

Kinetics of Decline of Maternal Measles Virus-Neutralizing Antibodies in Sera of Infants in France in 2006[∇]

Arnaud Gagneur,^{1,2*} Didier Pinquier,³ Marie Aubert,⁴ Laurent Balu,⁵ Olivier Brissaud,⁶ Loïc De Pontual,⁵ Christèle Gras Le Guen,⁷ Isabelle Hau-Rainsard,⁸ Olivier Mory,⁹ Georges Picherot,⁷ Jean-Louis Stephan,⁹ Bernard Cohen,¹⁰ Evelyne Caulin,⁴ Benoît Soubeyrand,⁴ and Philippe Reinert⁸

CHU Brest, Brest, France¹; Département de Pédiatrie, CHUS Sherbrooke, Québec, Canada²; Hôpital Charles Nicolle, Pôle Mère-Femme-Enfant, CHU Rouen, Rouen, France³; Sanofi Pasteur MSD, Lyon, France⁴; Hôpital Jean Verdier, Bondy, France⁵; CHU Bordeaux, Bordeaux, France⁶; Hôpital Mère-Enfant et Centre d'Investigation Clinique Pédiatrique, CHU Nantes, Nantes, France⁷; CHI Créteil, Créteil, France⁸; CHU Nord, Saint-Etienne, France⁹; and Health Protection Agency, London, United Kingdom¹⁰

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The optimal age for measles vaccination is an important health issue, since maternal antibodies may neutralize the vaccine antigen before a specific immune response develops, while delaying vaccination may increase the risk of complicated diseases in infants. However, measles vaccination impacts the duration of protection afforded by transplacental transfer of maternal antibodies: vaccination-induced maternal antibodies disappear faster than disease-induced antibodies. In order to maintain protection against measles in infants, it is important to monitor the dynamics of this phenomenon in vaccinated populations. To assess the current situation in France, a multicenter, prospective seroepidemiological study was conducted in seven French hospitals between October 2005 and January 2007. Maternal measles antibody concentrations from 348 infants 0 to 15 months old were measured using the plaque reduction neutralization assay. Geometric mean concentrations and the percentage of infants with maternal measles antibody concentrations above the protection threshold (≥ 120 mIU/ml) were assessed according to age. Results show that after more than 20 years of routine measles vaccination in France, maternal measles-neutralizing antibodies decrease dramatically in French infants by 6 months of age, from 1,740 mIU/ml for infants 0 to 1 month old to 223 mIU/ml for infants 5 to 6 months old, and that 90% of infants are not protected against measles after 6 months of age. Infant protection against measles could be optimized both by increasing herd immunity through an increased vaccine coverage and by lowering the age of routine vaccination from 12 to 9 months.

Large-scale measles vaccination has led to a dramatic decrease in measles incidence and deaths from measles worldwide (54). In France, the estimated number of measles cases dropped from 300,000 in 1985 to less than 10,400 cases in 2003 (3, 48), and mortality has declined from 30 deaths per year in the 1980s to less than 10 per year in recent years (3, 48). However, despite the success in controlling measles, the disease has not been eliminated in Europe; outbreaks still occur (2, 3, 13, 18, 29, 34, 35, 45, 48, 50, 52, 53), and measles can still represent a serious health threat, especially in infants under 1 year of age (7, 18).

The optimal age for infant measles vaccination is an important health issue, since maternal antibodies may neutralize the vaccine antigen before a specific immune response develops, while delaying vaccination may increase the risk of complicated diseases in infants. However, the introduction of measles vaccine in a country particularly impacts the duration of protection afforded by maternal antibodies: levels of vaccine-induced maternal antibodies are lower, and they disappear faster than disease-induced antibodies. As vaccine coverage of a pop-

ulation increases, measles virus circulation declines, and more infants are born with vaccine-induced maternal antibodies. These infants will be protected for a shorter period of time than those in the prevaccine era. To maintain protection against measles in infants, it is thus important to monitor the dynamics of this phenomenon in vaccinated populations.

Although the measles vaccine was licensed in France in 1966, it was not included in the vaccination schedule until 1983, as a bivalent vaccine in combination with rubella, and then in 1986, as a trivalent measles-mumps-rubella (MMR) vaccine for infants 12 to 15 months old. In 1996, recommendations were extended to include a second dose of MMR vaccine for children 11 to 13 years old. This second dose does not constitute a booster, with long-term immunity acquired following the first vaccination. It constitutes a catch-up for infants who did not seroconvert, for one of several antigens, with the first vaccination (10).

