Modelling measles re-emergence as a result of waning of immunity in vaccinated populations

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Abstract

An age-structured mathematical model of measles transmission in a vaccinated population is used to simulate the shift from a population whose immunity is derived from natural infection to a population whose immunity is vaccine-induced. The model incorporates waning of immunity in a population of vaccinees that eventually will become susceptible to a milder form of vaccine-modified measles with a lower transmission potential than unvaccinated classical measles. Using current estimates of duration of vaccine-derived protection, measles would not be expected to re-emerge quickly in countries with sustained high routine vaccine coverage. However, re-emergence is possible to occur several decades after introduction of high levels of vaccination. Time until re-emergence depends primarily on the contagiousness of vaccine-modified measles cases in comparison to classical measles. Interestingly, in a population with a high proportion of vaccinees, vaccine-modified measles and classical measles would occur essentially in the same age groups. Although waning of humoral immunity in vaccinees is widely observed, re-emergence of measles in highly vaccinated populations depends on parameters for which better estimates are needed.

Keywords: Measles; Waning immunity; Vaccination; Mathematical model

1. Introduction

Measles is still one of the major causes of morbidity and mortality among children in the world. It is estimated that annually 900,000 deaths can be attributed to measles, mainly in Africa and Southeast Asia [1]. In the late 1990s, the WHO established a time frame for measles elimination in the different global regions. The difficulties in reaching this goal have shifted the emphasis towards improving control in countries with the highest measles mortality [2].

Although measles immunization is widely regarded as one of the safest and most cost-effective public health interventions, serological studies indicate that vaccine-induced immunity might be less protective and less durable than immunity conferred by natural measles infection [3–7]. The decline of MV-antibodies is also faster in vaccinees than in children who recovered from the disease [10]. The role of circulating wild-type measles virus for boosting immunity is not fully understood. It is therefore possible that waning of antibodies may be accelerated in the absence of re-exposure to MV. Although recent outbreak studies in developed countries suggest that vaccine efficacy is very high with 90–95% of exposed vaccinees being protected from measles infection [10,11], this may change in the future, as the vaccinated population grows older. Antibody titres in vaccinated individuals are subject to substantial waning, which may not only result in typical measles, but also in susceptibility to a milder or subclinical form of infection [12,13].

The epidemiological implications of vaccinees having lost their immunity, becoming susceptible to a milder form of measles and being able to transmit the virus have been investigated previously using a simple mathematical model [14]. In this study, we extend this model to include age structure to simulate the dynamics of transmission more accurately and to evaluate the long-term evolution of immunity and infection in a setting with several decades of high levels of routine measles vaccination.

The model describes the shift from a population in which measles immunity was acquired through natural infection to a population of individuals with vaccine-induced immunity. We investigate whether and when this shift could lead to a re-emergence of measles under the assumptions that...
(i) vaccinated individuals are protected for a limited time only as an effect of waning of immunity and that (ii) they will become susceptible to a milder form of measles infection during which virus can be transmitted to other susceptible persons.

2. Methods

The simple model of vaccine-modified measles transmission developed earlier by us [14] is extended by including implicit age structure using partial differential equations according to a standard method [15]. This permits to model age-dependent force of infection, which has been shown to be an important characteristic of measles epidemiology in developed countries. The contact patterns of five age classes (0–4, 5–9, 10–14, 15–19, >20) are described using a “who acquires infection from whom” (W AIFW) matrix, a two-dimensional step function (see Table 1).

Details of the model equations can be found in Appendix A. Briefly, the equations describe the transmission of infection from infectious to susceptible individuals in a population subject to demographic processes (birth and death) and a routine single dose vaccination at 12 months of age. In addition to the five standard compartments (protected by maternal antibodies $M$, susceptible to classical measles infection $S_c$, individuals with latent measles infection $E_c$, infectious individuals $I_c$, immune following infection $R_c$) we consider four additional compartments to model the varying immunity levels of vaccinated individuals and vaccine-modified infection. Following vaccination, we assume that individuals are protected from any form of measles infection ($W$), after which they become susceptible to the vaccine-modified form of infection ($S_v$). After exposure to measles virus, infected individuals ($E_v$) will incubate virus (latent period) before becoming infectious ($I_v$). As in our previous study, we assume that the vaccinated individuals with the vaccine-modified form of infection or disease are less contagious than unvaccinated individuals with natural measles (i.e. they have a lower basic reproduction number [14]). This lower contagiousness is implemented by multiplying the transmission parameter of vaccinated individuals who contract measles by a factor $\phi$ (Eq. (A.3) in Appendix A). Their basic reproduction number is then simply the basic reproduction number of unvaccinated individuals with natural measles multiplied by $\phi$. Following infection (either natural or vaccine-modified), individuals remain immune for life.

