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MAJOR ARTICLE

Infectivity and Immunogenicity of Live-Attenuated Respiratory Syncytial Virus Vaccines in Human Immunodeficiency Virus–Exposed Uninfected Children

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Background. Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory illness among young children. Human immunodeficiency virus (HIV)–exposed, uninfected (HEU) children experience a higher burden of RSV disease and have immune abnormalities that may influence their responses to live-attenuated RSV vaccines.

Methods. In a pooled analysis of clinical trials of 7 live-attenuated, intranasal RSV vaccines conducted by the IMPAACT Network among children 6 to <25 months of age with serum RSV-neutralizing titers of <1:40, the infectivity and immunogenicity of these vaccines were compared among HEU and HIV-unexposed, uninfected (HUU) children. Nasal washes were collected during the first 28 days after vaccination. Serum RSV-neutralizing and anti-RSV F glycoprotein immunoglobulin G (IgG) antibodies were measured prior to and 56 days after vaccination, and before and after the following winter season.

Results. Of 156 children, 90 (58%) were HUU and 66 (42%) were HEU. Seventy-six (84%) HUU and 63 (95%) HEU participants were infected with vaccine (shed vaccine virus and/or had a ≥4-fold rise in serum RSV antibodies at 56 days after vaccination). HUU children had higher serum RSV-neutralizing and anti-RSV F IgG titers prior to vaccination. Compared to HEU children, lower percentages of HUU children had ≥4-fold rises in RSV-neutralizing (67% vs 88%) and anti-RSV F IgG (70% vs 89%) titers at 56 days after vaccination.

Conclusions. Live-attenuated RSV vaccines are highly immunogenic in HEU children. Given their increased burden of RSV disease and higher early childhood mortality in some settings, HEU children should be prioritized for vaccination against RSV as these vaccines become available.

Keywords. antibody interference; live-attenuated RSV vaccine; maternal HIV infection; transplacental antibody transfer; vaccine-elicited immunogenicity.

Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory illness (ALRI) among infants and young children. Globally, it is estimated that RSV caused 33 million ALRI episodes, 3.6 million hospital admissions, and >100 000 deaths among children <5 years of age in 2019 [1]. Fortunately, RSV vaccine development has accelerated over the past decade, with several vaccine candidates currently being evaluated for use in children [2]. A bivalent RSV prefusion F protein–based vaccine for pregnant women and an extended half-life monoclonal antibody for infants were recently approved by the United States Food and Drug Administration for the passive protection against RSV disease among infants <6 months of age [3, 4]. However, there remains an urgent need for a pediatric vaccine that effectively induces active immunity to RSV and prevents RSV disease among infants and children >6 months of age, who account for approximately 50% of RSV-associated child deaths globally [5].

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Approximately 1.2 million infants are born to women with human immunodeficiency virus (HIV) each year, and >1 million of these infants do not acquire HIV [6]. Despite the absence of HIV infection, these HIV-exposed, uninfected (HEU) children have higher early childhood morbidity and mortality from infections, including ALRI caused by RSV (RSV-ALRI) [7–10]. In a study conducted in South Africa, HEU infants had a 40% higher incidence and more than twice the odds of death from RSV-ALRI during the first 6 months of life than HIV-unexposed, uninfected (HUU) infants [10]. Although multiple factors are likely to contribute to their higher burden of infections, HEU children have a broad range of immune abnormalities postulated to be related to in utero exposure to HIV or antiretroviral medications [11]. In particular, compared to HUU children, HEU children have differences in lymphocyte subsets, have lower neutrophil counts and altered T-lymphocyte function, and acquire lower titers of maternal antibodies specific to several common pathogens [12–17]. These differences in cellular and humoral immunity among HUU and HEU children could have important implications for the effectiveness of vaccines currently in development for the prevention of RSV disease during early childhood.

In this study, pooled analyses of data from phase 1 clinical trials that evaluated 7 live-attenuated intranasal RSV vaccines in children with serum RSV-neutralizing titers of <1:40 were performed. These pooled data were used to compare the infectivity and immunogenicity of these vaccines among HUU and HEU children.

