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

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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 2,872 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.

Keywords

Measles; Measles Vaccine; Measles Virus; Measles-Mumps-Rubella Vaccine; Continental Population Groups; Sex Factors; Immunity; Cellular; Immunity; Humoral

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 1,000 patients left with permanent deafness or other

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Competing Interests:

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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 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 2,872 children and adults from three separate cohorts across multiple geographical locations across the U.S.

Methods

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 to 41 years), consisting of three independent cohorts: a Rochester cohort (n=1,062); a San Diego cohort (n=1,071); and a U.S. cohort (n=1,058). The recruitment efforts, demographic and clinical characteristics of these cohorts have been previously published [35–37, 41].

Specifically, 1,062 healthy children and young adults, ranging in age from 11 to 22 years, were recruited from Rochester, MN, between 2001–2009 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 1,071 healthy older adolescents and adults (age 19 to 40 years) from military personnel in San Diego, CA, enrolled by the Naval Health Research Center (NHRC) between 2005–2006, 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 1,058 healthy adults with proven MMR vaccine-induced immunity from armed forces (age 19 to 41 years), enrolled between 2010–2011 [41]. Of these, 1,008 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) approved the study, and written informed consent was obtained from each adult subject or parents of subject children.

Measles-neutralizing antibody assay

Measles-specific neutralizing antibody titer measurements were conducted as previously published [12, 43, 44] using a high-throughput plaque-reduction microneutralization (PRMN) assay utilizing a recombinant GFP-measles virus (MV) strain. Subject samples were assayed using six replicates with strict quality control and quality assurance procedures, with both an internal standard serum with known antibody concentration and the international 3rd WHO anti-measles antibody standard [12]. Karber's formula was used to calculate the 50% neutralizing dose (ND_{50}) and transformed into mIU/mL using the international WHO anti-measles antibody standard [43]. The coefficient of variation (CV) for this assay was 5.7%, and the mean limit of detection was 15 mIU/mL [12].

IFNγ ELISPOT

Details of IFN-γ ELISPOT responses to the Edmonston strain of measles virus were measured using Human IFN-γ ELISPOT kits (R&D Systems; Minneapolis, MN) as previously published [36, 44, 45]. ELISPOT results are presented as spot-forming units

(SFU) per 2×10^5 cells. Intraclass correlation coefficients (ICCs) were previously shown to be 0.94 for stimulated and 0.85 for unstimulated values [45].

Statistical methods

Demographics—Select patient characteristics were summarized using counts and percentages for discrete variables and measures of center, variability, and spread for continuous variables.

Principal Component Analysis (PCA) stratification of ancestry—Genetic data from Illumina SNP arrays (San Diego: Human Hap550v3, HumanHap650Yv3; Rochester: HumanOmni1-Quadv1; US: HumanOmni2.5-8v1) were used to assign ancestry groups (African, Caucasian, or Asian) to individuals using the STRUCTURE software [46] and 1000 Genomes data as a reference. These estimates were done within cohort and platform. Further details of this analysis are provided in Supplemental Information.

Across cohorts, 145 subjects were classified as Asian and excluded due to low sample size. Thirty-five subjects of Somali ancestry in the Rochester cohort showed genetic profiles distinct from those of African-Americans and were removed from further analysis.

Ancestry and sex analyses—Outcomes were transformed as follows: IFN-γ ELISPOT values by taking the probit (i.e., normal distribution quantiles) of the difference of mean stimulated and mean unstimulated values; neutralizing antibody titers were transformed by taking the natural log of the ID_{50} (mIU/mL). Potential confounders differed by cohort. To permit data amalgamation, confounders were regressed out and residuals were extracted to be used in subsequent modeling procedures. These residuals were produced separately for each analysis (IFN-γ/neutralizing antibody correlation analysis, ancestry analysis, sex analysis). Details of this analysis are provided in Supplemental Information.

