

Estimation of the time-dependent vaccine efficacy from a measles epidemic

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Summary

We present a method to estimate the time-dependent vaccine efficacy from the cohort-specific vaccination coverage and from data on the vaccination status of cases and apply it to a measles epidemic in Germany which involved 529 cases, 88 of whom were vaccinated and 370 unvaccinated (for the remaining 71 cases the vaccination status is unknown).

Our epidemiological model takes into account that maternal antibodies prevent successful vaccination and that vaccine immunity may be lost over time. Model parameters are estimated from the data using maximum likelihood.

Vaccination coverage, as determined in school surveys, ranged from 27.6% for the cohort born in 1974 to 85% for the 1986 cohort, which is far too low to prevent measles transmission. Cohorts for which no school surveys were performed, are omitted from analysis. Thus, sufficient data are available for only 282 cases, 69 of whom are vaccinated. According to our estimates, measles vaccinations provided no immunity before 1978 (95% CI: 0 to 47%), for the period 1978-82, the estimated vaccine efficacy was 80% (95% CI: 67 to 89%), and for 1982-90 it was 97% (95% CI: 93 to 99%). After 1990, the estimated value dropped to 89%, but its confidence interval widely overlaps with that of the previous period (95% CI: 74 to 97%). Loss of immunity was estimated to be zero (95% CI: 0 to 0.003/year).

Several sensitivity analyses were performed with respect to the model assumptions. A modified model which assumed constant efficacy at all vaccination times yielded a high estimate of 96% (95% CI: 92 to 98%) for primary vaccine efficacy but also a high loss rate of immunity of 0.007/year (95% CI: 0.001 to 0.012) to explain the high fraction of vaccinated cases among older individuals. The likelihood score value is however significantly inferior compared to the score value of the model with time-dependent vaccine efficacy.

1 Introduction

Measles epidemics are still quite common in Germany. The necessary accumulation of susceptible individuals can often be attributed to a low vaccination coverage, but even vaccinated individuals may still be susceptible if the vaccination failed or if their immunity was lost¹. Disentangling the web of factors which caused the epidemic can be rather difficult, especially if data are only available from the cases, but not from the unafflicted fraction of the population.^{2,3} In this paper, we present the development and the assumptions of a mathematical model, which allows to extract some of the missing information on the unafflicted population from the case reports and from external information on the vaccination coverage in the population. Using this model, we estimate the age-specific vaccination coverage and the time-dependent vaccine efficacy.

Our model is based on the following idea: if the vaccination coverage v and the proportion f_v of vaccinated individuals among the cases are known, we can calculate the vaccine efficacy r from the formula which defines f_v :^{1,4,5}

$$f_v = \frac{v(1-r)}{v(1-r) + (1-v)} = \frac{v(1-r)}{1-vr}. \quad (1)$$

To use this idea for the measles epidemic studied in this paper, we need to make some refinements: (1) We have to account for the fact that individuals who were vaccinated in earlier years, are highly over-represented among the cases. This can be accomplished by allowing the vaccine efficacy r to change over time or by considering the loss of vaccine immunity.^{6,7} (2) We assume that infants are temporarily protected by maternal antibodies which not only prevent infection but also successful vaccination.

2 Description of the data

From January 1992 to June 1993, a measles epidemic occurred in the municipality of Ansbach (Bavaria), Germany. Figure 1 depicts the monthly incidence during the epidemic. Data were collected by sending questionnaires to general practitioners and pediatricians who were asked to supply detailed clinical information about the measles cases they had seen during the epidemic. Out of 85 physicians, 54 returned the questionnaire, 34 of whom had seen measles cases during the epidemic. The resulting data set describes 529 measles cases. Besides the information on the clinical condition of the patients, data are generally available on the cases' date of birth, the date and type of vaccination (if any) and the date of onset of measles prodromi or exanthemata. We also have access to vaccination coverage data obtained from school surveys in the area where the epidemic occurred (Table 1). Cohorts for which no such information is available (i. e. 194 patients) are excluded from the main analysis, but are included in one of the sensitivity analyses. From the remaining patients, 53 are excluded because their vaccination status is unknown. This leaves 282 patients for evaluation, 213 of them unvaccinated and 69 vaccinated. For

Table 1: Information on the cohorts. The cohort-specific vaccination coverage v_c was determined by school surveys in the first and fifth grade, respectively (n denotes the number of children with vaccination records involved in the vaccination survey). The expected numbers of cases refer to the full model with time-dependent vaccine efficacy $r(t)$.

year of cohort	date of birth		grade of school survey	vaccination coverage		observed (expected) number of cases			
	from	to		v_c [%]	(n)	unvaccinated		vaccinated	
1973	7/72	6/73	5th	45.1	(1,253)	3	(3.1)	2	(1.9)
1974	7/73	6/74	5th	27.6	(1,509)	3	(4.1)	2	(0.9)
1975	7/74	6/75	5th	42.4	(1,548)	9	(11.4)	7	(4.6)
1976	7/75	6/76	5th	35.7	(1,690)	7	(8.1)	3	(1.9)
1977	7/76	6/77	1st	43.7	(1,747)	20	(19.5)	5	(5.5)
1978	7/77	6/78	1st	54.2	(1,871)	22	(22.5)	6	(5.5)
1979	7/78	6/79	1st	67.7	(1,810)	17	(16.7)	7	(7.3)
1980	7/79	6/80	1st	66.8	(1,903)	17	(15.6)	4	(5.4)
1981	7/80	6/81	1st	72.6	(2,027)	22	(18.9)	3	(6.1)
1982	7/81	6/82	1st	74.3	(2,020)	24	(22.4)	4	(5.6)
1983	7/82	6/83	1st	73.7	(2,076)	15	(17.1)	6	(3.9)
1984	7/83	6/84	1st	79.6	(2,081)	18	(18.9)	7	(6.1)
1985	7/84	6/85	1st	83.7	(2,089)	20	(18.3)	6	(7.7)
1986	7/85	6/86	1st	85.0	(2,147)	16	(15.9)	7	(7.1)
Total						213	(212.5)	69	(69.5)

55 of the 69 vaccinated individuals, the date of vaccination is known. Two children received inactivated as well as live measles vaccine and six received a booster vaccination. Considering a possible loss of protection following vaccination, we use the date of the last vaccination rather than the first one for all these children.

3 Description of the model

The proposed model describes the dynamics of five different epidemiological states: individuals are either protected by maternal antibodies (unvaccinated or vaccinated), or susceptible (unvaccinated or vaccinated), or immune. A schematic representation of the model is given in Figure 2.