In 1997, the recommended age range for the second dose was lowered to 3 to 6 years (42). In 2005, within the framework of the WHO congenital measles and rubella elimination program, the recommendation was modified again, and the age of vaccination was lowered to 12 months for the first dose of MMR vaccine, with the second dose given between 13 and 24 months of age (11). For children attending day care centers or traveling to countries where measles is highly endemic, the recommendation for the first dose is 9 months of age, with the

* Corresponding author. Present address: Département de Pédiatrie, Unité de Néonatalogie, CHUS Fleurimont 3001, 12ème Avenue Nord, Sherbrooke, QC J1H 5N4, Canada. Phone: (819) 346-1110. Fax: (819) 564-5398. E-mail: arnaud.gagneur@usherbrooke.ca.

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second dose given between 12 and 15 months of age. Monovalent measles vaccine can be used in infants 6 to 8 months old who have been in contact with measles cases (10, 11, 16). Lowering the recommended age of vaccination was also prompted by several reports showing a rapid decline in maternal measles antibody concentrations in other well-vaccinated populations (12, 24, 32, 40, 44).

In France, measles vaccine coverage increased significantly only after the official recommendation in 1983 and the subsequent availability of the combined MMR vaccine in 1986. Measles vaccine coverage of infants (with a single dose at 24 months of age) increased from 19% in 1979 to 35% in 1983, 57% in 1987, and 80% in 1994 and then remained relatively unchanged until 2004, when it reached 87% (4, 10).

The present study is the first to assess the seroepidemiology of measles in infants in France, a country where the population is well vaccinated against measles. The main objective of this study was to determine the kinetics of the decline of passively transferred maternal measles antibodies in infants 0 to 15 months old. The second objective was to define the proportion of infants protected against measles (with neutralizing serum antibody concentrations of ≥ 120 mIU/ml).

MATERIALS AND METHODS

Study design. This prospective multicenter study was conducted between 6 October 2005 and 31 January 2007 in seven hospitals located in six regions throughout France, as follows: Normandie, Bretagne, Pays de Loire, the greater Paris area, Rhône-Alpes, and Aquitaine.

Study population. Seven hospitals consecutively recruited infants, who consulted or were hospitalized in a pediatric department and/or a pediatric emergency service, who met the following inclusion criteria: between 0 and 15 months of age, born at term (mother with ≥ 37 weeks amenorrhea), with a birth weight of ≥ 2.8 kg and a medical condition requiring blood sampling, and with informed consent for the present study given by at least one parent.

Infants were excluded from the study if they met any of the following criteria: previous vaccination against measles or a clinical history of measles, contact with a measles case in the previous 3 weeks, a known or suspected immunodeficiency, and previous treatment with immunoglobulins or a blood transfusion. Infants were also excluded if their mother received a blood transfusion during pregnancy or had been living in metropolitan France for less than 3 years. In addition, if collection of an additional 0.5 ml of blood posed a medical risk or if an infant was enrolled in any other study, the infant was excluded from this study.

The study was performed in accordance with the Helsinki Declaration, the good epidemiology practice guidelines of the Association of French-speaking Epidemiologists, and the procedures established by French law. It was approved by the Consultative Committee for the Protection of Persons Participating in Biomedical Research of Saint-Germain-en-Laye. Informed consent was given by at least one of the parents of all infants participating in the study. Children enrolled in the study were listed in the National File of Persons Participating in Biomedical Research without Direct Individual Benefit.

Sampling. For each infant, a 0.5-ml blood sample was collected in a dry tube for determination of measles antibody concentration in addition to the volume collected for the infant's medical management.

The additional 0.5-ml blood sample was processed by the local hospital laboratory. Blood was centrifuged at 3,000 rpm for 10 to 15 min, and serum was separated, placed in a tube labeled with the patient's identification code (tag), and stored at -20°C until the end of the study. Coded serum samples were shipped at the end of the study to the Centre for Infections, Health Protection Agency, London, United Kingdom, for analysis.

PRN assay to determine measles-neutralizing serum antibodies. Measles antibodies were measured by a plaque reduction neutralization (PRN) assay as described previously (8). In brief, each serum dilution was mixed with an equal volume of challenge virus (Edmonston wild-type strain) containing a standard virus dose. After incubation, to allow virus neutralization to proceed, the virus-serum mixtures were inoculated onto Vero cells and incubated for an additional 5 to 7 days. The highest dilution of serum giving a 50% reduction in plaque count was defined as the endpoint concentration. Results were transformed into

mIU/ml by comparing sample endpoint concentrations with the concentration of the second international standard for measles antibody containing 5,000 mIU/ml (National Institute of Biological Standards and Control, South Mimms, United Kingdom), which was tested in parallel with each batch of test samples.

