulation (*a*). However, the gap in the male profile can be reduced (*b*).

by foreigners over the period 1980–2. This difference between their estimated level of import and the level of import needed in the model to eliminate discrepancies indicates that import cannot be the only factor contributing to virus circulation.

Another factor contributing to virus circulation could come forward if vaccine effectiveness is interpreted as partial protection. In the model a vaccine effectiveness of 95% means that one dose of vaccine is expected to provide complete protection against infection in 95% of the cases of vaccination of susceptible persons and no protection at all in the remaining 5%. If it is supposed that vaccination provides complete protection against disease, but only partial protection against infection, then vaccination would result in a lower level of susceptibility to infection with a probably lower level of infectivity when infected, a shorter duration of the infectious period, and less or no symptoms. Vaccinated people would then be able to contribute to the spread of the virus in the population. They would help to maintain circulation functioning as asymptomatic carriers. Susceptibles in well vaccinated municipalities with vaccination coverage above the critical coverage of elimination would not be protected as much as expected by herd immunity. Some data support this theory. Reported cases of rubella are not restricted to municipalities with a lower vaccination coverage. MMR coverage data for the birth cohort of 1993 show that only a few of the municipalities have a coverage below 80% (Fig. 7*a*). Notification data from 1993 to 1996 show that 19% of the reported cases were among vaccinated people, who were not clustered to specific birth cohorts. From literature it is known that reinfection can arise in individuals with serologically confirmed naturally acquired rubella infection or with successful immunization [27–37]. Reinfection is more likely to occur in those with vaccine-induced immunity than in

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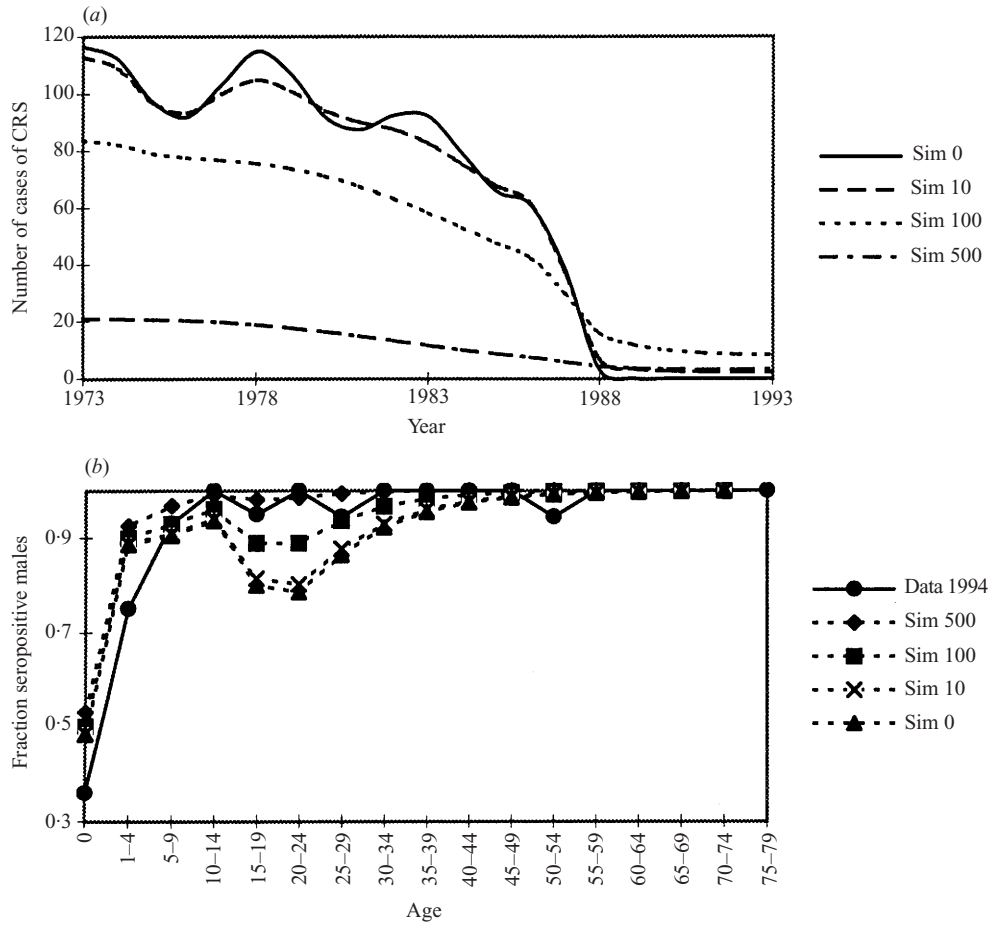