3.1 Model structure

We assume that every newborn is protected by maternal antibodies (M_n) which prevent infection. Maternal protection is assumed to be lost at rate $\delta = 2/\text{year}$, corresponding to an average protective duration of six months. Vaccination during this time (modelled by a transition from M_n to M_v ; Fig. 2) is assumed not to confer any protection. Irrespective of their vaccination status, individuals become fully susceptible after losing maternal protection. Unvaccinated individuals become vaccinated at a cohort- and age-specific rate $\varphi_c(a)$. As a consequence of vaccination, a time-dependent fraction $r(t)$ of previously susceptible individuals (S_n) becomes immune (R), whereas a fraction $1 - r(t)$ is vaccinated in vain and remains susceptible (S_v). We assume that unvaccinated and unsuccessfully vaccinated individuals are equally likely to be infected and to develop the disease during an epidemic.

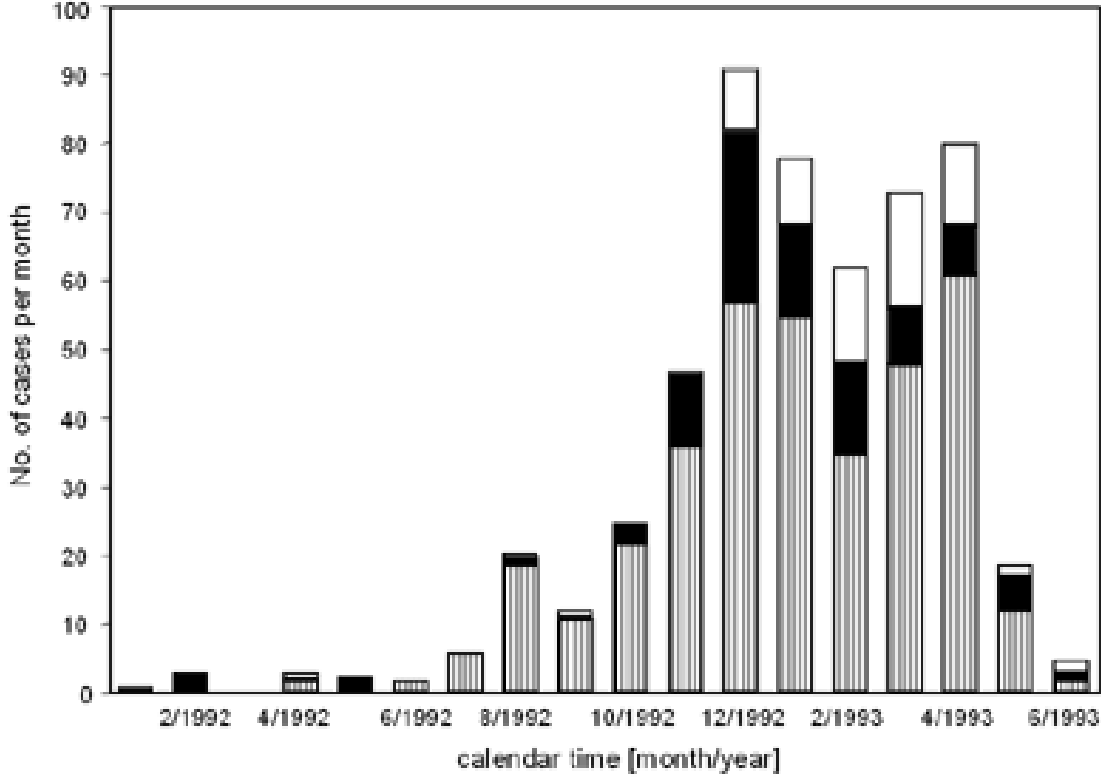


Figure 1: Monthly measles incidence in the municipality of Ansbach, Germany, (all 529 cases combined; grey = unvaccinated, black = vaccinated, white = unknown vaccination status)

The above assumptions are translated into the following equations:

$$\begin{aligned}
\frac{\partial M_{n,c}(a,t)}{\partial a} + \frac{\partial M_{n,c}(a,t)}{\partial t} &= -(\delta + \varphi_c(a))M_{n,c}(a,t), \\
\frac{\partial M_{v,c}(a,t)}{\partial a} + \frac{\partial M_{v,c}(a,t)}{\partial t} &= \varphi_c(a)M_{n,c}(a,t) - \delta M_{v,c}(a,t), \\
\frac{\partial S_{n,c}(a,t)}{\partial a} + \frac{\partial S_{n,c}(a,t)}{\partial t} &= \delta M_{n,c}(a,t) - \varphi_c(a)S_{n,c}(a,t), \\
\frac{\partial S_{v,c}(a,t)}{\partial a} + \frac{\partial S_{v,c}(a,t)}{\partial t} &= \delta M_{v,c}(a,t) + (1 - r(t))\varphi_c(a)S_{n,c}(a,t), \\
\frac{\partial R_c(a,t)}{\partial a} + \frac{\partial R_c(a,t)}{\partial t} &= r(t)\varphi_c(a)S_{n,c}(a,t),
\end{aligned} \tag{2}$$

with the boundary conditions $M_{n,c}(0,t) = 1$ and $M_{v,c}(0,t) = S_{n,c}(0,t) = S_{v,c}(0,t) = R_c(0,t) = 0$. The subscript c relates to the cohort.

Solving these equations, allows to calculate the following proportions that can be interpreted as probabilities or densities, respectively:

1. The probability that an individual of cohort c has not been vaccinated and is susceptible at age a is

$$P_{n,c}(a) = (1 - e^{-\delta a}) e^{-\int_0^a \varphi_c(\alpha) d\alpha}. \tag{3}$$

2. The probability density that an individual of cohort c with birth date t_b has been vaccinated at age a_v and is susceptible at age $a \geq a_v$ in spite of the vaccination is

$$\begin{aligned}
p_{v,c}(t_b, a_v, a) &= \varphi_c(a_v) e^{-\int_0^{a_v} \varphi_c(\alpha) d\alpha} \times \\
&\times \left[e^{-\delta a_v} (1 - e^{-\delta(a-a_v)}) + (1 - e^{-\delta a_v}) (1 - r(t_b + a_v)) \right].
\end{aligned} \tag{4}$$

