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Determining rubella immunity in pregnant Alberta women 2009–2012

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ABSTRACT

Rubella IgG levels for 157,763 pregnant women residing in Alberta between 2009 and 2012 were analyzed. As there have been no reported cases of indigenous rubella infection in Canada since 2005, there has been a lack of naturally acquired immunity, and the current prenatal population depends almost entirely on vaccine induced immunity for protection. Rubella antibody levels are significantly lower in younger maternal cohorts with 16.8% of those born prior to universal vaccination programs (1971–1980), and 33.8% of those born after (1981–1990) having IgG levels that are not considered protective (<15 IU/mL). Analysis across pregnancies showed only 35.0% of women responded with a 4-fold increase in antibody levels following post-natal vaccination. Additionally, 41.2% of women with antibody levels <15 IU/mL had previously received 2 doses of rubella containing vaccine. These discordant interpretations generate a great deal of confusion for laboratorians and physicians alike, and result in significant patient follow-up by Public Health teams. To assess the current antibody levels in the prenatal population, latent class modeling was employed to generate a two class fit model representing women with an antibody response to rubella, and women without an antibody response. The declining level of vaccine-induced antibodies in our population is disconcerting, and a combined approach from the laboratory and Public Health may be required to provide appropriate follow up for women who are truly susceptible to rubella infection.
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1. Introduction

Rubella infection is generally regarded as a mild, self-limited illness when it affects young healthy children. However, if rubella is acquired during the first 10 weeks of pregnancy, the fetus is at high risk of congenital rubella syndrome (CRS) [1], with manifestations ranging from deafness, cardiac disease, and cognitive impairment to miscarriage and fetal death [2–4]. The incidence of CRS in Canada is rare, with an average of 0.69 cases per year between 1998 and 2010 [5]. Since Canada introduced the rubella vaccine in 1969, rubella incidence has markedly decreased; no indigenous rubella cases have been reported since 2005 [5].

The ideal marker for immunity to a viral pathogen is the detection of virus-specific neutralizing antibodies [6–9]. As the rubella neutralization assay is labor intensive, time consuming and not amenable to automation, detection of total rubella IgG via high throughput enzyme immunoassays has replaced neutralization as the primary screening methodology [10]. It is important to note that neutralization assays were used to determine the initial antibody cut off recommendations, and that total IgG levels represent a surrogate marker for immunity. Furthermore, the measurement of total antibody levels can vary by manufacturer depending upon the selection of antigens and reference standards employed in the assay [11–13]. Studies on the development of the rubella vaccine showed long-lasting antibody responses were elicited [14], however waning levels of IgG have been noted in post-vaccine

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populations [15,16]. Rubella IgG levels were lower in younger age groups compared to those born prior to universal childhood vaccination [17–19], suggesting that vaccine induced immunity may elicit lower IgG levels than natural infection. Therefore, the level of IgG used to indicate immunity prior to vaccine implementation may not accurately represent the level of rubella IgG required to mount an effective immune response in a vaccinated population.

Here we report rubella antibody levels among pregnant women in the Canadian province of Alberta, and evaluate the current Alberta antibody cut off of >15 IU/mL. The proportion of women who had low antibody levels was assessed by age, ethnicity and geographic region. History of rubella vaccination was correlated with rubella antibody levels across multiple pregnancies to examine the effect of vaccination on circulating rubella IgG antibody levels. Finally, latent class modeling using a two class fit model was used to examine the level of rubella IgG antibodies, and assess the level of Public Health involvement at variable antibody cut off values.

2. Methods

2.1. Rubella antibody testing

Prenatal rubella antibody testing in Alberta is performed centrally at the Provincial Laboratory for Public Health (ProvLab). All prenatal specimens submitted from Alberta residents for rubella serology between October 2009 and December 2012 were included in this study. Only the first rubella serological test per pregnancy (defined as all samples collected from the same woman within a 365-day period) was included in this analysis and any repeat tests within one year of the initial test were excluded.

Demographic data including, Personal Health Number (PHN), date of birth, specimen collection date, test platform and rubella test results were extracted from ProvLab's laboratory information system. These data were linked with the Alberta Health Care Insurance Plan Central Stakeholder Registry (CSR) to identify the area of residence, First Nations status, and immigration information. First Nations were defined as any aboriginals who hold treaty registration status under the Indian Act of Canada. The CSR captured all interprovincial and international immigration to Alberta since 1984, however secondary migration was not captured (e.g., international immigration to Ontario followed by immigration to Alberta). Interprovincial migrants and immigrants with unknown country of origin were therefore reported together. All provincial immunization records were linked to these data through the Alberta Immunization Repository with the exception of First Nations persons living on reserve, as First Nations maintain independent repositories of these data.

