Measles Antibody Levels in Young Infants

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abstract

BACKGROUND: Infants are often assumed to be immune to measles through maternal antibodies transferred during pregnancy and, in many countries, receive their first measles-containing vaccine at 12 to 15 months. Immunity may wane before this time in measles-eliminated settings, placing infants at risk for measles and complications. We investigated humoral immunity to measles in infants <12 months of age in Ontario, Canada.

METHODS: We selected sera collected at a tertiary pediatric hospital from infants <12 months who were born at ≥37 weeks' gestational age. We excluded infants with conditions that affect antibody levels. We selected ≤25 sera from 8 predetermined age bands and tested them for measles-neutralizing antibody using the plaque-reduction neutralization test. We calculated the proportion immune at each age band, and predictors of infant susceptibility were assessed by using multivariable logistic regression and Poisson regression.

RESULTS: Of 196 infant sera, 56% (110 of 196) were from boys, and 35% (69 of 196) were from infants with underlying medical conditions. In the first month, 20% (5 of 25) of infants had antibodies below the protective threshold, which increased to 92% (22 of 24) by 3 months. By 6 months, all infants had titers below the protective threshold. In a multivariable analysis, infant age was the strongest predictor of susceptibility (odds ratio = 2.13 for each additional month increase; 95% confidence interval: 1.52–2.97).

CONCLUSIONS: Most infants were susceptible to measles by 3 months of age in this elimination setting. Our findings inform important policy discussions relating to the timing of the first dose of measles-containing vaccine and infant postexposure prophylaxis recommendations.

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Drs Science and Bolotin conceptualized the study, provided input into the study design and interpretation of results, drafted the initial manuscript, and analyzed the data; Drs Severini, McLachlan, Savage, and Hughes tested the sera and/or analyzed the data, provided input into the study design and interpretation of results, and contributed to authoring the manuscript; Mr Arnold and Drs Richardson, Crowcroft, Deeks, Halperin, Brown, Hatchette, Gubbay, and Mazzulli provided input into the study design and interpretation of results and contributed to authoring the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Infants <12 months of age are often assumed to be immune to measles from maternal antibodies transferred during pregnancy. However, this may not be the case in infants of vaccinated mothers living in measles-eliminated settings, where there is less circulating virus.

WHAT THIS STUDY ADDS: We found that most infants were susceptible to measles by 3 months of age, which has important public health implications regarding infant postexposure management to protect infants and prevent spread.

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Measles is a highly infectious acute viral illness that can lead to severe complications, such as pneumonia, encephalitis, and death.[1] Compared with older children and adults, infants <12 months of age are vulnerable to measles, with elevated attack rates during outbreaks,[2] and children younger than 5 years have been reported to have high rates of complications, hospitalization, and death.[3–5]

Historically, infants have been assumed to be protected from measles for much of their first year by antibodies acquired transplacentally from their mothers.[6–8] However, this assumption was based on studies performed in settings where measles circulated endemically. In these settings, many mothers are immune through natural infection and are continually exposed to measles, leading to repeated immunologic boosting and more robust antibody levels. However, in measles-elimination settings, defined as settings where no endemic transmission of the virus persists for ≥12 months,[9] many women of childbearing age are immune through vaccination, which has been associated with lower antibody titers compared with natural infection.[10,11] Furthermore, because the measles virus does not circulate endemically in elimination settings, immunologic boosting of vaccinated individuals from exposure to measles is greatly reduced.[12,13] This may lead to infants in measles-elimination settings having lower titers of transplacentally acquired antibodies that fall below the threshold of protection earlier.[14,15] These infants are then left susceptible to measles until they receive their first dose of the vaccine,[8,11] which, in elimination settings, is not administered until 12 to 15 months of age.[16] To date, few researchers have measured the duration of measles maternal antibody protection in infants living in elimination settings.[17] The limited number of studies that have been conducted are hindered by small sample sizes and a focus on either immunity at birth or immunity in older infants, and researchers have not evaluated infant immunity at small intervals across the first year of life.[18–23]

Our goal for this study was to assess infant susceptibility to measles in Ontario, Canada. Canada has had a routine measles immunization program since 1963, and vaccine coverage in Ontario is generally high.[24] Furthermore, Canada eliminated measles in 1998.[25] Therefore, we hypothesized that infant immunity to measles in our elimination setting would wane in the first 6 months of life because of vaccine-induced immunity, rather than natural infection–induced immunity, in women of childbearing age. This is concerning because of continued measles circulation elsewhere in the world,[26] putting infants at risk for disease and disease-related complications.

