Epidemiol. Infect. (2002), **128**, 47–57. © 2002 Cambridge University Press
DOI: 10.1017/S0950268801006409 Printed in the United Kingdom

Protecting the vaccinating population in the face of a measles epidemic: assessing the impact of adjusted vaccination schedules

S. VAN DEN HOF[1]*, J. WALLINGA[1], M.-A. WIDDOWSON[1,2] AND M. A. E. CONYN-VAN SPAENDONCK[1]

[1] *National Institute of Public Health and the Environment, Department of Infectious Diseases Epidemiology, P.O. Box 1, 3720 BA Bilthoven, The Netherlands*
[2] *European Programme for Intervention Epidemiology*

(*Accepted 3 September 2001*)

SUMMARY

We investigated which vaccination schedule gives best protection to the vaccinating population, in case there is a measles epidemic in an area with low vaccine coverage. We considered combinations of an early measles vaccination (none, at 6 months or at 9 months), a measles–mumps–rubella (MMR) vaccination around the first birthday (at either 11 or 14 months), and MMR vaccination at an older age (at either 4 or 9 years). The different estimates on measures of protection (percentage of susceptibles, number of reported cases in an epidemic year, percentage of lifetime spent susceptible) relied on a mathematical model of decline of maternal antibody levels with age, and the impact of that antibody level on seroconversion and immunity. Model parameters were estimated from a Dutch population-based serological survey on measles antibodies. Different measures of protection favoured different vaccination schedules, but dropping the age of second MMR vaccination prevents considerably more cases than an extra early measles vaccination or dropping the age of first MMR vaccination.

INTRODUCTION

The purpose of high measles vaccine coverage is to protect as many people as possible from clinical measles infection and its complications, and to prevent transmission of the virus within a population. If the proportion of immune individuals is high enough, transmission can be completely interrupted and measles will be eliminated. It has been estimated that to achieve this, vaccine coverage levels of 95% for two doses are required [1]. However, pockets of low vaccine coverage within areas of otherwise high coverage may prevent elimination of measles [2].

Pockets of low vaccine coverage exist in several countries, either due to religious reasons, e.g. Amish communities in the United States, orthodox Jewish communities in the United Kingdom [3, 4] or for programmatic reasons, e.g. low uptake in parts of Dublin, Ireland [5]. In the Netherlands, pockets of low vaccine coverage exist as a result of socio-geographic clustering of orthodox reformed communities that decline vaccination on religious grounds. Although national measles vaccine coverage has been 94–96% in the Netherlands since 1986, some municipalities have vaccine coverage as low as 53% [6].

This large group of vaccine decliners has been an important factor in the occurrence of regular measles epidemics in the Netherlands since vaccination started in 1976. In the most recent epidemic, from June 1999 to April 2000, 3292 cases were reported, most of whom were unvaccinated for religious reasons. There were, however, also 96 cases in individuals too young to be vaccinated, whose parents would have vaccinat-

* Author for correspondence.

ed their child at the recommended time. Additionally there were 157 cases with primary vaccine failure. Nearly all of these cases among vaccine acceptors occurred in areas with low vaccine coverage.

The objective of this study was to investigate which vaccination schedule gives best protection from measles in vaccine acceptors. We considered various combinations of three key changes to the regular Dutch measles vaccination schedule (two doses of measles–mumps–rubella (MMR) vaccine, at 14 months and 9 years). These were administering an extra early measles vaccination at the age of 6 or 9 months followed by the regular two-dose MMR vaccination schedule, giving the first MMR vaccination at 11 months or giving the second MMR vaccination at 4 years.

It is widely believed that the level of (maternal) antibodies determines whether an individual will seroconvert or not, and whether an individual is protected against natural infection or not. We propose a stochastic model that relates age-specific levels of antibodies to age-specific seroconversion rates. We fitted this model to Dutch serological data, and used the fitted model to evaluate the impact of alternative vaccination schedules on age-specific levels of immunity. We have discussed our results in the light of published literature. We hope that our findings will be helpful in deciding on a vaccination schedule that will best protect those vaccinated during a measles epidemic in areas of low herd immunity.

METHODS

First, we estimated the age-specific decline in maternal levels of antibodies and its relation to age-specific seroconversion rates, using data from a Dutch population-based serological survey [7]. Second, we assessed how different vaccination schedules result in different age-specific percentages of susceptibles on a population level immediately after each new schedule with a catch-up campaign was implemented, and we translated these age-specific percentages of susceptibility into the number of reported cases in this population in an epidemic year. Third, besides assessing the impact of a new schedule with catch-up on the short term, we estimated the average percentage of entire lifetime spent susceptible when following a particular vaccination schedule, an indication for the performance of the schedule on susceptibility in the long term.

Description of age-specific levels of maternal antibodies, and probability of susceptibility and seroconversion

Log-transformed levels of antibodies, at any particular age, are well described by a normal distribution [8, 9]. We denoted an individual's log-transformed antibody level by x. This is a stochastic variable with a normal probability distribution with age-dependent mean $m(a)$ and a constant standard deviation s. That is, $x \sim N(m(a), s^2)$. The log-transformed maternally derived antibody levels decline approximately linearly with age in the first months of life, with an approximately constant standard deviation [8, 9]. This rate of decline levels off to a low, but detectable antibody level [10]. The mean log-transformed level of maternal measles antibodies in individuals not vaccinated against measles, and not naturally infected, varies with age according to the following equation:

$$m(a) = \ln(M_0 e^{-da} + B). \quad (1)$$

For low ages, this relation shows a linear decline, with rate d, for log-transformed maternal levels of antibody from $\ln(M_0 + B)$ at low age, and approaches a constant baseline level B for higher ages (Fig. 1), which correlates with 97% chance on seroconversion.

