

## Detection of delayed vaccinations: a new approach to visualize vaccine uptake

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### SUMMARY

For the prevention of pertussis and invasive *Haemophilus influenzae* type b (Hib) infections, each with a peak for mortality and serious complications in the first year of life, early vaccination is important and needs adequate monitoring. In a 1999 national coverage survey the timing of uptake of these vaccines in German children was therefore assessed conventionally at defined age thresholds and with a new adaptation of the Kaplan–Meier (KM) method estimating immunization uptake over time by 1 minus the survival function  $s(t)$ . Only 6% and 9% of children were vaccinated against pertussis and Hib in accordance with the national recommended primary vaccination schedule. Coverage levels for the primary vaccination course of 50% and 90% were attained for pertussis after 6·6 and 16·3 months respectively and for Hib after 7·0 and 24·3 months. These estimates were only possible with the KM method which proved useful to monitor vaccination programmes and will allow the comparison of vaccination uptake in different populations.

### INTRODUCTION

The aim of childhood vaccination programmes is to provide protection at the earliest possible age. This is especially important for invasive *Haemophilus influenzae* b (Hib) disease and pertussis, which have their highest morbidity, mortality and rate of complications in the first year of life [1]. Moreover it also applies to upcoming immunization strategies such as vaccination against pneumococci. Therefore there is an increasing need for methods that describe the time course of vaccination uptake in populations.

The most commonly used method is computing vaccination coverage at certain age thresholds e.g. 7, 13, 19, 24 months of age in the United States [1, 2]. The limitations of this approach, however, are that

the vaccination coverage can only be determined for the preset age groups and that the age when defined coverage levels are attained cannot be measured. The Kaplan–Meier method, a classical technique to describe time to event data, is often used to describe patient survival but, to our knowledge, has never been used to characterize vaccination uptake.

We applied this method to assess timing of Hib and pertussis vaccination in German children based on data from a 1999 national vaccination coverage survey.

This paper compares this new approach with traditional methods, describes the timing of Hib and pertussis vaccination in Germany and discusses possible further applications of this approach to depict vaccine uptake in populations.

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## METHODS

### Sampling and data collection

A total of 1345 households with children up to 3 years of age were identified by screening a random-digit-dialed sample of 24292 private German households. Between July and September 1999 computer-assisted telephone interviews on children's vaccination status were completed in 775 households representing 837 children aged up to 3 years. The response rate for eligible households was 58%. The distribution of sociodemographic variables of responding parents was comparable to those in the parents who were initially randomly identified and to data provided by the Federal Statistical Office, Germany. Non-German nationality households, however, were not fully represented in the sample due to language difficulties.

To collect detailed information on the child's vaccination history parents were asked to read out all the information given in the vaccination booklet of their child (date of each vaccination, kind of vaccine, brandname) assisted by two trained interviewers.

### Analysis

The analyses presented here were confined to 782 children aged 0–35 months (born between 1 July 1996 and 30 June 1999) excluding 22 and 23 children due to ineligible age and insufficient vaccination-information respectively. 1 July 1999 was set as a reference for age calculations and vaccinations given after this date were excluded. Outcome measures were coverage with first dose, completed primary vaccination series and complete vaccination series (including booster dose) for pertussis and *Haemophilus influenzae b* (Hib) vaccinations. These are nationally recommended and reimbursed in Germany. The current recommended schedule for pertussis and Hib is primary vaccination at 3, 4 and 5 months and booster between the 12th and 15th month of life [3]. Primary vaccination series was defined as three doses for pertussis and Hib if part of a combination vaccine containing pertussis antigen. Primary vaccination with a monovalent vaccine was defined as two doses of Hib. Complete vaccination series (including booster) was defined as primary vaccination plus one dose.

### Statistical analysis

The Kaplan–Meier method [4] was used as an approach to describe the time to defined vaccination

outcome and to estimate the immunization coverage at any given age. Information on birthdates and dates of vaccination from all eligible children 0–35 months ( $n = 782$ ) was included in the analysis as the Kaplan–Meier method takes into account different lengths of individual observation periods. Basically the Kaplan–Meier method transforms calendar time to observation time (starting at birth and stopping for each child at its age on 1 July 1999). The overall period of observation (0–35 months) was split into small time intervals each limited by one vaccination. For each time interval the proportion of children still unvaccinated at the end divided by those unvaccinated at the beginning of the interval was calculated. The subsequent products of these proportions gives a 'survival' function  $s(t)$  representing proportions of unvaccinated children at any given age  $t$  (classical Kaplan–Meier curve). Immunization coverage at any given age  $t$  is estimated by the inverse function  $1 - s(t)$ . 95% Confidence intervals (CI) were calculated using the Greenwood formula (5). As the number of persons under observation decreases with time, the very right part of the curve is unstable and interpretation of this part should be careful. There is only one main assumption required which is independence of censoring from the event. That means that the date of interview (censoring) has nothing to do with the probability of being vaccinated (event). This is always fulfilled as long as the cutpoint-date (here 1 July 1999) is set at random. A concise description of the Kaplan–Meier method may be found in the Statistics Notes series of the British Medical Journal [6].