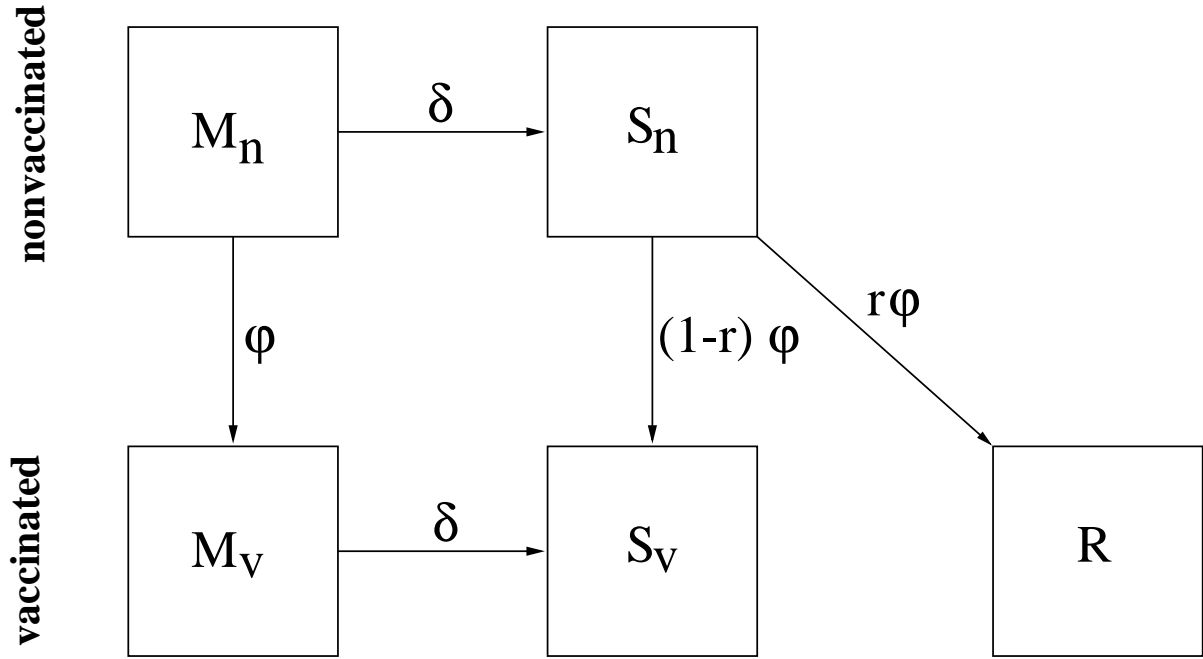


Figure 2: Schematic representation of the model dynamics (M_n, M_v : maternally protected individuals, S_n, S_v : susceptible individuals, R : immune individuals; δ : maternal loss rate, φ : vaccination rate; for explanations see text.

3. The probability that an individual of cohort c with birth date t_b is susceptible at age a in spite of an earlier vaccination (performed at an unknown age $a_v \leq a$) is

$$P_{v,c}(t_b, a) = \int_0^a p_{v,c}(t_b, s, a) ds. \quad (5)$$

3.2 Assumptions concerning the vaccination rate

Determining a sequence of age- and cohort-specific vaccination rates $\varphi_c(a)$ from the available information is difficult. The only source of information are cross-sectional school surveys during first and fifth grade (corresponding to ages seven and eleven years), respectively, during which the vaccination certificates of pupils in the Ansbach region were collected by a public health official (Table 1). Thus, the vaccination coverage in the population is only given at one age for each cohort (see the markers in Figures 4 and 5). Additional information is needed to determine the shape of the age- and cohort-specific vaccination rates. The observed distribution of vaccination ages among cases does not by itself determine the shape of $\varphi_c(a)$, because it is also influenced by the vaccine efficacy $r(t)$. Only if the values of $r(t)$ are known, the observed distribution of vaccination ages can be used to calculate the shape of $\varphi_c(a)$. To solve this problem, we estimate the parameters which determine $\varphi_c(a)$ simultaneously with the other model parameters from the data.

We choose a step function for the vaccination rate $\varphi_c(a)$ to keep the number of unknown

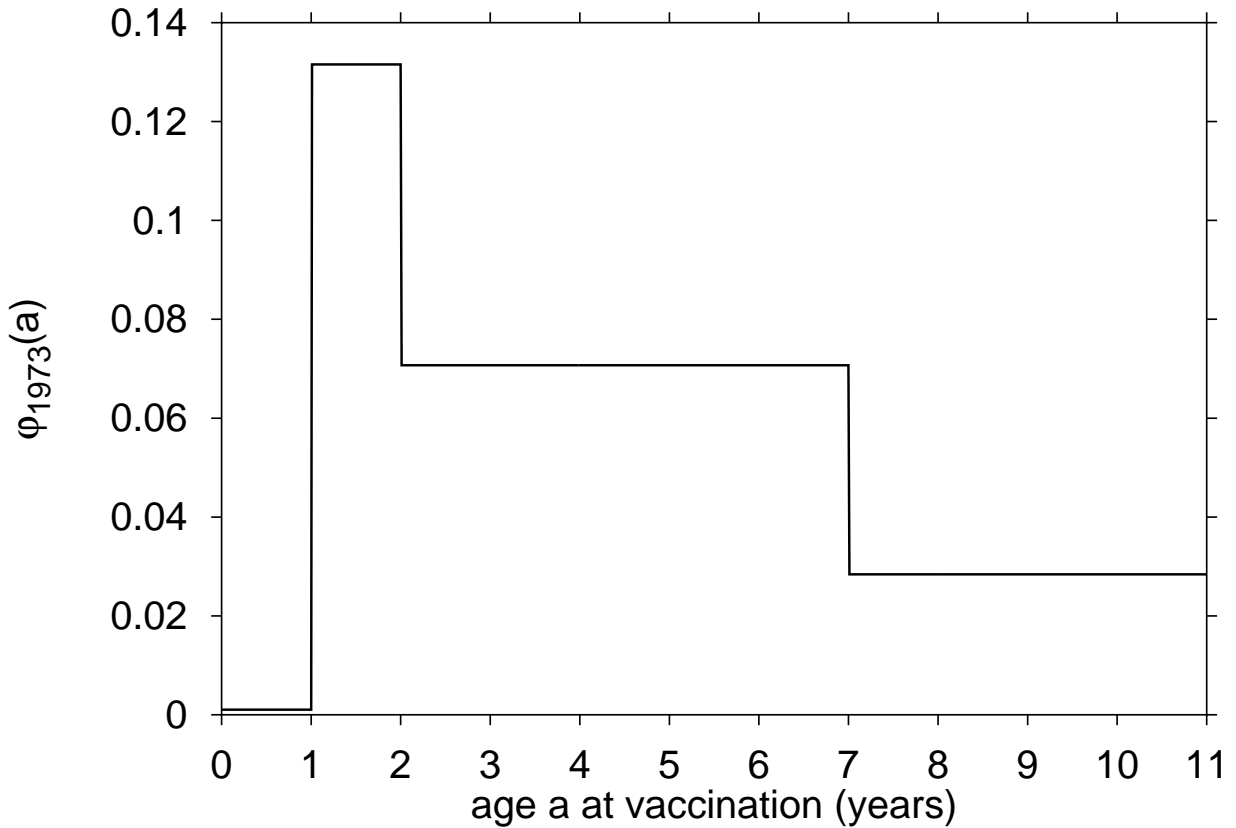


Figure 3: Age-specific vaccination rate $\varphi_c(a)$ for the 1973 cohort (see Table 1). Vaccination rates of other cohorts can be derived from this figure by multiplication with a cohort-specific factor (see text for explanations).

parameters as small as possible (Figure 3):

$$\varphi_c(a) = \begin{cases} q_1 \psi_c & \text{if } a < 1 \text{ year,} \\ \psi_c & \text{if } 1 \text{ year} \leq a < 2 \text{ years,} \\ q_2 \psi_c & \text{if } 2 \text{ years} \leq a < 7 \text{ years,} \\ q_3 \psi_c & \text{if } 7 \text{ years} \leq a < 11 \text{ years,} \\ 0 & \text{if } 11 \text{ years} \leq a. \end{cases} \quad (6)$$

It is assumed that the coefficients q_1, q_2 and q_3 of the step functions $\varphi_c(a)$ are the same for every cohort c whereas ψ_c is a cohort-specific parameter which has to be estimated from the data (cf. equation 8).