The interpretation of the relation between antibody level and age that is maintained here is the following: each individual of a particular age has the same expected value, and the variation around this expected value is not correlated in time (like measurement noise).

We denote the probability that an unvaccinated and uninfected child is susceptible for measles infection at age a by $w(a)$. This is the probability that an unvaccinated individual at age a has a level of antibodies below the critical level for protection W:

$$w(a) = \Pr(x \leqslant \ln W).$$

We used the value of 0·2 international units per millilitre (IU/ml) for W, which is often used in other studies [7, 8, 10, 11].

We denote the probability that a susceptible individual of age a will seroconvert by $v(a)$. It is the age-specific proportion of unvaccinated children with a level lower than the critical level for seroconversion V:

$$v(a) = \Pr(x \leqslant \ln V). \quad (2)$$

Seroconversion results in effective protection

https://doi.org/10.1017/S0950268801006409 Published online by Cambridge University Press

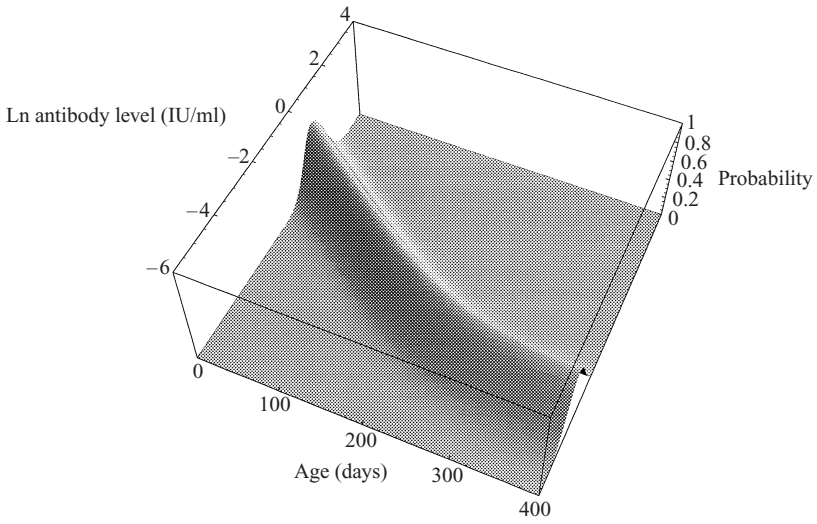

Fig. 1. Stochastic relation between age and maternal measles antibody levels in infants not vaccinated against measles, and not naturally infected (see equation (1)).

Table 1. *Maximum likelihood estimates* (*MLE*) *of parameter values with* 95% *credible intervals* (*CI*)

	MLE	(95% CI)	Units	Interpretation
V	0·084	(0·072–0·136)	IU/ml	Critical level for seroconversion
M_0	3·038	(2·659–4·230)	IU/ml	Mean level of antibodies at birth
B	0·025	(0·022–0·029)	IU/ml	Baseline level of antibodies
d	0·019	(0·018–0·022)	IU/(ml day)	Rate of decay of maternal antibodies
s	0·647	(0·455–0·991)	IU/ml	Standard deviation of level of antibodies before seroconversion
f	10·9	(8·1–13·4)	Day	Lag between vaccination and onset of immunity

against measles infection. The time lag between vaccination and onset of protection is denoted by f.

With equations (1) and (2) we can specify the probability of having a certain level of antibodies at a certain age, given the values of the parameters V, M_0, B, d, s and f. The likelihood function for these parameters can be derived in a straightforward manner. We have observations on the level of measles antibody over a wide age range from a serological cross-sectional survey of the Dutch population in 1995–6 [7]. The parameter values were estimated as those values that maximize the likelihood given the observations from the serological cross-sectional survey (Wallinga, unpublished results). A quantification of the uncertainty in the estimates was obtained by Markov chain Monte Carlo methods [12], which allowed us to sample plausible values for each parameter, from which we estimated 95% credible intervals (CI). The maximum likelihood estimates of V, M_0, B, d, s and f with corresponding CI are given in Table 1. Figure 2 shows a comparison of predicted seroconversion levels with observed seroconversion levels according to re-analysis of published data on a field trial in the Netherlands in 1990–1 [13].

Vaccination schedules

We denote the probability for a vaccine-accepting individual to be susceptible at age a by $u(a)$. We denote the ages at which an individual receives vaccination by A_1 and A_2. From equations [1] and [2], that describe the probability of susceptibility and seroconversion of an unvaccinated individual, we can derive that the probability of susceptibility of an individual as a result of a vaccination schedule at any age is described as follows:

$$u(a) = \begin{cases} w(a) \text{ if } 0 \leqslant a \leqslant A_1 + f \\ w(a) - v(A_1) \text{ if } A_1 + f < a \leqslant A_2 + f \\ (1 - v(A_1))(w(a) - v(A_2) \text{ if } A_2 + f < a \leqslant L \end{cases}$$

where L is the life expectancy (assumed to be 75 years), and f again is the lag between vaccination and onset of effective immunity (10·9 days, see Table 1). It is assumed that vaccine-induced immunity does not

https://doi.org/10.1017/S0950268801006409 Published online by Cambridge University Press