METHODS

Population and Study Design

We used residual sera collected for clinical testing at The Hospital for Sick Children, a large pediatric tertiary care hospital in Toronto, Canada, with ~15 000 admissions and >50 000 emergency department visits per year. Sera were collected between January 1, 2014, and December 31, 2016, from infants <12 months of age who were born at ≥37 weeks' gestational age. The study was approved by the hospital research ethics board. Infant serum is routinely stored for 5 years at −80°C when blood is sent for serology. On the basis of a chart review, we excluded infants with a suspected or confirmed immunodeficiency, an underlying condition associated with antibody loss (eg, nephrotic syndrome, protein-losing enteropathy), if they had received intravenous immunoglobulin, intramuscular immune globulin, or blood transfusions or had a history of measles or measles vaccination.

We randomly selected up to 25 sera from 8 predetermined age bands: 0 months (0–30 days), 1 month (31–60 days), 2 months (61–89 days), 3 months (90–119 days), 4 months, 5 months, 6 to 9 months, and 9 to 11 months. The sample size was chosen based on the number of tests that could be conducted, taking into account feasibility and resource considerations. The choice of age bands was informed by a systematic literature review of measles maternal antibody waning in elimination settings, which was recently completed by our team,[17] that revealed a paucity of data on infant susceptibility to measles in elimination settings, particularly in those <6 months of age.

One physician (M.S.) extracted demographic information, which included gestational age, age at time of sera collection, sex, underlying medical conditions, admission reason and location, pregnancy and neonatal factors including feeding type (breastfeeding versus formula feeding), maternal age, country of birth, and vaccination history.

Outcome

Sera were tested for neutralizing antibody by using the plaque-reduction neutralization test (PRNT)[27,28] at Canada's National Microbiology Laboratory. The primary outcome of interest was measles susceptibility, defined by a threshold neutralization titer of <192 mIU/mL (previously determined by our group[29]). Detection of neutralizing antibodies revealed a reliable measurement of the protective immunity transferred from the mother to the infant. All antibody titers were above the limit of detection of 15.5 ± 2.6 mIU/mL, and those that exceeded the upper detection limit (700.8 ± 110.3

mIU/mL) were further diluted and retested.

Statistical Analysis

We reported continuous variables using the mean and SD for normally distributed variables and the median and range for nonnormally distributed data. We reported numbers and percentages for dichotomous outcomes. We calculated the proportion of samples considered susceptible at each age band and assessed statistical significance using Pearson's χ^2 test, Student's *t* test, or the Cochran-Armitage test for trend.

We used multivariable logistic regression with a forward-fitting approach to predict infants' susceptibility to measles by age. We included infant age, sex, and maternal age a priori, followed by other covariates that were associated with infants' susceptibility status at the $P < .20$ level in univariable analyses using Pearson's χ^2 test or Student's *t* test. Adjusted marginal predictions of infants' susceptibility at each month of age were calculated by using the average maternal age of 32 years and the postestimation "margins" command in Stata (Stata Corp, College Station, TX). We used the Hosmer-Lemeshow goodness-of-fit test with 10 groups to assess model fit.

We then used a multivariable Poisson regression model to predict mean measles antibody titers because measles antibody titers are nonnegative and positively skewed. This approach has been suggested as a better alternative to log-linear regression because of its flexibility to handle natural zeros and its treatment of small nonzero values.[30,31] Because of the potential for overdispersion, which would violate Poisson model assumptions, we used robust SEs in the model.[32] We used the same approach of adding covariates to the model as in the logistic model. Because the relationship between infant age and antibody titer was nonlinear, we modeled age using restricted cubic spline terms, with 5 knots placed at the fifth (age 0.4 months), 27th and a half (2.1 months), 50th (4.0 months), 72nd and a half (5.7 months), and 95th percentiles (10.0 months). We calculated the adjusted marginal predictions of infant mean antibody titers using the average maternal age of 32 years as well as 4 maternal age time points (25, 30, 35, and 40 years).

