Increased Susceptibility to Measles in Infants in the United States

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ABSTRACT. *Background.* **Women born in the United States after measles vaccine licensure in 1963 transfer less measles antibody to their infants than do older women. This may result in increased susceptibility to measles among infants.**

Objective. **To determine the effect of maternal year of birth on the risk for measles in infants.**

Methods. **We enrolled 128 unvaccinated infants ≤15 months of age who had documented exposure to measles from 1990 through 1992 in a retrospective cohort study. We interviewed their mothers by telephone to obtain demographic data, medical and vaccination history, and details of measles exposure and outcome. We used logistic regression analysis to estimate the effect of maternal year of birth.**

Results. **Infants whose mothers were born after 1963 had a measles attack rate of 33%, compared with 12% for infants of older mothers. In logistic regression analysis, the adjusted odds ratio for maternal year of birth (born after 1963) was 7.5 (95% confidence interval 1.8, 30.6). Other significant risk factors were older infant age, mothers who developed measles after delivery, and exposure within 2 days of the rash onset of the exposing case.**

Conclusions. **Infants whose mothers were born after 1963 are more susceptible to measles than are infants of older mothers. An increasing proportion of infants born in the United States may be susceptible to measles. Infants at high risk of exposure to measles should be vaccinated at 12 months of age. Vaccination programs that reduce transmission of the measles virus in the general population reduce the risk of infant exposure to measles.** *Pediatrics* **1999;104(5). URL: http://www.pediatrics.org/cgi/content/full/104/5/e59; *measles, maternal antibody, measles vaccine, infants.***

ABBREVIATION. CI, confidence interval.

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Most infants are protected from measles by passively acquired maternal antibody from birth until the antibody is depleted. The duration of protection is dependent to a great extent on the amount of antibody received by the infant during pregnancy, which is directly related to the maternal antibody titer.[1] Women who have had measles disease have high measles antibody titers, women who have not had measles but have been vaccinated effectively have lower antibody titers,[2] and women who have neither had measles nor been vaccinated effectively have no measles antibody.

Because it is difficult to obtain an accurate history of maternal measles disease, many studies of maternal antibody have used the maternal year of birth as a proxy indicator for the history of measles disease. People born in the United States after measles vaccine licensure in 1963 have a lower probability of having had measles than do those born before 1963. In studies conducted before 1963, >85% of the population developed measles by 10 years of age.[3] United States Immunization Surveys, conducted from 1965 to 1978, showed that the percentage of 10-year-old children with a reported history of measles decreased progressively from 70% for children born in 1955 to 14% for children born in 1968.[4,5]

Serologic studies have shown that mothers born in the vaccine era (since 1963) had significantly lower measles antibody titers and were more likely to have no detectable antibody to measles, compared with older mothers.[1,6–8] Compared with infants whose mothers were born when measles disease was common, infants whose mothers were born in the vaccine era had 1) lower measles antibody titers at birth,[1,7,8] 2) higher rates of seronegativity at 6, 9, and 12 months of age,[1,6,7] and 3) higher seroconversion rates to measles vaccine at 6, 9, and 12 months of age.[6] Although these serologic studies suggest that infants whose mothers were born in the vaccine era would be more susceptible to measles disease than would infants of older mothers, no study actually has documented increased susceptibility to clinical measles disease.

During the 1989 to 1991 measles resurgence in the United States, the age-specific incidence of measles was highest among infants ≤15 months of age (the standard age for measles vaccination at that time).[9] Despite comprising only 2% of the general population,[10] infants ≤15 months of age accounted for 24% of the 55 622 reported measles cases from 1989 to 1991.[9,11] This is the highest proportion of cases accounted for by this age group since detailed age

reporting began in 1985,[9] and this supports the theory of increased susceptibility to measles in this age group. To determine whether infants whose mothers were born in the vaccine era are more susceptible to measles than are infants of older mothers, we conducted a cohort study in unvaccinated infants ≤ 15 months of age with documented exposure to measles.