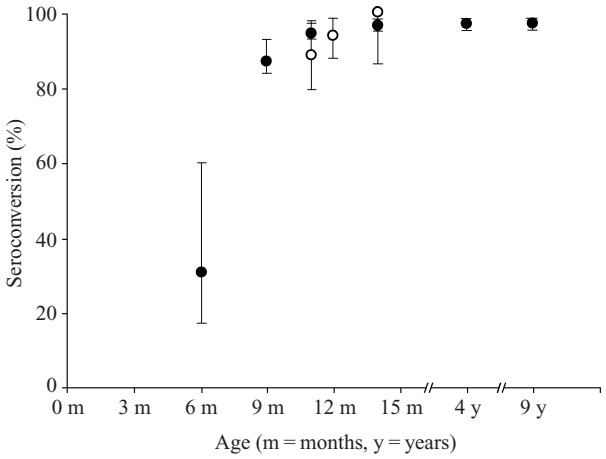

Fig. 2. Predicted seroconversion levels (●) with 95% credible intervals by age, and observed seroconversion levels (○) by age in a field trial in the Netherlands in 1990–1 (see reference 13).

wane. The implications of this assumption will be discussed later. The extension to three ages at which vaccine is offered, is straightforward.

Measures of protection of vaccine acceptors

Percentage of susceptibles shortly after introducton of a new vaccination schedule

A measure of the impact of a new vaccination schedule in the short term is the percentage of susceptibles within the population shortly after the introduction of the new vaccination schedule with concomitant catch-up campaign. It is assumed that vaccine acceptors followed the old schedule (14 months and 9 years) before the new schedule was introduced. We then assessed for each age group whether individuals were entitled to a catch-up vaccination according to the new schedule. For example, with a new vaccination schedule of 6 months, 14 months and 4 years, all children aged 6–14 months and all children 4–9 years are entitled to a catch-up vaccination. Thus, A_1 and A_2, the ages at which individuals were administered doses of measles or MMR vaccine, may differ between individuals due to the catch-up campaign.

The probability of being susceptible was assessed immediately after the time lag f between vaccination and onset of immunity had expired. We then took the weighted average over all age groups, assuming everybody has a lifetime expection at birth of 75 years, and multiplied it by 100%. The result is the percentage of susceptibles in the whole population.

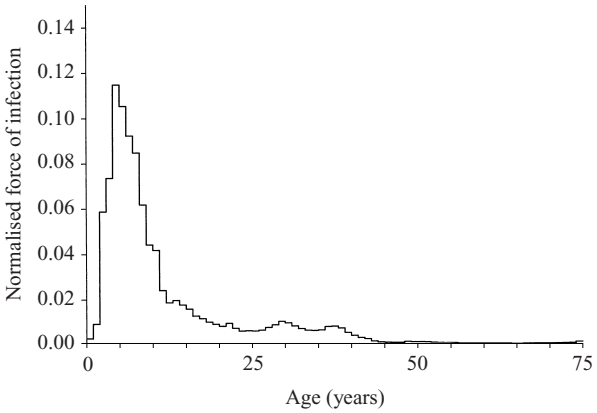

Fig. 3. Probability by age, for a susceptible vaccine acceptor to become a reported case in an epidemic year.

Number of reported cases shortly after introduction of a new vaccination schedule

Another, related, measure of protection in the short term is the number of reported cases in an epidemic year shortly after implementation of the new vaccination schedule and concomitant catch-up programme. This gives an idea of the public health impact of a new vaccination schedule.

We estimated the age-dependent probability of contracting infection and becoming a reported case as follows. From the national population survey from 1995–6 [7] we reconstructed the number of susceptibles per age cohort in the Dutch population. From the database of reported measles cases we extracted the number of cases per age cohort per year from 1988 until 2000. We estimated the average annual number of reported cases per number of susceptibles for each age cohort. We then calculated the relative increase of number of reported cases in the epidemic year 1988 over the annual average. The arbitrary choice for this particular epidemic year affects absolute outcome only; as the relative age-dependent risk of infection does not change between epidemic years, it does not affect relative outcomes. From the database, we estimated the relative proportion of vaccine acceptors among the reported cases to be 6%. This makes it possible to calculate the age-specific probability for a susceptible vaccine acceptor to become a reported case in an epidemic year (Fig. 3).

For each vaccination schedule, the age-specific probability of being a susceptible vaccine acceptor was multiplied with the age-specific probability of being reported (conditional on being a susceptible vaccine acceptor). The age-specific probabilities of being reported, while accepting vaccine, were averaged over the vaccinating population, thus giving an

https://doi.org/10.1017/S0950268801006409 Published online by Cambridge University Press

estimate of the number of reported cases. We assumed that all cases among vaccine acceptors were infected by vaccine decliners, and that transmission between vaccine acceptors is negligible.

Percentage of lifetime spent susceptible as a result of a vaccination schedule

A measure of the long-term impact of a vaccination schedule on immunity is the average percentage of entire lifetime spent susceptible. Here, we consider only individuals that follow the same specific vaccination schedule throughout their lives (and not, as we did in the previous section, a whole population adjusting to a new vaccination schedule with concomitant catch-up programme). Therefore, A_1 and A_2 are simply the ages at which vaccinations are offered, and they are the same for everybody.

We averaged the age-specific probabilities of being susceptible over an entire lifetime (assuming everybody has a lifetime expection at birth of 75 years and is not infected with wild measles virus), and multiplied by 100%. The resulting expected percentage of entire lifetime spent susceptible is considered to be a projection of long-term impact of a new vaccination schedule on population susceptibility levels.

