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Seroprevalence of rubella antibodies and determinants of susceptibility to rubella in a cohort of pregnant women in Canada, 2008–2011

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ABSTRACT

Long term control of rubella and congenital rubella syndrome relies on high population-level immunity against rubella, particularly among women of childbearing age. In Canada, all pregnant women should be screened so that susceptible new mothers can be offered vaccination for rubella before discharge. This study was undertaken to estimate rubella susceptibility in a cohort of pregnant women in Canada and to identify associated socio-economic and demographic factors. Biobanked plasma samples were obtained from the Maternal-Infant Research on Environmental Chemicals (MIREC) study, in which pregnant women were recruited between 2008 and 2011. Socio-demographic characteristics and obstetric histories were collected. Second trimester plasma samples (n = 1,752) were tested for rubella-specific IgG using an in-house enzyme-linked immunosorbent assay. The percentage of women with IgG titers <5 IU/mL, 5–10 IU/mL, and ≥10 IU/mL were 2.3%, 10.1%, and 87.6%, respectively. Rates of seronegativity, defined as <5 IU/mL, were 3.1% in women who had no previous live birth and 1.6% in women who had given birth previously. Among the latter group, seronegativity was higher in women with high school education or less (adjusted OR (aOR) 5.93, 95% CI 2.08–16.96) or with a college or trade school diploma (aOR 3.82, 95% CI 1.45–10.12), compared to university graduates, and those born outside Canada (aOR 2.60, 95% CI 1.07–6.31). In conclusion, a large majority of pregnant women were found to be immune to rubella. Further research is needed to understand inequalities in vaccine uptake or access, and more effort is needed to promote catch-up measles-mumps-rubella vaccination among socioeconomically disadvantaged and immigrant women of childbearing age.

1. Introduction

Rubella, one of the classic childhood exanthems, is caused by rubella virus, a positive-sense, single-stranded RNA virus of the *Togaviridae* family [1–3]. In children, the disease is characterized by a self-limiting rash and fever. Up to 50% of infections are subclinical [4]. Complications such as meningoencephalitis, thrombocytopenia and post-infectious encephalomyelitis occur but are very rare [1]. In adults and particularly in post-pubertal women, rubella infection is an important cause of arthralgia/arthritis [3]. The most severe complications of rubella in adult women occur during pregnancy when infection can lead to miscarriage, stillbirth, or congenital rubella syndrome (CRS), a constellation of congenital anomalies including microphthalmia and other eye defects, sensorineural deafness, heart defects, and brain damage such as microcephaly [1]. The rate of vertical transmission and CRS is highest when maternal infection occurs in the first ten weeks of pregnancy and decreases afterwards [2].

In Canada, routine vaccination with rubella-containing vaccine has been publicly-funded in most provinces since the 1970s, and by 1983 a combined measles-mumps-rubella vaccine (MMR) was incorporated into all provincial and territorial routine vaccination programs. As a result, the average annual incidence of rubella fell from 18.9 cases per 100,000 in 1979–1983 to 5.0 cases per 100,000 in 1984–1997 [5]. In parallel, the rate of CRS fell from 3.0 cases per 100,000 live births in 1979–1983 to 0.8 cases per 100,000 live births in 1984–1997 [5]. After the introduction of a second dose of MMR vaccine into all provincial and territorial

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vaccination programs between 1996 and 1997, the average annual rubella and CRS incidence rates decreased further to 0.1 cases per 100,000 and 0.2 cases per 100,000 live births in 1998–2008, respectively [5]. Canada achieved elimination of both rubella and CRS by 2005, with an annual average of only 4.3 rubella cases reported per year between 2006 and 2011 and no reported cases of CRS due to exposure in Canada since 2000 [5,6].

The long-term control of rubella and CRS relies on maintaining high coverage with a rubella-containing vaccine. Seroconversion after a single dose of live attenuated rubella vaccines, including MMR, have consistently exceeded 95% [7] and vaccine-induced anti-rubella titres can be remarkably robust [8]. Nonetheless, antibody titres tend to fall after vaccination [9] and at least some of those who have been previously vaccinated mount primary responses upon revaccination [10]. Although global inclusion of a rubella-containing vaccine in routine childhood vaccination programs has increased steadily in the last two decades, vaccination programs in one third of the world's low- and middle-income countries did not include a rubella-containing vaccine in 2009 [11]. Of all World Health Organization (WHO) Regions, only the Americas have interrupted the endemic transmission of rubella so far [1]. Finally, widely publicized and fraudulent claims linking MMR vaccination to autism [12] may have negatively affected vaccine uptake, though their actual impact remains difficult to measure. All of these factors highlight the need to maintain high vaccination coverage.