Because of the large degree of missing data for maternal age (49%) and breastfeeding status (47%), we used single random-regression imputation for missing values under the missing-at-random assumption. We also performed a sensitivity analysis using a complete-case analysis (ie, observations restricted only to infants who had complete data for these covariates) for both models.

All estimates are presented with 95% confidence intervals (CIs). Comparisons between study groups were made by using Pearson's χ^2 test or Student's *t* test with a type 1 error rate of $\alpha = .05$ to test the null hypothesis of no difference between groups. We performed all analyses in Stata version 15.1 (Stata Corp).

RESULTS

We included a total of 196 infant sera in the study (Table 1); 56% of the sera were from boys. Approximately one-third (35%) of sera came from individuals with an underlying condition, the majority of which were central nervous system or developmental delay and a gastrointestinal or liver condition. Most of the samples were obtained from infants admitted to the hospital (47%) or seen in outpatient clinics (48%), including the infectious diseases and gastroenterology clinics or the outpatient laboratory. A small number of individuals ($n = 9$) contributed 2 sera samples, collected at 2 different time points, to the analysis. A post hoc sensitivity analysis was conducted, in which 1 randomly selected serum sample was removed to ensure that the removal of the sample did not impact the results. The mean maternal age was 32 years (range 18–47).

In univariable analyses (Table 1), the proportion of infants who were susceptible to measles increased as the age in months increased (Cochran-Armitage test for trend $P < .001$). We found no significant differences in the proportion of infants susceptible to measles between boys and girls ($P = .29$) or across gestational ages from 37 to 41 weeks ($P = .27$). A higher proportion of infants with an underlying condition were susceptible to measles compared with those without such conditions (83% vs 68%; $P = .03$). Susceptibility in those who had received any breast milk (58%) was lower compared with that in those who had not (76%), although this difference was not statistically significant ($P = .11$).

In the logistic regression analysis (Table 2), forward stepwise regression added no additional variables to the model beyond those chosen a priori. The odds of susceptibility more than doubled for each month increase in infant age (unadjusted odds ratio [OR] = 2.38; 95% CI: 1.81–3.12). Adjusting for infant sex and maternal age by using cases with the maternal age data available (complete-case analysis) did not impact the association (adjusted OR = 2.13; 95% CI: 1.52–2.97, $n = 100$). Results were similar by using an imputed data set (adjusted OR = 2.39; 95% CI: 1.81–3.16, $n = 196$). Using logistic regression modeling, we predicted the probability of measles susceptibility in infants with a mother aged 32 years (mean age of cohort) to be 0.31 (95% CI: 0.19–0.43) at 1 month and to increase to 0.97 (95% CI: 0.94–1.00) at 6 months, at which age (and above)

TABLE 1 Characteristics of Study Population (n = 196)

Variable	Overall (N = 196)	Nonimmune (n = 143)	Immune (n = 53)	P
Infant age, mo, n (%)				<0.001
0	25	5 (20.0)	20 (80.0)	
1	25	8 (32.0)	17 (68.0)	
2	24	16 (66.7)	8 (33.3)	
3	24	22 (91.7)	2 (8.3)	
4	24	22 (91.7)	2 (8.3)	
5	25	21 (84.0)	4 (16.0)	
6	7	7 (100.0)	0 (0.0)	
7	7	7 (100.0)	0 (0.0)	
8	11	11 (100.0)	0 (0.0)	
9	12	12 (100.0)	0 (0.0)	
10	3	3 (100.0)	0 (0.0)	
11	9	9 (100.0)	0 (0.0)	
Infant age, mo, mean (SD)	4 (3)	5 (3)	2 (1)	<.001
Infant sex, n (%)				.29
Male	110	77 (70.0)	33 (30.0)	
Female	86	66 (76.7)	20 (23.3)	
Underlying condition, n (%)				.03
Yes	69	57 (82.6)	12 (17.4)	
No	127	86 (67.7)	41 (32.3)	
Admission setting, n (%)				.12
Inpatient	92	66 (71.7)	26 (28.3)	
Outpatient	93	66 (71.0)	27 (29.0)	
ED	11	11 (100.0)	0 (0.0)	
Gestational age, wk[a], n (%)				.27
37	21	19 (90.5)	2 (9.5)	
38	28	20 (71.4)	8 (28.6)	
39	35	22 (62.9)	13 (37.1)	
40	21	14 (66.7)	7 (33.3)	
≥41	24	17 (70.8)	7 (29.2)	
Any breastfeeding[b], n (%)				.11
Yes	79	46 (58.2)	33 (41.8)	
No	25	19 (76.0)	6 (24.0)	
Maternal age, y, mean (SD, range)[c]	32 (6, 18–47)	33 (6, 18–47)	31 (6, 21–42)	.31
Antibody titer, mIU/mL, GMT	81.72	44.35	425.14	