RESULTS

Measures of protection of vaccine acceptors

The estimated impact of various measles vaccination strategies among vaccine acceptors on susceptibility levels is shown in Table 2. The lowest percentage of measles susceptibles in the short term, that is, shortly after introduction of the new strategy was established, is achieved by vaccinating at age 6 months, 14 months, and 4 years with catch-up; the highest percentage results from the regular schedule (14 months and 9 years, no catch-up). The differences in the estimated percentages of susceptibles between vaccination schedules are the result of a decrease in measles susceptibility in children under 10 years of age, since none of the evaluated vaccination schedules affects the vaccination status in those aged 10 years and older. The estimated rates of reported measles cases among vaccine acceptors in an epidemic year are also shown in Table 2. The results show that a lower percentage of susceptibles does not guarantee a lower number of cases, due to the fact that force of infection differs with age (Fig. 3). For example, the strategy of offering vaccine at 11 months and 9 years results in a lower percentage of susceptibles than offering vaccine at 14 months and 4 years, but leads to more reported cases.

The long-term consequences of the various measles vaccination schedules on susceptibility (i.e. the average percentages of the lifetime spent susceptible when following a schedule throughout life) if not infected, are also shown in Table 2. The lowest percentage lifetime spent susceptible is achieved by vaccinating at 9 months, 14 months, and 4 years; the highest percentage results from the regular schedule. The percentages of lifetime spent susceptible (range 0·95–1·48%) are higher than or equal to the percentages of susceptible in the population in the short term (range 0·53–1·48%).

Impact of an extra, early measles vaccination

The seroconversion at 6 months of age was estimated to be 30% (CI 17–60%), and the seroconversion at 9 months was estimated to be 86% (CI 84–93%) (Fig. 2). When an extra early vaccination with catch-up campaign is introduced, all 6–14-month-old infants or 9–14-month-old infants are vaccinated at the same time. In this case an extra vaccination at 6 months leads to a smaller percentage of susceptibles shortly after introduction of the new vaccination schedule than an extra early vaccination at 9 months. However, as the risk of susceptible infants to acquire measles infection in an epidemic year is relatively small (Fig. 3), this difference in percentage of susceptibles leads to a small difference in expected number of reported cases. Following a schedule with an extra vaccination at 6 months leads to a higher percentage of lifetime spent susceptible than an extra vaccination at 9 months (Table 2).

Impact of dropping the age of first MMR vaccination

The seroconversion at 11 months of age was estimated to be 94% (CI 93–97%), and the seroconversion at 14 months was estimated to be 97% (CI 95–98%) (Fig. 2). When a new vaccination schedule with a dose at 11 months with catch-up campaign is introduced, all 11–14-month-old children are vaccinated. In this case a vaccination at 11 months leads to less susceptibles shortly after introduction of the new vaccination schedule compared to a vaccination at 14 months. As the risk of susceptible children aged 11–14 months to acquire measles infection during an epidemic is relatively small (Fig. 3), a vaccination at 11 months results in slightly less reported cases as compared to

https://doi.org/10.1017/S0950268801006409 Published online by Cambridge University Press

Table 2. *Estimated percentage of susceptibles and estimated rate at which new cases are reported in an epidemic year among vaccine-acceptors*, and estimated percentage of entire lifetime spent susceptible for an individual* (0–75 *years*) *for different vaccination schedules*

Vaccine and age at vaccination					
Measles	First MMR	Second MMR	% Susceptible (95% CI)	Rate of cases reported (year^{-1})†	% Lifetime spent susceptible (95% CI)
6 months	14 months	4 years	0·53 (0·31–0·63)	24	0·95 (0·59–1·07)
6 months	14 months	9 years	0·74 (0·37–0·89)	80	1·09 (0·64–1·26)
9 months	14 months	4 years	0·75 (0·55–0·84)	25	0·68 (0·54–0·75)
9 months	14 months	9 years	0·96 (0·60–1·10)	81	0·70 (0·54–0·78)
	11 months	4 years	0·95 (0·76–1·04)	26	1·09 (0·80–1·20)
	11 months	9 years	1·16 (0·81–1·31)	83	1·43 (0·92–1·61)
	14 months	4 years	1·27 (1·08–1·37)	34	1·27 (1·08–1·37)
	14 months	9 years	1·48 (1·13–1·63)	90	1·48 (1·13–1·63)

* Note that vaccine accepting population also includes infants too young to be vaccinated.
† Note that 1 reported case may stand for 40–70 real cases (see reference 14).

vaccination at 14 months. Vaccinating at 11 months also leads to a slightly lower average percentage lifetime spent susceptible than vaccinating at 14 months (Table 2).

Impact of dropping the age of second MMR vaccination

The seroconversion at both 4 and 9 years was estimated to be 97% (CI 95–98%) (Fig. 2). The purpose of this second MMR vaccination is to provide a second opportunity for immunity in those individuals who did not respond to the first MMR vaccination. Vaccinating at 4 years of age leads to a lower percentage of susceptibles shortly after introducing the new vaccination schedule as compared to vaccinating at 9 years of age. Because the risk of susceptible children of 4–9 years of age to acquire measles infection during an epidemic is relatively high (Fig. 3), the vaccination at 4 years of age results in less than half the number of reported cases as compared to vaccinating at 9 years of age (in absence of an extra, early measles vaccination, Table 2). Vaccinating at 4 years of age also leads to a lower expected percentage of lifetime spent susceptible than vaccinating at 9 years of age.

