(Hib) after immunization with diphtheria-tetanus-acellular pertussis-Hib-hepatitis B combined vaccine in infants. J Infect Dis 1999;180:1390–3.
13. Anttila M, Eskola J, Ahman H, Kayhty H. Avidity of IgG for *Streptococcus pneumoniae* type 6B and 23F polysaccharides in infants primed with pneumococcal conjugates and boosted with polysaccharide or conjugate vaccines. J Infect Dis 1998; 177:1614–21.
14. Anttila M, Eskola J, Ahman H, Kayhty H. Differences in the avidity of antibodies evoked by four different pneumococcal conjugate vaccines in early childhood. Vaccine 1999;17: 1970–7.
15. Campbell JD, Lagos R, Levine MM, Losonsky GA. Full and fractionated doses of *Haemophilus influenzae* type b (Hib) PRP-T vaccine induce similar IgG antibody avidity in Chilean infants [Abstract 628]. Presented at the 38th Annual Meeting of the Infectious Diseases Society of America, New Orleans, LA, September 7 to 11, 2000.

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Consequences of delayed measles vaccination in Germany

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Background. **In recent surveillance data there are still many cases of measles and even local epidemics in Germany. We studied whether delayed measles vaccination contributes to this situation.**

Methods. **Vaccine coverage data in children <3 years of age were assessed by a telephone survey. Three data sources for measles surveillance were analyzed: official measles notifications; sentinel data; and official hospital discharge diagnoses.**

Results. **After the time recommended for completion of measles vaccination at Month 15, only 22% of German children had received their first vaccine dose. This percentage increased to 77% at the age of 24 months and to 87% at 36 months of age. According to all three surveillance instruments, the number of measles cases was highest in children age 1 to 4 years with a peak in the second year of life.**

Conclusions. **More than 50% of measles cases in 1-year-old children would be prevented if presently observed vaccine coverage rates in the third year of life could be achieved 12 months earlier. Delayed measles vaccination is responsible for a large number of measles cases still occurring in the German population, where measles has not yet been eliminated. If vaccination were delivered according to the recommended time schedule, the incidence of measles would be considerably reduced.**

INTRODUCTION

In the strategic framework for the elimination of measles in the European Region promulgated by WHO in 1997, Germany was categorized into Group 3, namely countries with poor control and weak surveillance of measles.[1, 2] Virus circulation was ongoing, but valid data were lacking for estimating the epidemiologic situation. A national program for improving surveillance was implemented in 1999 with a nationwide sentinel system for active surveillance of measles cases, AGM-Sentinel. The measles working group, AGM, is a joint initiative of the Robert Koch-Institute (RKI) and the three vaccine manufacturers, Chiron Behring, Aventis Pasteur MSD and GlaxoSmithKline. The German Green Cross has been entrusted with the field work and data management. The RKI does not receive any outside funding for this activity.[3, 4] In addition measles became a notifiable disease according to the new "infectious diseases protection law" [Infektionsschutzgesetz (IfSG)] in January 2001.[5] Measles cases must be reported by physicians and also by diagnostic laboratories confirming this diagnosis.

Recently available epidemiologic data in Germany confirm what had been previously suspected, that

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there are many measles cases and even local epidemics. Although the German Standing Committee on Vaccination (Ständige Impfkommission) recommends administering the first dose of measles vaccine between ages 11 and 14 months,[6] this is accomplished in only ~22% of children, and only ~85% of children receive a first measles vaccine dose by age 35 months.[7] Strategies to reduce measles-associated morbidity in the population might be targeted at increasing vaccination coverage and at administering the vaccine earlier in life. Using recently available epidemiologic data, we studied whether timely vaccination might have a substantial impact on the number of measles cases in Germany.

METHODS

Vaccination coverage study. The vaccination status of children <3 years of age was investigated in summer 1999 by telephone interview in a randomly selected sample of households in Germany. For each child the date of birth as well as all available information on vaccines administered were obtained, including date of administration and the product used. Vaccine coverage by age in months was calculated according to the Kaplan-Meier method and then illustrated with a survival curve. This curve shows the ratio between the number of vaccinated children at age t (nominator) and the number of age eligible children for vaccination at the same age (denominator). Time of "survival" is the period from birth to receiving the first measles vaccine dose. The probability of survival $S(t)$ is the probability of not being vaccinated at time t and thus, $1 - S(t)$ is the probability of being vaccinated at this time, which is the coverage rate for measles vaccination at a certain age.

