Vaccine 34 (2016) 4913–4919

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Genetically defined race, but not sex, is associated with higher humoral and cellular immune responses to measles vaccination

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ARTICLE INFO

Article history:
Received 10 June 2016
Received in revised form 17 August 2016
Accepted 18 August 2016
Available online 30 August 2016

Keywords:
Measles
Measles vaccine
Measles virus
Measles-mumps-rubella vaccine
Continental population groups
Sex factors
Immunity, cellular
Immunity, humoral

ABSTRACT

In addition to host genetic and environmental factors, variations in immune responses to vaccination are influenced by demographic variables, such as race and sex. The influence of genetic race and sex on measles vaccine responses is not well understood, yet important for the development of much-needed improved measles vaccines with lower failure rates. We assessed associations between genetically defined race and sex with measles humoral and cellular immunity after measles vaccination in three independent and geographically distinct cohorts totaling 2872 healthy racially diverse children, older adolescents, and young adults. We found no associations between biological sex and either humoral or cellular immunity to measles vaccine, and no correlation between humoral and cellular immunity in these study subjects. Genetically defined race was, however, significantly associated with both measles vaccine-induced humoral and cellular immune responses, with subjects genetically classified as having African-American ancestry demonstrating significantly higher antibody and cell-mediated immune responses relative to subjects of Caucasian ancestry. This information may be useful in designing novel measles vaccines that are optimally effective across human genetic backgrounds.

1. Introduction

Measles is the most contagious known human infectious disease, with an estimated transmissibility to susceptible contacts of 70–100% [1]. Before the introduction of measles vaccine in the U. S., measles caused over 500,000 reported cases annually, resulting in 500 measles-related deaths and nearly 1000 patients left with permanent deafness or other neurological impairment [2]. Due to measles' high transmissibility, a herd-immunity level of 96–98% vaccination is estimated to be necessary to protect populations from measles outbreaks, and must be uniform across subpopulations to effectively prevent measles transmission among the unvaccinated [3,4].

Despite widespread vaccination, measles outbreaks continue to occur throughout the world, including within the United States [2,5,6]. While insufficient vaccine coverage is a clear and major contributor to many outbreaks [7], both primary and secondary vaccine failures also play a role. In outbreaks in developed countries since 2000, many have involved previously immunized individuals [2,6,8–11]. Studies have demonstrated vaccine failure rates of 2–10% in individuals immunized with the recommended two doses of the measles vaccine [12–14]. These data suggest the development of a new measles vaccine will be necessary to achieve full herd immunity and achieve the WHO-declared goal of measles eradication that has not been met [11,15,16]. A better understanding of the underlying factors driving inter-individual differences in measles vaccine antibody and cellular responses would aid in the design of new vaccines that could be targeted to individuals' or subpopulations' profiles and reduce measles vaccine failure rates [17,18].

For many vaccines, heterogeneity in vaccine responses has been traced to inter-individual differences in sex, age at vaccination, race (genetic ancestry), and genetic host determinants, in addition to other environmental and clinical variables (e.g., nutrition, immunization route, maternal antibodies, etc.) [14,19–27]. Sex is frequently, but not always, a strong determinant of vaccine responses, with females demonstrating higher humoral immune responses to vaccines [19]. The relationship of humoral responses to measles vaccine with biological sex is not yet clear. Female children have been shown to be less likely to seroconvert than males in response to measles vaccine [28,29], yet published studies both support [29,30] and refute [31,32] findings of higher measles

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http://dx.doi.org/10.1016/j.vaccine.2016.08.060
0264-410X/

antibody responses in females than males. Little information is known about differences in cellular immune responses to measles vaccine associated with biological sex.

Genetic ancestry has also been noted to be a significant determinant of vaccine responses. Caucasians and Hispanics have, for example, been shown to have lower humoral responses to rubella vaccination than African-Americans and individuals from Somali backgrounds [33]. Previous studies suggest higher humoral responses to measles vaccine in native versus non-native Canadian children [24], and a significantly higher measles seropositivity rate in non-Hispanic blacks throughout the U.S. population than non-Hispanic white Americans and Mexican Americans [34]. Genetic ancestry has not been systematically studied as a possible factor underlying humoral or cellular measles vaccine response heterogeneity in large, diverse cohorts.

We hypothesized that sex and genetic ancestry contribute to inter-individual heterogeneity in immune responses to measles vaccine, and studied these hypotheses in a diverse human population representing 2872 children and adults from three separate cohorts across multiple geographical locations across the U.S.