For simplicity, a vaccination program is considered where children get one dose of vaccine at the age of 12 months. It is assumed that as of 1980, 90% of 12-month-old children were vaccinated and seroconverted.

The demographic parameters are taken to be representative of a developed country assuming a type I mortality profile of the population where all individuals die at age 80. The birth rate is considered to be 1/80 units per person per year, so that the total population remains constant over time. The epidemiological parameters used for classical unvaccinated measles cases in the model are shown in Table 2 and correspond to those found in the literature [12]. Estimates of the force of infection correspond to those observed in the United Kingdom prior to the introduction of vaccines and are assumed to be representative of the force of measles infection in most developed countries. Since estimates of the duration of vaccine-induced protection widely vary in the literature, several values were used for this parameter. Similarly a range of values for the relative transmission potential of vaccines $\phi$ was assumed. All model simulations were started at equilibrium prior to vaccination.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth rate</td>
<td>$\mu$</td>
<td>1/80 per person per year</td>
</tr>
<tr>
<td>Life expectancy</td>
<td></td>
<td>80 years</td>
</tr>
<tr>
<td>Effective vaccine coverage at 12 months of age</td>
<td></td>
<td>90%</td>
</tr>
<tr>
<td>Mean duration of latency (for both types of infection)</td>
<td>$\lambda/v$</td>
<td>7 days</td>
</tr>
<tr>
<td>Mean duration of infectiousness (for both types of infection)</td>
<td>$\phi/v$</td>
<td>7 days</td>
</tr>
<tr>
<td>Mean duration of passive immunity due to maternal antibodies</td>
<td>$\phi/v$</td>
<td>3.5 months</td>
</tr>
<tr>
<td>Force of infection (per person per year)</td>
<td>$\lambda(a, t)$</td>
<td>0.154 0.518 0.255 0.102 0.095</td>
</tr>
<tr>
<td>Transmission potential of vaccine-modified infection compared to classical infection</td>
<td>$\phi$</td>
<td>10–50%</td>
</tr>
<tr>
<td>Mean duration of vaccine protection</td>
<td>$\phi/v$</td>
<td>20, 25 or 33 years</td>
</tr>
</tbody>
</table>

This particular matrix was chosen as it results in plausible transmission coefficients for all five age groups with the highest contact rate among 5–9-year-olds [16].
3. Results

Fig. 1 shows how the time interval until the first re-emergence of measles—sometimes referred to as the honeymoon period [17]—varies depending on the duration of vaccine-induced protection and the transmission potential of vaccine-modified infection. Assuming vaccine protects for 20, 25 or 30 years and 90% of 12 months old children were effectively vaccinated, increasing the transmission potential has the effect of decreasing the honeymoon period. The duration of vaccine protection also influences the duration of the honeymoon period, but to a lesser degree than the transmission potential.

Fig. 2 depicts the prevalence of classical measles as a function of the transmission potential of vaccine-modified infection assuming the mean duration of protection is 25 years. If the transmission potential of vaccines with vaccine-modified measles was assumed to be 10, 20 or 30% of fully susceptible individuals with measles, three scenarios emerged. For all three scenarios, classical measles disappears for a certain time period following the introduction of the vaccination programme. The time to a first re-emergence of measles is shorter if the transmission potential $\phi$ of vaccinees is larger.

The more contagious individuals with vaccine-modified infection are, the earlier a re-emergence of measles must be expected. This occurs because the threshold level of susceptibles needed for continued chains of transmission is lower when the basic reproduction number of individuals with vaccine-modified measles is higher. For instance in the case of a transmission potential of 10%, re-emergence will not be a problem until almost 70 years after the beginning of large scale vaccination which in Fig. 2 was supposed to be in 1980. Assuming a transmission potential of 30%, the virus would have re-emerged already before the year 2000. Furthermore, Fig. 2 shows that with an assumed transmission potential of 20% the circulation of the virus would re-emerge after 30 years and will not disappear anymore. With a mean duration of protection of 20 years, re-emergence would occur approximately 10 years earlier for the scenarios where the transmission potential is between 10 and 30% (see Fig. 1).

More importantly, the model assesses the change of the immunity profile in the population following the start of the vaccination programme. In Fig. 3, we can see how this shift from a population whose immunity was induced by classical infection is replaced by vaccine-induced immunity, which is less protective. For these simulations an average duration of vaccine protection of 25 years and a vaccine-modified transmission potential of 10% was assumed. It is clear that while high routine vaccine coverage achieves a temporary elimination of measles infection in the population, the proportion of vaccinees becoming susceptible to the vaccine modified form of infection increases slowly. As shown in Fig. 3, 25 years after starting vaccination, 28% of the total population will be vaccinated, 18% will still have protective vaccine-derived immunity and 10% will be susceptible to vaccine-modified infection. It is clear that as time passes, the pool of susceptible individuals will increase until a critical threshold is reached where sustained vaccine-modified measles transmission occurs.