Measles surveillance. Three data sources were analyzed: the AGM-Sentinel network data; official notifications of measles cases (IfSG); and data on hospital discharges from the German Official Health Statistics (Statistisches Bundesamt).

More than 1200 physicians, mainly pediatricians, responsible for the primary medical care of children in Germany, participate in the sentinel network. As confirmed by official statistical data, the regional and the sociodemographic distribution of sentinel physicians was comparable with that of all pediatricians in Germany.[8] Participants received monthly report cards from the study office at the German Green Cross asking whether patients with measles had been observed during the previous month. The cards had to be returned, even if no case of measles had been observed (null option). If there was at least one case, the reporting physician was asked to report the following details on patients in a questionnaire: month and year of birth; date of onset of symptoms; vaccination status; source of infection; complications (otitis media, pneumonia, central nervous system-related symptoms, others); hospital admission; single case; or epidemiologically linked cases. The measles case definition included fever, exanthema and at least one other symptom including cough, rhinitis or conjunctivitis. Laboratory confirmation of measles was offered free of charge by the National Reference Center for Measles, Mumps and Rubella at the RKI. Microbiologic confirmation was encouraged, particularly for single cases and for confirmation of first cases in an outbreak. The total number of measles cases in one year was estimated by extrapolation. The number of reported cases per participating pediatrician per month and per region was multiplied by the number of pediatricians in the respective region and then calculated for Germany.

The second data source used was official case notifications according to the infection protection law (IfSG), available since January 1, 2001, to June 30, 2001 (RKI, data unpublished when this article was accepted for publication). Any case of measles diagnosed clinically or by a laboratory must be reported to local public health departments, and the information is sent to the national surveillance center at the RKI. For each reported case in a child <5 years, the age in months at the onset of measles symptoms was calculated.

Data gathered by sentinel surveillance as well as case notifications were compared with hospital discharge data from the German Statistical Office,[9] which are available from mandatory reporting of the International Classification of Diseases, 9th revision, classifications (Code 055 for measles) of all German hospitals by age group (<1 year, 1 to 4 years, 5 to 14 years, 15 to 24 years and 25 years and older).

RESULTS

Of the 1400 contacted households with children <3 years of age, 775 participated in the study (response rate, 55%).

The vaccination status of 837 children could be assessed. 55 children had to be excluded because there

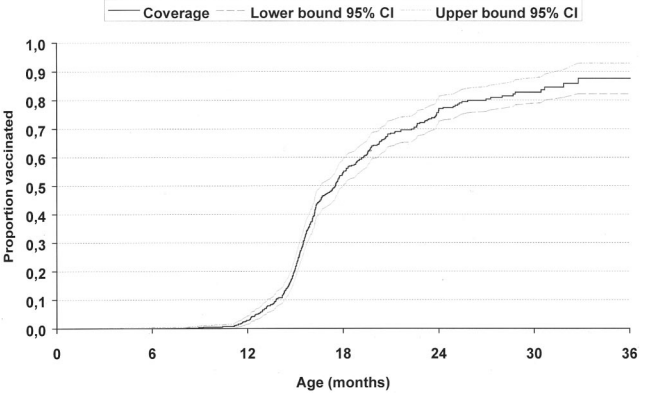

FIG. 1. Vaccination coverage rate by age. *CI,* confidence interval.

was either incomplete information on the vaccination history or because the child was not in the target age group (children born between July 1, 1996, and June 30, 1999). Thus 782 children age 0 to 35 months were included in the analysis.

Figure 1 shows the increment in measles vaccination coverage rate by age as calculated by the Kaplan-Meier method. At age 15 months only 21.7% (confidence interval, 18.0 to 25.3) of the children had received their first dose of measles vaccine. By 24 months this proportion increased to 77.0% (confidence interval, 72.7 to 81.4), with the steepest increase between Months 15 and 17. By age 36 months 87.6% of children had received their first measles vaccination.

From October 1999 to May 2001, a total of 1486 measles cases were reported to the AGM. Most cases were in children age 1 to 4 years, and the highest number of measles complications was observed in this age group (Fig. 2).