The seroconversion threshold was defined as the detection limit of the technique. The detection limit varied slightly between assay runs, ranging from 27 to 63 (average 45.3) mIU/ml in the nine assay runs performed to test the samples from this study. The protection threshold was defined as a concentration of ≥ 120 mIU/ml (6). Antibody concentrations were reported in mIU/ml, and the geometric mean concentration (GMC), extreme values (minimum and maximum range), and 95% confidence intervals (CI) were calculated. Only antibody concentrations over the limit of detection were taken into account for the calculation of GMCs.

Data collection. A case report form was compiled for each participant and included identification of the infant and investigator; the place and date of inclusion; the date of birth, gestational age, birth weight, and sex of the infant; and the date of and reason for blood sampling for the infant's medical management. Information about the mother, including her date of birth and her measles history (natural infection or vaccination), was obtained during the interview with the parents and was noted in the case report form.

Statistical analysis. Quantitative variables were analyzed using a two-sided Student *t* test or analysis of variance. Qualitative variables were studied using a two-sided chi-square test or a Cochran-Mantel-Haenszel test. Data analysis was conducted using SAS version 8. A *P* value below 0.05 was considered statistically significant.

The evaluable population was defined as the infant population with no major deviation from the protocol. Factors such as a history of vaccination or the absence of the information form or the data for gestational age or a blood sample were considered major deviations. Infants with a birth weight between 2.6 and 2.8 kg were taken into account in the evaluation.

Measles antibody concentrations were analyzed by 1-month age groups. For statistical tests, 3-month age groups were used if a sufficient sample size could not be obtained for each 1-month age group. The relationship between measles antibody concentrations and age was assessed using exponential nonlinear regression analysis weighted by age.

RESULTS

A total of 353 infants were enrolled in the study. Five infants were excluded due to previous measles vaccination ($n = 2$) or missing data or blood samples ($n = 3$). Of the 348 evaluable infants, 51.1% were males and 48.9% were females. Their median gestational age at birth was 39 weeks (mean, 39.3 ± 0.2 weeks), and the median birth weight was 3.330 kg (mean, 3.392 ± 0.424 kg; minimum to maximum, 2.610 kg to 5.050 kg). The median age at inclusion was 8.7 months (mean, 7.9 ± 3.8 months; minimum to maximum, 0.03 to 15.57 months). The distribution according to age was as follows: 0 to 3 months, 13.8% ($n = 48$); 3 to 6 months, 12.9% ($n = 45$); 6 to 9 months, 27.0% ($n = 94$); 9 to 12 months, 33.0% ($n = 115$); and >12 months, 13.2% ($n = 46$).

The age of the mother was known for 347/348 infants. At delivery, the median age of the mothers was 29 years (mean, $28.9 \text{ years} \pm 5.05 \text{ years}$; range, 17 to 45 years). Among the 348 mothers, 113 (32.5%) said they had been vaccinated, and 141 (40.5%) reported a history of natural infection.

Measles-neutralizing serum antibody concentrations in infants. A total of 40.2% of infants (140/348) had measles antibody concentrations above the detection limit. The proportion of infants with detectable measles antibodies decreased dramatically with age, from 95.8% in infants 0 to 3 months old to 39.4% in infants 6 to 9 months old and 10.9% in infants over 12 months.

The GMCs of measles antibodies for each 1-month age group were determined for the 140 serum samples with antibody concentrations above the detection level. Measles-neu-