The ages which determine the step function are motivated by the following facts: (1) In Germany, it was formerly recommended to vaccinate children around the age of 15 months (recently the recommendation has been changed to vaccinate at 12-15 months of age)⁹, so we assume that the vaccination rate was about constant between one and two years of age. (2) School surveys were performed during first and fifth grade, so we use the ages of 7 and 11 years as further endpoints. (3) None of the cases was vaccinated after the age of 11 years, so we assume that the vaccination coverage for older children was zero. The shape of the vaccination functions $\varphi_c(a)$ may have changed over time, but it seems unreasonable to attempt estimating such a change, because in all evaluated cohorts combined, there are only 55 individuals with known vaccination dates.

The vaccinated fraction v_c of seven (or eleven) year old children of cohort c is known from school surveys (Table 1). The relationship between $v_c(a)$ and $\varphi_c(a)$, as depicted in

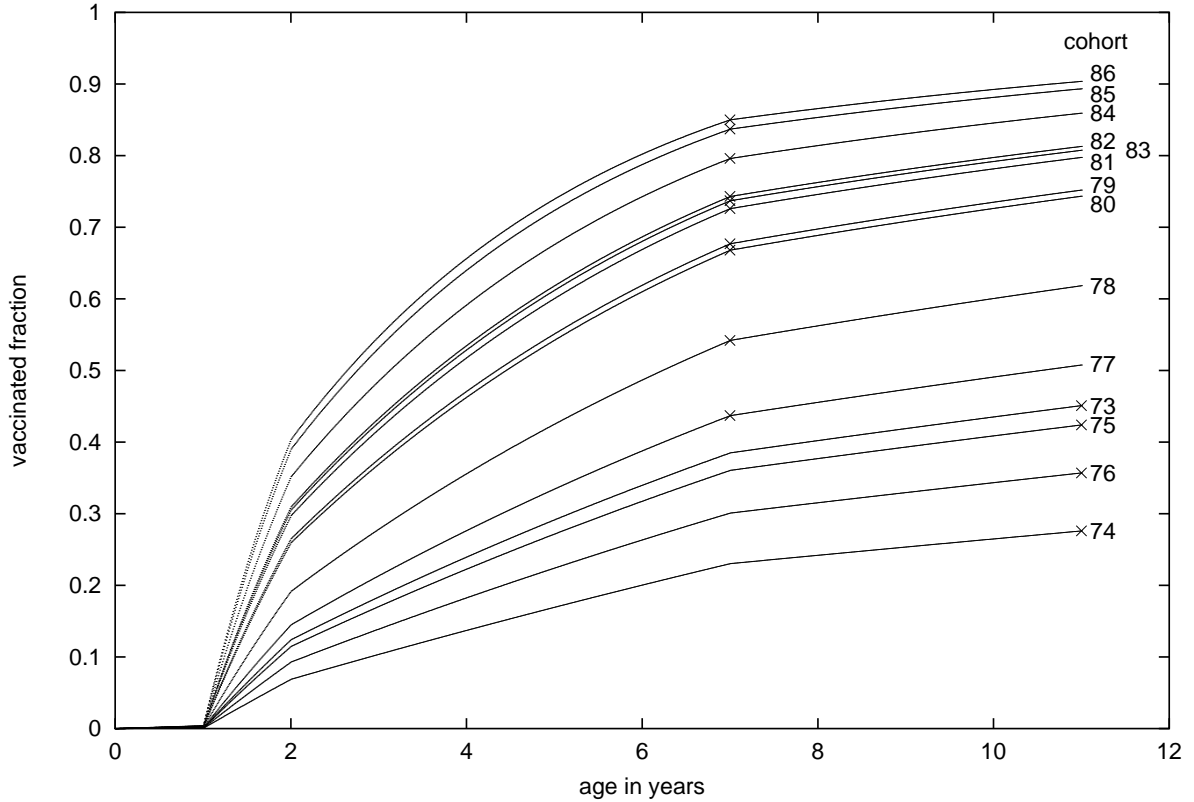


Figure 4: Age- and cohort-specific fraction of vaccinated individuals. The numbers on the right side denote the cohorts and the markers denote the results of the school surveys.

Figure 4 is given by

$$v_c = \begin{cases} 1 - e^{-\int_0^7 \varphi_c(a) da} = 1 - e^{-(q_1+1+5q_2)\psi_c} & \text{for school surveys in first grade,} \\ 1 - e^{-\int_0^{11} \varphi_c(a) da} = 1 - e^{-(q_1+1+5q_2+4q_3)\psi_c} & \text{for school surveys in fifth grade.} \end{cases} \quad (7)$$

For given values v_c and q_1, q_2, q_3 , these equations can be solved for ψ_c which yields

$$\psi_c = \begin{cases} -\frac{\ln(1-v_c)}{q_1+1+5q_2} & \text{for school surveys in first grade,} \\ -\frac{\ln(1-v_c)}{q_1+1+5q_2+4q_3} & \text{for school surveys in fifth grade.} \end{cases} \quad (8)$$

3.3 Assumptions concerning the vaccine efficacy

We assume that the probability $r(t)$ that the vaccination of a susceptible individual (S_n) leads to immunity (R), depends on the time when the vaccination was administered (cf. 6):

$$r(t) = \begin{cases} r_1 & \text{if } t \leq 6/1978, \\ r_2 & \text{if } 7/1978 \leq t \leq 6/1982, \\ r_3 & \text{if } 7/1982 \leq t \leq 6/1986, \\ r_4 & \text{if } 7/1986 \leq t \leq 6/1990, \\ r_5 & \text{if } t \geq 7/1990. \end{cases} \quad (9)$$

The function $r(t)$ is chosen arbitrarily (the number of steps is limited by the information contained in the data); different choices are explored in the sensitivity analysis section.