As CRS is a severe consequence of rubella infection during pregnancy, rubella immunity in post-pubertal women is of particular interest. The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends that (i) every opportunity be taken to assess rubella immunity in women of childbearing age (e.g., preconception consultation); (ii) all pregnant women be screened to determine their rubella serostatus; and (iii) susceptible women be immunized either pre-conception or post-partum before hospital discharge [13]. While rubella seroprevalence studies have previously been conducted in Canada, they focussed on specific provinces and lacked detailed information on risk factors for rubella susceptibility. Moreover, although screening studies on pregnant women conducted in Ontario [14] and Alberta [15] identified those tested more than once for rubella IgG during the study period, neither could distinguish women who had at least one previous live birth from those who had not. Knowing the seroprevalence of rubella antibodies among women who have had a previous live birth is of particular importance, as it provides a proxy for compliance with recommendations to screen pregnant women and to immunize at-risk mothers post-partum.

This study was undertaken to (i) determine the seroprevalence of rubella IgG antibodies in a cohort of pregnant women in Canada (overall, for those who had no previous live birth, and for those who had at least one); and (ii) to identify the socio-economic and demographic factors associated with higher susceptibility to rubella infection.

2. Methods

2.1. The MIREC study

The Maternal-Infant Research on Environmental Chemicals (MIREC) study was undertaken to examine potential adverse health effects of prenatal exposure to specific environmental chemicals on pregnancy and infant health. The study participants were pregnant women recruited during their first trimester between 2008 and 2011 in ten Canadian cities within six provinces (British Columbia, Alberta, Manitoba, Ontario, Québec, and Nova Scotia) [16]. Enrolment occurred between the 6th and 13th week of pregnancy, at which time participants completed a questionnaire documenting their socio-demographic characteristics and obstetrical history. Maternal blood samples were collected in each trimester and at delivery. Plasma from the second trimester were used in this study because of their availability in the biobank. Samples were centrifuged within two hours of collection, aliquoted, and stored at −20 °C until tested.

2.2. Laboratory methods

Plasma samples were tested for rubella-specific IgG using an in-house enzyme-linked immunosorbent assay (IH-EIA) based upon a highly purified GMP-quality rubella virus lysate antigen (Rubella K2S: Microbix, Mississauga, ON). Briefly, 96-well microtiter round-bottom plates (Greiner bio-one, Monroe, NC) were coated overnight with 50 μL of rubella virus antigen at a concentration of 0.25 μg/well in a carbonate buffer (pH 9.6) at 4 °C. After washing three times in PBS-T (phosphate-buffered saline [pH 7.4] containing 0.05% [vol/vol] Tween 20), 300 μL of blocking buffer (ELISA Blocker Blocking Buffer – Thermofisher Scientific, Ottawa, ON) was added per well, and the reaction mixture was incubated for two hours at room temperature to block nonspecific binding. Plates were washed three times with PBS-T, and then 10 μL of control or sample was diluted in 240 μL of blocking buffer, added to each well and incubated at 37 °C for one hour. After washing three times with PBS-T, 100 μL of mouse anti-human IgG conjugated to horseradish peroxidase (Fisher Scientific, Ottawa, ON) diluted 1:50,000 in blocking buffer was added to each well, and the reaction mixture was incubated for one hour at 37 °C. After washing four times, 100 μL of substrate, 3,3′,5,5′-tetramethylbenzadine was added to each well, and the reaction mixture was incubated in the dark at room temperature for 20 min. The reaction was stopped with the addition of 50 μL of 5% sulfuric acid. The optical density of each control and sample was read at 450 nm.

Each microtiter plate contained a 7-point standard curve constructed using duplicate, serial 2-fold dilutions of the WHO RUBI-1-94 starting at a concentration of 40 IU/mL (range 40–0.625 IU/mL). An internal anti-rubella virus IgG quality control sample diluted with negative human serum to 20 IU/mL (based on the Architect assay: Abbott Diagnostics, Abbott Park, IL) was tested at least once in each plate.