To back up the validity of our results from the Kaplan–Meier analysis, prevalences of vaccinated children at certain age thresholds were calculated and results from both methods were compared. Calculation of prevalences was confined to children at least 19 months of age ( $n = 367$ , born between July 1996 and November 1997) as these were old enough to have received all vaccinations according to the national recommendations, allowing for a 4 month grace-period of delay. Exact 95% CI were calculated on the basis of the binomial distribution (Pearson–Clopper values) [7].

## RESULTS

Vaccination coverage estimates by the Kaplan–Meier method and the traditional prevalence calculation are shown in Table 1. The Kaplan–Meier estimates are

Table 1. Vaccination coverage of pertussis- and Haemophilus influenzae type b vaccine (Hib) among children 7, 19, 13, 24 months of age as calculated by Kaplan–Meier method and prevalences

Vaccination coverage	Children at age								Method of analysis
	7 months		13 months		19 months		24 months		
	%	95% CI*	%	95% CI*	%	95% CI*	%	95% CI*	
<b>Pertussis vaccine</b>									
Primary Immunization§	58.1	54.4, 61.9	86.7	83.9, 89.4	91.2	88.8, 93.6	92.6	90.3, 94.9	KM†
Booster¶			6.2	4.2, 8.3	49.0	44.2, 53.8	74.1	69.4, 78.7	KM†
			6.0	3.8, 8.9	47.1	41.9, 52.4	70.0	65.1, 74.7	P‡
<b>Hib-vaccine</b>									
Primary Immunization§	49.6	45.8, 53.4	72.3	68.7, 75.8	83.0	79.9, 86.2	88.2	85.3, 91.1	KM†
Booster¶	45.8	40.6, 51.0	65.1	60.0, 70.0	79.3	74.8, 83.3	84.7	80.6, 88.3	P‡
			4.9	3.1, 6.8	38.5	33.9, 43.1	56.9	51.8, 61.9	KM‡
			4.6	2.7, 7.3	36.2	31.3, 41.4	53.1	47.9, 58.3	P‡

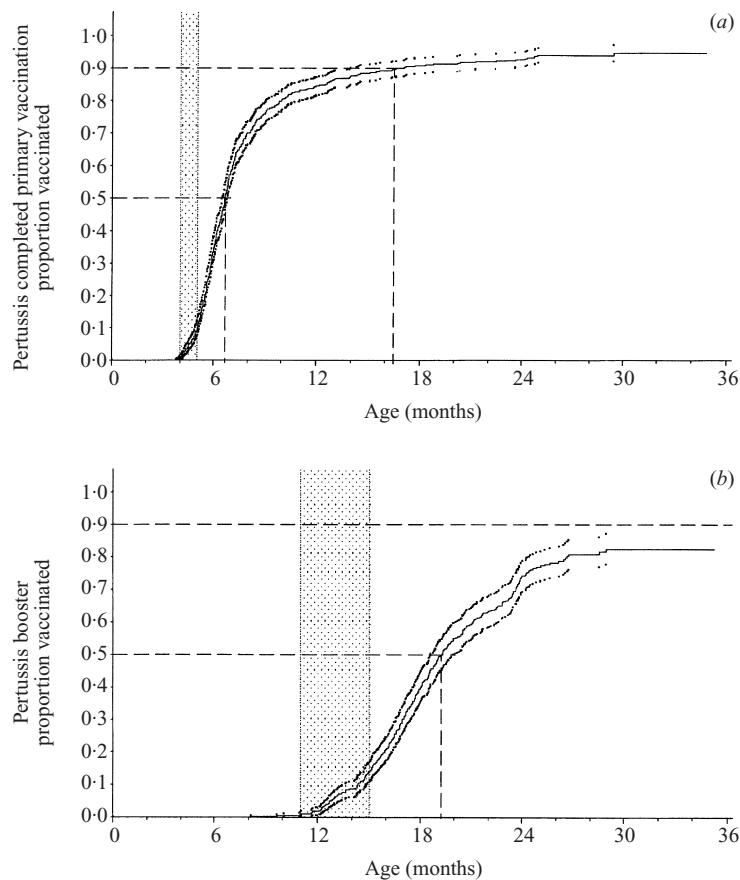
\* CI = Confidence interval.