METHODS

Study Design

We performed a retrospective cohort study of infants exposed to measles during two large measles outbreaks. The outbreaks occurred in New Jersey from November 1990 to September 1991 (824 confirmed cases reported),[9] and in southern Texas from November 1991 to July 1992 (990 confirmed cases reported).[12] These outbreaks predominantly affected preschool-aged children; children <5 years of age accounted for 65% of cases in New Jersey[9] and 75% of cases in Texas.[12]

The New Jersey and Texas Departments of Health investigated each reported case of suspected measles and confirmed or discarded the cases based on standard criteria for measles cases. A confirmed measles case had laboratory evidence of measles infection or met the clinical definition (generalized rash for at least 3 days, and fever (>101°F, if measured), and cough or coryza or conjunctivitis) and had an epidemiologic link to a confirmed case. Routine investigation of each reported case included identification of all persons potentially exposed during the infectious period and recommendation that every susceptible person be protected with measles vaccine or immune globulin. The study was conducted at the conclusion of each outbreak and did not interfere with state efforts to identify and vaccinate susceptible persons exposed to measles.

We reviewed the case investigation forms of all confirmed measles cases to identify potential cohort members. Infants ≤15 months of age with mothers born in the United States were enrolled in the cohort if they were exposed for ≥5 hours (to ensure adequate exposure to measles virus) during the period from 3 days before to 3 days after the rash onset of the confirmed case (defined as the appearance of the first visible lesion). We excluded infants who received measles vaccination before or within 3 days after exposure or immune globulin within 6 days after exposure or who had onsets of measles rash before or within 10 days after the documented exposure.

Study Procedures

We contacted mothers of exposed infants by telephone, explained the purpose of the study, and asked each mother to participate. We telephoned each mother until we contacted her or at least 10 times, with at least 3 calls made in the evening, 3 during the day-time, and 3 during weekends. We conducted telephone interviews in English or Spanish at the mother's preference and collected information on the child's age, gender, medical history, details of measles exposure, history of receiving measles vaccine or immune globulin, and history of any symptoms of measles illness during the 3 weeks after exposure. The interviews were conducted 2 to 8 months after the child's exposure. If a mother reported that her child had received measles vaccine or immune globulin or was unsure, we contacted the child's health care providers by telephone to confirm the date of administration and the type of immunobiologic agent given. We also collected data on the maternal year of birth, race, ethnicity, and history of measles disease or vaccine. For infants exposed to measles in day care centers, we telephoned the center to ascertain the duration and timing of the exposure.

Statistical Analysis

Cohort infants who had symptoms consistent with the clinical case definition of measles within 21 days after the documented exposure were classified as measles cases; those who did not were classified as not measles cases. With measles classification as the outcome variable, we performed χ^2 tests of association and calculated risk ratios for characteristics of the study cohort.[13,14] We used logistic regression to estimate the effect of the maternal year of birth on the risk of measles in infants, while controlling simultaneously for potentially confounding variables.[15,16] Variables controlled for in the multivariable model were selected by considering their univariate associations with measles classification, the degree of their confounding the association between the maternal year of birth and measles classification, and their clinical importance, while avoiding overfitting and collinearity of variables.[17,18] We assessed interaction between each pair of variables in the multivariable model. In constructing the interaction variables, we treated the main effect variables as continuous whenever possible to avoid problems (eg, zero cell counts) in fitting the logistic regression model. We built a second model in which main effect variables were treated as continuous, whenever possible, to represent the risk of measles on a continuous scale. We evaluated how well the multivariable models fit the data using log-likelihood statistics and Hosmer-Lemeshow goodness-of-fit tests.[15]

Distribution of Maternal Year of Birth, United States

To assess the distribution of birth years among women giving birth, we performed a separate analysis using birth certificate data from the United States Detail Natality Files.[19] We calculated the proportion of mothers born since 1963 from the maternal age distribution in the birth certificate records for each year from 1970 to 1993. For birth cohorts from 1994 to 2000, we extrapolated the proportion of mothers born since 1963, assuming the age distribution of mothers for these years would be similar to the age distribution in 1993.

RESULTS

Study Population

We identified 557 potential cohort members through review of the confirmed cases records in New Jersey and Texas. Approximately 25% (152) of the mothers were unreachable by telephone; only a few of these mothers did not have a telephone number. The median age of the infants whose mothers were unreachable by telephone was the same as the median age of the final cohort (7 months). Each of the contacted mothers gave verbal consent to be interviewed. Of the 405 infants in the families interviewed, 277 were excluded for the following reasons (some infants had multiple exclusions): duration of exposure <5 hours (99), actual age >15 months (35), vaccinated (39), received immune globulin (16), rash onset <10 days after exposure (74), and mother not born in the United States (19).