In preliminary work to optimize the IH-EIA, variance between duplicate wells was less than 15% and inter-assay variance was 23%. The IH-EIA was validated essentially as described by Dimech et al. [17] against a commercial EIA (Architect: Abbott Diagnostics) using a panel of human sera and the WHO international anti-rubella immunoglobulin standard (RUBI-1-94). The Architect assay is a micro-particle chemiluminescent enzyme immune-assay that is FDA-approved for clinical diagnostic use. A total of 126 samples, including 33 with IgG titers <10 IU/mL, were analysed in both assays and the ability of IH-EIA to detect sero-negative samples was compared to the commercial platform. Overall, the positive and negative percent agreements between the two assays were 86% and 92% respectively, and the negative and positive predictive values were 82% and 94% respectively.

2.3. Data analysis

Data were analysed using SAS Enterprise Guide 5.1. Participant year of birth was categorized as follows: those born from 1983 onwards (i.e. after the initiation of MMR vaccination at 12 months of age in Canada), those born between 1978 and 1982, those born between 1974 and 1977, and those born between 1960 and 1973.

The distribution of anti-rubella IgG titers was assessed as one of three categories: rubella susceptible/seronegative (<5 IU/mL), indeterminate susceptibility (5 to <10 IU/mL), and rubella

immune/seropositive (≥10 IU/mL). Geometric means of rubella IgG titers with their 95% confidence intervals were calculated by birth year categories, and compared using generalized linear models (GLM). This analysis was repeated after excluding women who had had a previous live birth (to prevent effect modification by post-partum vaccination) and women born outside Canada (to examine the effect of MMR introduction).

For the analysis of factors associated with rubella susceptibility, the threshold of <5 IU/mL suggested by Lai et al. [15] was used to identify those who were definitively seronegative. In contrast, the use of a higher threshold (i.e. <10 IU/mL) to identify all those who *may not* be immune is clinically appropriate [18] as they could benefit from vaccination.

Associations between sociodemographic factors and rubella seronegativity were determined by simple and multiple logistic regressions. Factors with *p* values below 0.10 in simple regressions were included in multiple regression models and retained in models as long as their *p* values remained below 0.10. The standard errors of parameter estimates in the multiple regression models were compared to those in the simple regression models to find co-linearity, but none were identified. Unadjusted odds ratios (OR) and adjusted odds ratios (aOR) and their respective 95% confidence intervals were calculated. This analysis was carried out for the entire study population, and then separately for women who had no previous live births and those who had at least one live birth, to account for effect modification by post-partum vaccination.

2.4. Ethics

This study was reviewed and approved by Health Canada and the Public Health Agency of Canada's Research Ethics Board (REB).

The MIREC study had previously been reviewed and approved by the REBs of the Centre Hospitalier Universitaire Sainte-Justine, all recruitment sites and Health Canada and Public Health Agency of Canada. The consent provided by participants allowed for the use of anonymized data and bio-banked biological samples for further research.

3. Results

Of the 1,928 participants enrolled in the MIREC study, 1,752 had a second-trimester plasma sample available for testing. Their age at enrollment ranged between 18 and 48 years, 64% of them were university graduates, and 55% had had at least one previous live birth (Table 1).

Anti-rubella IgG antibody titers in the second trimester of pregnancy ranged from 0.9 to 897 IU/mL. The percentage of women with IgG titers <5 IU/mL, between 5 and 10 IU/mL, and ≥10 IU/mL were 2.3%, 10.1%, and 87.6%, respectively (Table 2).

Anti-rubella IgG antibody titers were lower in younger participants (Table 3), with the greatest gap between those born in 1974–1977 compared to those born in 1978–1982. Similar trends were observed after excluding women who had had at least one live birth (i.e., potentially vaccinated post-partum) and those born outside Canada (i.e., possibly vaccinated according to a different schedule or not vaccinated at all). There was no significant difference between those born on or after 1983 and those born immediately before that milestone (Table 3).