† Kaplan–Meier estimate (KM) of proportion vaccinated in 782 children (0–35 months) born July 1996–June 1999.

‡ prevalence (P) of vaccinated children in 367 German children (19–35 months) born July 1996–November 1997.

§ ≥ 3 doses of pertussis-vaccine and Hib-vaccine if combined with pertussis antigen, otherwise ≥ 2 doses of Hib.

¶ ≥ 4 doses of pertussis-vaccine and Hib-vaccine if combined with pertussis antigen, otherwise ≥ 3 doses of Hib.



**Fig. 1** (a) Pertussis vaccination in Germany (completed primary) in 782 children aged 0–3 years. Inverse Kaplan–Meier curves ( $1-s(t)$ ) with 95% confidence interval. The shaded area marks the nationally recommended age-periods for vaccination (3rd to 5th month of life). (b) Pertussis vaccination in Germany (completed primary + booster) in 782 children aged 0–3 years. Inverse Kaplan–Meier curves ( $1-s(t)$ ) with 95% confidence interval. The shaded area marks the nationally recommended age-periods for vaccination (12th–15th month of life).

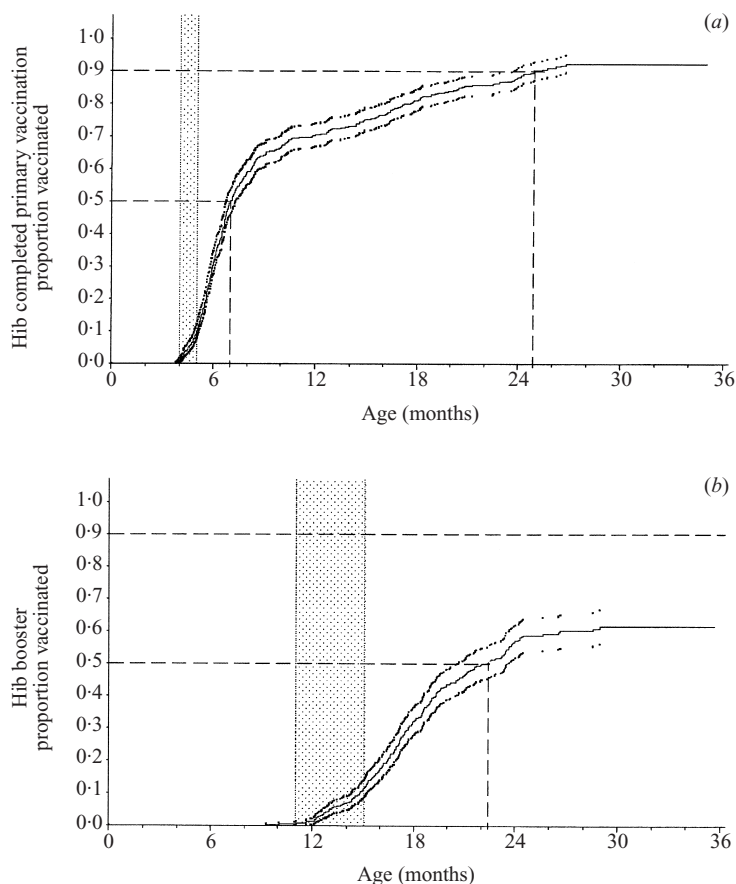
slightly but systematically higher. Completion of primary vaccination is scheduled for the fifth month of life by national recommendations. However, for both vaccines there is a significant rise of coverage between age 7 months and 13 months, indicating considerable delay in vaccination. Similarly booster coverage rises between 19 and 24 months although it is recommended from 12–15 months of age.

The time course of completion of primary pertussis and Hib vaccination is described graphically in Figure 1a and 2a respectively. These figures show that both for pertussis and for Hib completion of primary vaccination, recommended by month five, is achieved in at maximum 10% of the population and that it takes until month 6.6 for pertussis and until month 7 for Hib for 50% of the German children to have completed primary vaccination.