The final cohort included 128 infants. The median year of birth of the mothers in the cohort was 1966, and 69% were born after 1963. Of the mothers, 10 had measles after the infant's birth. Most infants (55%) were exposed in a household setting. The median duration of exposure was 16 hours. The duration of exposure was greater among infants exposed in households than among those exposed in day care centers (median: 108 hours vs 8 hours). Most of the infants (73%) were exposed to a confirmed case during the period from 2 days before to 2 days after the rash onset of the confirmed case, while 27% were exposed only on day 3 before the rash onset of the index case (Table 1).

Univariate Analysis

Of the 128 exposed infants, 34 developed measles, an attack rate of 27%. For the 34 infants who developed measles, the interval between initial exposure and rash onset ranged from 10 to 21 days, with a median of 14 days. Infants whose mothers were born since 1963 had an attack rate of 33%, compared with

TABLE 1. Measles Attack Rates in Infants, New Jersey and Texas, 1990–1992

Characteristic	Total	Measles Attack Rate (%)	*P* Value*
Maternal year of birth			
1948–1963	40	12	.02
1964–1976	88	33	
Mother had measles after delivery			
No	118	22	<.01
Yes	10	80	
Child age (mo)			
0–5	53	15	
6–11	52	35	.047
12–15	23	35	
Exposure duration (h)			
5–15	51	14	.01
16–168	77	35	
Exposure setting			
Day care	58	16	.01
Household	70	36	
Exposure within 2 days of rash onset of exposing case†			
No	34	3	<.01
Yes	94	35	
Breastfeeding at age when exposed			
Yes	14	0	.02
No	114	30	
Mother had measles before delivery			
Yes	47	19	
No	63	35	.11
Cannot recall	18	17	
Mother received measles vaccine			
Yes	102	27	
No	14	36	.26
Cannot recall	12	8	
Mother's race/ethnicity			
White	34	18	
Black	21	14	.07
Hispanic	73	34	
State of residence			
Texas	99	24	.27
New Jersey	29	34	
Child's gender			
Male	56	21	.25
Female	72	31	
Infant born >3 wk prematurely			
Yes	10	10	.22
No	118	28	
Infant's birth weight (g)			
<2500	15	20	.54
2500+	113	27	

* χ^2 test for difference in measles attack rates.
† Exposed to a confirmed case during the period from 2 days before to 2 days after the rash onset of the confirmed case.

12% for infants of older mothers (risk ratio: 2.6; 95% confidence interval [CI]: 1.1, 6.3). Infants whose mother had measles after delivery had an attack rate of 80%, compared with 22% for infants whose mothers did not have measles after delivery (risk ratio: 3.6; 95% CI: 2.3, 5.8). The risk of measles for infants <6 months of age was lower than for infants in both the 6 to 11 and 12 to 15 months of age groups (attack rate 15% vs 35% for both older age groups). Infants whose exposure to the confirmed case occurred within 2 days (ie, from 2 days before to 2 days after) of the rash onset of the confirmed case had an attack rate of 35%, compared with 3% in other infants. Infants who were exposed in a household setting were more likely to develop measles than were those exposed in a day care center. The risk for measles increased with the duration of exposure. Infants who were breastfeeding were less likely to develop measles than were infants who were not breastfeeding. None of the other characteristics of the study cohort were associated significantly with the risk of measles (Table 1).

Multivariable Analysis

We fit a multivariable model that included four factors: maternal year of birth, occurrence of measles in the mother after delivery, the child's age, and exposure timing. No pair-wise interaction was identified among the variables in the multivariable model. After adjusting for other significant variables, infants whose mothers were born since 1963 were significantly more likely to develop measles than were infants of older mothers (adjusted odds ratio: 7.5; 95% CI: 1.8, 30.6). The Hosmer-Lemeshow goodness-of-fit test statistic was 5.2 with 6 degrees of freedom ($P = .52$), indicating good agreement between the outcomes predicted by the model and those observed in the dataset (Table 2).