These observations correspond well with recently available hospital discharge diagnoses (1999).[9] In this system children age 1 to 4 years accounted for the largest group hospitalized with measles (172 of 582 patients; 30%). Similarly this age group accounted for most reported measles cases according to IfSG: 1113 of 4500 reports (25%) from January to June 2001.

Data from the AGM demonstrate that 4% of 1- to 4-year-old patients with measles were admitted to a hospital, with an overall admission rate of 3% for patients of all ages. According to IfSG data the rate of hospital admissions was 7% for patients age 1 to 4 years and 9% for all patients.

Measles reports from the AGM-Sentinel survey and from measles notifications within the IfSG allowed for further differentiation by age to estimate the impact of delayed measles vaccination on the overall burden of disease in Germany. Within the age group 1 to 4 years, most cases were seen in 1-year-old children (400 of 1113 or 36% in the IfSG reports; 223 of 597 or 37% of cases reported to the AGM). Only ~20% of cases were observed in each of the older age groups.

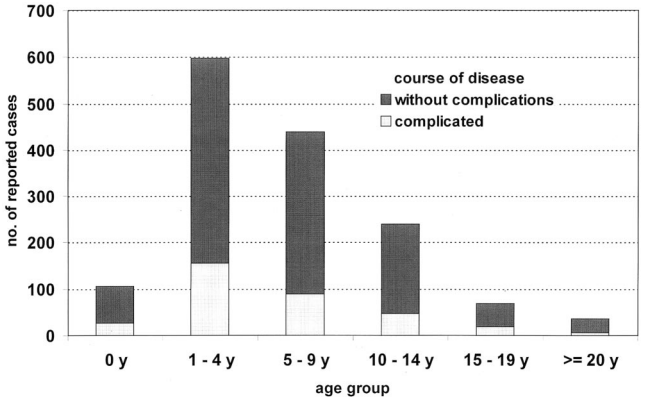

FIG. 2. Reported measles by age group with and without complications (source, AGM-Sentinel). *y,* years.

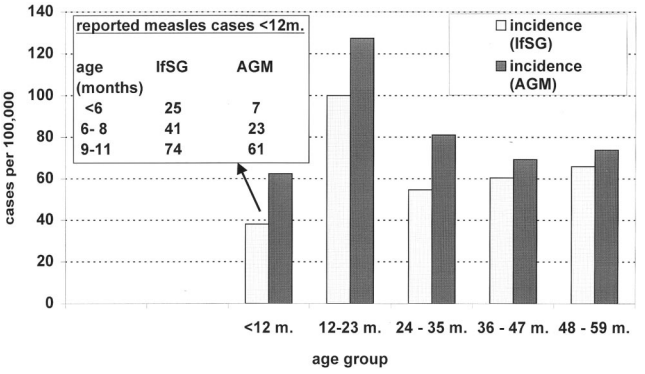

FIG. 3. Incidence of measles in children <5 years of age (estimates per year and 100 000 of age group) and number of cases in <12-month (*m.*)-old infants according to different data sources.

Reports from both systems were used to estimate incidences to allow for identical scales (Fig. 3). The expected number of cases per year and per 100 000 per age group was calculated by extrapolation for all reported AGM cases of the respective age. The number of cases observed after mandatory IfSG reports from January to June 2001 (half a year) was simply doubled for incidence estimation per year. In both reporting systems the highest age-specific incidence was in the second year of life. The estimated incidence rates in this age group were between 100 (IfSG reports) and 125 (AGM-Sentinel survey) cases per 100 000 children which results in a total of ~800 to 1000 measles cases in that age group per year. In both reporting systems ~35% of children with measles were 12 to14 months old, which is the recommended time for the administration of the first dose of measles vaccine.

A considerable number of cases occurred during the first 11 months of life. Both data sources indicated that the steepest increase as well as the highest number of measles cases in infants occurred in the second half of the first year. With an estimated incidence of ~50 cases per 100 000 infants and a birth cohort of ~800 000, there might be some 400 cases per year in that age. Incidences at 2, 3 and 4 years, respectively, were well below 80 cases per year and 100 000 children, and the yearly number of cases is estimated to be 500 to 600 for each group.