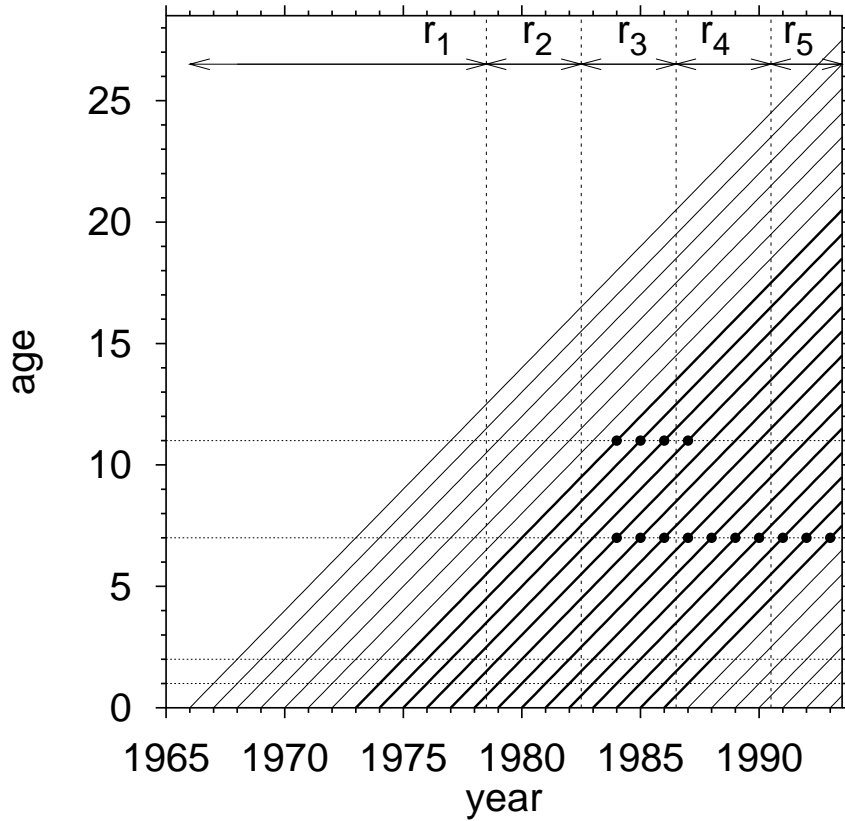


Figure 5: Lexis diagram of the cohorts which were affected by the measles epidemic. Each line represents one cohort; fat lines denote cohorts which are used for parameter estimation. School surveys are depicted as round marks. Horizontal dotted lines show the ages at which the values of the vaccination functions $\varphi_c(a)$ change and vertical dashed lines show the times at which the values of the vaccine efficacy $r(t)$ change.

Figure 5 shows a Lexis diagram which illustrates the assumptions concerning $\varphi_c(a)$ and $r(t)$. Each line depicts the ageing of one cohort as time passes. Bold lines are used for the cohorts where school surveys are available (cf. Table 1). The marks denote the ages and times when these surveys were performed. Horizontal dotted lines show the ages at which the values of the vaccination functions $\varphi_c(a)$ change and vertical dashed lines show the times at which the values of the vaccine efficacy $r(t)$ change.

4 Maximum likelihood estimation

The values of the parameters r_1, \dots, r_5 , q_1, q_2 and q_3 are estimated by maximum likelihood⁸. To estimate the values of the parameters, we calculate the probabilities that a susceptible individual was unvaccinated or vaccinated at the age of infection.

1. For each unvaccinated individual i of cohort c with birth date $t_b^{(i)}$ and onset of disease at age $a_d^{(i)}$, the contribution to the likelihood is given by

$$f_n^{(i)} = \frac{P_{n,c}(a_d^{(i)})}{P_{n,c}(a_d^{(i)}) + P_{v,c}(t_b^{(i)}, a_d^{(i)})}. \quad (10)$$

Table 2: Estimated parameter values with 95% confidence intervals (not determined for $q_1 \dots q_3$); for details see text.

parameter		estimate	95% CI
vaccine efficacy ($t \leq 6/78$)	r_1	0.00	0.00 - 0.47
vaccine efficacy ($7/78 \leq t \leq 6/82$)	r_2	0.80	0.67 - 0.89
vaccine efficacy ($7/82 \leq t \leq 6/86$)	r_3	0.97	0.94 - 0.99
vaccine efficacy ($7/86 \leq t \leq 6/90$)	r_4	0.96	0.93 - 0.99
vaccine efficacy ($7/90 \leq t$)	r_5	0.89	0.74 - 0.97
vaccination parameter ($0 \leq a < 1$)	q_1	0.008	n.d.
vaccination parameter ($2 \leq a < 7$)	q_2	0.54	n.d.
vaccination parameter ($7 \leq a < 11$)	q_3	0.22	n.d.

2. For each vaccinated individual i of cohort c with birth date $t_b^{(i)}$, vaccination age $a_v^{(i)}$ and onset of disease at age $a_d^{(i)}$, the contribution to the likelihood is

$$\tilde{f}_v^{(i)} = \frac{p_{v,c}(t_b^{(i)}, a_v^{(i)}, a_d^{(i)})}{P_{n,c}(a_d^{(i)}) + P_{v,c}(t_b^{(i)}, a_d^{(i)})}. \quad (11)$$

3. For each vaccinated individual i of cohort c with birth date $t_b^{(i)}$ and onset of disease at age $a_d^{(i)}$ for whom the vaccination age is unknown, the contribution to the likelihood is given by

$$f_v^{(i)} = \frac{P_{v,c}(t_b^{(i)}, a_d^{(i)})}{P_{n,c}(a_d^{(i)}) + P_{v,c}(t_b^{(i)}, a_d^{(i)})}. \quad (12)$$

The log-likelihood function based on all observations is calculated by

$$\log(\mathcal{L}) = \left(\sum_{i=1}^{213} \log(f_n^{(i)}) \right) + \left(\sum_{i=214}^{268} \log(\tilde{f}_v^{(i)}) \right) + \left(\sum_{i=269}^{282} \log(f_v^{(i)}) \right), \quad (13)$$

where the first 213 terms correspond to the unvaccinated individuals, the following 55 terms correspond to those with known vaccination age and the last 14 terms correspond to vaccinated individuals with unknown vaccination age.

Parameters which maximise the log-likelihood are estimated by using an optimization routine of the NAG Fortran library. Confidence intervals (CI), are calculated using the profile log-likelihood⁸.