To analyze for correlation between IFN-γ ELISPOT and neutralizing antibody titers in individuals, the Spearman correlation between the adjusted IFNγ and neutralizing antibody traits was calculated. For ancestry and sex analyses, linear models were constructed by regressing the adjusted traits (IFN-γ or neutralizing antibody) of interest onto an indicator for cohort and our variable of interest (sex or genetic ancestry). Time since vaccination and age at enrollment were among the list of potential covariates considered; however, these were not found to be statistically significant covariates across the cohorts, did not affect our main conclusions, and were not finally included as adjusting covariates.

Further details are also provided in Supplemental Information.

Results

1. Genetic classification of subjects

Genome-wide genetic differences between racial populations were captured by a STRUCTURE analysis as described above. This analysis allowed for unbiased racial ancestry categorization, as well as classification of study subjects with unclear racial self-declaration. Major genetic ancestry groups included African-American and Caucasian. One-

hundred forty-five subjects classified as Asian and 35 subjects of Somali background found to be genetically distinct from African-American subjects were removed from further analysis.

2. Overall study demographic information

Demographic data are summarized in Table 1. In total, 2,872 subjects met all inclusion criteria, were successfully genotyped, met QC criteria, and were included in the final analysis. Of these, 780 (27.2%) were female and 2,092 (72.8%) were male. This male overrepresentation is largely due to the San Diego and U.S. cohorts comprising predominantly male military populations. 13.9% of the study subjects (n=400) self-identified as of Hispanic ethnicity, of which 387 were genetically classified as part of the Caucasian ancestry group and 13 as part of the African-American ancestry group. The average age of the study population was 21.4 years (SD=6.14 years), and median age was 22 years. Mean time since last vaccination (when recorded data was available) was 3.98 years.

3. Measles-specific antibody and IFN-γ ELISPOT immune responses to MMR vaccination

Of the total subjects, 54 failed QA/QC for neutralizing antibody titer, and 254 subjects failed to meet QA/QC standards for the IFN-γ ELISPOT assay. The summary statistics for the remaining subjects' immune outcomes unadjusted for confounders are presented in Table 2.

4. Neutralizing antibody and IFN-γ ELISPOT results differ significantly by genetic ancestry

When immune response outcomes were adjusted for covariates and stratified by subjects' genetic ancestry (Table 3) and further adjusted for covariates, significant differences were observed between individuals genetically classified as African-American and those classified as Caucasian. These differences were significant with both measles-specific neutralizing antibody ($p=1.4 \times 10^{-11}$) and measles-specific cellular responses measured by IFN-γ ELISPOT (p=0.0013).

We repeated these analyses excluding the 670 subjects without vaccination record data, and further corrected for time since vaccination and age at enrollment as covariates. While controlling for other covariates, time since vaccination and age at enrollment did not reach statistical significance in any of the cohorts (see Supplemental information for further details). Our results demonstrating higher measles-specific humoral responses in African-Americans than Caucasians remained statistically significant ($p=2.4 \times 10^{-8}$), indicating that our observations of genetic race-based differences in measles vaccine-induced immunity are not a result of inappropriate assumptions made due to lack of full records for our genetically diverse cohorts.

In a single cohort from a region with less racial diversity (Rochester, MN), no differences were seen in measles-specific antibody or IFN-γ ELISPOT immune responses to measles vaccine. This large study (2,872 subjects) provided sufficient statistical power to identify ancestry differences in immune responses to measles vaccine, which were not previously found due to smaller cohort sizes and limited racial diversity. The statistical significance of these ancestry differences in immune responses cannot be explained by the presence or

absence of self-declared Hispanic subsets within each cohort's genetically defined Caucasian group (analysis not shown).

5. Measles vaccine-induced antibody and IFN-γ ELISPOT outcomes show no associations with sex

Neutralizing antibody and IFN-γ ELISPOT measures across cohorts were adjusted for covariates, as decribed in the Methods sections. Unadjusted data stratified by subjects' biological sex is presented in Table 4. No differences were found for either confounder-adjusted neutralizing antibody or IFN-γ ELISPOT (p=0.62) responses in males versus females.