The maternal year of birth and the child's age were significant when they were included in the model as continuous variables. The adjusted odds ratio for maternal year of birth was 1.15 (95% CI: 1.04, 1.27) for each 1-year increment, and the adjusted odds ratio for the child's age was 1.20 (95% CI: 1.05, 1.36) for each one month increment. We estimated risk of measles among infants from a multivariable model that included child age, maternal year of birth, and exposure timing. The adjusted risk for measles among infants 7 months of age increased from 6% for infants whose mothers were born in 1948 to 59% for infants whose mothers were born in 1976 (Fig 1).

The variables that were significant in the univariate analysis but not included in the logistic regression model were highly associated with variables that were included in the logistic regression model. Both exposure duration and setting of exposure were highly associated with the timing of exposure. Compared with other infants, infants who were exposed within 2 days of rash onset of the exposing case were more likely to have >15 hours of exposure (81% vs 3%; $P < .01$) and to have been exposed in a household setting (71% vs 9%; $P < .01$). Breastfeeding was highly associated with the child's age ($P < .01$); al1 14 children who were breastfeeding were <12 months of age, and 12 were <6 months of age. Breastfeeding was not associated with the maternal year of birth ($P = .70$).

Distribution of Maternal Year of Birth, United States

The proportion of women giving birth in the United States who were born after 1963 increased from 3% in 1980 to 51% by 1990. By the year 2000, 95% of women giving birth in the United States will have been born after 1963 (Fig 2).

TABLE 2. Association Between Maternal Year of Birth and Risk for Measles in Infants, Univariate Analysis and Multivariable Model Controlling for Other Risk Factors, New Jersey and Texas, 1990–1992

Characteristic	Univariate Risk Ratio (95% CI)	Multivariable* Odds Ratio (95% CI)
Maternal year of birth		
1948–1963	1.0 (referent)	1.0 (referent)
1964–1976	2.6 (1.1, 6.3)	7.5 (1.8, 30.6)
Mother had measles after delivery		
No	1.0 (referent)	1.0 (referent)
Yes	3.6 (2.3, 5.8)	17.9 (2.9, 110.8)
Child age (mo)		
0–5	1.0 (referent)	1.0 (referent)
6–11	2.3 (1.1, 4.8)	4.3 (1.4, 13.4)
12–15	2.3 (1.0, 9.6)	7.8 (1.9, 31.9)
Exposure within 2 d of rash onset of exposing case†		
No	1.0 (referent)	1.0 (referent)
Yes	12.0 (1.7, 84.1)	15.0 (1.9, 121.9)

* Odds ratios for each characteristic are adjusted for the other characteristics listed in this table. Hosmer-Lemeshow goodness-of-fit statistic = 5.2; 6 *df*; $P = .52$.
† Exposed to a confirmed case during the period from 2 days before to 2 days after the rash onset of the confirmed case.

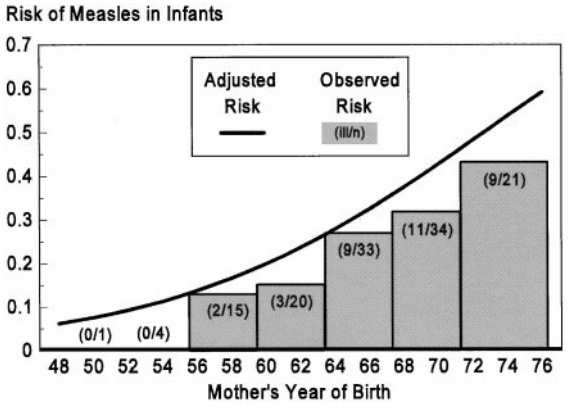

Fig 1. Risk of measles in infants by maternal year of birth. Risk is derived from a multivariable model that includes child age (risk estimated for infants 7 months of age, the observed median), maternal year of birth, and exposure timing (risk estimated for infants who were exposed within 2 days of rash onset of the exposing case). The model does not include the variable for whether the mother had measles disease after delivery. For observed risk, maternal year of birth is grouped into 4-year intervals because of the small sample size for each year.