Adjusting for year of birth, education, and history of previous live birth, the odds of rubella seronegativity were significantly (i) lower in women born in 1978–1982 compared to those born in 1960–1973 (aOR 0.35, 95% CI 0.14–0.90), (ii) higher in women with a trade school or college diploma compared to university graduates (aOR 2.15, 95% CI 1.03–4.51), and (iii) higher in women with one or more live births compared with those with none (aOR 0.47, 95% CI 0.24–0.92) (Table 4). Among those who had had no previous live births (and therefore no opportunity for postpartum vaccination), the odds of rubella susceptibility were even greater for those with (i) a high school education or less [5.93 (2.08–16.96)] or (ii) a college or trade school diploma [3.82 (1.45–10.12)] compared to university graduates. Similarly, the association between being born outside Canada and the risk of rubella seronegativity was statistically significant in women with no previous live births, whereas it was non-significant for the entire population (Table 5). In women who had had a previous live birth, none of the demographic factors analysed were associated with rubella seronegativity (Table 6).

Table 1
Socio-demographic characteristics and birth history of MIREC study participants with a second-trimester plasma sample available for testing (n = 1,752).

Characteristic	n	%
Province of residence		
Nova Scotia	263	15.0
Quebec	334	19.1
Ontario	922	52.6
Manitoba	77	4.4
Alberta	17	1.0
British Columbia	139	7.9
Year of birth		
1960–1973	470	26.8
1974–1977	478	27.3
1978–1982	581	33.2
1983–1992	223	12.7
Age at enrollment		
18–29	521	29.7
30–34	640	36.5
35–48	591	33.7
Education		
High school or less	232	13.2
College or trade school diploma	403	23.0
University graduate	1,115	63.6
Not stated	2	0.1
Household Income		
$1 - $60,000	371	22.1
$60,001 - $100,000	620	36.9
$100,001 or more	689	41.0
Not stated	72	4.3
Born outside Canada		
No	1425	81.3
Yes	327	18.7
Number of previous live births		
0	781	44.6
1	704	40.2
≥2	267	15.2

4. Discussion

Plasma concentrations of anti-rubella IgG in pregnant women were clearly lower in those born after the introduction of monovalent (early 1970s) and subsequently combined rubella-containing vaccines (i.e. MMR, 1983). This trend is consistent with decreased circulation of wild-type rubella virus in Canada following vaccine introduction [5]. A similar pattern has been observed in countries as diverse as Spain [19] and Peru [20]. As higher vaccination rates are achieved and fewer exposures to wild-type virus occur, populations are increasingly dependent upon vaccine-induced immunity alone. Even though rubella-containing vaccines are highly immunogenic, they generally produce a lower and less durable antibody response than natural infection [21]. To date however, decreasing antibody levels in highly vaccinated populations have

Table 2
Distribution of anti-rubella IgG titers in pregnant women by history of live birth.

Rubella IgG titers (IU/mL)	All participating women (n = 1,752)		Women with no previous live birth (n = 781)		Women with ≥1 previous live birth (n = 971)	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
0–4.99	40	2.3 (1.6–3.1)	24	3.1 (2.0–4.5)	16	1.6 (0.9–2.7)
5.00–9.99	177	10.1 (8.7–11.6)	90	11.5 (9.4–14.0)	87	9.0 (7.2–10.9)
≥10.00	1535	87.6 (86.0–89.1)	667	85.4 (82.7–87.8)	868	89.4 (87.3–91.3)

Table 3
Participant anti-rubella IgG titers (IU/mL) by birth year, live birth history, and place of birth.

Year of birth	All participating women (n = 1,752)			Women with no previous live birth (n = 781)			Canadian-born women with no previous live birth (n = 640)		
	N	Geometric mean (95% CI)	*p*	N	Geometric mean (95% CI)	*p*	N	Geometric mean (95% CI)	*p*
1960–1973	470	30.3 (27.9–33.0)	Reference	167	30.1 (26.2–34.7)	Reference	121	29.7 (25.4–34.8)	Reference
1974–1977	478	29.0 (26.8–31.2)	0.4097	170	26.7 (23.5–30.3)	0.2052	131	24.9 (21.7–28.6)	0.0908
1978–1982	581	23.8 (22.3–25.4)	<0.0001	308	22.9 (20.9–25.2)	0.0012	264	21.8 (19.8–24.0)	0.0006
1983–1992	223	22.9 (20.4–25.8)	<0.0001	136	21.4 (18.2–25.1)	0.0007	124	20.4 (17.5–23.7)	0.0004

p values are for the comparison with the 1960–1973 birth cohort.