Table 3 shows that following the start of the vaccination programme, the average age of infection increases faster for the vaccine-modified type of infection than for classical
measles. Within 10–15 years after the beginning of routine vaccination, modified measles would occur in the same age groups as classical infection, i.e. among adolescents. Thus, vaccine-modified measles would not necessarily be found primarily in older individuals as one might expect given the long average duration of protection. Moreover, the number of vaccine-modified measles cases (relative to the number of classical measles cases in unvaccinated individuals) increases in a population with the proportion of vaccinees. For instance, after 30 years, the number of vaccine-modified measles cases will exceed classical cases by a factor of 2–3 under the scenario of Table 3.

Table 3

<table>
<thead>
<tr>
<th>Years after start of vaccination programme</th>
<th>Average age at classical infection (years)</th>
<th>Average age at vaccine-modified infection (years)</th>
<th>Ratio of cases with classical to cases with vaccine-modified infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>6.5</td>
<td>3.3</td>
<td>45.2</td>
</tr>
<tr>
<td>10</td>
<td>8.8</td>
<td>7.4</td>
<td>1.7</td>
</tr>
<tr>
<td>15</td>
<td>10.5</td>
<td>9.8</td>
<td>0.8</td>
</tr>
<tr>
<td>20</td>
<td>11.3</td>
<td>12.0</td>
<td>0.6</td>
</tr>
<tr>
<td>25</td>
<td>11.9</td>
<td>13.3</td>
<td>0.5</td>
</tr>
<tr>
<td>30</td>
<td>13.2</td>
<td>15.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Mean duration of vaccine protection $\omega = 25$ years and transmission potential $\phi = 0.1$ for these scenarios.

4. Discussion

If natural immunity against measles is thought to last life-long, vaccine-induced protection is well documented to be less durable and less robust [3–7]. While the dynamics of antibody decay are still poorly understood, even less is known about waning of cell-mediated immunity. Most of these studies are based on antibodies and little is known about the role of the T cell response in vaccines [18]. As time passes, the proportion of vaccinees increases in the general population and individuals gradually replace individuals with a life-long protection with a waning immunity. Although it is difficult to assess at the present time the impact of such a shift on the epidemiology of measles this may well become a critical aspect of future measles control strategies.

Here, we show that in a population with a sustained high routine coverage over several decades, the duration of the honeymoon period depends on two main factors. First and probably most important is the transmission potential of vaccinees who have lost their protection against disease or infection. Unfortunately, no estimates exist for this parameter from empirical studies. In the absence of any estimates, the transmission potential was assumed to be reduced to 10–30% of the infectivity of naïve individuals with classical measles. Second, the modelling shows that the time period until re-emergence of disease is also sensitive to the duration of vaccine-induced protection. We have previously estimated duration of protection to be approximately 25 years (95% CI 18–48 years) in the absence of boosting from wild
type virus [10], but the confidence interval of these estimates are rather wide and might depend on the setting and vaccine. Depending on the above assumptions (long duration of vaccine-induced immunity and low transmission potential in vaccinees), measles would not return until many decades after the beginning of routine vaccination (e.g. 2030) when more than 80% of the population has been vaccinated. Under less optimistic assumptions (short duration of vaccine-induced immunity or high transmission potential of vaccinees) a first outbreak due to waning immunity in vaccinees could occur already within 40 years or less after the beginning of routine vaccination. According to current terminology, such outbreaks would be attributed to secondary vaccine failure.

Our model assumes that routine vaccination covered 90% of all children of 12 months of age as from 1980. For some countries like the United States this may be a realistic estimate but for many others it is not, because their high routine vaccination started later and or their coverage is much lower. In many developing countries (and in some developed countries), routine vaccination rates are typically much lower than 90%. Measles epidemics have been and are still observed in countries with low (<90%) routine coverage. Previous modelling has suggested that measles is very likely to continue to circulate in these settings even if we assume that the vaccine is "perfect" (i.e. offers full protection for a lifetime) [16]. As long as vaccination coverage is not high enough, unvaccinated susceptibles rather than vaccinated individuals with waning immunity (secondary vaccine failures) will be responsible for sustaining chains of measles transmission. In this setting, the contribution to overall measles virus transmission of vaccinated individuals who have lost their immunity might be easily overlooked and difficult to assess in practice.

