The Journal of Infectious Diseases

BRIEF REPORT

Persistence of Maternal Anti-Rotavirus Immunoglobulin G in the Post–Rotavirus Vaccine Era

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To assess whether titers of anti-rotavirus immunoglobulin G persist during the post–rotavirus vaccine era, the Pediatric Respiratory and Enteric Virus Acquisition and Immunogenesis Longitudinal (PREVAIL) Cohort analyzed serum samples collected from Cincinnati-area mothers and young infants in 2017–2018. Rotavirus-specific antibodies continue to be transferred from US mothers to their offspring in the post–rotavirus vaccine era, despite dramatic decreases in childhood rotavirus gastroenteritis.

Keywords. rotavirus; vaccine; cohort; IgG; immunity; maternal antibodies.

After the US introduction of rotavirus vaccines in 2006, national rotavirus vaccine coverage among eligible US infants born in 2016 and 2017 was 75.3% (95% confidence interval, 74.1%–76.5%) [1]. A corresponding, precipitous decrease in medically attended childhood rotavirus gastroenteritis incidence has been observed during the post–rotavirus vaccine era [2]. Diminished rotavirus incidence in children has also been associated with concomitant reductions in rotavirus-associated medical visits among adults [3, 4]. Despite these vaccine-associated reductions in severe rotavirus gastroenteritis outcomes, rotavirus vaccines do not offer sterilizing immunity and rotavirus community transmission has been interrupted but not extinguished [5].

Humoral immunity matures over repeated rotavirus exposures, eventually leading to asymptomatic or paucisymptomatic infections that are not captured by medical event–based surveillance [6]. Following lifetime exposures to rotavirus, maternal pathogen-specific immunoglobulin (Ig) G antibodies are typically transferred from mother to child before birth and are present in neonatal blood [7]. Maternal anti-rotavirus IgG protects neonates and unvaccinated infants during the period of immune system maturation and can be protective during this time of high risk for experiencing severe rotavirus gastroenteritis. Despite this naturally acquired passive immunity, maternal anti-rotavirus IgG has also been shown to inhibit vaccine-induced immune responses from oral, live, attenuated rotavirus vaccines [8, 9].

Post–rotavirus vaccine era US maternal anti-rotavirus IgG antibody levels are currently unknown. We hypothesize that these maternal anti-rotavirus IgG levels remain robust, more than a decade after the commencement of the US rotavirus vaccination program, owing to continued exposures. This topic is deserving of investigation because, alternatively, if these antibody levels have declined, the dynamics of anti-rotavirus immunologic transfer from mothers to infants may have changed. The objective of the current study was to measure US maternal anti-rotavirus IgG antibody levels during the post–rotavirus vaccine era and to explain how these findings could affect rotavirus epidemiology and vaccine performance.

METHODS

The Pediatric Respiratory and Enteric Virus Acquisition and Immunogenesis Longitudinal (PREVAIL) Cohort is a longitudinal birth cohort study of mother-infant pairs around Cincinnati, Ohio. Institutional review board approvals were obtained from the US Centers for Disease Control and Prevention and from the study site. The PREVAIL Cohort includes healthy mothers enrolled in the third trimester of pregnancy and their offspring, who are actively followed up with routine specimen and epidemiologic data collection. Further methodologic details have been reported by Morrow et al [10]. To assess titers of US maternal/infant anti-rotavirus IgG during the post–rotavirus vaccine era, the PREVAIL Cohort analyzed serum samples collected from Cincinnati-area mothers in 2017–2018 during their third trimesters of pregnancy. Maternal anti-rotavirus IgG results were compared with results from corresponding cord blood samples obtained at delivery and from infants at 6–8 weeks of age, before the recommended age of first rotavirus vaccination [11]. Pearson correlation coefficients were calculated.

Anti-rotavirus IgG results were compared across maternal variables, including race, age, health insurance status, partner cohabitation status, number of previous pregnancies, number of previous live births, number of children <5 years old in the household, and number of children <18 years old in the household. Results were also compared across the infant variables of breastfeeding status (ever vs none) and infant age. Kruskal-Wallis or Wilcoxon rank sum tests were used.

Received 13 August 2020; editorial decision 10 November 2020; accepted 16 November 2020; published online November 19, 2020.

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The Journal of Infectious Diseases® 2021;224:133–6

DOI: 10.1093/infdis/jiaa715

As a secondary objective, we assessed whether antibodies appear to have changed from the pre– to post–rotavirus vaccine eras. We compared 2017–2018 PREVAIL Cohort anti-rotavirus IgG results with those from US infants identified from a phase II clinical trial (V260-002) conducted by Merck & Co in 1993–1994 [12], a randomized, controlled trial (RCT). This RCT was a randomized, double-blinded, placebo-controlled trial of a quadrivalent rotavirus vaccine. RCT specimens were collected from healthy infants at 10 US study sites. Serum anti-rotavirus IgG results analyzed here were not published in the original report of the phase II clinical trial by Clark et al [12]. Although the RCT enrolled infants <6 months of age, we analyzed prevaccine/preplacebo samples from a subset of those aged 1–3 months, for better comparability with the PREVAIL Cohort subject ages. The RCT data received for this analysis did not include sociodemographic variables other than age, although approximately 10% of the RCT subjects were reported to be of nonwhite race [12]. A memorandum of agreement between study investigators and Merck & Co was signed permitting this use of data.