DISCUSSION

Our objective was a very specific one, that has not been addressed before: the minimization of risk of measles infection for vaccine-accepting people living in and around areas of low vaccine coverage. We have estimated age-specific levels of susceptibility to measles infection in the vaccinating population and the resulting number of measles cases in an epidemic year, that would result from various vaccination schedules. The percentages of lifetime spent susceptible when following a given schedule throughout life, are higher than or equal to the percentages of susceptibles shortly after introduction of the same schedule with catch-up (Table 2). This shows that there are substantial effects from the concomitant catch-up campaigns on susceptibility levels in the short term.

Our results indicate that relative differences between vaccination strategies are large, but that differences are small in absolute terms. Furthermore, none of the vaccination schedules can prevent all cases among vaccine acceptors, because maternal antibodies interfere with vaccination in infants, and because vaccine efficacy is below 100%. There are two points to keep in mind, when interpreting the results. First, the numbers presented here refer to the proportion of susceptibles and number of reported measles cases among the vaccine-accepting population, and they should not be confused with the proportion of susceptibles and reported cases among the entire Dutch population. Second, due to underreporting, the number of reported cases does not stand for the number of real cases of measles: each reported case might represent up to 40–70 real cases of measles [14].

Strengths and limitations of the modelling approach

Our methodological approach is new in that we have constructed a stochastic model that allows us to

https://doi.org/10.1017/S0950268801006409 Published online by Cambridge University Press

estimate parameter values from serological data, as well as predict the impact of alternative vaccination schedules. A major advantage is that we can use this model to translate uncertainty in the estimated parameter values into uncertainty in the model outcome, and quantify this uncertainty by means of a credible interval. We have presented the stochastic model as if it were a mechanistic model that explains seroconversion in terms of antibody levels whereas other modelling studies have adapted a more descriptive approach [15–18].

The particular interpretation that we give to the model (that is, absence of correlation in individual antibody levels) is simply the most parsimonious mechanistic explanation we could imagine, given the lack of information on correlation of antibody levels and vaccine failure at an individual level, and given the relatively small differences in individual antibody levels at any particular age as compared to differences in antibody levels across ages (Fig. 1). However, the mathematical structure of the model allows more interpretations, and therefore one should see the model as a descriptive model with parameter values that allow a direct epidemiological interpretation. For example, the stochastic model enabled us to estimate a threshold antibody level of 0·084 IU/ml (CI 0·072–0·136 IU/ml) above which vaccination will not result in immunity, and this estimate is well within range of the previous estimate of 0·05 IU/ml [8, 9]. The good performance of the model, as indicated by the small credible intervals for parameter estimates (Table 1) and good predictions (Fig. 2), do not signify any proof of a causal relation between antibody levels and seroconversion, but show that there is a good (non-linear) association that can be used for prediction. Predictions should not extend beyond the range of antibody levels and ages (< 10 years) that were used to estimate the parameter values; the model does not inform on, for instance, waning of vaccine-induced immunity. Very few studies have estimated the impact of measles epidemics in a group of vaccine decliners on a surrounding population of vaccine acceptors. Salmon et al. provide a method to quantify the risk of contracting measles that vacine decliners pose to the vaccine accepting population, given the degree of mixing between decliners and acceptors [19]. However, estimating the degree of mixing between decliners and acceptors is a difficult, if not impossible, task. By contrast, our approach presumes that an epidemic outbreak of measles is maintained entirely by vaccine decliners, and that transmission between vaccine acceptors is negligible. All one needs to know is the force of infection as experienced by the vaccine acceptors during epidemic years, which can be estimated from case reports. In the Netherlands, measles cases among vaccine acceptors do not appear to be clustered in time and place [20], suggesting that the assumption of negligible transmission of measles among vaccine acceptors is justified.

Our estimations do not take into account all factors that may affect the applicability of a particular measles vaccination schedule. These include an effect of concomitant vaccines, logistical aspects, and acceptance of an altered vaccination schedule. We will discuss these factors in the light of published literature. Furthermore, we will consider the influence of adjusted vaccination schemes on protection against mumps and rubella.

Impact of an extra, early measles vaccination

In case that an additional vaccination at either 6 or 9 months is used for improving protection of infants during an epidemic, the results show that offering vaccine at 9 months is preferable (Table 2): the difference on projected number of reported cases is rather small (24 *vs.* 25), while the difference in time spent susceptible is considerably greater (1·09% *vs.* 0·70%, in case of second and third vaccination at 14 months and 9 years).

The level of measles antibodies below which individuals seroconvert is lower than the level required for protection. Thus, at certain antibody levels, an individual will not be immune nor seroconvert after vaccination. Infants who do not seroconvert after an early vaccination as a result of residual maternal antibodies, will have already lost or lose this maternal immunity shortly afterwards. Because of this, and because seroconversion rates are higher at 9 than at 6 months of age, an extra measles vaccination at 6 months results in higher average percentage of lifetime spent susceptible than an extra vaccination at 9 months. Furthermore, most of this susceptible time is during infancy, when the risk of complications upon infection is higher than later in childhood [21].

Findings of previous studies show that measles antibody titres may be lower after one early vaccination in the presence of maternal antibodies and a revaccination (at 14–15 months) than after one vaccination as scheduled [22–25], but findings on seroconversion rates and vaccine effectiveness conflict [22, 26–28].

https://doi.org/10.1017/S0950268801006409 Published online by Cambridge University Press

Administering an extra vaccination is likely to be a burden for vaccine acceptors and the health care system. Since it will only protect a small number of children who are at increased risk, an extra early vaccination seems warranted only in epidemic years.