However, the fact that no large scale outbreaks among vaccinees have been observed in countries with sustained high vaccine coverage (e.g. the United States or Finland) indicates either (i) that the transmission potential of vaccinees is low compared to individuals with classical measles infection (much less than 1) or (ii) that duration of vaccine-induced immunity is long (longer than 25 years), (iii) that for most developed countries, high vaccination rates were only achieved after 1980 as assumed here, (iv) that the second dose implemented in most developed countries further delays re-emergence or a combination of several of these factors. However, subclinical vaccine-modified measles with reduced severity of disease have been observed in developing countries with concomitant immunological boosting [19]. One implication is that immunity of vaccinees may become more robust because of exposure to circulating virus.

It is well known that mothers whose immunity to measles is vaccine-derived transfer lower levels of antibody to their children than unvaccinated mothers who had natural infection [15]. Children born to vaccinated mothers tend thus to become susceptible to infection (and vaccination) 1–3 months earlier than children born to mothers with natural immunity [15]. We have not included this aspect in the model, as its impact on transmission levels is minimal for the following reasons. First, at least in developed countries, the contact rate in this age group is lowest of all age groups [15]. Second, the additional few weeks months of susceptibility would increase the proportion of susceptibles in the population by a tiny fraction as an example, in a population with type I life expectancy of 80 years assuming 90% of individuals aged 12 months and above are effectively protected (through vaccination or infection), changing the duration of maternal antibody protection from a mean of 4–3 months would increase the fraction of total susceptibles in the population from 10.7 to 10.8%, a small increase of 0.1%. However, this small fraction of very young susceptibles bears a high burden of complications due to measles infection.

We have only considered a one-dose strategy in our model. Clearly this is not realistic, given the two-dose strategy currently advocated in developed countries. The effects of a two-dose strategy depend on how vaccinees react upon re-vaccination. If revaccination simply boosts titres, then it can be assumed to delay the waning by approximately 5 or 10 years (assuming a second dose at either 6 or 12 years of age). However if, as some studies suggest, only low titres are boosted then the impact of the second dose might be simply to delay waning by 5 or 10 years for only a small proportion of vaccinees. Furthermore, it is possible that the second vaccination influences the speed of waning and the resulting transmission potential of those that are no longer protected against disease and infection.

Although the lack of reliable estimates of some of the critical parameters limits predictive capabilities, the model contributes to a better understanding of the potential future bottlenecks of measles control. It also shows that further studies investigating vaccine immunity and protection are warranted. Within its limitations, the model highlights nevertheless the importance from a public health perspective of investigating the long-term efficacy of measles vaccines to provide children, adolescents and adults with durable protection from disease and infection [6,20]. One of the principal insights gained from this model is that waning of immunity and subsequent mild subclinical infection in vaccinees would not necessarily result in a rapid re-emergence of measles, but that the re-emergence is realistic and essentially depends on parameters for which no good estimates exist.

Acknowledgements

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Appendix A

The model of vaccine-modified measles transmission [14] is extended by including implicit age structure according to
standard methods [15]. The model attempts to capture the transmission dynamics of measles in a developed nation (i.e., constant population size and rectangular age structure, or type 1 survival).

The investigated model can be written as a system of partial differential equations:

\[
\begin{align*}
\frac{\partial M}{\partial t} + \frac{\partial M}{\partial a} &= -\mu(a)M(a, t) \\
\frac{\partial E}{\partial t} + \frac{\partial E}{\partial a} &= \lambda(a, t)S(a, t) - (\mu(a) + \sigma)E(a, t) \\
\frac{\partial S}{\partial t} + \frac{\partial S}{\partial a} &= \delta M(a, t) - (\mu(a) + \lambda(a, t))S(a, t) \\
\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} &= \sigma E(a, t) - (\mu(a) + \gamma)I(a, t) \\
\frac{\partial W}{\partial t} + \frac{\partial W}{\partial a} &= - (\mu(a) + \omega)W(a, t) \\
\end{align*}
\]

where \(\lambda(a, t)\) represents the effective contact rate between susceptibles of age \(a\) and infectious individuals of age \(a'\) and \(\psi\) is the transmission potential of vaccine-modified infection compared to classical infection.

Note that the force of infection is calculated as the normalized product of the effective contact rate of individuals with classical infection (\(I_c\)) and individuals with vaccine-modified measles infection (\(I_v\)). To account for the fact that individuals with vaccine-modified infection are assumed to be less contagious, their contribution is reduced by multiplication with the transmission potential \(\psi < 1\).

Vaccination is implemented by transferring 90% of children who reach 1 year of age in the S_c class directly to the W class.

The force of infection is then given by

\[
\lambda(a, t) = \int_0^\infty \beta(a, a')I_v(a', t) + \psi I_c(a', t) \, da' \quad \text{(A.3)}
\]

where \(\beta(a, a')\) is the effective contact rate between susceptibles of age \(a\) with infectious individuals of age \(a'\) and \(\psi\) is the transmission potential of vaccine-modified infection compared to classical infection.

References