Serum anti-rotavirus IgG levels for both studies were measured with enzyme-linked immunosorbent assay at Cincinnati Children's Hospital Medical Center in the Laboratory for Specialized Clinical Studies. While there were likely minor testing differences over time between the 2 studies, the same laboratory protocol [13] was used for both the 2017–2018 cohort and the 1993–1994 RCT, the same reference standard and reagent qualifications were used in both studies, and efforts were made to maintain performance consistency to the extent possible.

RESULTS

From 265 mothers enrolled in the PREVAIL Cohort, 210 (79%) corresponding infants had blood samples collected between 1 and 3 months of age (median, 46 days; range, 37–83 days), before receipt of rotavirus vaccination. Approximately half (47%) of mothers were nonwhite race, with a median age of 30 years (range 18–45 years). Of the 210 matched maternal-infant blood samples, 186 (89%) were further matched to a cord blood sample.

Infant anti-rotavirus IgG titers were normally distributed on the log scale and were positively correlated with maternal anti-rotavirus IgG titers ($P < .001$; $r = .86$). Cohort anti-rotavirus IgG geometric mean titers (GMTs) for maternal, cord, and infant blood were 240, 341, and 121 U/mL, respectively. (Figure 1) Weekly testing demonstrated that just 1 infant had a wild-type rotavirus infection (<1%), a G12[P8] strain. This infant, infected at 4 months of age, had opportunity to receive just 1 dose