6. Individuals' neutralizing antibody and IFN-γ ELISPOT outcomes are not correlated

Adjusted and transformed measles-neutralizing antibody titers and measles-reactive IFN-γ ELISPOT assay results for each individual subject were plotted against one another as described above, and correlations between these outcomes were assessed. No correlation was found using Spearman rank correlation analysis for immune outcome traits (p=0.32, r=0.02).

Discussion

Several factors have been previously correlated with the development of immune responses after vaccination, including biological sex, heritable genetic factors, and environmental effects. To investigate the effects of biological sex and race on measles immunity after MMR vaccination, we assessed measles-specific humoral (neutralizing antibody, PRMN) and cellular (IFN-γ ELISPOT) immune responses after vaccination in a large, racially diverse cohort across several geographic locations in the US. Instead of relying on self-reported race, which can be erroneous or ambiguous, we were able to estimate genetic ancestry with available genetic data from prior genome-wide association studies of our subjects. The strengths and weaknesses of self-reported race versus genetic ancestry have been highlighted elsewhere [47]. No differences were seen in either humoral or cellular immunity between groups of different biological sex, nor were correlations found between measles-specific IFN-γ ELISPOT and neutralizing antibody assay results – reaffirming that antibody and IFN-γ ELISPOT responses are driven by separate mechanisms. However, ancestry-related differences were found, with African-Americans developing, on average, significantly higher responses than Caucasians for both humoral and cellular immunity. Differences in antibody responses, in particular, were highly significant with a p-value of 1.4×10^{-11}, suggesting that Caucasians and African-Americans respond much differently to measles vaccine.

For many vaccines, including influenza, smallpox, mumps, rubella, and hepatitis A and B vaccines [19, 25, 48], women have been shown to have significantly higher humoral immune responses than men. However, little evidence of sex dependency has been found in humoral responses to some other vaccines, such as yellow fever 17D vaccine [19]. Relatively little information is known about differences in cellular immune responses to measles vaccine associated with biological sex. Previous studies of measles vaccine-induced immune

responses have not resulted in definitive conclusions regarding the relationship of immune responses and biological sex. Female children have been shown to be less likely to seroconvert than males in response to measles vaccine [28, 29], yet some published and well-regarded studies suggest higher measles antibody responses in females than males [29, 30]. Other studies demonstrated no sex-based differences in antibody responses [31, 32]. Our results demonstrate no significant sex-based difference in either measles-specific IFN-γ ELISPOT or neutralizing antibody responses to measles vaccine, suggesting that sex-related factors in measles vaccine responses may be short-term or linked to other demographic factors for which we have corrected. Our combined cohort size exceeds that of any of these previous studies, and likely represents a more racially diverse population than studies reported from Catalonia, Spain [31]; Japan [32]; Israel [30]; or Newfoundland, Canada [29].

Measles vaccine studies have identified both human leukocyte antigen (HLA) and non-HLA-based genetic influences on vaccine-induced measles-specific humoral responses, with these factors accounting for ~30% of the inter-individual heterogeneity in measles antibody responses (reviewed in [49]). This knowledge suggests that genetic ancestry, and therefore racial background, is a significant determinant of immune responses to measles vaccine. Our previous report on the Rochester cohort (764 children and young adults) included an analysis of immune response by race; however, no significant findings were found, likely due to the predominantly Caucasian background of the cohort members [12]. The addition of larger numbers of genetically diverse study subjects in this report increased statistical power and allowed us to observe new significant genetic ancestry differences in measles humoral and cellular responses between subjects of African-American and Caucasian genetic backgrounds (see Table 4). To date, this is the largest and most diverse study in the literature that examines ancestry effects on measles vaccine-induced immunity.

The importance of cell-mediated immunity in measles vaccine-induced protection is not well understood; antibody titers have traditionally been used as the correlate of protection. Low cellular responses to measles vaccine have been demonstrated in the past not to correlate well with low measles antibody responses [12, 44]. Similarly, our results in this study demonstrate a lack of correlation between neutralizing antibody and IFN-γ ELISPOT immune responses to measles vaccine consistent with previous studies, suggesting separate mechanisms for cellular and humoral immunity to measles and possible protection from measles in vaccinees with low antibody titers, as reported in other studies [50].