5 Results

The estimated parameter values are listed in Table 2 with their 95% confidence limits, the resulting vaccine efficacy $r(t)$ with its 95% confidence limits (dashed lines) is shown in Figure 6 and one of the resulting vaccination rates $\varphi_c(a)$ is depicted in Figure 3. Table 1 compares for each cohort the observed proportion of unvaccinated cases with the proportion expected by the model, using the most likely parameter values as given in Table 2. The expected number $E_{n,c}$ of unvaccinated individuals in each cohort c is calculated according to

$$E_{n,c} = \sum_{i \in c} f_n^{(i)}. \quad (14)$$

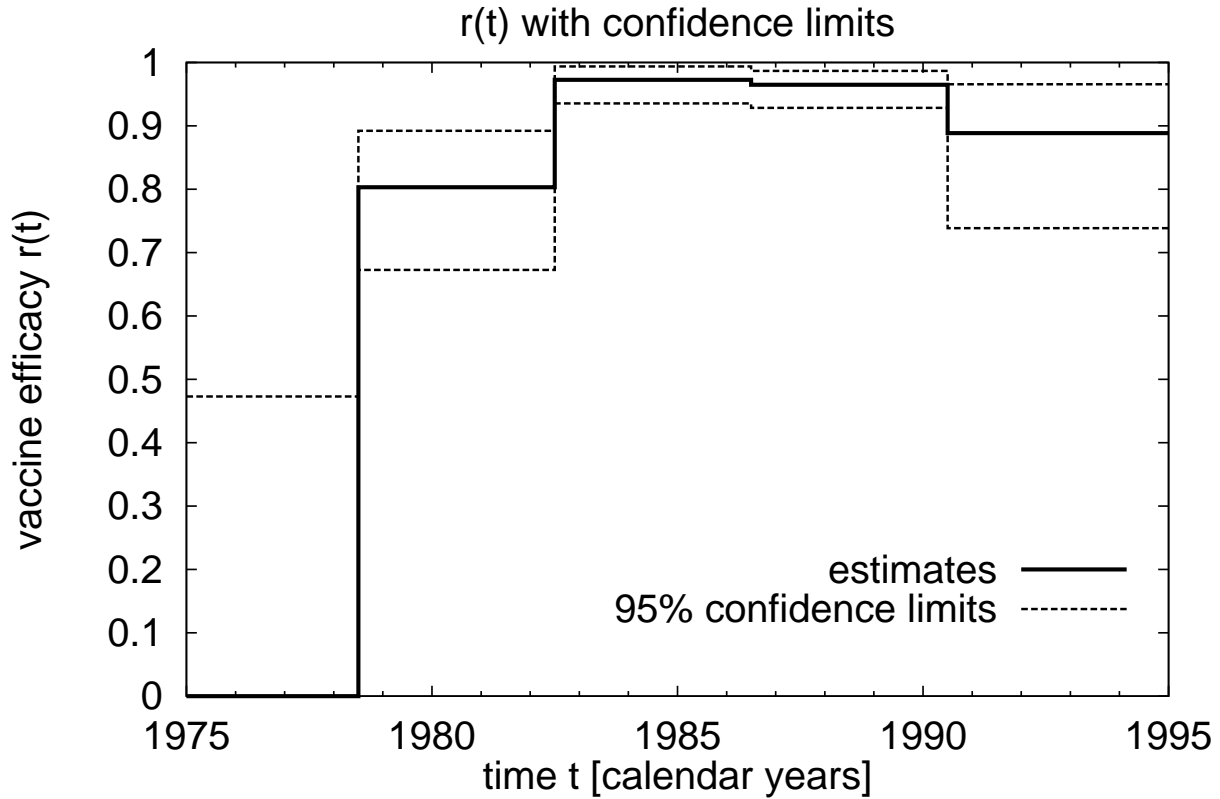


Figure 6: Time-dependent vaccine efficacy $r(t)$: the most likely values for $r_1 \dots r_5$ are given as a full line, 95% confidence limits as dashed lines.

6 Sensitivity analyses

6.1 Waning immunity

Let us assume that immune individuals lose their protective immunity at a constant rate σ and become susceptible again (S_v), and that no measles infections occurred prior to the epidemic. The last two equations of the model (equation 2) have to be changed to

$$\begin{aligned} \frac{\partial S_{v,c}(a,t)}{\partial a} + \frac{\partial S_{v,c}(a,t)}{\partial t} &= \delta M_{v,c}(a,t) + (1 - r(t))\varphi_c(a)S_{n,c}(a,t) + \sigma R_c(a,t), \\ \frac{\partial R_c(a,t)}{\partial a} + \frac{\partial R_c(a,t)}{\partial t} &= r(t)\varphi_c(a)S_{n,c}(a,t) - \sigma R_c(a,t), \end{aligned} \quad (15)$$

and the probability density (equation 4) changes to

$$\begin{aligned} p_{v,c}(t_b, a_v, a) &= \varphi_c(a_v) e^{-\int_0^{a_v} \varphi_c(\alpha) d\alpha} \left[e^{-\delta a_v} (1 - e^{-\delta(a-a_v)}) + \right. \\ &\quad \left. + (1 - e^{-\delta a_v})(1 - r(t_b + a_v) + r(t_b + a_v)(1 - e^{-\sigma(a-a_v)})) \right]. \end{aligned} \quad (16)$$

The maximum likelihood estimate for σ turns out to be 0/year (95% CI from 0 to 0.003) and the total likelihood and the values of the other parameters remain unchanged.

For a reduced model which uses a constant value for $r(t)$ instead of the step function shown in Figure 6, we get the estimates $r = 96\%$ (95% CI: 92-98%) and $\sigma = 0.007/\text{year}$ (95% CI: 0.001-0.012/year). The log-likelihood for this estimate is -264.2, which is highly significantly inferior to the value -245.3 of the full model. The results of these two models

have very different interpretations. The full model explains the relatively high fraction of vaccinated individuals among the older cases by an early deficiency in vaccine efficacy which was overcome in later years. It also suggests that successfully vaccinated individuals virtually never lose their protection. According to the reduced model, the immediate success of vaccination was always high, but immune individuals gradually lose their protection. We decided to reject the reduced model because the model with time-dependent r yields significantly better log-likelihood values and because the expected values of the full model (Table 1) fit better to the observed ones (results for the reduced model not shown).

6.2 Choice of the step function for $r(t)$

Further sensitivity checks are necessary because of our arbitrary definition of the vaccine efficacy function (equation 9): we assume that $r(t)$ is stepwise constant within 4-year intervals (see Figures 5 and 6). We extended the model by estimating one more parameter which allows to keep the interval length in the function $r(t)$ variable within the limits of 3.5 and 4.5 years, but the estimated interval length is close to four years and the likelihood of the extended model does not improve significantly. Likewise, we incorporated a new parameter in the model which allows to shift the endpoints of the 4-year-intervals up to plus or minus six months from the values shown in Figures 5 and 6, but the estimated value of this parameter is close to zero and the likelihood does not improve significantly.