2. Methods

2.1. Study subjects

The study population and recruitment methods described herein are identical to or similar to those published for our previous studies [12,35–41]. Subjects from previously described cohorts were used for this study [12,35–37,41]. The study cohort was a large population-based combined sample of healthy children, older adolescents and young adults (age 11–41 years), consisting of three independent cohorts: a Rochester cohort (n = 1062); a San Diego cohort (n = 1071); and a U.S. cohort (n = 1058). The recruitment efforts, demographic and clinical characteristics of these cohorts have been previously published [35–37,41].

Specifically, 1062 healthy children and young adults, ranging in age from 11 to 22 years, were recruited from Rochester, MN, between 2001 and 2009 and comprise the Rochester cohort, as previously published [12,35,38,39]. Each subject had written records of having received two doses of measles-mumps-rubella (MMR, Merck) vaccine. Of the study subjects, 982 (93%) were successfully genotyped and assayed for immune response outcomes (Table 1). The San Diego cohort consisted of 1071 healthy older adolescents and adults (age 19–40 years) from military personnel in San Diego, CA, enrolled by the Naval Health Research Center (NHRC) between 2005 and 2006, as previously published [37,40,42]. After excluding subjects without genotyping and immune response outcome data, 882 subjects (82%) remained for analysis. The U.S. cohort consisted of 1058 healthy adults with proven MMR vaccine-induced immunity from armed forces (age 19–41 years), enrolled between 2010 and 2011 [41]. Of these, 1008 subjects (95%) were successfully genotyped and assayed for immune response outcomes.

The Institutional Review Boards of the Mayo Clinic (Rochester, MN) and the Naval Health Research Center (San Diego, CA)

Table 1
Demographic and immune characteristics of the study subjects.

	Rochester cohort (n = 982)	San Diego cohort (n = 882)	U.S. cohort (n = 1008)	Total (n = 2872)
Sex				
Female	444 (45.2%)	240 (27.2%)	96 (9.52%)	780 (27.2%)
Male	538 (54.8%)	642 (72.8%)	912 (90.5%)	2092 (72.8%)
Race (self-declared)				
White	888 (90.4%)	492 (55.8%)	826 (81.9%)	2206 (76.8%)
Black or African-American	51 (5.19%)	164 (18.6%)	125 (12.4%)	340 (11.8%)
American Indian/Alaska Native	4 (0.407%)	10 (1.13%)	15 (1.49%)	29 (1.01%)
Asian/Hawaiian/Pacific Islander	7 (0.713%)	4 (0.454%)	9 (0.893%)	20 (0.696%)
Multiple	21 (2.14%)	74 (8.39%)	14 (1.39%)	109 (3.8%)
Other	5 (0.509%)	118 (13.4%)	0 (0%)	123 (4.28%)
Unknown	6 (0.611%)	20 (2.27%)	19 (1.88%)	45 (1.57%)
Ethnicity (self-declared)				
Hispanic/Latino	19 (1.93%)	200 (22.7%)	181 (18%)	400 (13.9%)
Not Hispanic/Latino	956 (97.4%)	648 (73.5%)	818 (81.2%)	2422 (84.3%)
Unknown	7 (0.713%)	34 (3.85%)	9 (0.893%)	50 (1.74%)
Genetic Ancestry				
Caucasian	942 (95.9%)	718 (81.4%)	895 (88.8%)	2555 (89%)
African-American	40 (4.07%)	164 (18.6%)	113 (11.2%)	317 (11%)
Age at enrollment (years)				
Number missing	0	245	0	245
Mean (SD)[a]	15 (2.23)	24.5 (3.74)	25.7 (4.59)	21.4 (6.14)
Q1, Q3	13, 17	22, 26	22, 27	16, 25
Median	15	24	24	22
Range	11–21	19–39	19–41	11–41
Age at last vaccination (years)				
Number missing	0	245	439	684
Mean (SD)[a]	8.39 (3.48)	20.5 (3.41)	25.8 (4.43)	16.4 (8.41)
Q1, Q3	5, 12	18, 22	23, 28	11, 23
Median	9.5	19	25	18
Time from last vaccination to enrollment (years)				
Number missing	0	245[b]	439[b]	684
Mean (SD)[a]	6.66 (2.9)	3.41 (1.72)	0.012[c] (0.008)	3.98 (3.47)
Q1, Q3	4.7, 8.6	2.16, 4.06	0.005, 0.014	0.033, 6.4
Median	6.4	3.03	0.011	3.4

[a] Standard Deviation: Q1, first quartile; Q3, third quartile.
[b] Military subjects had demonstrated MMR-induced measles immunity; complete vaccination records for some subjects proved unobtainable.
[c] The U.S. cohort was recently vaccinated with a booster dose of MMR vaccine as part of standard military pre-deployment procedures. This booster vaccination was conducted shortly before our samples were drawn, and too recently for effects to be seen in long-term measles immunity measures (antibody and ELISPOT).