Hospital admission rates due to measles at age 1 to 4 years were 4% according to AGM data and 7% according to IfSG data. For an estimated 100 to 180 hospitalizations in Germany per year, this number is consistent with the officially registered number of 172 hospital discharge diagnoses according to International Classification of Diseases, 9th revision, in 1999.[9]

DISCUSSION

The consequence of insufficient coverage of vaccination on measles epidemiology in general is well-

TABLE 1. Potentially preventable measles cases by increasing vaccine coverage in the second year of life

Age Group (mo)	Present Stage (According to Vaccination Rates in the Second yr of Life)			Potential Stage (if Present Vaccination Rates in the Third yr Were Already Reached in the Second yr of Life)			
	Vaccine coverage (%)	No. not vaccinated	No. of cases	Vaccine coverage (%)	No. not vaccinated	No. of cases	No. of potentially prevented
12–14	20	160000	315	75	50000	100	215
15–17	50	100000	205	79	42000	85	120
18–20	66	68000	190	82	36000	100	90
21–23	75	50000	190	85	30000	115	75
Sum		378000	900		158000	400	500

known,[1, 2, 10] we focused on the aspect of delayed vaccination in the youngest age group.

To estimate the number of measles cases in Germany that could be prevented by strictly adhering to the recommended time schedule for measles vaccination, we used three sources for detecting measles cases in the population. By arriving at similar results the three sources validated one another.

The calculated incidence rates are rough estimates. Underreporting occurs in mandatory, passive reporting systems,[11] resulting in underestimation when using measles notifications systems alone. Incidence rates estimated from the AGM-Sentinal data were higher than the IfSG notifications. However, even the AGM incidence figures may be an underestimation, because underreporting cannot be excluded even with active surveillance systems.[12] On the other hand a proportion of cases reported according to the IfSG as well as to AGM may not be measles cases given that laboratory confirmation is not required in the case definition. Caring for a patient with measles is a rather rare event for many physicians in Germany, and the clinical picture alone cannot with certainty be distinguished from the clinical presentation of other diseases. Thus only microbiologically confirmed cases are definite cases.

Microbiologic confirmation was sought in ~40% of all AGM-cases and ~60% of these samples tested positive. Vaccination status, age, complications, sporadic *vs.* endemic cases are factors that influence the threshold for taking samples for microbiologic testing and the predictive value of the tests. However, the high laboratory confirmation rate of cases is a clear marker of an epidemic situation of measles in Germany that is far from measles elimination. Only a laboratory confirmation rate of <10% is regarded as a criterion for the elimination phase of the disease.[1, 10, 13]

The high proportion of cases in the first 4 years of life, consistently found in all three data sources, and the sharp increase of cases after 6 months of age are biologically plausible. Protection by maternal antibodies is rapidly waning during the second half of the first year of life; therefore measles vaccination has recently been scheduled at 11 to 14 rather than at 15 to 18 months of age.[6] This problem might increase because today many infants are protected by maternal antibodies induced by vaccination rather than by infection with the wild virus. Measles vaccination results in lower maternal antibody concentration and in a shorter period of protection from passively transferred immunity. Measles cases reported in the first 6 months of age may result from vaccine-induced early waning passive immunity.

The World Health Organization has set forth age-specific immunity targets as a prerequisite for measles elimination. The rate of susceptible children should not exceed 15% in children age 1 to 4 years, 10% in children 5 to 9 years and 5% in children older than 10 years.[2] In Germany an 85% measles vaccination coverage rate is achieved only at the end of the third year of life. Vaccination coverage may even be overestimated, because participation in the telephone interview was far from complete and because unvaccinated children may be overrepresented in those not willing to participate in the telephone survey. This assumption is supported by data from a survey of measles antibody prevalence in infants.[13] These data from the National Reference Center for Measles, Mumps and Rubella at the RKI showed a lack of specific measles antibodies of >30% at the age of 2 years and of ~25% in 3-year-old children in 1995/1996.[13]