Data are presented as n or n (%) unless indicated. ED, emergency department; GMT, geometric mean titer.
[a] Excludes 67 with missing data.
[b] Excludes 92 with missing data.
[c] Excludes 96 with missing data.

virtually all infants were predicted to be susceptible (Table 3, Fig 1).

We used the same models to investigate the effect of maternal age on infant measles susceptibility. We generated predictions for a range of maternal ages (25, 30, 35, and 40 years) and observed a modest increase in the probability of infant susceptibility as maternal age increased (Supplemental Fig 4). For example, our model predicted that a 1-month-old infant had a probability of being susceptible to measles of ∼25% if the mother was 25 years of age but a ∼40% probability of being susceptible if the mother was 40 years of age. There was no significant difference in the model predictions by sex (data not shown).

The relationship between infant antibody titer and month of infant age is shown in Fig 2. In the Poisson regression analysis that was used to control for infant sex and maternal

TABLE 2 Logistic Regression Analysis (Model 1) of the Association Between Infant Age and Susceptibility to Measles

Variable	Unadjusted, N = 196		Adjusted (Imputed), N = 196		Adjusted (Complete Case), N = 100	
	OR	95% CI	OR	95% CI	OR	95% CI
Infant age per 1-mo increase	2.38	1.81–3.12	2.39	1.81–3.16	2.13	1.52–2.97
Maternal age per 1-y increase	—	—	1.05	0.98–1.12	1.07	0.97–1.17
Infant sex female	—	—	1.35	0.59–3.11	0.85	0.29–2.49

Hosmer-Lemeshow goodness-of-fit χ^2 test (g = 10) = 9.33, P = .315. —, not applicable.

TABLE 3 Predicted Probabilities of Infant Susceptibility to Measles (Model 1) and Mean Antibody Titer (Model 2) for Infants With a Mother Aged 32 Years Based on Models That Were Controlled for Infant Sex and Maternal Age

Infant Age, mo	1: Logistic Regression		2: Poisson Regression	
	Predicted (Susceptibility)	95% CI	Mean Titer, mIU/mL	95% CI
0	0.16	0.05–0.26	610	323–897
1	0.31	0.19–0.43	541	368–714
2	0.51	0.41–0.62	365	218–512
3	0.72	0.63–0.81	142	106–178
4	0.86	0.78–0.93	60	35–84
5	0.93	0.88–0.99	53	35–70
6	0.97	0.94–1.00	64	45–83
7	0.99	0.97–1.00	67	43–91
8	0.99	0.99–1.00	61	41–81
9	1.00	1.00–1.00	49	37–62
10	1.00	1.00–1.00	37	27–48
11	1.00	1.00–1.00	27	14–40

age, the predicted standardized mean antibody titer in infants 1 month of age with a mother aged 32 years was 541 mIU/mL (95% CI: 368–714) (Table 3, Fig 3). However, by 3 months of age, the predicted mean antibody titer dropped to 142 mIU/mL (95% CI: 106–178), well below the measles threshold of susceptibility of 192 mIU/mL. By the time infants reached 6 months of age, the predicted mean antibody titer declined to 64 mIU/mL (95% CI: 45–83). Predicted titers were similar across a range of maternal ages (Supplemental Fig 5) and for both sexes (data not shown).

DISCUSSION

To our knowledge, this study includes 1 of the largest cohorts used to describe infant susceptibility to measles over the first year of life in an elimination setting. Our findings reveal that the majority of infants are susceptible to measles by 3 months of age, well before immunization with a first dose of measles-containing vaccine, which, in Ontario, is administered at 12 months.