Fig. 11. Simulated effect of variation in import on the incidence of CRS (*a*), and on the male serological profile from 1994 compared to data (*b*). Import of infectious sources can both maintain virus circulation (*a*) and reduce the gap in the male profile (*b*).

those with natural acquired immunity. Most cases of rubella reinfection are inapparent. Virus can be shed from the throat, but a viraemia is rare. Therefore maternal rubella reinfection is considered to be of minimal risk to the fetus. Nevertheless cases of fetal infection after maternal reinfection have been reported [30, 31, 33, 35, 36]. Simulation of a lower all-or-nothing type effectiveness, as carried out in this study, can be seen as a simplified way of modelling contribution to virus circulation of vaccinated people, but might not yield the same results in terms of persistence of the virus as a model with different levels of susceptibility and infectivity.

Rubella vaccination strategies in England and Wales, and in Sweden have been similar to the Dutch strategy: selective vaccination followed by mass vaccination. However, in both countries the gap in the male serological profile was present [38–40]. Outbreaks among young adult males were responsible for an increase in infection in pregnant women. Instead of younger siblings affecting their mother, young men became the main source of infection of young women in their first pregnancy. Because the gap in the male profile was present for England and Wales, and for Sweden, reinfection of vaccinated people cannot be the major factor explaining the absence of the predicted gap in The Netherlands.

In The Netherlands people who refuse vaccination on religious grounds are both geographically and socially clustered. Social clustering might account for the reported cases not being restricted to municipalities with a lower vaccination coverage. It is not known if reported cases occur mainly among members of this group. The presence of virus circulation will reduce the upward shift in average age at infection and therefore reduce the risk of CRS for non-vaccinated women in these socially and geographically clustered communities.

Although cases of rubella are often subclinical, cases of CRS are almost always clinical and therefore

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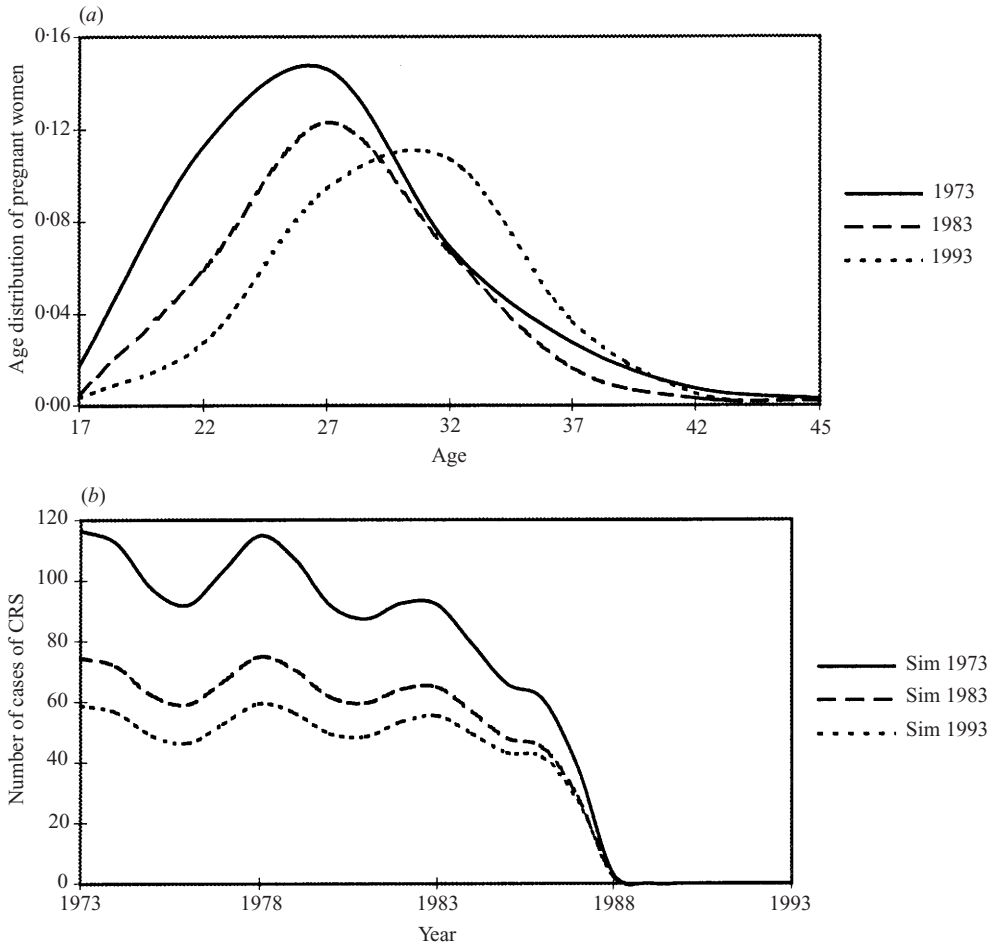