Impact of dropping the age of the first MMR vaccination

According to the results of our analysis, dropping the age of the first MMR vaccination from 14 to 11 months has relatively little impact on the percentage of susceptible vaccine acceptors, on the number of cases reported among vaccine acceptors, and on the long-term estimates of susceptibility.

From outbreaks and vaccine trials there is evidence that children vaccinated at 15 months are more likely to make and maintain measles antibodies and are less likely to be infected in outbreak situations than those children vaccinated earlier [27, 29–33]. De Serres et al. showed an incremental increase in protection with age at vaccination: the vaccine efficacy in an outbreak situation rose from 84% in children vaccinated before 12 months to 94% in those vaccinated at 15–17 months to 97% in children vaccinated at 18 months or later [34]. Many of these children were born of naturally immune mothers. Other studies have shown that maternal antibodies in children of mothers who were vaccinated and raised in an era with less measles virus circulation, are below protective levels quicker than those of naturally immune mothers [8, 35]. In accordance with this, vaccinating infants just under 12 months of age of vaccinated mothers yields seroconversion rates similar to those in infants vaccinated over 12 months [31, 33, 36].

In the Netherlands approximately 90% of the children are currently still born from naturally immune mothers [37]. In the present situation vaccinating infants under 12 months may result in a poorer immune response, as confirmed by a Dutch study [13], see Fig. 2. It is possible that in the future when most mothers have vaccine-induced immunity, antibody levels in infants will allow a MMR vaccination under 12 months with high vaccine efficacy to the measles component. Further serological studies are required on which to base this change.

For mumps and rubella, the age of vaccination does not seem to be as critical as for measles. Mumps vaccination given at 12–14 months has not been associated with vaccine failure [38, 39]. For rubella, succesful vaccination is even likely from 9 months on [40].

Impact of dropping the age of the second MMR vaccination

We showed that dropping the age of the second MMR vaccination causes a small reduction in the percentage of susceptibles on a population level in the short and long term, but a substantial reduction of cases among vaccine acceptors in case of a measles epidemic (Table 2), since almost all children who did not respond to the first MMR will seroconvert upon a second vaccination.

Our estimations did not take into account waning of antibodies over lifetime. Measles, mumps, and rubella antibodies are all known to decrease after vaccination [7, 41–43]. This becomes a problem if antibodies wane to non-protective levels after vaccination, leading to secondary vaccine failures. The risks of complications for measles, mumps, and especially rubella, are greater after than during childhood [21]; the purpose of rubella vaccination is sustained immunity through childbearing age, in order to avoid congenital rubella syndrome (CRS). Until now, no problems with secondary vaccine failures have been observed for all three diseases in industrialised countries, even when the second MMR vaccine is given at 4–6 years [21, 44–50]. If waning of, particularly, rubella antibodies and of measles and mumps antibodies is no problem, a drop in the age of the second MMR vaccination could be considered.

Immunogenicity and reactogenicity of adjusted vaccination schedules

A decline in immunogenicity (vaccine efficacy), and an increase in reactogenicity (adverse events) as a result of a different vaccination schedule may eventually lead to reduced vaccine coverage within the population. In the particular situation of the Dutch vaccination schedule, dropping the age of second MMR vaccine to 4 years implies giving vaccinations simultaneously, that normally are not given together (MMR and DT–IPV). Many studies have shown that giving live and inactivated vaccines simultaneously, does not affect immunogenicity [51–57], and that the number of adverse events after simultaneous vaccinations is on average smaller than after the same number of injections given at different times [58]. Also, it seems unlikely that adding an extra, early measles vaccination or dropping the age of the first MMR

vaccination will lead to an increase in the number of adverse events [40].

In conclusion, in case of an epidemic, giving an extra, early vaccination at 9 months could be implemented temporarily, since this provides good protection for infants in the short term, and the thrice vaccinated cohort also has low susceptibility levels in the long term. In the current Dutch situation, with most mothers having naturally acquired immunity, a first MMR vaccination at 11 months only leads to a small reduction in cases in the short term, while it has no impact on population susceptibility levels in the long term. Bringing forward the age of second MMR vaccination to approximately 4 years would lead to the greatest reduction in number of cases in the short and long term. To prevent cases in the long term and to increase the proportion of immunes in the vaccinating population, lowering the age of the second vaccination in the regular measles vaccination schedule is worth considering.

ACKNOWLEDGEMENTS

The authors thank the members of the Outbreak Management Team who, in the face of the Dutch 1999/2000 measles epidemic, posed the question addressed in this manuscript: How to best protect the vaccinating population? We acknowledge the DGV of the European Commission for funding the European Programme for Intervention Epidemiology (agreement number: SI2.74030 (99CVVF4-003-0)).