Testing for quantitative rubella IgG antibodies was performed on the Architect platform (Abbott Laboratories, Saint-Laurent, Québec). While the manufacturer's recommended cut off is 10 IU/mL, where antibody levels <10 IU/mL are considered negative and ≥10 IU/mL are considered protective, Alberta has adopted a modified structure. Specimens with antibody levels <10 IU/mL are reported as negative, 10–15 IU/mL reported as indeterminate, and >15 IU/mL as positive. Rubella antibody IgG results were stratified by year of test, maternal birth cohort, and geographical region of residence. Differences in proportions were compared using Chi-square test.

2.2. Change in antibody levels between pregnancies

In Alberta, women who have rubella IgG antibody levels are ≤15 IU/mL, and who have received less than 2 doses of rubella vaccine, are offered postnatal MMR (measles–mumps–rubella) vaccination [20]. Rubella IgG levels were compared across pregnancies by analyzing the antibody levels from initial and repeat prenatal screening in subsequent pregnancies. The change in antibody levels between those with and without MMR immunization between their pregnancies was assessed. Changes in antibody IgG levels were reported as median and interquartile range (IQR).

2.3. Cutoff for sero-positivity

Two latent classes were developed to assess appropriate rubella IgG antibody level cutoffs: women with an antibody response to rubella, and women without an antibody response to rubella. This two-class model was used to fit the rubella IgG data. Log-normal distributions of IgG values were assumed. All data management and statistical analyses in this study were undertaken in SAS 9.3 (SAS Institute, USA).

2.4. Research ethics approval

Ethics approval for this study was granted by the University of Alberta Research Ethics Board.

3. Results

3.1. Demographic data

During the study period, 171,821 prenatal specimens were submitted to ProvLab for rubella serology testing. Specimens from non-Alberta residents, or specimens with missing or invalid date of birth were removed from the analysis ($n = 1015$) leaving 157,763 test results available for analysis. Demographic evaluation shows 92,682 (58.7%) were born prior to universal childhood vaccination implementation in 1982. In total, 10,952 (6.9%) specimens were collected from First Nations, and 87,056 (55.2%) specimens from immigrants who moved to Alberta since 1984. Among immigrants with information on the country of origin ($n = 30,733$), 17,934 (58.4%) came from Asia, 3726 (12.1%) from Africa, 3203 (10.4%) from Europe, and 2028 (6.6%) from USA.

3.2. Proportion of seronegative (<10 IU/mL) and indeterminate (10–15 IU/mL)

Overall, 15.9% of the specimens were found to be seronegative (<10 IU/mL) and 11.7% indeterminate (10–15 IU/mL). Cumulatively, 27.6% of the specimens had rubella antibodies ≤15 IU/mL, which was consistent across all years (Table 1). The proportion of low-level rubella IgG (≤15 IU/mL) was higher in the younger maternal birth cohorts. Among those women born in or before 1980 (i.e. before the universal immunization program was implemented, as those born in 1981 would have been the first cohort vaccinated in the 1982 vaccine implementation for 12 month old infants), 16.8% showed antibody levels ≤15 IU/mL. This proportion increased to 31.6% among those born between 1981 and 1985, 37.7% among those born between 1986 and 1990, and to 47.2% among those born in 1991 and after.

Overall, 60.7% of First Nations women showed rubella IgG ≤15 IU/mL; 42.4% of those were seronegative while 18.3% were indeterminate. This represented a 2-fold increase compared to non-First Nations Albertans (60.7% vs. 28.6%, $p < 0.001$). Immigrants from the USA showed the highest proportion of antibody levels ≤15 IU/mL (23.3%), followed by immigrants from Asia (17.9%) and Africa (15.0%). Women living in non-urban areas were more likely to have low antibody levels ($p < 0.001$). 43.9% of women in remote-rural areas, 34.8% in rural, 29.6% in urban and 24.1% in metro cities had antibody levels ≤15 IU/mL, despite consistent vaccination uptake in these regions for Alberta women born after 1981

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