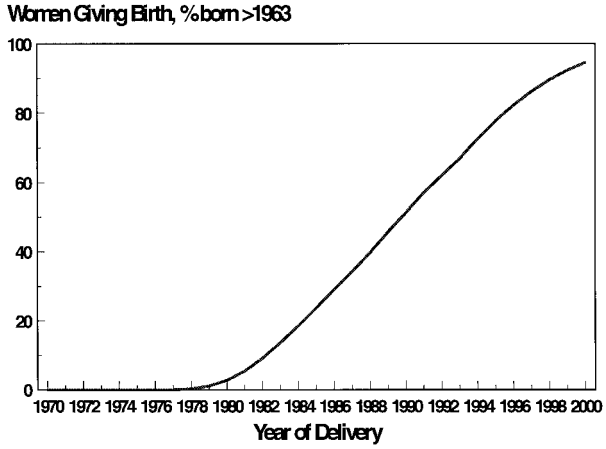

Fig 2. Distribution of maternal year of birth calculated from data in US birth certificate records. Distribution for years 1994–2000 projected, assuming a similar age distribution of mothers as in 1993.

DISCUSSION

To our knowledge, these data are the first to show increased susceptibility to clinical measles disease in a cohort of infants born to younger women. Our results suggest that infants whose mothers are born since measles vaccine licensure in 1963 are significantly more susceptible to measles than are infants of older mothers and that the risk of measles increases incrementally with each year increase in the maternal year of birth. In addition, older infants in our study were more susceptible to measles than were younger infants. These findings are consistent with the patterns of declining antibody titers in women born in the United States and declining seroprevalence in children <12 months of age.[1,6–8] A large study of US infants demonstrated that seroprevalence of measles antibody in unvaccinated infants decreased from 79% at 6 months of age to 48% at 9 months and to 16% at 12 months of age for infants of mothers born before 1963, compared with seroprevalence rates of 44%, 23%, and 5%, respectively, for the same age groups among infants of mothers born after 1963.[6] For comparison with our results, we fit a logistic regression model to these seroprevalence rates and plotted the rates estimated from the model on the same graph with the results derived from our multivariable model on the effect of infant age by the maternal year of birth (Fig 3). Our clinical data corroborate previous serologic evidence of early susceptibility to measles in children born to vaccinated women. Infants of mothers born after 1963 may become susceptible to measles at a younger age than do infants with older mothers because they receive less maternal antibody and become seronegative more quickly.

The extremely high risk for measles among infants whose mothers developed measles after delivery occurred because these mothers had no maternal antibody to transfer during pregnancy. Lennon and Black[1] found that 4.6% of women born after 1959 had no detectable antibody for measles, compared with 1.3% of older women. An increased proportion of infants who lack maternal antibody at birth may be one cause of increased measles susceptibility among infants of mothers born after 1963. Infants who re-