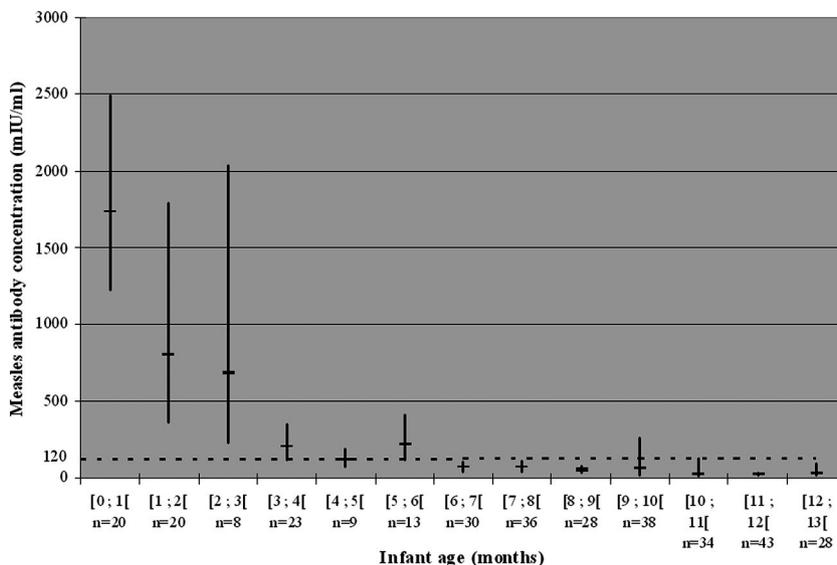


FIG. 1. Distribution of measles-neutralizing serum antibody concentrations (GMC) in infants 0 to 15 months old (1-month age groups) in France, 2006.

tralizing antibody GMCs decreased rapidly from 1,740 mIU/ml for infants in the 0- to 1-month age group to 223 mIU/ml (5- to 6-month age group) to 65 mIU/ml (6- to 7-month age group). Among the 13- to 14-month and the 14- to 15-month age groups, 11/12 and 6/6 children, respectively, had measles antibody concentrations under the limit of detection. Consequently, these concentrations were not taken into account for the calculation of GMCs (Fig. 1). When results for infants in the different 3-month age groups were compared (Table 1), a statistically significant difference ($P < 0.001$) in GMCs was observed.

Proportion of infants with measles-neutralizing serum antibody concentrations at or above the seroprotection threshold (≥ 120 mIU/ml). The proportion of infants with protective measles antibody concentrations at or above 120 mIU/ml dropped from 100% in infants 0 to 1 month old to 10% in infants 6 to 7 months old (Fig. 2). A statistically significant difference in the proportion of infants with protective measles antibody concentrations was observed between the 3-month age groups ($P < 0.001$) (data not shown).

TABLE 1. Measles-neutralizing serum antibody concentrations by 3-month age groups in France in 2006

Age group (mo)	No. of infants evaluated	No. of infants with Ab concn over detection limit ^a	GMC (mIU/ml) ^b	95% CI	Range (minimum-maximum) (mIU/ml)
0-3	48	46	1,094.56	746.69-1604.50	44.00-7,968.00
3-6	45	38	186.97	137.06-255.06	33.80-1,596.50
6-9	94	37	64.52	50.51-82.41	18.00-400.50
9-12	115	14	40.61	20.68-79.74	13.50-1,277.00
>12	46	5	34.18	16.7-69.93	21.30-80.00
Total	348	140			

^a Ab, antibody.

^b A significant difference ($P < 0.001$) was observed between the GMCs of the five age groups.

Measles-neutralizing antibody concentrations in infants according to the mother's year of birth. The GMC of measles-neutralizing antibodies was lower in infants whose mothers were born after 1983 than in infants whose mothers were born before 1983 (128.6 mIU/ml versus 212.1 mIU/ml, respectively) (Table 2), but this difference was not statistically significant ($P = 0.43$).

The proportion of infants with protective measles antibody concentrations was also lower in infants whose mothers were born after 1983 than in infants whose mothers were born before 1983 (9.1% versus 22.2%, respectively). This difference, however, was not statistically significant ($P = 0.15$).

Measles-neutralizing antibody concentrations in infants according to the mother's reported history of measles (natural infection versus vaccination). Infants 0 to 3 months old whose mothers had a reported history of measles vaccination had lower antibody concentrations (GMC, 155.0 mIU/ml; 95% CI, 95.6 to 251.5) than infants whose mothers had a reported history of measles infection (GMC, 263.8 mIU/ml; 95% CI, 172.8 to 402.8), but the difference was not statistically significant ($P = 0.11$) and disappeared rapidly (Fig. 3). For infants 6 to 9 months of age, the level of maternal measles antibodies was the same for all infants, whether their mothers had had natural measles infections or had been vaccinated.

DISCUSSION

Early measles infection may lead to severe complications such as bacterial superinfection and subacute sclerosing pan-encephalitis; the highest hospitalization rates for measles are observed for infants under 1 year of age (7, 18, 33). Newborns are protected against measles by maternal antibodies actively transferred via the placenta during the last trimester of pregnancy (41, 46). These maternal antibodies disappear during the first months of life as the newborn's own immune system develops.