Fig. 12. Simulated effect of the fertility distribution on the incidence of CRS. The age distribution of pregnant women (source: Central Bureau of Statistics) is plotted for 1973, 1983, and 1993 against midpoint of age classes 15–19, 20–24, 25–29, 30–34, 35–39, 40–44, and 45 years (*a*). Sensitivity of the incidence of CRS to fertility data from 1973, 1983, and 1993 (*b*). The fertility distribution in the population heavily influences the incidence of CRS.

should be recognized except for some misdiagnosis of the cause of complications. The model without import probably overestimates the equilibrium incidence of 116 cases of CRS in the prevaccination period. Depending on the level, import lowers this CRS incidence by increasing the force of infection and thus shifting the average age at infection downwards below childbearing age.

If virus circulation is eliminated or close to elimination then immunity cannot be boostered by natural infection and immunity might start to wane. Vaccine-induced immunity might even be less persistent than naturally acquired immunity. The serological profile for males from 1994 indicates that sufficient virus circulation seems to be present to reduce the gap in immunity. Therefore effects of waning immunity are assumed to be negligible.

For further evaluation of the impact of the vaccination programme against rubella and CRS and a better fit of the model to data, the model should include age-related transmission, import of infectious cases, probably declining over time as a result of vaccination programmes in surrounding countries, and vaccine effectiveness implemented with varying levels of susceptibility and infectivity. If the virus is eliminated and import is low, then waning immunity should be included in the model. A more realistic demography should be considered with respect to birth, mortality, immigration, emigration, fertility and clustering. Offering vaccine to pregnant women should be included in the model. Being close to elimination, numbers of infectives will become small and stochastic effects cannot be ignored. Therefore stochastic models should be preferred for the evaluation of elimination strategies. If data on vaccine effectiveness with respect to susceptibility to infection are not available, then the model can be used to explore the effects of a variety of effectiveness levels. Sensitivity

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analysis of the model shows that caution should be taken with quantitative predictions based on limited available data.

The Dutch rubella elimination programme will only benefit substantially from vaccination programmes in other countries if these programmes also aim at elimination of rubella. If in The Netherlands import of infectious cases from other countries remains a major factor and if vaccinated people can maintain virus circulation, then elimination will be hard to achieve.

In conclusion, case-notification data show that cases of rubella infection and CRS have further decreased by changing from a selective to a mass vaccination strategy. Even though the number of infections is much higher than the number of reported cases of rubella infection and CRS, limited serosurveillance shows that women of childbearing age are well protected by immunization. However, virus circulation seems to be still present and not restricted to municipalities with a lower vaccination coverage. Simulation studies indicate that import of infectious cases and a lower vaccine effectiveness related to possible asymptomatic reinfection of vaccinated people could contribute to the present virus circulation. In order to monitor the impact of rubella vaccination more clearly, reported cases of rubella infection and CRS should be reported separately and be serologically confirmed.