REFERENCES

1. World Health Organization. Strategic plan for the elimination of measles in the European Region. Copenhagen, Denmark, 1997.
2. World Health Organization. A strategic framework for the elimination of measles in the European Region. Copenhagen, Denmark, 1999.
3. Briss PA, Fehrs LJ, Hutcheson RH, Schaffner W. Rubella among the Amish: resurgent disease in a highly susceptible community. Pediatr Infect Dis J 1992; **11**: 955–9.
4. McCann R, Bosche C van den, White J, Cohen B. Outbreak of measles in an orthodox jewish community. Eurosurveill Weekly 2000; **4**: 119.
5. Cronin M, O'Connell T. Measles outbreak in the Republic of Ireland. Eurosurveill Weekly 2000; **4**: 210.
6. Inspectie voor de Gezondheidszorg. Vaccinatietoestand Nederland per 1 januari 1999. Den Haag, the Netherlands, December 1999.
7. Hof S van den, Berbers GAM, Melker HE de, Conyn-van Spaendonck MAE. Sero-epidemiology of measles antibodies in the Netherlands; a study in a national sample and in municipalities with low vaccine coverage. Vaccine 1999; **18**: 931–40.
8. Brugha R, Ramsay M, Forsey T, Brown D. A study of maternally derived measles antibody in infants born to naturally infected and vaccinated women. Epidemiol Infect 1996; **117**: 519–24.
9. Williams BD, Cutts FT, Dye C. Measles vaccination policy. Epidemiol Infect 1995; **115**: 603–21.
10. Chen RT, Markowitz LE, Albrecht P et al. Measles antibody: reevaluation of protective titers. J Infect Dis 1990; **162**: 1036–42.
11. Christenson B, Böttiger M. Methods for screening the naturally acquired and vaccine-induced immunity to the measles virus. Biologicals 1990; **18**: 207–11.
12. Gilkes WR, Richardson S, Spiegelhalter DJ, eds. Markov Chain Monte Carlo in Practice. London: Chapman and Hall, 1996.
13. Smeets-Driessen MDH, Zwan CW van der, Plantinga AD, Rümke HC, Spijker C van 't. BMR-vaccinatie volgens een alternatief schema? Voor- en nadelen overwogen. Tijdschr Soc Gezondheidsz 1995; **73**: 295–9.
14. Zwan CW van der, Plantinga AD, Rümke HC, Conyn-van Spaendonck MAE. Mazelen in Nederland; epidemiologie en de invloed van vaccinatie. Ned Tijdschr Geneeskd 1994; **138**: 2390–5.
15. Cvjetanovic B, Grab B, Dixon H. Epidemiological models of poliomyelitis and measles and their application in the planning of immunization programmes. Bull WHO 1982; **60**: 405–22.
16. Katzmann W, Dietz K. Evaluation of age-specific vaccination strategies. Theor Popul Biol 1984; **25**: 125–37.
17. Hethcote HW. Optimal ages of vaccination for measles. Math Biosci 1988; **89**: 29–52.
18. McLean AR, Nokes DJ, Anderson RM. Model-based comparisons of measles immunization strategies using high dose Edmonston–Zagreb type vaccines. Int J Epidemiol 1991; **20**: 1107–17.
19. Salmon DA, Haber M, Cangarosa EJ, Philips L, Smith NJ, Chen RT. Health consequences of religious and philosophical exemptions from immunization laws. JAMA 1999; **282**: 47–53.
20. Hof S van den, Kerkhof JHTC van den, Ham PBG ten, Binnendijk RS van, Conyn-van Spaendonck MAE, Steenbergen JE van. Mazelenepidemie in Nederland, 1999–2000. Ned Tijdschr Geneesk 2001. In press.
21. Redd SC, Markowitz LE, Katz SL, Measles vaccine. In: Plotkin SA, Orenstein WA, eds. vaccines. London: WB Saunders, 1999.
22. Murphy MD, Brunell PA, Lievens AW, Shehab ZM. Effect of early immunization on antibody response to reimmunization with measles vaccine as demonstrated by enzyme-linked immunosorbent assay (ELISA). Pediatrics 1984; **74**: 90–3.