Table 4
Determinants of rubella IgG seronegativity[a] in participants (n = 1,752).

Characteristic	N	n	%	Unadjusted OR (95% CI)	Adjusted[b] OR (95% CI)
Year of birth					
1960–1973	470	13	2.8	Reference	Reference
1974–1977	478	10	2.1	0.75 (0.33–1.73)	0.76 (0.33–1.77)
1978–1982	581	7	1.2	0.43 (0.17–1.08)	0.35 (0.14–0.90)
1983–1992	223	10	4.5	1.65 (0.71–3.82)	0.98 (0.39–2.47)
Education					
High school or less	232	9	3.9	2.46 (1.09–5.55)	2.38 (0.97–5.84)
College or trade school diploma	403	13	3.2	2.03 (0.99–4.19)	2.15 (1.03–4.51)
University graduate	1,115	18	1.6	Reference	Reference
Not stated	2	0	0.0		
Household Income					
$1 - $60,000	371	12	3.2	2.06 (0.90–4.72)	
$60,001 - $100,000	620	13	2.1	1.32 (0.59–2.97)	
$100,001 or more	689	11	1.6		
Not stated	72	4	5.6	3.63 (1.12–11.70)	
Born outside Canada					
No	1,425	29	2.0	Reference	
Yes	327	11	3.4	1.68 (0.83–3.39)	
Previous live birth					
No	781	24	3.1	Reference	Reference
Yes	971	16	1.6	0.53 (0.28–1.00)	0.47 (0.24–0.92)

[a] Seronegativity defined as IgG titers <5 IU/mL.
[b] Model includes all variables for which values are shown in the column.

not led to major outbreaks of rubella or an increased incidence of CRS [22].

The overall percent of pregnant women immune to rubella in this study (88% with ≥10 IU/mL) was lower than the 90% measured in Ontario pregnant women in 2006–2010 [14], but higher than the 84.1% measured in Alberta in 2009–2012 [15]. Rubella seropositivity in our study was also slightly lower than the 91.5% measured in the United States in non-pregnant women aged 20–49 [23]. The different assays used in these studies may have influenced rubella seroprevalence results, particularly at low antibody titers [17]. Nonetheless, all of these studies send the same message: that some women of child-bearing age may be susceptible to rubella.

Although not truly national in scope, our rubella seroprevalence study is the first to be conducted across multiple Canadian provinces representing 92.5% of the country's total population in 2016 [24] and with good geographic coverage.

Unfortunately, the number of foreign-born women in this study (total 327, seronegative 11) was too small to undertake a detailed analysis by country or region of birth as the numbers of women from specific regions would not allow valid inferences. However, because of varying rubella vaccination programs and disease incidence rates, differences between countries or regions of birth can be expected. The SOGC recommends vaccinating all immigrant and refugee women at their first encounter with the Canadian health care system, unless they have documentation of effective vaccination or natural immunity [13]. A chart review of 1,987 Canadian-born and 3,796 foreign-born pregnant women found that, among the latter, those born in the Middle East or in North Africa were at higher risk of seronegativity than those Canadian-born, while those born in Sub-Saharan Africa were at lower risk. Women from other parts of the world were not statistically different from those Canadian-born [25]. In a study of 1,480 immigrants in Montreal, rubella seronegativity rates (<10 IU/mL) ranged from

Table 5
Determinants of rubella IgG seronegativity[a] in participants who had no previous live birth (n = 781).

Characteristic	N	%	Unadjusted OR (95% CI)	Adjusted[b] OR (95% CI)
Year of birth				
1960–1973	167	3.6	Reference	
1974–1977	170	2.4	0.65 (0.18–2.33)	
1978–1982	308	1.6	0.44 (0.13–1.47)	
1983–1992	136	6.6	1.90 (0.66–5.48)	
Education				
High school or less	90	7.8	5.47 (1.93–15.49)	5.93 (2.08–16.96)
College or trade school diploma	164	5.5	3.77 (1.43–9.93)	3.82 (1.45–10.12)
University graduate	527	1.5	Reference	Reference
Household Income				
$1 - $60,000	170	5.3	3.41 (1.12–10.34)	
$60,001 - $100,000	272	2.2	1.38 (0.42–4.56)	
$100,001 or more	310	1.6		
Not stated	29	13.8	9.76 (2.46–38.66)	
Born outside Canada				
No	640	2.5	Reference	Reference
Yes	141	5.7	2.35 (0.98–5.60)	2.60 (1.07–6.31)

[a] Seronegativity defined as IgG titers <5 IU/mL.
[b] Model includes all variables for which values are shown in the column.