APPENDIX: MATHEMATICAL ASPECTS

Model description

The model is described by the following set of differential equations. Index i represents gender, where $i = 1$ denotes males and $i = 2$ denotes females. Index j represents age. M refers to the number of maternally immune individuals, X to the number of susceptible individuals, H to the number of latent infected individuals, Y to the number of infectious individuals, and Z to the number of natural and vaccine-induced immune individuals.

$$\frac{\mathrm{d}M_{i0}}{\mathrm{d}t} = -r_M M_{i0} + b_{Mi}, \quad M_{ij} = 0 \text{ for } j > 0,$$

$$\frac{\mathrm{d}X_{i0}}{\mathrm{d}t} = r_M M_{i0} - pcX_{i0}\frac{Y}{N} + b_{Xi}(1 - v_{i0}) - \frac{X_{i0}}{d} - \frac{X_{i0}}{N_{i0} - M_{i0}}\frac{M_{i0}}{d},$$

$$\frac{\mathrm{d}X_{ij}}{\mathrm{d}t} = -pcX_{ij}\frac{Y}{N} + \left(\frac{X_{ij-1}}{d} + \frac{X_{ij-1}}{N_{ij-1} - M_{ij-1}}\frac{M_{ij-1}}{d}\right)(1 - v_{ij}) - \frac{X_{ij}}{d}, \quad j > 0,$$

$$\frac{\mathrm{d}H_{i0}}{\mathrm{d}t} = pcX_{i0}\frac{Y}{N} - r_H H_{i0} - \frac{H_{i0}}{d} - \frac{H_{i0}}{N_{i0} - M_{i0}}\frac{M_{i0}}{d},$$

$$\frac{\mathrm{d}H_{ij}}{\mathrm{d}t} = pcX_{ij}\frac{Y}{N} - r_H H_{ij} + \frac{H_{ij-1}}{d} + \frac{H_{ij-1}}{N_{ij-1} - M_{ij-1}} \times \frac{M_{ij-1}}{d} - \frac{H_{ij}}{d}, \quad j > 0,$$

$$\frac{\mathrm{d}Y_{i0}}{\mathrm{d}t} = r_H H_{i0} - r_Y Y_{i0} - \frac{Y_{i0}}{d} - \frac{Y_{i0}}{N_{i0} - M_{i0}}\frac{M_{i0}}{d},$$

$$\frac{\mathrm{d}Y_{ij}}{\mathrm{d}t} = r_H H_{ij} - r_Y Y_{ij} + \frac{Y_{ij-1}}{d} + \frac{Y_{ij-1}}{N_{ij-1} - M_{ij-1}}\frac{M_{ij-1}}{d} - \frac{Y_{ij}}{d}, \quad j > 0,$$

$$\frac{\mathrm{d}Z_{i0}}{\mathrm{d}t} = r_Y Y_{i0} + b_{Xi} v_{i0} - \frac{Z_{i0}}{d} - \frac{Z_{i0}}{N_{i0} - M_{i0}}\frac{M_{i0}}{d},$$

$$\frac{\mathrm{d}Z_{ij}}{\mathrm{d}t} = r_Y Y_{ij} + \left(\frac{X_{ij-1}}{d} + \frac{X_{ij-1}}{N_{ij-1} - M_{ij-1}}\frac{M_{ij-1}}{d}\right)v_{ij} + \frac{Z_{ij-1}}{d} + \frac{Z_{ij-1}}{N_{ij-1} - M_{ij-1}}\frac{M_{ij-1}}{d} - \frac{Z_{ij}}{d}, \quad j > 0,$$

with

$$N = M + X + H + Y + Z.$$

Description of ageing, mortality and birth

During 1 year exactly N individuals have to move to the next age class. Per day and per age class N_{ij}/d individuals move, with d the number of days per year. So terms of the form $-(S_{ij}/d)$, with S being one of the states M, X, H, Y, Z, represent an outflow per day of males or females moving from a particular age class to the next older age class, while terms of the form S_{ij-1}/d represent an inflow per day of ageing from the younger age class to that particular age class. As maternal immunity lasts for about 6 months from birth, maternally immunes cannot move to an older age class. In order to keep a population structure with constant and equal class size, an extra term M_{ij}/d, representing maternally immune individuals who loose their immunity, is distributed over the states X, H, Y, Z, weighted by their fraction of the total population minus maternally immunes. The whole terms look like