6.3 Patients with unknown vaccination status

So far, we have excluded 53 patients from evaluation, because their vaccination status is unknown. If the majority of them were unvaccinated, the fraction of unvaccinated individuals among the cases might be under-estimated and the vaccine efficacy might have higher values. If, on the other hand, most of them were vaccinated, the fraction of vaccinated individuals among the cases might be under-estimated and the estimated vaccine efficacy might turn out to be lower. We first examine the “best case scenario” by assuming that all 53 individuals are unvaccinated. Under these assumptions, the most likely parameter values are $r_1 = 0\%$, $r_2 = 85\%$, $r_3 = 98\%$, $r_4 = 97\%$, $r_5 = 91\%$, $q_1 = 0.007$, $q_2 = 0.63$, $q_3 = 0.25$ (log-likelihood = -259.3). It is noteworthy that the vaccine efficacy r_1 for early vaccinations is again estimated to be zero. To examine the “worst case scenario”, we declare all 53 individuals to be “vaccinated at unknown age”. Under these assumptions, the most likely parameter values are $r_1 = 0\%$, $r_2 = 63\%$, $r_3 = 92\%$, $r_4 = 93\%$, $r_5 = 79\%$, $q_1 = 0.010$, $q_2 = 0.37$, $q_3 = 0.16$ (log-likelihood = -307.6). Whereas the “best case scenario” gives slightly higher estimates for $r_2 \dots r_5$, the opposite is true for the “worst case scenario”. This suggests that omitting the 53 patients from analysis should not have introduced a severe bias in the estimates.

6.4 Cohorts with unknown vaccination coverage

In the analyses described above, we have mainly used the data of 282 out of a total of 529 cases, i. e. those individuals with known vaccination status who belong to a cohort for which the vaccination coverage is known from school surveys. To include the data of individuals of other cohorts, we have to make assumptions about the vaccination coverage of these cohorts: (a) For individuals who are born after June 1986, we apply the same age-specific vaccination rate $\varphi_c(a)$ as for the 1986 cohort. (b) For the cohorts 1966 to

1973 we assume that the vaccination coverage v_c of eleven year old children increased linearly from 0% to 45.1% (the value of the 1973 cohort). (c) It is further assumed that nobody of the older cohorts was vaccinated against measles (accordingly, individuals of these cohorts do not contribute to the likelihood and are omitted). After omitting all individuals with unknown vaccination status, we can evaluate data of 458 individuals, 88 of them vaccinated (69 with known vaccination date). The newly added cohorts are shown in the Lexis diagram (Figure 5) as thin lines. Under these assumptions, the most likely parameter values (and their 95% CI) are $r_1 = 23\%$ (0-63%), $r_2 = 81\%$ (68-90%), $r_3 = 97\%$ (93-99%), $r_4 = 96\%$ (92-98%), $r_5 = 91\%$ (84-96%), $q_1 = 0.005$, $q_2 = 0.44$, $q_3 = 0.16$ (log-likelihood = -311.9). The main difference between the previous and the current estimates concerns the early vaccine efficacy r_1 which shifts from 0% (0-47%; Table 2) to the slightly more optimistic value of 23% (0-63%). Comparison between the observed and expected fractions of vaccinated individuals among the cases revealed a rather poor fit (results not shown), especially for the older cohorts which were added here, which indicates that the assumption of a linearly increasing vaccination coverage was far too crude and which casts doubts on the reliability of the new estimate for r_1 .

7 Discussion

We assume in the model that each individual is vaccinated only once. It is remarkable that some individuals developed measles in spite of more than one vaccination, but this is difficult to interpret as we do not know the prevalence of multiple vaccinations in the population. Considering multiple vaccinations in the model would require additional assumptions for which we have no data. In general, uptake of the second MMR vaccine has been low in Germany so that the vaccine efficacy $r(t)$ should only be slightly over-estimated by our model.

Various ideas have been discussed concerning the degree and duration of maternal protection.^{10,11,12} Among the cases with known vaccination age, there is only one child who was vaccinated before one year of age (cf. Fig. 7). Therefore, our estimates of the vaccine efficacy should not be strongly influenced by the assumptions made in our model.

Of the 85 physicians who were asked to supply information, only 54 returned the questionnaire; nothing is known about the remaining 31. It cannot be excluded that mainly such doctors refused to participate who oppose vaccination and, therefore, are more likely to be confronted with unvaccinated cases. If this was the case, vaccinated patients should be over-represented and all estimated vaccine efficacies should be biased towards lower values, but such a bias cannot easily explain the zero efficacy before 1978.

Patients who develop severe measles are more likely to consult a physician and, thus, the data may be biased towards severe cases. We assume that unsuccessfully vaccinated individuals remain completely susceptible. Contrary to this assumption, it has been argued that “unsuccessfully” vaccinated individuals may still profit from the vaccination by being at least partly protected against infection or by having only mild symptoms upon infection¹³. If this was the case, the bias towards severe cases would lead to an under-estimation of measles cases among vaccinated individuals which would imply even lower vaccine efficacies.

The vaccine efficacy is estimated from the fraction of vaccinated individuals among cases of the same age (cf. equation 1). Thus, our estimates cannot be affected by age-dependent differences in infection rates, in case detection probabilities or in the reliability of the measles diagnosis, if unvaccinated and unsuccessfully vaccinated individuals are equally susceptible.