23. Wilkins J, Wehrle PF. Additional evidence against measles vaccine administration to infants less than 12 months of age: altered immune response following active/passive immunization. J Pediatr 1979; **94**: 865–9.
24. Linneman CC Jr, Dine MS, Roselle GA, et al. Measles immunity after revaccination: results in children vaccinated before 10 months of age. Pediatrics 1982; **69**: 332–5.
25. Brunell PA, Weigle K, Murphy MD. Antibody response following measles-mumps-rubella vaccine under conditions of customary use. JAMA 1983; **250**: 1409–12.
26. Black FL, Berman LL, Libel M, et al. Inadequate immunity to measles in children vaccinated at an early age: effect of revaccination. Bull WHO 1984; **62**: 315–9.
27. Shasby DM, Shope TC, Downs H, et al. Epidemic measles in a highly vaccinated population. N Engl J Med 1977; **296**: 585–9.
28. Ceyhan M, Kanra G, Erdem G, Kanra B. Immunogenicity and efficacy of one dose measles-mumps-rubella (MMR) vaccine at twelve months of age as compared to monovalent measles vaccination at nine months followed by MMR revaccination at fifteen months of age. Vaccine 2001; **19**: 4473–8.
29. Yuan L. Measles outbreak in 31 schools: risk factors for vaccine failure and evaluation of a selective revaccination strategy. CMAJ 1994; **150**: 1093–8.
30. Singh R, John TJ, Cherian T, Raghupathy P. Immune response to measles, mumps & rubella vaccine at 9, 12 & 15 months of age. Indian J Med Res 1994; **100**: 155–9.
31. Orenstein WA, Markowitz LE, Preblud SR, et al. Appropriate age for measles vaccination in the United States. Dev Biol Stand 1986; **65**: 13–21.
32. Shelton JD, Jacobson JE, Orenstein WA, et al. Measles vaccine efficacy: influence of age at vaccination vs duration of time since vaccination. Pediatrics 1978; **62**: 961–4.
33. Volti SL, Giammanco-Bilancia G, Grassi M, Garozzo R, Gluck R, Giammanco G. Duration of the immune response to MMR vaccine in children of two age-different groups. Eur J Epidemiol 1993; **9**: 311–4.
34. De Serres G, Boulianne N, Meyer F, Ward BJ. Measles vaccine efficacy during an outbreak in a highly vaccinated population: incremental increase in protection with age at vaccination up to 18 months. Epidemiol Infect 1995; **115**: 315–23.
35. Maldonado YA, Lawrence EC, DeHovitz R, Hartzell H, Albrecht P. Early loss of passive measles antibody in infants of mothers with vacine-induced immunity. Pediatrics 1995; **96**: 447–50.
36. De Serres G, Boulianne N, Ratnam S, Corriveau A. Effectiveness of vaccination at 6 to 11 months of age during an outbreak of measles. Pediatrics 1996; **97**: 232–5.
37. Central Bureau of Statistics. Statistical yearbook. The Hague, the Netherlands, 1999.
38. Wharton M, Cochi SL, Hutcheson RH, Bistowish JM, Schaffner W. A large outbreak of mumps in the postvaccine era. J Infect Dis 1988; **158**: 1253–60.
39. Hersh BS, Fine PE, Kent WK, et al. Mumps outbreak in a highly vaccinated population. J Pediatr 1991; **119**: 187–93.
40. Klinge J, Lugauer S, Korn K, Heininger U, Stehr K. Comparison of immunogenicity and reactogenicity of a measles, mumps and rubella (MMR) vaccine in German children vaccinated at 9–11, 12–14 or 15–17 months of age. Vaccine 2000; **18**: 3134–40.
41. Johnson CD, Kumar ML, Whitwell JK, et al. Antibody persistence after primary measles–mumps–rubella vaccine and response to a second dose given at four to six vs. eleven to thirteen years. Pediatr Infect Dis J 1996; **15**: 687–92.
42. Haas R de, Hof S van den, Berbers GAM, Melker HE de, Conyn-van Spaendonck MAE. Prevalence of antibodies against rubella virus in the Netherlands nine years after changing from selective to mass vaccination. Epidemiol Infect 1999; **123**: 263–70.
43. Christenson B, Böttiger M. Changes of the immunological patterns against measles, mumps and rubella. A vaccination programme studied 3 to 7 years after introduction of a two-dose schedule. Vaccine 1991; **9**: 326–9.
44. Cheek JE, Baron R, Atlas H, et al. Mumps outbreak in a highly vaccinated school population. Evidence for large-scale vaccination failure. Arch Pediatr Adolesc Med 1995; **149**: 774–8.
45. Briss PA, Fehrs LJ, Parker RA, et al. Sustained transmission of mumps in a highly vaccinated population: assessment of primary vaccine failure and waning immunity. J Infect Dis 1994; **169**: 77–82.
46. Markowitz LE, Preblud SR, Fine PE, et al. Duration of live measles vaccine-induced immunity. Pediatr Infect Dis J 1990; **9**: 101–9.
47. Anders JF, Jacobson RM, Poland GA, et al. Secondary failure rates of measles vaccines: a metaanalysis of published studies. Pediatr Infect Dis J 1996; **15**: 62–6.
48. Ramsay ME, Moffatt D, O'Connor M. Measles vaccine: a 27-year follow-up. Epidemiol Infect 1994; **112**: 409–12.
49. Christenson B, Böttiger M. Long-term follow-up study of rubella antibodies in naturally immune and vaccinated young adults. Vaccine 1994; **12**: 41–5.
50. Peltola H, Davidkin I, Paunio M, Valle M, Leinikki P, Heinonen OP. Mumps and rubella eliminated from Finland. JAMA 2000; **284**: 2643–7.
51. Begg NT, Miller E, Fairly CK, et al. Antibody responses and symptoms after DTP and either tetanus or diphteria *Haemophilus influenzae* type B conjugate vaccines given for primary immunisation by separate or mixed injection. Vaccine 1995; **13**: 1547–50.
52. Clemens JD, Ferreccio C, Levine MM, et al. Impact of *Haemophilus influenzae* type b polysaccharide-tetanus protein conjugate vaccine on responses to concurrently administered diphtheria–tetanus–pertussis vaccine. JAMA 1992; **267**: 673–8.
53. Gold R, Scheifele D, Barreto L, et al. Safety and immunogenicity of *Haemophilus influenzae* vaccine (tetanus toxoid conjugate) administered concurrently

or combined with diphtheria and tetanus toxoids, pertussis vaccine and inactivated poliomyelitis vaccine to healthy infants at two, four and six months of age. Pediatr Infect Dis J 1994; **13**: 348–55.
54. Deforest A, Long SS, Lischner HW, et al. Simultaneous administration of measles–mumps–rubella vaccine with booster doses of diphtheria–tetanus–pertussis and oral poliovirus vaccines. Pediatrics 1988; **81**: 237–46.
55. McBean AM, Gateff C, Manclark CR, Foster SO. Simultaneous administration of live attenuated measles vaccine with DTP vaccine. Pediatrics 1978; **62**: 288–93.
56. King GE, Hadler SC. Simultaneous administration of childhood vaccines: an important public health policy that is safe and efficacious. Pediatr Infect Dis J 1994; **13**: 394–407.
57. Miller E, Waight P, Laurichesse H, et al. Immunogenicity and reactogenicity of acellular diphtheria/tetanus/pertussis vaccines given as a pre-school booster: effect of simultaneous administration of MMR. Vaccine 2001; **19**: 3904–11.
58. Anonymous. Measles, mumps, and rubella – vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1998; **47**: 1–57.