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Rubella virus neutralizing antibody response after a third dose of measles-mumps-rubella vaccine in young adults

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ABSTRACT

Background: Third doses of measles-mumps-rubella (MMR) vaccine have been administered during mumps outbreaks and in various non-outbreak settings. The immunogenicity of the rubella component has not been evaluated following receipt of a third dose of MMR vaccine.
Methods: Young adults aged 18–31 years with documented two doses of MMR vaccine received a third dose of MMR vaccine between July 2009 and October 2010. Rubella neutralizing antibody titers were assessed before, 1 month, and 1 year after receipt of a third dose of MMR vaccine.
Results: Among 679 participants, 1.8% had rubella antibody titers less than 10 U/ml, immediately before vaccination, approximately 15 years after receipt of a second dose of MMR vaccine. One month after receipt of a third dose of MMR vaccine, average titers were 4.5 times higher and >50% of participants had a 4-fold boost. Response was highest among those with titers less than 10 U/ml prior to vaccination (geometric mean titer ratio = 18.8; 92% seroconversion) and decreased with increasing pre-vaccination titers. Average titers declined 1 year postvaccination but remained significantly higher than pre-vaccination levels. The proportion classified as low-positive antibody levels increased from 3% 1 month postvaccination to 24% 1 year postvaccination.
Conclusions: Vaccination with a third dose of MMR vaccine resulted in a robust boosting of rubella neutralizing antibody response that remained elevated 1 year later. Young adults with low rubella titers are more likely to benefit from a third dose of MMR vaccine.

1. Background

Acute infection with rubella virus often results in a mild fever and rash. However, rubella infection in pregnant women, especially during the first trimester, can result in miscarriages, stillbirths, and congenital rubella syndrome (CRS), a constellation of birth defects that often includes cataracts, hearing loss, congenital heart defects, and developmental delay [1].

Rubella vaccines have been available since the late 1960s and are highly effective in preventing clinical disease [2–4]. In the United States, rubella vaccine was combined with measles and mumps vaccines as measles-mumps-rubella (MMR) vaccine in 1971. Although only 1 dose of rubella-containing vaccine is currently recommended in the United States by the Advisory Committee on Immunization Practices (ACIP) [5], most people receive 2 doses of MMR vaccine as a result of the recommended 2-dose MMR vaccine schedule for school-aged children (age 12–15 months and 4–6 years) for improved measles control starting in 1989 [6]. High 2-dose MMR vaccination coverage contributed to the end of endemic transmission of rubella and CRS in the United States, which was declared in 2004 [7]. In 2011, an expert panel reviewed available data and unanimously agreed that rubella and CRS elimination has been maintained in the United States [8].

Serologic studies have shown nearly all (≥99%) children have detectable rubella antibody and over half have a fourfold increase in rubella titer following receipt of a second dose of MMR vaccine [9–11]. Additionally, between 2004 and 2011, a median of 10 cases were reported annually in the United States, of which, 88% were

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unvaccinated or had unknown vaccination status [8]. Although it is unlikely a third dose is currently needed to maintain elimination of endemic rubella transmission, information on a third dose in the United States may be important in the future for maintenance of rubella elimination, since population immunity may change. Illustrating the evolution of MMR vaccination recommendations is the fact that a third dose of MMR vaccine has been administered during mumps outbreaks [12–14] and recently recommended for persons identified by public health as being at increased risk during mumps outbreaks [15]. A third dose has also been administered in non-outbreak settings to healthcare personnel, military recruits, international travelers, and college students who may have been vaccinated with two doses previously but lacked documentation of receipt [16,17]. Additional vaccination is also recommended for women of childbearing age or pregnant women with a negative rubella titer (after delivery for pregnant women) even if they have had two previous doses of MMR vaccine [5]. The immunogenicity of the rubella component following receipt of a third dose of MMR vaccine has not been systematically evaluated among persons with documented receipt of two doses of MMR vaccine. We measured the rubella neutralizing antibody response one month after receipt of a third dose of MMR vaccine in a healthy, young adult population and persistence of the response one year after receipt. We also assessed persistence of rubella neutralizing antibody levels among young adults who have received two doses of MMR vaccine in childhood.

2. Methods

2.1. Study population and procedures

From July 2009 through October 2010, young adults aged 18–31 years were contacted by mail and telephone to assess study eligibility and invite participation. Individuals were eligible for the study if they (1) had previously participated in a longitudinal study at the Marshfield Clinic examining immunogenicity and adverse events following the second dose of MMR vaccine (MMR2 study) [9,18–20], or (2) were aged 18–25 years and lived in or around Marshfield, Wisconsin with two doses of MMR vaccine documented in the Marshfield Clinic's electronic immunization registry (www.recin.org).