The optimal age for measles vaccination is an important

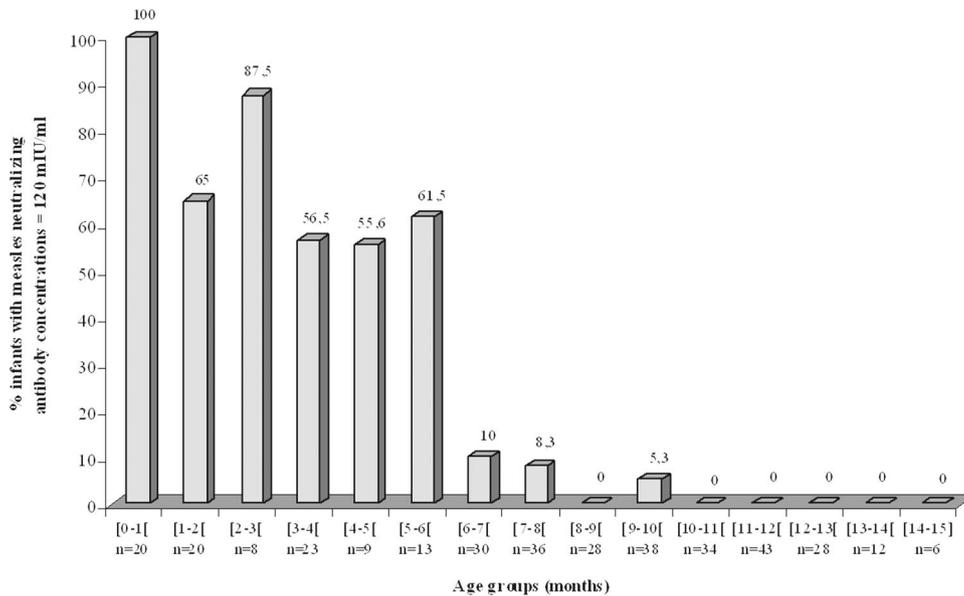


FIG. 2. Proportion of infants 0 to 15 months old (1-month age groups) with protective measles antibody concentrations according to age in France, 2006.

public health issue. Vaccination at an early age may fail because of immaturity of the immune system and also because of the presence of maternal antibodies, which neutralize the vaccine antigens before a specific immune response develops (19, 25, 36). However, any delay in vaccination may increase the risk of complicated disease in infants. It is consequently important for each country to adapt the timing of vaccination to its measles seroepidemiological situation (27). This study is, to our knowledge, the first to determine the kinetics of maternal measles antibody decline in infants in France. It involved seven hospitals located in six regions throughout France: Normandie, Bretagne, Pays de Loire, greater Paris, Rhône-Alpes, and Aquitaine.

A rapid decline in levels of maternal measles-neutralizing antibodies after birth was observed, as measured by the PRN assay. This test is currently considered the gold standard due to its high sensitivity and ability to measure functional neutralizing antibodies (6, 9, 51). Although the percentage of infants with detectable measles-neutralizing antibody levels remained around 40% for infants 7 to 8 months old, 90% of the infants included in the study had antibody concentrations under 120

mIU/ml after 6 months of age. Studies carried out in other countries have also shown that infants over 6 months of age in a well-immunized population may be poorly protected against measles (5, 12, 24, 32, 40, 44).

The 120-mIU/ml antibody level correlates with protection in actively immunized (vaccinated) children; it may not correlate with protection in passively immunized children because cell-mediated immunity, which also plays an important role in protection, is lacking in passive immunity. Thus, while some children vaccinated against measles could be protected even in the absence of detectable circulating antibodies through cell-mediated immunity (47), infants passively immunized through maternal antibodies may not be protected against disease, even with antibody levels of >120 mIU/ml.

The rate of decline of maternal antibodies in infants is dependent upon initial levels of maternal antibody, which reflect both maternal antibody levels at the time of pregnancy and the extent of placental transfer. Since antibody transfer occurs mainly during the third trimester of pregnancy, preterm infants have low levels of maternal antibodies (5, 21, 26, 28, 31, 41, 46).

TABLE 2. Measles-neutralizing serum antibody concentrations in infants in 2006 according to their mothers' year of birth in France

Mothers' birth year ^a	No. of infants born (n = 347)	No. of infants with Ab concn over detection limit ^b	GMC (mIU/ml) (95% CI) ^c
Before 1983	325	132	212.1 (159.7–281.6)
After 1983	22	7	128.6 (28.1–588.4)

^a The measles vaccination schedule was introduced in France in 1983.
^b Ab, antibody.
^c GMCs were available for 140 infants; the year of the mother's birth was available for 139 infants. No significant differences were observed for GMCs between the two infant groups ($P = 0.43$).