Figures 1b and 2b show time courses for booster dose (booster after primary vaccination had been completed). Primary vaccination is completed more

often and reaches its maximum faster than the booster dose, as the level of plateau is higher and the curve is steeper. For pertussis population coverage levels of 92–95% are required for elimination [8]. For Hib thresholds are less well defined but generally goals are coverage of at least 90% (9, 10). It is also obvious from the graphs, that for both vaccinations these coverage rates were not achieved for primary vaccination during the first year of life and not at all for the booster dose (Figs 1a, b, 2a, b, Table 2).

To quantify more precisely how much vaccinations are delayed in comparison to the recommended schedule, unvaccinated children were excluded from the analysis. The reason for this is the assumption that vaccination in these children is not delayed but will never take place, so their data cannot contribute to actual timing of vaccination. Fifty percent of the children who completed primary vaccination did so by age 7 months and 50% of the children who received the booster did so by age 18 months (Table



**Fig. 2** (a) Hib vaccination in Germany (completed primary) in 782 children aged 0–3 years. Inverse Kaplan–Meier curves ( $1-s(t)$ ) with 95% confidence interval. The shaded area marks the nationally recommended age-periods for vaccination (3rd to 5th month of life). (b) Hib vaccination in Germany (completed primary + booster) in 782 children aged 0–3 years. Inverse Kaplan–Meier curves ( $1-s(t)$ ) with 95% confidence interval. The shaded area marks the nationally recommended age-periods for vaccination (12th–15th month of life).

3). Compared to the recommended vaccination schedule there is a median delay of vaccination of 6 weeks and 10 weeks respectively.

## DISCUSSION

The immunization status measure most commonly used in populations is the proportion of children with adequate immunizations at a certain age threshold ('up-to-date') or adequate vaccination for their age ('age-appropriate') [2]. This approach does not require as detailed data as the Kaplan–Meier method does (exact birth dates and vaccination dates) but it also gives less information. The progress of immunization coverage between the defined ages cannot be judged and restriction of the study population to children who are equal or older than the highest age threshold used (e.g.  $\geq 24$  months old) is required.

These limitations may be overcome by a method which allows visualization of the increase in vac-

ination uptake over time. The Kaplan–Meier method is one such way. To our knowledge this method, though being a well established method of analysis in other fields of medicine, e.g. oncology (analysis of survival time), has not yet been used to describe timing of vaccination. Information from each child, independently of its age and individual observation time, can be taken into account. Therefore the Kaplan–Meier method gives slightly higher results than the conventional method. This difference was not due to a cohort effect (data not shown) but results from the censoring, as Kaplan–Meier reduces the population at risk at the time point when censoring occurs. Identical values compared to the conventional method would be obtained in a data set with identical follow-up periods for all subjects under observation. The Kaplan–Meier method also provides some further advantages: The graphic presentation gives a quick and comprehensive overview of the complex issue of vaccination over time in a population. The estimation

Table 2. Age of children\* at defined coverage levels for pertussis- and *Haemophilus influenzae b* (Hib)-vaccination as calculated by Kaplan–Meier method

	Vaccination coverage							
	50%¶		90%**		92%**		95%**	
	Age (days)	95% CI†	Age (days)	95% CI†	Age (days)	95% CI†	Age (days)	95% CI†
Primary immunization‡								
Pertussis-vaccine	202	197, 207	497	421, 680	615	496, 893	893	713, ††
Hib-vaccine	212	203, 221	753	713, ††	802	731, ††	NA‡‡	
Booster§								
Pertussis-vaccine	581	563, 605	NA		NA		NA	
Hib-vaccine	666	612, 717	NA		NA		NA	

\* 782 German children aged 0–35 months (born July 1996–June 1999).

† CI, Confidence interval.

‡ 3rd dose pertussis, 3rd dose Hib if combination vaccine with pertussisantigen, otherwise 2nd dose Hib.

§ 4th dose pertussis, 4th dose Hib if combination vaccine with pertussisantigen, otherwise 3rd dose Hib.

¶ Age at which 50% of all children were vaccinated with respective dose.

\*\* Immunization coverage levels of 92–95% are considered necessary for elimination of *Bordetella pertussis* [8] and coverage levels of  $\geq 90\%$  are generally aimed for with *Haemophilus influenzae b* vaccination [9].

†† Upper limit of confidence interval could not be terminated in the sample due to lacking observations

‡‡ NA, not achieved.

Table 3. Median delay of vaccination among vaccinated children\* in comparison to national recommendations in Germany 1999 (Kaplan–Meier method)

	n†	Age in days		National recommendation¶	Median delay#
		Median age at vaccination‡	95% CI§		
Primary immunization††					
Pertussis-vaccine	591	196	189, 201	113–152	+ 6 weeks
Hib-vaccine	554	199	194, 203	113–152	+ 6 weeks
Booster‡‡					
Pertussis-vaccine	315	529	515, 542	334–456	+ 10 weeks
Hib-vaccine	243	521	510, 535	334–456	+ 10 weeks

\* of 782 German children aged 0–35 months (born July 1996–June 1999).