The strength of this study is the large sample size (2,872 subjects) and the diverse nature of the overall study cohort. These cohort characteristics allowed for the discovery of previously undetected genetic ancestry-related differences in measles-specific immune responses following MMR vaccine. Measurement of humoral immunity by neutralizing antibody rather than enzyme immunoassay (which measures circulating IgG) also provides more accurate measurement of protective immunity than some previous studies [31, 32].

Limitations in this study include an overrepresentation of the male sex (72.8% of total), largely due to the inclusion of two military cohorts, resulting in lower statistical power to detect sex-based immune response differences. Similarly, while numbers of minority subjects are substantially larger in this study than our previous studies, African-Americans

still represent only 11% of the overall cohort. Higher proportions of African-American subjects would substantially increase the statistical power of this study, and inclusion of substantial numbers of other racial groups (Asian, east African, etc.) would extend the generalizability of the study.

Further limitations include the lack of full vaccination records from a subset of our U.S. and San Diego military cohorts. While these subjects demonstrated MMR-induced measles immunity, full vaccination records that included dates for the first and second MMR doses proved impossible to obtain for some subjects. However, our analyses determined that even removing these subjects from our analysis did not change the conclusions of this study. Additional statistical analysis determined that the effects of time since vaccination and age of vaccination/enrollment on our measures of measles immunity were of minimal significance, as consistent with other studies [51]; therefore, we retained these subjects in our final analyses.

Differing vaccine responses between racial groups may pose a challenge for future vaccination efforts. Since an extremely high population immunity rate is necessary to maintain herd immunity, subpopulations of different ethnic groups with lower vaccine-induced immune responses may present a serious impediment to stopping measles outbreaks. Even with high population-wide immunity that exceeds herd immunity levels, pockets of more susceptible people have been shown to allow the spread of measles, resulting in an increased rate of infection [3]. Caucasians (including most Hispanics), who we demonstrate show significantly lower measles vaccine responses than African-Americans, represent nearly 80% of the U.S. population. Lower vaccine-induced immunity to measles in this large population is concerning to U.S. vaccination and eradication efforts.

Future studies in our laboratory will examine the role of cellular immunity in measles vaccine-induced immunity. Additional studies of measles vaccine responses in other genetically distinctive groups should also be conducted, including in Native Americans and those of Asian heritage, both substantial U.S. minority populations. Further studies will also aim to better define the genetic factors behind apparent racial differences in measles vaccine responses, and elucidate their interplay with the biological processes involved in forming and maintaining humoral and cellular immune responses. Such knowledge may be used to design better measles vaccines that are optimally effective across human genetic and ethnic backgrounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Poland is the chair of a Safety Evaluation Committee for novel investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland offers consultative advice on vaccine development to Merck & Co. Inc., CSL Biotherapies, Avianax, Dynavax, Novartis Vaccines and Therapeutics, Emergent Biosolutions, Adjuvance, Microdermis, Seqirus, NewLink, Protein Sciences, GSK Vaccines, and Sanofi Pasteur. Drs. Poland and Ovsyannikova hold two patents related to measles and vaccinia peptide research. Dr. Kennedy has received funding from Merck Research Laboratories to study waning immunity to mumps vaccine.

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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=2,872)
Sex				
Female	444 (45.2%)	240 (27.2%)	96 (9.52%)	780 (27.2%)
Male	538 (54.8%)	642 (72.8%)	912 (90.5%)	2,092 (72.8%)
Race (self-declared)				
White	888 (90.4%)	492 (55.8%)	826 (81.9%)	2,206 (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%)	2,422 (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%)	2,555 (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) *	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) *	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 †	439 †	684
Mean (SD) *	6.66 (2.9)	3.41 (1.72)	0.012 ≠ (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

* Standard Deviation;

Q1, first quartile, Q3, third quartile

† Military subjects had demonstrated MMR-induced measles immunity; complete vaccination records for some subjects proved unobtainable.