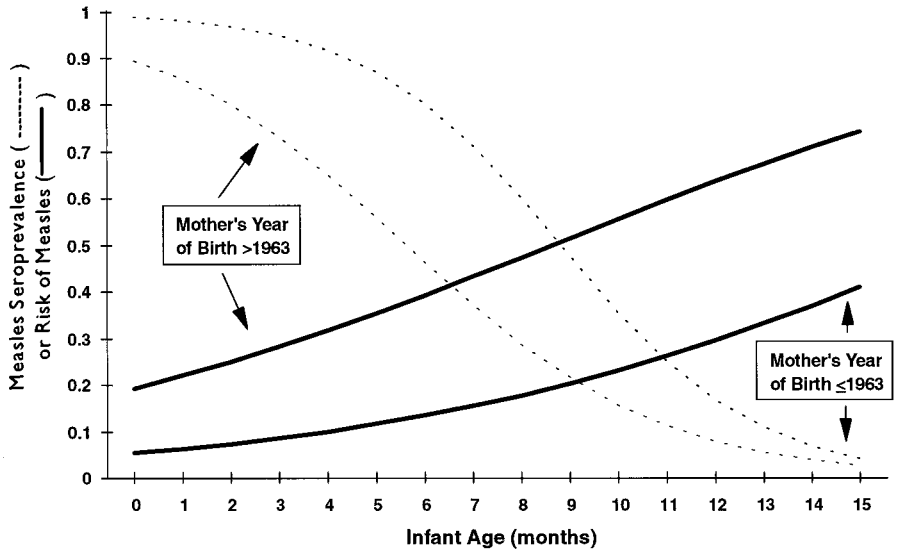

Fig 3. Measles seroprevalence and the risk of measles in infants by infant age. Measles seroprevalence was estimated by a logistic regression analysis of published data from a study of unvaccinated US infants.[6] Measles seroprevalence was defined as an antibody titer of ≥1:8 dilution, using the plaque reduction neutralization technique. The risk of measles disease was estimated from the present study and was derived from a multivariable model that includes child age, maternal year of birth (born after 1963 vs born in 1963 or before), and exposure timing (risk estimated for infants who were exposed within 2 days of rash onset of the exposing case). The model does not include the variable for whether the mother had measles disease after delivery. The broken lines indicate the seroprevalence for measles disease. The solid lines indicate the risk of measles disease.

ceive no maternal antibody are susceptible to measles from birth until they are vaccinated or infected with the measles virus.

Our study has several limitations. The medium-sized dataset was sufficient to demonstrate the effect of maternal year of birth, while controlling for important potentially confounding variables, but there were not enough infants to perform subgroup analyses, such as determining the effect of the maternal year of birth in different age groups of infants. In addition, because we were not able to reach ~25% of the potential cohort, our results may not be representative of infants from this population.

More than 20 years ago, increased susceptibility to measles among infants was predicted as a consequence of lower maternal antibody titers attributable to a sustained effective vaccination program.[20] The potential negative impact of increased infant susceptibility can be limited by vaccinating against measles at a younger age and by preventing exposure to measles among infants. Vaccination at younger ages increases the likelihood of vaccine failure. However, multiple studies have shown that seronegative infants are more likely to respond to vaccines than those who have maternal antibody. Markowitz and coworkers[6] demonstrated that 98% of children whose mothers were born after 1963 had a serologic response to measles vaccine at 12 months of age, compared with 90% of children whose mothers were born from 1957 to 1963 and 83% of children whose mothers were born before 1957. This parallels trends in maternal antibody seroprevalence in those groups of children. A recent smaller study confirmed these findings but also raised questions concerning responsiveness to vaccine in infants 6 months of age, even in the absence of detectable passively acquired neutralizing antibodies.[21] The routine age for measles vaccination in the United States was lowered from 15 months to between 12 and 15 months in January 1994.[22,23] This change was based on the increased susceptibility and better response to vaccination among infants whose mothers were born after 1963, the fact that the vast majority of women giving birth in the United States were born after 1963, and the hope that ability to vaccinate at a younger age may result in increased coverage rates.[24]

The second strategy to limit the impact of increasing infant susceptibility is decreasing the risk of exposure to measles in infants. Since the 1989 to 1991 resurgence of measles, increased vaccination efforts in the United States have achieved record high coverage rates, both in 1-dose coverage among preschool children and in 2-dose coverage among school-aged children. These efforts and the vaccination efforts of other countries in the Americas, which have resulted in reduced importation of the measles virus,[25] have driven measles incidence in the United States to record low levels. Despite increasing infant susceptibility to measles, only 62 cases of measles were reported in the United States among infants ≤15 months of age in 1996.[26]

The historically low incidence of measles in the United States has decreased the risk of exposure to measles among infants in the United States. However, many countries, both developing and industrialized, still have endemic measles transmission. Infants leaving the United States for international travel should be given measles vaccine or immune globulin, according to current guidelines before departure. Infants ≥6 months of age who are known to be exposed to measles or at high risk of exposure in outbreak settings also should be vaccinated.[23] The use of immune globulin is indicated for infants <6

months of age whose mothers have developed measles after delivery.

In countries with endemic measles transmission, young women with immunity to measles from vaccination are entering the child-bearing age group. These countries may experience a surge in infant measles incidence similar to that seen in the United States from 1989 to 1991. To prevent increased infant morbidity and mortality attributable to measles, timely vaccination of infants and intensive efforts to decrease the transmission of measles disease by ensuring immunity in older children are now more important than ever. This potential increase in infant mortality should provide additional impetus to strengthen efforts toward global eradication of measles disease.

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