About 15% of German children at age 3 years are left unprotected against measles, and the morbidity observed because of delayed vaccination is considerable. To assess the benefit possibly achieved by measles vaccination in accordance with the national recommendations in Germany, the number of cases preventable by early vaccination was estimated under the assumption that vaccination coverage presently attained during the third year of life could be attained during the second year of life (Table 1). On the basis of an age cohort of ~800 000 children, 200 000 children belong to each of the 3-months age groups from which the number of unvaccinated children was calculated using current ("real") as well as a potential earlier vaccination coverage. The number of cases at the present stage was given according to the estimated incidence. The potential number of cases was estimated under the

assumption that the relation between the number of cases and the number of unvaccinated children is the same regardless of vaccination coverage. If present vaccine coverage rates could be achieved 12 months earlier, >50% of measles cases (500 of 900) in the second year of life would be prevented. The total number of preventable cases in all age groups would even be higher as the number of measles susceptible children beyond the age of 2 years would decrease. Most of the benefit would be achieved in children age 12 to 14 months, where more than two-thirds of the presently occurring cases (215 of 315) could be prevented if vaccination were conducted according to the recommended schedule.

Our results show that in countries like Germany where vaccination coverage in young children is below the coverage necessary for measles elimination and where there still is a considerable circulation of measles wild virus, early vaccination could lead to a considerable reduction of measles-related morbidity.

REFERENCES

1. Expanded Programme on Immunization (EPI). Meeting on advances in measles elimination: conclusions and recommendations. Wkly Epidemiol Rec 1996;71:305–12.
2. Expanded Programme on Immunization in the European Region of WHO: Measles: a strategic framework for the elimination of measles in the European Region. Copenhagen: WHO, 1999:26 pp.
3. Robert Koch-Institute. Interventionsprogramm Masern, Mumps, Röteln (MMR). Epidemiol Bull 1999;45:335–41.
4. Tischer A, Siedler A, Rasch G. Laboratory supported results of the measles sentinel in Germany. Infection 2001;29(Suppl 1):50.
5. Bundesgesetzblatt Teil 1 Nr.33/2000: 1045–78.
6. Robert Koch-Institute. Impfempfehlungen der Ständigen Impfkommission (STIKO) am RKI. Epidiol Bull 2001;28:203–18.
7. Laubereau B, Hermann M, Weil J, et al. Durchimpfungsraten bei Kindern in Deutschland 1999. Monatsschr Kinderheilkd 2001;149:367–72.
8. INKAR-Indikatoren und Karten zur Raumentwicklung. Bonn: Bundesamt für Bauwesen und Raumordnung, 2000.
9. Federal Health Monitoring System. Information system of the Health Monitoring System. Available at: www.gbe-bund.de. Hospital discharges 1999 (search results for "measles").
10. Gay N, Hesketh M, Morgan-Capner P, et al. Interpretation of serologic surveillance data for measles using mathematical models: implications for vaccine strategy. Epidemiol Infect 1995;115:139–56.
11. Kirschner W. Sentinel-Surveillance von HIV und anderen sexuell übertragbaren Krankheiten: Ergebnisse der ANOMO-Studie 1988 bis 1994. German Ministry of Health, ed. Baden-Baden: Nomos Verlagsgeselschaft, 1996.
12. von Kries R, Heinrich B, Hermann M. Pädiatrische Epidemiologie in Deutschland: Forschungsinstrument ESPED. Monatsschr Kinderheilkd 2001;149:1191–7.
13. Gerike E, Tischer A, Santibanez S. Einschätzung der Masernsituation in Deutschland: Ergebnisse der laborgestützten Überwachung von 1990 bis 1998. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 2000;43:11–21.

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Infectious diseases in sub-Saharan African immigrant children in Madrid, Spain

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Background. **Immigration flow from developing countries to European countries is growing continually, but data about imported infectious diseases in immigrant children are few.**

Methods. **Descriptive and retrospective study of 125 sub-Saharan African children <14 years of age attending a tropical medicine referral unit in Madrid, Spain, between 1989 and 2001.**

Results. **Of the 125 children 79% had 1 or more symptoms. The remaining 21% (26 cases) were asymptomatic and were screened for infectious diseases. Of them 57.7% (15 cases) had 1 or more infectious diseases. Significant association ($P < 0.05$) was found between fever and malaria, between cutaneous pruritus and filariasis and between eosinophilia and filariasis and intestinal helminthiasis. Seventy-nine percent had infectious pathology and 33.3% were in-**

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