† n = number of children vaccinated with respective dose.

‡  $t_{50\%}$  = median age at vaccination = age at which 50% of the children vaccinated had received vaccination.

§ CI, Confidence interval.

¶ 113–152 days = 5th month, 334–456 days = 12th–15th month [3].

# median delay = difference between  $t_{50\%}$  and upper limit of recommendations.

†† 3rd dose pertussis, 3rd dose Hib if combination vaccine with pertussis antigen, otherwise 2nd dose Hib.

‡‡ 4th dose pertussis, 4th dose Hib if combination vaccine with pertussis antigen, otherwise 3rd dose Hib.

of the proportion immunized by any chosen time and vice versa gives two main measures. It allows an estimation of the age at which the vaccination coverage required for elimination of the target disease (mostly 90%–95% [8]) is reached in a population. Moreover, looking at vaccination uptake *per se*, the median vaccination age is a measure of how well

recommended schedules are implemented in a population. This measure corresponds to the median survival time often used in interpreting survival analysis.

Applying this approach to the assessment of *Haemophilus influenzae type b* (Hib) and pertussis vaccination coverage in a representative sample of



German children up to 3 years of age we found a dramatic delay in primary vaccination during the first year of life (Figs 1a, 2a). Less than 10% of children were vaccinated on-schedule and 90% and 92% coverage was not reached for pertussis and Hib-vaccination during the first year of life but only at age 19 and 25 months respectively. For booster doses of both vaccines 90% coverage was not attained at all (Figs 1b, 2b). Age at coverage 90–95% cannot be estimated precisely in our population because the remaining number of children under observation at the relevant time points was small. The age-range of the study population should thus be extended to at least 4–5 years of age for more precise estimation, taking into account the considerable delays in vaccination.

For a closer look at timing of vaccination unvaccinated children were excluded from the analysis, assuming that these would never be vaccinated and thus vaccination in them was not actually delayed but rather non-existent. Comparing vaccinations that had taken place to national recommendations still revealed considerable delay. On ‘average’ (median) these children were immunized with a delay of about 6 weeks for primary and 10 weeks for booster vaccinations (Table 3). For booster doses delay is probably underestimated by this measurement, as children might still get their booster after 3 years of age, the censoring age in our survey.

There is evidence from the literature that delays of vaccination are clinically important. Infants and young children remain most susceptible to pertussis-associated complications [11] even in populations with a high pertussis vaccination coverage such as the US, England and France [11–14]. In the United States 70% of cases < 5 years of age reported from 1989 to 1998 were children less than 12 months old and of 10650 cases aged 3 months to 4 years with known vaccination status 54% were not vaccinated with DTP appropriately to their age (15). Analysis of 216 children with pertussis complications admitted to a German paediatric department 1993–6 gave similar results [16]. In the United States an additional 636 cases of pertussis per year, 115 of which would be associated with complications, were projected to occur if the current schedule of vaccinating infants at 2, 4 and 6 months of age were delayed to 8, 10 and 12 months [17].

In the prevaccination era invasive Hib disease was most frequent in children 6–11 months of age [15]. Though widespread vaccination has diminished the

incidence of Hib cases children less than 1 year old (either too young for vaccination or incompletely vaccinated given their age) remain at greatest risk [15]. In Germany it has been shown that inappropriate age of vaccination increased the risk of systemic Hib disease by a factor of 4.74 [18]. Therefore efforts should be undertaken to increase the timeliness of vaccination.

We think the Kaplan–Meier method might also be used for comparison of different populations or regions in a country. This might be extended to an international level as well. Thus harmonization of vaccination programs in Europe might be followed by describing how well vaccination goals are met in each country. Moreover progress over time in any chosen area can be documented either by comparing graphs from different periods or by using stratified analysis in a study population with different birth cohorts.

Our results suggest that the WHO recommendation of early immunizations against pertussis and Hib is insufficiently achieved in Germany. Timely uptake of certain vaccines is clinically and epidemiologically important and thus should be monitored. We think the Kaplan–Meier method presents an instructive and comprehensive approach to describe timing of vaccination and it is a useful tool for comparisons of vaccination schedules in different populations or in the same populations over time, if the progress of a vaccination campaign is to be monitored.

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