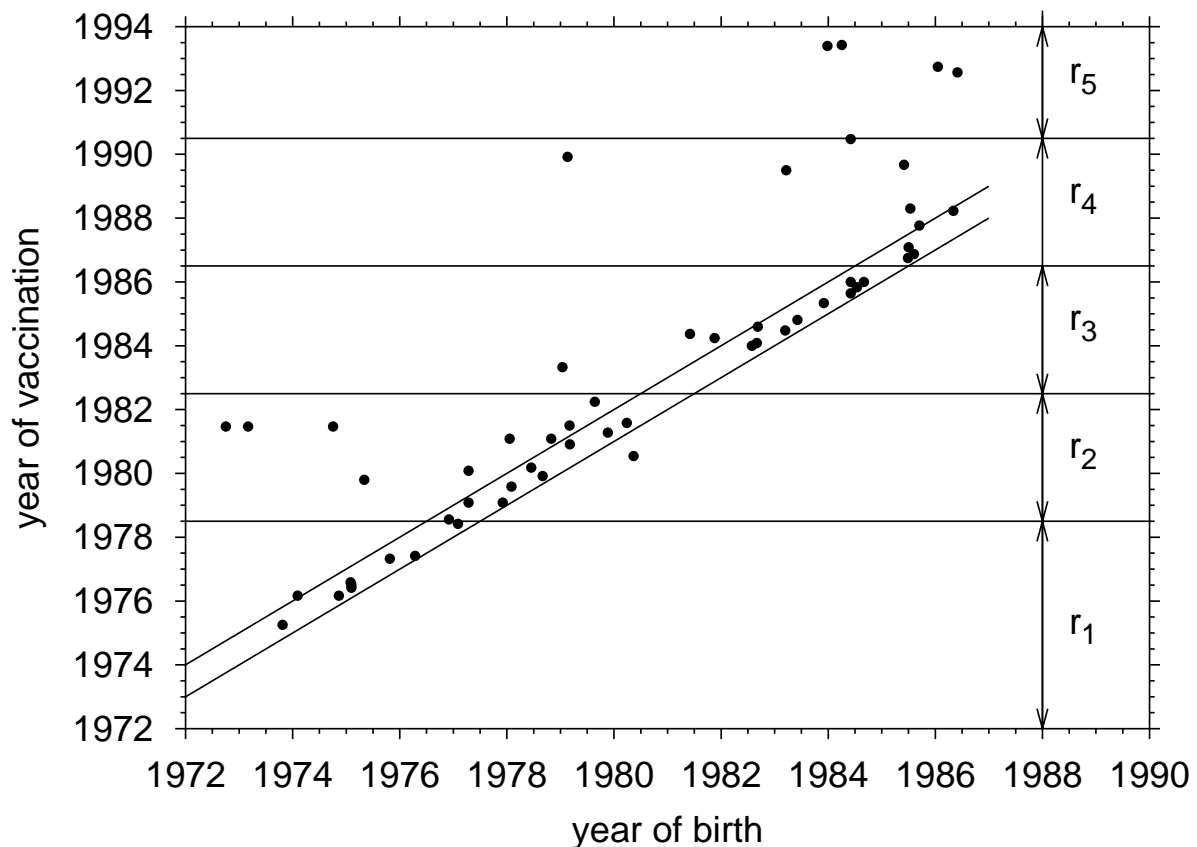


Figure 7: Vaccination dates of measles cases by birth date. Dots between the diagonal lines denote vaccinations between one and two years of age. Horizontal lines denote the times t at which the values of the vaccine efficacy $r(t)$ change.

If measles infections occurred in the Ansbach region before the epidemic, the fraction of unvaccinated and unsuccessfully vaccinated individuals should have been diminished by the same age-dependent fractions, which would have left the estimates of the vaccine efficacy unbiased (except for the sensitivity analysis models with immunity loss where prior exposure to measles infection would have caused an under-estimate in the immunity loss rate σ). A bias could have been caused by previous outbreaks if only those children were vaccinated who escaped infection, thus directing the (naturally) immune individuals to the unvaccinated group and the susceptible individuals to the vaccinated group. If the low estimate of the vaccine efficacy r_1 in early years was biased by such an unknown outbreak, one would expect that many of those cases who were vaccinated in early years, received vaccination when they were older. Figure 7 depicts the birth date and vaccination date of each patient; the markers of individuals who were vaccinated between one and two years of age lie between the two diagonal lines. None of the children who were vaccinated before July 1978 (and thus contributed to the estimation of r_1) was reported to be older than 25 months, i. e. the time window during which an outbreak could have created a bias (between loss of maternal protection and vaccination) was so small, that such an earlier outbreak seems to be a very unlikely explanation of the low estimate of r_1 .

According to our results, the large number of vaccinated individuals among older cases was more likely caused by changes in vaccine efficacy than by gradual loss of vaccine protection. It seems that the applied batches of vaccine have been of poor efficacy in the initial years of measles vaccination in Germany, and that efficacy has gradually improved thereafter to reach about 97 % in the late 80's (Table 2). There may have been problems with cold-chain maintenance during the early years, as the parents of the vaccinees fre-

quently had to buy and store the vaccine before it was applied by a doctor.¹⁴ The low estimate of only 89 % for the early 1990's is also rather disturbing and deserves further examination, but its wide confidence interval (95 % CI: 74 to 97 %) reveals that it is based on few data.

Literature

1. Orenstein, W. A., Bernier, R. H. and Hinman, A. R. 'Assessing vaccine efficacy in the field. Further observations.' *Epidemiological Reviews*, **10**, 212–241 (1988).
2. Mossong, J. and Muller, C. P. 'Estimation of the basic reproduction number of measles during an outbreak in a partially vaccinated population.' *Epidemiology and Infection*, **124**, 273–278 (2000).
3. Farrington, C. P. 'Relative incidence estimation from case series for vaccine safety evaluation.' *Biometrics*, **51**, 228–235 (1995).
4. Halloran, M. E., Haber, M., Longini, I. M. and Struchiner, C. J. 'Direct and indirect effects in vaccine efficacy and effectiveness.' *American Journal of Epidemiology*, **133**, 323–331 (1991).
5. Cutts, F. T., Smith, P. G., Colombo, S., Mann, G., Ascherio, A. and Soares, A. C. 'Field evaluation of measles vaccine efficacy in Mozambique.' *American Journal of Epidemiology*, **131**, 349–355 (1990).
6. Durham, L. K., Longini, I. M., Halloran, M. E., Clemens, J. D., Nizam, A. and Rao, M. 'Estimation of vaccine efficacy in the presence of waning: application to cholera vaccines.' *American Journal of Epidemiology*, **147**, 948–959 (1998).
7. Durham, L. K., Halloran, M. E., Longini, I. M. and Manatunga, A. K. 'Comparison of two smoothing methods for exploring waning vaccine efficacy.' *Applied Statistics*, **48**, part 3, 395–407 (1999).
8. Azzalini, A. *Statistical inference based on the likelihood*, Chapman and Hall, London, 1996.
9. STIKO 'Impfempfehlungen der ständigen Impfkommision (STIKO) am Robert-Koch-Institut.' *Epidemiological Bulletin*, **15**, 101–112 (1998).
10. Henigst, W. and Müller, F. 'Über die Wirksamkeit von Masernimpfstoff bei Säuglingen und Kleinkindern.' *Deutsche medizinische Wochenschrift*, **40**, 1773–1775 (1966).
11. Schlereth, B., Rose, J. K., Buonocore, L., Meulen, V. ter and Niewiesk, S. 'Successful vaccine-induced seroconversion by single-dose immunization in the presence of measles virus-specific maternal antibodies.' *Journal of Virology*, **74**, 4652–4657 (2000).
12. Williams, B. G., Cutts, F. T. and Dye, C. 'Measles vaccination policy.' *Epidemiology and Infection*, **115**, 603–621 (1995).
13. Halloran, M. E., Haber, M. and Longini, I. M. 'Interpretation and estimation of vaccine field efficacy under heterogeneity.' *American Journal of Epidemiology*, **136**, 328–343 (1992).

14. Fescharek, R., Quast, U., Maas, G., Merkle, W. and Schwarz, S. 'Measles-mumps vaccination in the FRG: an empirical analysis after 14 years of use. I. Efficacy and analysis of vaccine failures.' *Vaccine*, **8**, 333–336 (1990).