Table 6
Determinants of rubella IgG seronegativity[a] in participants who had at least one previous live birth (n = 971).

Characteristic	N	n	%	Unadjusted OR (95% CI)
Year of birth				
1960–1973	303	7	2.3	Reference
1974–1977	308	6	1.9	0.84 (0.28–2.53)
1978–1982	273	2	0.7	0.31 (0.06–1.52)
1983–1992	87	1	1.1	0.49 (0.06–4.05)
Education				
High school or less	142	2	1.4	0.83 (0.18–3.81)
College or trade school diploma	239	4	1.7	0.98 (0.31–3.17)
University graduate	588	10	1.7	Reference
Not stated	2	0	0.0	
Household Income				
$1 - $60,000	201	3	1.5	0.94 (0.23–3.81)
$60,001 - $100,000	348	7	2.0	1.28 (0.43–3.84)
$100,001 or more	379	6	1.6	Reference
Not stated	43	0	0.0	
Born outside Canada				
No	785	13	1.7	Reference
Yes	186	3	1.6	0.97 (0.28–3.45)

[a] Seronegativity defined as IgG titers <5 IU/mL.

5% to 30% depending upon the region of birth, with the lowest rates in Sub-Saharan Africa immigrants and the highest in those born in East Asia-Pacific countries [26]. These observations, together with our current findings, reinforce the message that more effort is needed to deliver catch-up vaccinations in immigrant women.

The association between lower educational attainment and increased rubella susceptibility may suggest socio-economic inequalities in rubella vaccine uptake. This possibility is consistent with inequalities observed in the general uptake of childhood vaccines in Canada [27]. More research is needed to determine the underlying causes of these inequalities, and to measure the relative contributions of vaccine hesitancy and systemic barriers.

Little is currently known regarding either the completeness of pre-natal screening or the uptake of postpartum rubella vaccination in Canada. In the 1990s, a chart review of prenatal rubella screening and its follow-up in 2,551 women who delivered in Québec hospitals found that among the 1.6% initially found to be seronegative, 33.5% were definitely vaccinated post-partum, 29.5% were definitely not vaccinated, and vaccination was not required for various reasons for 6%. The vaccination status of the remaining 31% could not be ascertained from the charts [28]. In the absence of more recent published data, it is unknown whether compliance with this health intervention changed over time. However, the difference in seronegativity rates in the current study between the women who had had a previous live birth and those who had not (1.6% versus 3.1% respectively) suggest that, while clearly not functioning optimally, the SOGC recommendation to vaccinate post-partum is having at least some impact.

This study has several limitations. MIREC was not designed to study vaccination or vaccine-preventable diseases so the vaccination history of participants was not recorded. Moreover, the study sample is not fully representative of the Canadian population as it is primarily a convenience sample, and was restricted to six out of ten provinces with no representation from the three territories. Further, the proportion of university graduates in this study, 64%, was much higher than the 35% measured in new mothers in a population-based survey conducted in 2006–2007 [29]. Therefore, the rates derived from our data may not be generalizable to all pregnant women in Canada.

5. Conclusion

Despite a general decrease over time in anti-rubella IgG titers after the introduction of rubella-containing vaccines, a large majority of pregnant women in the cohort were found to be immune to rubella. Among those who had at least one previous live birth, very few were susceptible to infection suggesting that post-partum vaccination recommendations, while not fully complied with, are having a positive impact. Lower educational attainment (possibly an indicator of low socio-economic status) and birth outside Canada were risk factors for rubella susceptibility. Further research is warranted to understand the socioeconomic inequalities in vaccine uptake or access, and more effort is needed to promote catch-up MMR vaccination among socioeconomically disadvantaged and immigrant women of childbearing age.

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