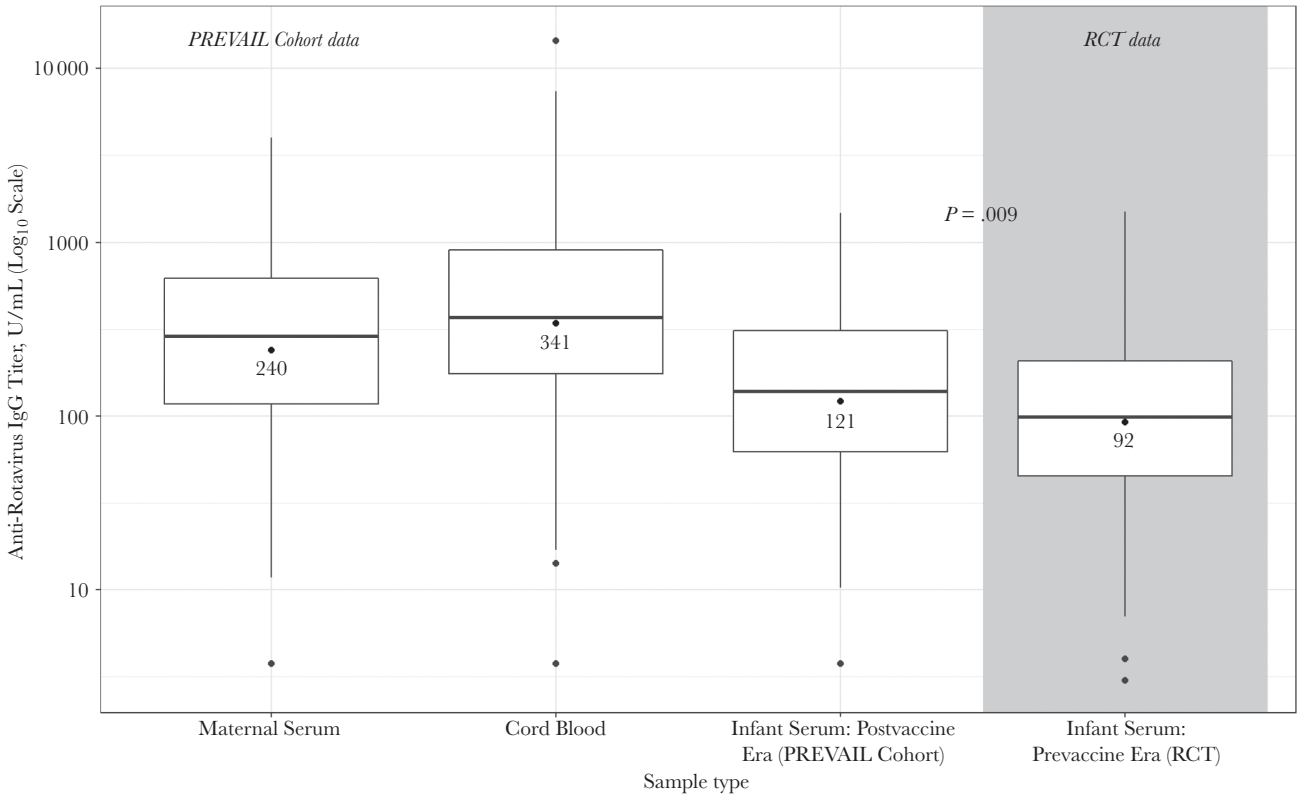

Figure 1. Anti-rotavirus immunoglobulin (Ig) GMTs titers for maternal serum, cord blood, and pre– and post–rotavirus vaccine era infant serum samples. Abbreviation: PREVAIL, Pediatric Respiratory and Enteric Virus Acquisition and Immunogenesis Longitudinal; RCT, randomized controlled trial.

of rotavirus vaccine before infection and did not seek medical care (maternal, cord, and infant blood IgG titers, 111, 77, and 46 U/mL, respectively).

No statistical difference in maternal anti-rotavirus IgG titers was observed by maternal age ($P = .15$). The only statistically significant finding was that anti-rotavirus IgG results for maternal and cord blood samples differed by race. Nonwhite mothers had higher GMTs than white mothers (342 and 175 U/mL, respectively; $P = .001$). Similarly, racial differences in anti-rotavirus IgG results were observed for cord blood (447 and 266 U/mL, respectively; $P = .02$), but infant blood results did not differ significantly between nonwhite and white infants (143 and 104 U/mL, respectively; $P = .16$). Infant serum anti-rotavirus IgG results from the 1993–1994 RCT pre-rotavirus vaccine era (GMT, 92 U/mL) were significantly lower than those from unvaccinated, similarly aged infants in the 2017–2018 PREVAIL Cohort post–rotavirus vaccine era ($P = .009$). (Figure 1)

DISCUSSION

The influence of anti-rotavirus IgG in conferring protection against severe rotavirus gastroenteritis has historically been considered less important than anti-rotavirus IgA titers. However, IgA is imperfectly correlated with protection [14], and recent in vivo experiments indicate a prominent intracellular role of VP6-specific anti-rotavirus IgG as part of the multifaceted approach to efficiently block rotavirus replication [15].

Our results indicate that these immunologically important rotavirus-specific IgG antibodies continue to be transferred from US mothers to their offspring during the post–rotavirus vaccine era, despite dramatic decreases in severe and medically attended rotavirus gastroenteritis. The persistence of passive maternal antibody transfer in 2017–2018 suggests that rotavirus exposure and humoral immunity maturation in US mothers continues to occur.

Anti-rotavirus antibodies inhibit efficacious immunologic take from oral, live-attenuated rotavirus vaccines in low- and middle-income countries [16]. The United States has observed sustained levels of good rotavirus vaccine performance [17], an indication that antibody-mediated interference is not occurring appreciably among our cohort.

Anti-rotavirus IgG titers differed significantly by race for maternal and cord blood, but the lack of a correlate of protection makes the clinical interpretation of these antibody results challenging. We suspect that extrinsic factors, such as the time since last exposure and the force and severity of previous infections, contribute to the observed differences in maternal and cord blood results by race.

No other sociodemographic variable was significantly different. Of note, our analyses did not find an association between anti-rotavirus IgG titers and previous live births or the number of children living in the household. Although young infants or children in the household could be a vehicle for rotavirus exposures and strengthen anti-rotavirus IgG titers among mothers, this lack of significance may indicate that such rotavirus exposures occur within the larger community as well.

When PREVAIL Cohort results were compared with the RCT results from the early 1990s, we unexpectedly found that median anti-rotavirus IgG titers during the post–rotavirus vaccine era were higher than those observed during the pre-vaccine era. While the meaning of that finding warrants further investigation, we could not precisely define infant ages from the RCT as we did for our cohort. This, along with differences in racial distributions between our cohort and the RCT, suggest the possibility that sociodemographic differences in these independent studies could affect their comparison. Although measures were taken to achieve consistency in laboratory test performance between the 1993–1994 and 2017–2018 serologic studies, there are likely factors that could not be controlled across this time period.

In conclusion, we found that, in the post–rotavirus vaccine era, US mothers still express antibodies produced from immunologic challenges against rotavirus, and these maternal anti-rotavirus IgG antibodies continue to be successfully passed to their infants. This advances our understanding that US infants may continue to be protected against rotavirus gastroenteritis by naturally acquired passive immunity, more than a decade after implementation of the US rotavirus vaccination program.

Notes

Acknowledgments. The authors recognize the participation of all mothers and children enrolled in the Pediatric Respiratory and Enteric Virus Acquisition and Immunogenesis Longitudinal (PREVAIL) Cohort.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

Financial support. This work was supported by the US Centers for Disease Control and Prevention (cooperative agreement IP16-004).

Potential conflicts of interest. M. G. G, is an employee of Merck Sharp & Dohme, a subsidiary of Merck & Co. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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