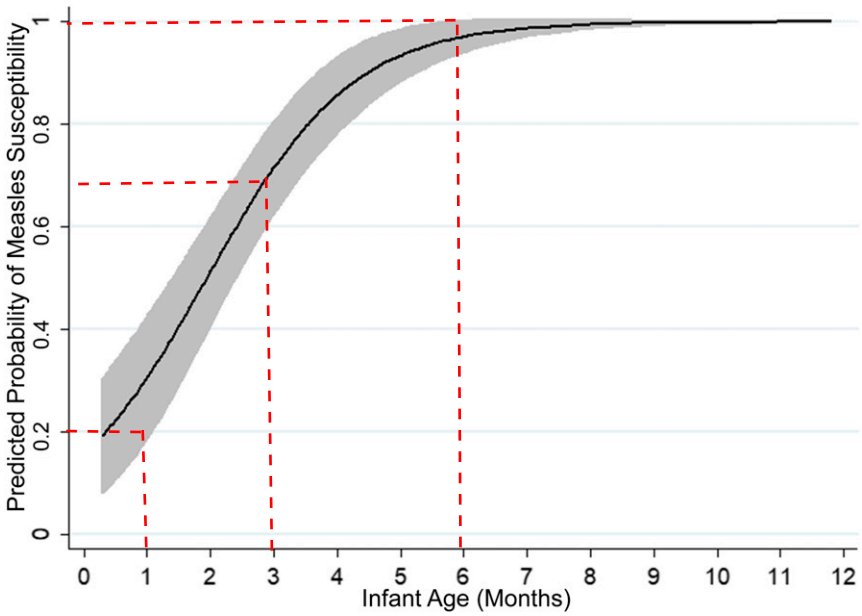

FIGURE 1
Predicted probability of measles susceptibility by infant age for mothers aged 32 years based on a logistic model that was controlled for infant sex and maternal age. The shaded area represents 95% CIs.

To date, studies used to measure infant susceptibility to measles in elimination settings have mainly been focused on older infants aged 6 to 12 months,[17] likely on the basis of the assumption that infants up to age 6 months are protected by their mother's antibodies.[33] Choudhury et al[18] examined younger infants and showed that American infants 3 to 7 months of age had no immunity to measles and that only 80% were protected at birth; however, findings were based on a small sample (n = 13). Although we report similar findings, it is difficult to make direct comparisons given differing methodologies. For example, in their study, Choudhury et al[18] used cord blood to assess protection against measles at birth, and our study's youngest age band was broader and included infants throughout the first month of life.

Despite the fact that we conducted our study in a measles-elimination setting, our findings are similar to those of some studies conducted in low-incidence, nonelimination settings. The authors of 2 large cross-sectional studies in the Netherlands[15] and China[34] also describe a significant loss of measles protection by 3 months. In the Netherlands, the median duration of antibody detection was 3.3 months

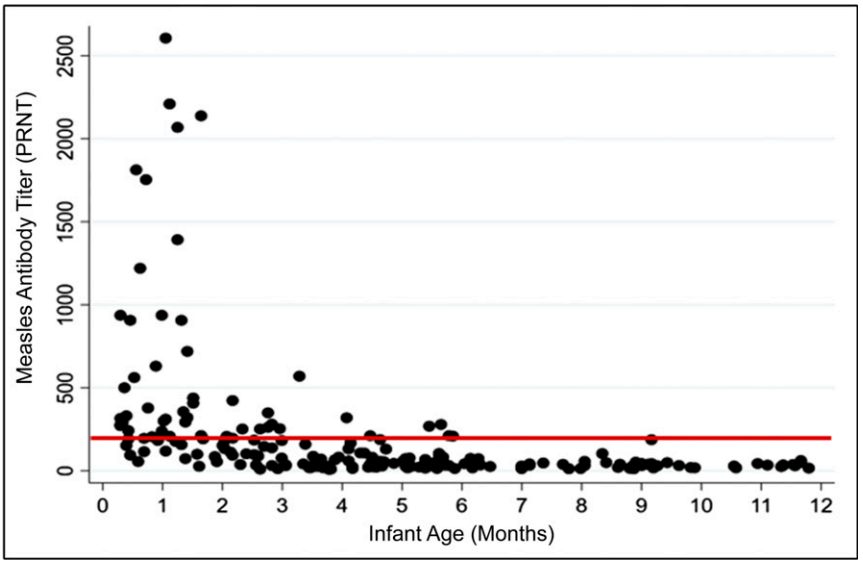

FIGURE 2
Scatterplot of the relationship between infant age in months and measles antibody titer in mIU/mL (N = 196). We considered infants above the threshold to be immune to measles infection and those below the threshold to be susceptible to measles infection.