Details of study procedures, including sample size determination and exclusion criteria were previously described [21,22]. Briefly, participants received a third dose of MMR vaccine (M-M-R II, Merck & Co) at the enrollment visit, and serum samples were collected for antibody testing immediately before vaccination, and approximately 1 month and 1 year postvaccination. Participants who had documented titers of ≥121 mIU/mL for measles, >10 for mumps, and >10 U/ml for rubella [21] during the follow-up period for the previous MMR2 study were not offered a third dose of MMR vaccine, but provided serum samples at the enrollment visit and approximately one year after enrollment. All participants were administered a survey to obtain information on demographics, clinical history (e.g., current illness and medications), history of potential exposures (e.g., military, university/college attendance), living conditions (e.g., type of housing, number of household members), and history of foreign travel at the enrollment visit. History of rash, exposure to measles, mumps, or rubella, and illness from measles, mumps, and rubella were assessed at every visit.

The study was approved by the Institutional Review Boards at the Marshfield Clinic and Centers for Disease Control and Prevention (CDC).

2.2. Laboratory methods

Serum samples were processed and stored at the Marshfield Clinic Research Institute at −80 °C until shipping to CDC for testing. Samples collected before receipt of the third dose of MMR vaccine (or at enrollment among those who did not receive a third dose), and approximately 1 month and 1 year postvaccination/enrollment were tested after completion of the 1 year postvaccination visit. All samples from the same individuals were tested in the same run.

A soluble immunocolorimetric neutralization assay (sICNA) was used to assess rubella neutralization titer at each time point as previously described [23]. Briefly, the ability of each serum to neutralize 30 plaque forming units of HPV-77 rubella virus was assessed as follows. Sera were serially diluted in duplicate in a 2-fold series beginning from 1:20 and continuing through 1:160 for pre-vaccination and 1 year postvaccination sera, and from 1:80 through 1:640 for 1 month postvaccination. Control sera were diluted similarly. The amount of remaining infectivity in the serum-virus mixtures was determined by infecting Vero cell monolayers. The standard control sera with known neutralization titers were included with each test. The end-point was defined as a 50% reduction in infectivity as measured 3 days postinfection. Serum-virus mixtures that had less than 50% of the input infectivity at the last dilution were retested in a more dilute dilution series. Serum-virus mixtures that had more than 50% of input infectivity at the first dilution were retested using a less dilute dilution series. The lowest dilution tested was 1:10. To confirm reproducibility, a total of 480 sera were retested 1 week to 1 month after the original tests. Final neutralization titers were calculated according to the previously described LOESS method [23].

2.3. Statistical analysis

Antibody titers were categorized into four groups: negative (titer <10 U/ml), low-positive (titers 10 U/ml to less than 40 U/ml), medium-positive (titers 40 U/ml to less than 120 U/ml), and high-positive (titers ≥120 U/ml).

Titers measured for specimens collected at enrollment for all participants were used to assess long-term persistence of rubella antibodies following receipt of a second dose of MMR vaccine. To assess antibody response and short term persistence following receipt of a third dose of MMR vaccine, only participants who received a third dose in this study were included (5 participants were excluded because they only had titer data at enrollment). The following endpoints were assessed: (1) geometric mean titer (GMT), using $\log_2$-transformed titers and reported as back-transformed value; (2) geometric mean of the titer ratio (GMT ratio), defined as the geometric mean of the difference between postvaccination $\log_2$-transformed titer and pre-vaccination $\log_2$-transformed titer (reported as back-transformed value); and (3) 4-fold boost, defined as a ratio of ≥4 for 1 month postvaccination titer to pre-vaccination titer. GMT ratio was assessed for both the 1 month and 1 year postvaccination visits. Logistic regression using backwards elimination (factors retained if $p < .05$) was used to assess factors associated with a 4-fold boost following vaccination with a third dose. Potential factors assessed included sex, age at first MMR dose (categorized as 12–15 and ≥16 months), time between second and third dose (categorized into tertiles: <14, 14–18, and ≥18 years), age at third dose (18–22 and 23–31 years), and prevaccination titer (continuous $\log_2$ transformed value). Secondary analysis was also conducted restricting to participants who (1) received their first dose of MMR vaccine at age 12–15 months and second dose at age 4–6 years, the ages recommended by ACIP [5], and (2) had rubella titer data for all three study visits.

Differences in characteristics between groups were assessed using χ^2 tests for categorical variables, ANOVA for normally distributed continuous variables, and Wilcoxon rank-sum test for log-transformed variables. All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

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