$$-\frac{S_{i0}}{N_{i0} - M_{i0}}\frac{M_{i0}}{d}$$

for extra outflow from the age class of 0-year-old individuals and

$$\frac{S_{ij-1}}{N_{ij-1} - M_{ij-1}}\frac{M_{ij-1}}{d}$$

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Table 2. *Parameters in the model: symbol, description, assigned value, and literature source*

Parameter	Description	Value	Source
N	Population size	14580000	[3]
t_M	Duration of maternally immune period	6 months	[3]
t_H	Duration of latent period	10 days	[3]
t_Y	Duration of infectious period	11 days	[3]
λ_0	Equilibrium force of infection in prevaccination period	0·12 per person per year	[2]
p_j	Fertility according to age (years)		
	15–19	0·0172 per year	[41]
	20–24	0·1128 per year	
	25–29	0·1459 per year	
	30–34	0·0687 per year	
	35–39	0·0273 per year	
	40–44	0·0071 per year	
	Otherwise	0·0000 per year	
v_{ij}	Proportion effectively vaccinated according to gender and age	Product of coverage and effectiveness	
	Coverage	See Table 1	[42]
	Effectiveness	95%	[43]
L	Life expectancy	75 years	[3]
d	Number of days per year	360 days	[3]
p_{crs}	Probability of CRS for a pregnant infected woman	0·1	[2]

for extra inflow of ageing from a younger age class. For a maternally immune period longer than 1 year this construction cannot be used. The proportion of susceptibles who move to a vaccination age are vaccinated. The number of males or females dying per day is equal to N_{iL-1}/d, with L, the life expectancy and d, the number of days per year. The number of births per day (b_i) is equal to this mortality term.

Whether newborns are maternally immune (b_{Mi}) or susceptible (b_{Xi}) depends on the distribution of immune and susceptible females weighted by their age dependent fertility (p_j).

$$b_{Mi} = b_i \frac{\sum_j (N_{2j} - X_{2j}) p_j}{\sum_j N_{2j} p_j},$$

$$b_{Xi} = b_i \frac{\sum_j X_{2j} p_j}{\sum_j N_{2j} p_j},$$

$$b_i = \frac{N_{iL-1}}{d},$$

$$p_j = \frac{\text{no. live newborns in 1973 from mothers of age } j}{\text{no. women in 1973 of age } j}.$$

The rate of transition from the compartments M, H and Y is equal to the reciproke of the time of residence in that compartment:

$$r_M = \frac{1}{t_M}, \quad r_H = \frac{1}{t_H}, \quad r_Y = \frac{1}{t_Y}.$$

The parameter pc, the effective contact rate per day, is the product of p and c, with p the probability of transmission per contact between a susceptible and an infectious person, and c the number of contacts per person per day. Separate estimated values for p and c are not known, but the product pc can be estimated from the basic reproduction number (R_0), which in turn is related to the equilibrium force of infection (λ_0) according to the following formulas:

$$pc = R_0 r_Y = \frac{\lambda_0 L}{1 - e^{-\lambda_0 L}} r_Y$$

for step function mortality [2, 20].

Parameter assignment

An overview of the data, from which parameter values used in the model were estimated, are shown in Table 2.

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Model extended with import

Import of infectives was implemented in the model. The number of imported infectives during one day (n_{imp}) was distributed over the gender- and age classes of the infectives. In order to keep population size and class size constant the number of imported infectives added was interchanged with susceptibles and immunes, one of which is usually large in every gender- and age class. A fraction $X_{ij}/(X+Z)$ of n_{imp} was subtracted from $\mathrm{d}X_{ij}/\mathrm{d}t$, and the complement fraction for each gender- and age class $Z_{ij}/(X+Z)$ of n_{imp} was subtracted from $\mathrm{d}Z_{ij}/\mathrm{d}t$. The term $[(X_{ij}+Z_{ij})/(X+Z)]$ n_{imp} was added to $\mathrm{d}Y_{ij}/\mathrm{d}t$ for each gender- and age class.