in infants of vaccinated mothers.[15] In China, almost all infants lost protection by 3 months.[34] This is not surprising given these settings are working toward measles elimination, and vaccinated mothers are likely being immunologically boosted less often than those in highly endemic settings, resulting in lower antibody levels. Other studies in low-incidence, nonelimination settings have revealed even faster waning of measles immunity. A longitudinal study in Belgium conducted from 2006 to 2008 revealed that the time to susceptibility was <1 month among infants born to vaccinated mothers.[14] Another study conducted in Portugal revealed only 81% protection at birth.[35] However, the authors of both these studies used enzyme-linked immunosorbent assays (ELISAs) with a protective threshold of ≥300 mIU/mL, which likely overestimated susceptibility.

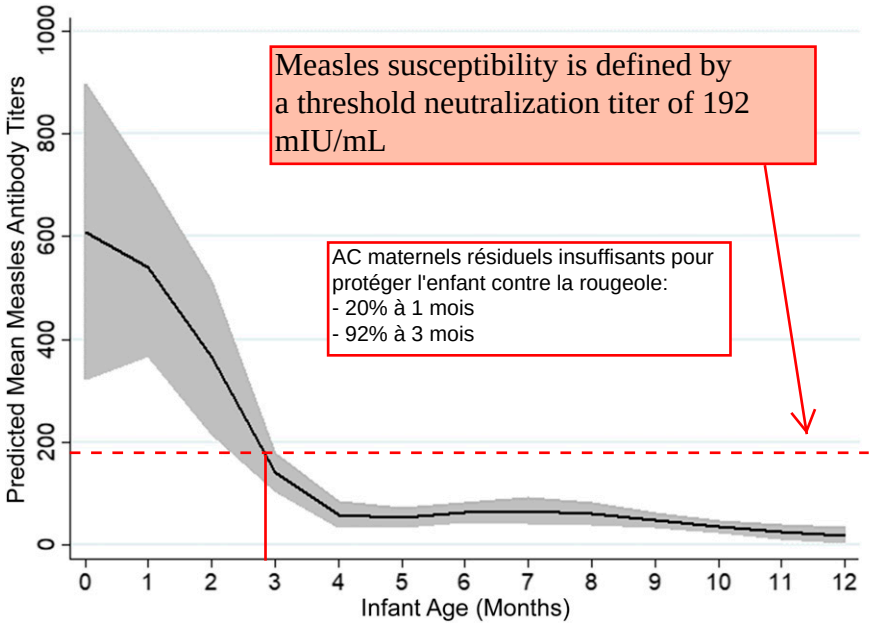

FIGURE 3
Predicted mean measles antibody titers by infant age for mothers aged 32 years based on a Poisson model that was controlled for infant sex and maternal age. The shaded area represents 95% CIs.

The study from Portugal also revealed that maternal age was a predictor of infant antibody level. Infants of older mothers had higher measles antibody levels than those of younger mothers because many older mothers in the study were immune through previous infection and not vaccination.[35] Our study revealed the opposite trend, but, this is not surprising given the majority of mothers in our cohort were likely vaccinated and would have had more remote vaccination than younger mothers; the oldest mothers in our cohort would have been born a decade after implementation of a routine measles immunization program in Canada. However, this finding did not reach statistical significance, which may be related to sample size.

Although most studies measure population susceptibility to measles using ELISA, our use of the gold standard PRNT to measure antibody titers is a strength of our study. We chose PRNT to ensure high test sensitivity because ELISA sensitivity decreases as antibody titers decrease,[29,36,37] and we anticipated much of our cohort to have low antibody levels.[14,17] Previous studies that have been focused on infants have revealed variable results, likely attributable to a combination of different testing methods, differing susceptibility cutoffs, and small sample sizes.[17] PRNT is a more accurate measure of functional immunity because it measures neutralizing antibodies regardless of isotype, compared with ELISA, which measures immunoglobulin G antibodies only, regardless of whether they are neutralizing or nonneutralizing.[27,38] The impact of this is highlighted in 1 of the largest comparable studies performed to date in an elimination setting, which was

conducted in South Korea in 2009–2010.[20] Cho et al[20] found that a much higher proportion of infants were protected from measles using PRNT versus ELISA (63.6% vs 23.1% at 2 months), emphasizing the sensitivity of PRNT relative to ELISA.