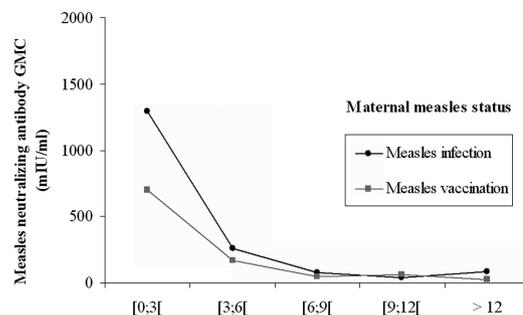


FIG. 3. Measles-neutralizing serum antibody concentration (GMC) according to infant age (3-month age groups) and maternal measles status (natural infection or vaccination) in France, 2006.

Placental transfer has also been found to be less efficient in infants in developing countries than in industrialized countries (22). Coexisting infections such as malaria and human immunodeficiency virus infections are also associated with decreased levels of maternal antibodies in infants (5, 17). These factors should not have complicated the results of the present study, since premature infants and infants whose mothers were not living in metropolitan France at the time of pregnancy were excluded from the study.

It is recognized that measles antibody levels induced by vaccination are lower than antibody levels induced by the disease (23, 24). Several studies have shown that newborns from vaccinated mothers have both lower levels of transplacentally transferred measles antibodies than infants born from women who had measles and an earlier decline in maternal antibodies (1, 4, 12, 15, 30, 37, 38, 40). In this study, the measles antibody levels determined for infants at 0 to 3 months of age were higher in infants born from mothers who had had natural measles infections than in infants of vaccinated mothers. This difference was not significant and disappeared rapidly (Fig. 3). However, one limitation to the study is that the mothers' histories were obtained only through interview, without any confirmation using individual health records or serology. The same trend was observed when antibody levels in infants were analyzed according to the mother's year of birth; for infants whose mothers were born before 1983 (measles vaccination was recommended in 1983), there was a nonsignificant trend toward higher antibody levels. This result should be interpreted with caution, taking into account the small sample size of infants with mothers born after 1983.

A seroepidemiological study carried out in France in 2005 to 2006 among women of childbearing age showed that the measles-neutralizing serum antibody GMCs were significantly lower in women born after 1983 and decreased significantly with increasing birth year, corresponding to increasing vaccine coverage (43). This decrease in antibody levels in women of childbearing age may be amplified with the increasing age at which the majority of women have children in the Western population, due to the increased interval between childhood vaccination and childbirth (27). In addition, boosting by wild-type viruses occurs less often as vaccination coverage increases, and this may contribute further to lower antibody levels in the adult population (either after vaccination or after natural disease) (39).

Conclusion. This study is the first to show that in France, passively transferred maternal antibodies against measles decline rapidly during the infant's first months of life, to reach mean concentrations under the seroprotection level at 6 months of age. Infants over 6 months are poorly protected by maternal antibodies against measles (90% of infants are no longer protected against measles at 6 months of age), which is consistent with observations in other countries, where populations are vaccinated routinely against measles. The progressive increase in measles vaccination coverage in infants born in France after 1983 led to a significant decrease in measles incidence and consequently a loss of natural boosters from wild-type measles virus. On the other hand, the current vaccination coverage (87% for one dose at 24 months of age in 2004) is not sufficient to eliminate the disease in France, and measles outbreaks are still occurring (10, 14). This places in-

fantas older than 6 months who have not yet been vaccinated in a critical window at risk for measles infection and potentially serious complications such as subacute sclerosing panencephalitis. While lowering the age for the first dose of measles vaccine to 6 months may not be optimal even in the absence of maternal antibody, because of the immaturity of the immune system (19, 20, 25, 36), lowering the age of routine vaccination from 12 to 9 months of age would reduce the immunity gap between passive and active protection.

High vaccine coverage is the most important factor needed to interrupt and control measles transmission (14). Efforts are also required to reach a vaccine coverage rate of at least 95% with two doses, estimated as necessary for measles elimination (3, 49).

Infant protection against measles could be optimized both by increasing herd immunity through an increased vaccine coverage and by lowering the age of routine vaccination from 12 to 9 months.

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