REFERENCES

1. Gezondheidsraad. Advies inzake Bof-/Rubella-vaccinatie (in Dutch). Staatsuitgeverij, Den Haag, 1984.
2. Druten JAM van, Boo Th de, Doesburg WH, et al. Incidentie van het congenitaal rubella syndroom, een mathematisch-epidemiologische benadering. T Soc Gezondheidsz 1984; **62**: 438–46.
3. Druten JAM van, Boo Th de, Doesburg WH, et al. Rubellavaccinatie, effecten op lange termijn van alternatieve strategieën. T Soc Gezondheidsz 1986; **64**: 210–8.
4. Druten JAM van, Boo Th de, Plantinga AD. Measles, mumps and rubella: control by vaccination. Develop Biol Standard 1986; **65**: 53–63.
5. Boo ThM de, Druten JAM van, Plantinga AD. Predicting the dynamic effects of rubella vaccination programmes. Stat Med 1987; **6**: 843–51.
6. Knox EG. Strategy for rubella vaccination. Int J Epidemiol 1980; **9**: 13–23.
7. Knox EG. Epidemiology of prenatal infections: An extension of the congenital rubella model. Stat Med 1983; **2**: 1–12.
8. Dietz K. The evaluation of rubella vaccination strategies. In: Hiorns RW, Cooke D, eds. The mathematical theory of the dynamics of biological populations, vol. II. London: Academic Press, 1981: 81–98.
9. Hethcote HW. Measles and rubella in the United States. Am J Epidemiol 1983; **117**: 2–13.
10. Anderson RM, May RM. Vaccintion against rubella and measles: quantitative investigations of different policies. J Hyg 1983; **90**: 259–325.
11. Anderson RM, May RM. Age-related changes in the rate of disease transmission: implications for the design of vaccination programmes. J Hyg 1985; **94**: 365–436.
12. Anderson RM, Grenfell BT. Quantitative investigations of different vaccination policies for the control of congenital rubella syndrome (CRS) in the United Kingdom. J Hyg 1986; **96**: 305–33.
13. Nokes DJ, Anderson RM, Anderson MJ. Rubella epidemiology in South East England. J Hyg 1986; **96**: 291–304.
14. Gay NJ, Hesketh LM, Morgan-Capner P, Miller E. Interpretation of serological surveillance data for measles using mathematical models: implications for vaccine strategy. Epidemiol Infect 1995; **115**: 139–56.
15. Edmunds WJ, Medley GF, Nokes DJ. Vaccination against hepatitis B virus in highly endemic areas: waning vaccin-induced immunity and the need for booster doses. Trans R Soc Trop Med Hyg 1996; **90**: 436–40.
16. Rouderfer V, Becker NG, Hethcote HW. Waning immunity and its effect on vaccination schedules. Math Biosci 1994; **124**: 59–82.
17. Schenzle D. An age-structured model of pre- and post-vaccination measles transmission. IMAJ Math Appl Med Biol 1984; **1**: 169–91.
18. Bolker BM, Grenfell BT. Chaos and biological complexity in measles dynamics. Phil Trans R Soc Lond B Biol Sci 1993; **251**: 75–81.
19. Babad HR, Nokes DJ, Gay NJ, Miller E, Morgan-Capner P, Anderson RM. Predicting the impact of measles vaccination in England and Wales: model validation and analysis of policy options. Epidemiol Infect 1995; **114**: 319–44.
20. Anderson RM, May RM. Infectious diseases of humans: dynamics and control. New York: Oxford University Press, 1991.
21. Veer M van der, Noorle Jansen LM van, Nagel J, Steenis G van, Plantinga AD, Rümke HC. Antistofpatronen in een doorsnede van de Nederlandse bevolking. Onderzoek peilstations in 1980 en 1985. RIVM-rapport nr 927901007, Januari 1993.
22. Druten JAM van, Reintjes AGM, Plantinga AD, et al. Bof, mazelen en rubella, een longitudinaal serologisch onderzoek naar de beschermingsgraad en besmettingsintensiteit. Eindverslag Praeventiefondsproject nr 28-1348, April 1990.
23. Melker HE de, Peet TE van der, Berbers GAM, et al. Pilot-onderzoek voor het Pienter-project. Seroprevalenties voor bof, mazelen, rubella, kinkhoest, Toxoplasma gondii, Toxocara, T. spiralis en hepatitis A. RIVM-rapport nr 213675004, December 1995.
24. Benenson AS (ed.). Control of communicable diseases in man. Washington: American Public Health Association, 1990.
25. Craddock-Watson JE. Laboratory diagnosis of rubella: past, present and future. Epidemiol Infect 1991; **107**: 1–15.
26. Morgan-Capner P, Wright J, Miller Cl, Miller E. Surveillance of antibody to measles, mumps, and rubella by age. BMJ 1988; **297**: 770–2.
27. Horstmann DM, Liebhaber H, Le Bouvier GL, Rosenberg DA, Halstead SB. Rubella: reinfection of vaccinated and naturally immune persons exposed in an epidemic. N Engl J Med 1970; **283**: 771–8.
28. Harcourt GC, Best JM, Banatvala JE. Rubella-specific serum and nasopharyngeal antibodies in volunteers with naturally acquired and vaccine-induced immunity after intranasal challenge. J Infect Dis 1980; **142**: 145–55.