The widening gap between loss of maternal antibodies and measles vaccination described in our study leaves infants vulnerable to measles for much of their infancy and highlights the need for further research to support public health policy. Potential considerations include (1) infant strategies, (2) maternal strategies, and (3) broader public health strategies. With respect to infant strategies, currently in Canada, infants are immunized with a first dose of measles-containing vaccine at 12 months of age, based on immune system maturity, optimizing community protection and avoiding potential antibody interference in the first year of life.[39] In other elimination settings, immunization is delayed up to 15 months. This results in a substantial measles susceptibility gap for infants in elimination settings. Although earlier vaccination between 6 and 12 months is safe and somewhat immunogenic,[40] there is evidence to suggest that the immune response may be blunted if the first dose is given before 9 months of age.[41] Despite these data being from nonelimination settings, where maternal antibodies may persist at higher levels, it is suggested that even in the absence of maternal antibodies, the proportion of infants who seroconvert after vaccination increases with age.[40] Vaccination earlier than 12 months is currently used only as a risk-mitigation strategy, reserved for infants traveling to measles-endemic areas or exposed infants without immunity 6 to 12 months of age.[16,33] With respect to maternal strategies, vaccination during pregnancy to boost antibody levels is not possible because both the measles, mumps, and rubella vaccine and the monovalent measles vaccine are contraindicated because of the fact that they are live-attenuated vaccines.[42] A strategy of immunizing women of childbearing age to boost antibody levels is unlikely to succeed considering the low vaccination coverage for adult immunization in many jurisdictions[43] as well as the fact that up to half of pregnancies are unplanned.[44] Therefore, the best strategy for protecting infants against measles is adequate community protection delivered through high coverage of 2 doses of measles-containing vaccine. As such, broader public health strategies to achieve and maintain adequate vaccine coverage remain critical, especially in the era of vaccine hesitancy.[45]

Currently, despite Canada's elimination status, measles exposures and sporadic outbreaks continue to occur annually because of importations from abroad,[26,46,47] with infants making up as much as 31% of cases in some years.[26] Our findings have implications for the management of infants exposed to measles. Susceptible exposed infants of all ages should be considered for interventions (vaccine or immune globulin) to prevent disease and should be isolated to prevent disease spread during the incubation period. However, currently infants <6 months of age are considered by some agencies to be immune if there is a maternal history of vaccination[33] but not by others. As such, consideration should be given to either testing exposed infants aged <6 months to establish immune status, if readily available and timely (rather than assuming immunity solely based on their age and mother's immunity status), or considering them nonimmune. Nonimmune infants <6 months of age could then be offered immune globulin as a postexposure prophylaxis, keeping with current guidelines.[1,33]

A key limitation of this study was its restriction to a single tertiary care center, which may affect the representativeness of the sample. To mitigate this, we only included children who did not have an underlying immunodeficiency or a condition that would impact antibody production. Although The Hospital for Sick Children is a tertiary care center that receives patient transfers from other hospitals, many admissions are directly from the emergency department and are patients who fall in the hospital catchment area. This population is similar to children admitted to other local hospitals. A second limitation was that we used a retrospective chart review to abstract data, which resulted in missing data, most notably for duration of breastfeeding and maternal age. We show, however, that the missing data were unlikely to affect study findings, with results robust across sensitivity analyses. In addition, maternal country of birth and vaccination history were not routinely recorded in infant charts and therefore could not be adjusted for in the analysis. However, it is interesting to note that Toronto has a high immigrant population, and despite the fact that many of the women may have been from countries where measles is still endemic, antibody levels were low.

CONCLUSIONS

We found that infants were susceptible to measles earlier than previously observed in nonelimination settings, with most infants becoming susceptible by 3 months of age. These findings have important implications for current infant postexposure prophylaxis recommendations because infants <6 months of age are often considered routinely immune to measles. Further research is needed prospectively to validate these findings and explore the impact of maternal age and breastfeeding on infant immunity in elimination settings.

ABBREVIATIONS

CI: confidence interval
ELISA: enzyme-linked immunosorbent assay
OR: odds ratio
PRNT: plaque-reduction neutralization test

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