[‡]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)

Table 2

Immune outcomes as a result of measles vaccination

	Rochester cohort (n=982)	San Diego cohort (n=882)	U.S. cohort (n=1008)	Total (n=2,872)
Neutralizing antibody titer[a]				
Mean (SD)*	1,336 (1,316)	1,444 (2,017)	1,307 (2,092)	1,359 (1,835)
Q1; Q3	435; 1,769	394; 1,666	346; 1,519	394; 1,683
Median	902	844	766	845
IFN-γ ELISPOT, SFU / 2×10^{5}cells[b]				
Mean (SD)*	39 (39.1)	14.9 (18.5)	21.4 (27.8)	25.1 (31.4)
Q1; Q3	8.33; 57.8	4; 21	7; 28.7	6; 32.7
Median	27	9.67	14.7	15

[a] Neutralizing antibody titer (mIU/mL), measured by the plaque reduction microneutralization assays (PRMN);

[b] IFN-γ ELISPOT spot forming units (SFU), measured per 2 × 10^5 PBMCs (mean of measles virus-specific response, measured in triplicate wells, minus the mean of unstimulated response, also measured in triplicate wells)

* Standard Deviation;

Q1, first quartile, Q3, third quartile

Table 3

Analysis of measles-specific immune responses to MMR vaccine by genetic ancestry, separated by cohort.

	Rochester cohort		San Diego cohort		U.S. cohort		Total	
	African-American (n=40)	**Caucasian (n=942)**	**African-American (n=164)**	**Caucasian (n=718)**	**African-American (n=113)**	**Caucasian (n=895)**	**African-American (n=317)**	**Caucasian (n=2,555)**
Neutralizing Ab titer, mIU/mL[a]								
Mean (SD)[*]	1,886 (2,179)	1,313 (1,263)	2,257 (3,376)	1,257 (1,486)	1,856 (2,051)	1,237 (2,088)	2,065 (2,821)	1,271 (1,652)
Median (IQR)[†]	894 (449; 2,593)	902 (435; 1,751)	1,224 (552; 2,637)	770 (372; 1,526)	1,238 (672; 2,598)	702 (334; 1,404)	1,180 (550; 2,632)	803 (383; 1,607)
Adjusted p-value	0.703		7.1×10^{-8}		2.41×10^{-6}		1.41×10^{-11}	
IFN-γ ELISPOT response (SFU / 5×10^5 PBMCs)[b]								
Mean (SD)[*]	49.5 (39.8)	38.6 (39)	18.7 (19.3)	14 (18.2)	24 (23.9)	21 (28.2)	24.4 (26)	25.2 (31.4)
Median (IQR)[†]	45 (21.3; 71.5)	26 (8.33; 57)	12.3 (6; 23.7)	9.33 (3.75; 20.6)	15.7 (8.58; 34.3)	14.3 (7; 27.8)	15 (7; 34.5)	15 (6;32.7)
Adjusted p-value	0.64		0.005		0.094		0.0013	

[a] Neutralizing antibody titer (mIU/mL), measured by the plaque reduction microneutralization assays (PRMN);

[b] IFN-γ ELISPOT spot forming units (SFU), measured per 2×10^5 PBMCs (mean of measles virus-specific response, measured in triplicate wells, minus the mean of unstimulated response, also measured in triplicate wells)

[*] Standard Deviation

[†] Interquartile Range

Table 4

Measles antibody and cellular immunity measures after MMR vaccination, according to subject biological sex

Immune measure	Male subjects (n=2,092) median (IQR)[†]	Female subjects (n=780) median (IQR)[†]	Adjusted p-value
Antibody titer, mIU/mL[a]	834 (389–1,659)	862 (419–1,737)	0.89
IFN-γ ELISPOT, SFU / 2×10^5PBMCs[b]	14 (⁻5.67–30.7)	18 (⁻7.33–42.1)	0.623

[a] Neutralizing antibody titer (mIU/mL), measured by the plaque reduction microneutralization assays (PRMN);

[b] IFN-γ ELISPOT spot forming units (SFU), measured per 2×10^5 PBMCs (mean of measles virus-specific response, measured in triplicate wells, minus the mean of unstimulated response, also measured in triplicate wells)

[†] Interquartile Range