29. Morgan-Capner P, Hodgson J, Sellwood J, Tippett J. Clinically apparent rubella reinfection. J Infect 1984; **9**: 97–100.
30. Bott LM, Eizenberg DH. Congenital rubella after successful vaccination. Med J Aust 1982; **1**: 514–5.
31. Best JM, Banatvala JE, Morgan-Capner P, Miller E. Fetal infection after maternal reinfection with rubella: criteria for defining reinfection. BMJ 1989; **299**: 773–5.
32. Morgan-Capner P., Hambling MH, Coleman TJ, et al. Detection of rubella-specific IgM in subclinical rubella reinfection in pregnancy. Lancet 1985; i: 244–6.
33. Gilbert J, Kydesia G. Fetal infection after maternal reinfection with rubella. BMJ 1989; **229**: 1217.
34. Cusi MG, Rossolini GM, Valensin PE, Cellesi C, Zanchi A. Serological evidence of reinfection among vaccinees during rubella outbreak. Lancet 1990; **336**: 1071–3.
35. Ross R, Harvey DR, Hurley R. Reinfection and congenital rubella syndrome. Practitioner 1992; **236**: 246–51.
36. Aboudy Y, Fogel A, Barnea B, et al. Subclinical rubella reinfection during pregnancy followed by transmission of virus to the fetus. J Infect 1997; **34**: 273–6.
37. Best JM. Rubella vaccines: past, present and future. Epidemiol Infect 1991; **107**: 17–30.
38. Miller E, Tookey P, Morgan-Capner P, et al. Rubella surveillance to June 1994: third joint report from the PHLS and the National Congenital Rubella Surveillance Programme. CDR Rev 1994; **4**: R146–52.
39. Miller E, Waight P, Gay N, et al. The epidemiology of rubella in England and Wales before and after the 1994 measles and rubella vaccination campaign: fourth joint report from the PHLS and the National Congenital Rubella Surveillance Programme. CDR Rev 1997; **7**: R26–32.
40. Böttiger M, Forsgren M. Twenty years' experience of rubella vaccination in Sweden: 10 years of selective vaccination (of 12-year-old-girls and of women postpartum) and 13 years of a general two-dose vaccination. Vaccine 1997; **15**: 1538–44.
41. Netherlands Central Bureau of Statistics. Pocket Yearbook 1975. 's Gravenhage: staatsuitgeverij, 1975.
42. Inspectie voor de Gezondheidszorg. Vaccinatietoestand Nederland per 1 januari 1994 en per 1 januari 1995. Rijswijk: 1996.
43. Burgmeijer RJF, Bolscher DJA. Vaccinaties bij kinderen. Uitvoering en achtergronden van het Rijksvaccinatieprogramma en andere vaccinaties bij kinderen. Assen: Van Gorcum, 1995.