METHODS

Study Design and Analysis Population

This was a retrospective analysis of data from 6 double-blind, randomized, placebo-controlled clinical trials that evaluated the safety, infectivity, and immunogenicity of 7 recombinant live-attenuated RSV vaccines (Supplementary Table 1) [18–23]. Studies were conducted at International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network sites in the United States (Supplementary Table 2) and the Johns Hopkins Center for Immunization Research (Baltimore, Maryland) between October 2013 and September 2020. Although no efforts were made to specifically recruit HEU children into these clinical trials, a high proportion of enrolled children were HEU because of the study populations of other trials being conducted by these IMPAACT Network sites. Eligible participants were 6 to <25 months of age, healthy, without lung disease, and had RSV 60% plaque neutralizing serum antibody titers of <1:40 at screening. In each study, participants were randomly assigned 2:1 to receive a single dose of RSV vaccine or placebo intranasally (day 0). For each of these trials, recruitment occurred outside the time period during which RSV typically circulates (between 1 April and 14 October for most sites), and study participants were followed through the subsequent winter season (RSV surveillance period; between 1 November and 31 March for most sites). Nasal washes were collected on days 3, 5, 7, 10, 12, 14, 17, and 28 (±1 day) relative to vaccination to assess vaccine infectivity, including the magnitude and duration of vaccine virus shedding; in 2 studies (P1114 and IMPAACT 2000), nasal washes were also collected on days 19 and 21. RSV serum antibody titers were measured prior to vaccination, 56 days after vaccination, and before and after the RSV surveillance period. During the RSV surveillance period, a study visit involving a clinical assessment and nasal wash ("illness visit") was performed for infants who developed medically attended acute respiratory illness, identified based on the presence of fever, symptoms of upper or lower respiratory tract infection, or a diagnosis of acute otitis media. The population analyzed included HUU and HEU children who were randomized to and received an intranasal RSV vaccine. Participants who were randomized to placebo, randomized to vaccine but did not receive the study product, or who had no study visit after vaccine receipt were excluded. No participants were enrolled in >1 study.

Patient Consent Statement

Written informed consent was obtained from a legal guardian for all study participants. These studies were approved by each site's institutional review board, conducted in accordance with the principles of the Declaration of Helsinki and Standards of Good Clinical Practice as defined by the International Conference on Harmonisation, and monitored by the independent data safety and monitoring board of the Division of Clinical Research at the National Institute of Allergy and Infectious Diseases.

Laboratory Methods

To evaluate kinetics of vaccine virus shedding, nasal washes collected during the first 28 days after vaccination were evaluated by immunoplaque assay on Vero cells and by a reverse-transcription quantitative polymerase chain reaction (qPCR) assay specific to the RSV matrix gene, as previously described [24]. Negative cultures and qPCR measurements were assigned values equal to the lower limits of detection (LLD) for these assays (0.5 $\log_{10}$ plaque-forming units [PFU]/mL and 1.7 $\log_{10}$ copies/mL, respectively). Nasal washes collected prior to vaccination and at illness visits conducted during the RSV surveillance period were tested for RSV by qPCR to identify wild-type RSV infections; these samples were also tested for common adventitious agents by multiplex reverse-transcription qPCR (Respiratory Pathogens 21 Assay, Fast-Track Diagnostics, Esch-sur-Alzette, Luxembourg). Serum RSV-neutralizing antibodies (RSV-$PRNT_{60}$) were measured using a complement-enhanced 60% plaque reduction neutralization assay [25]. Serum immunoglobulin G antibodies to the RSV F glycoprotein (anti-RSV F IgG) were measured using an enzyme-linked

immunosorbent assay (ELISA) based on the RSV F glycoprotein derived from strain A2, as previously described [24]. The LLD was 1:10 for the RSV-PRNT$_{60}$ assay and 1:50 for the anti-RSV F IgG ELISA. Antibody titers were analyzed on the reciprocal $\log_2$ scale. For numerical summaries, measurements below the LLD for the RSV-PRNT$_{60}$ and anti-RSV F IgG assays were assigned reciprocal $\log_2$ titers equal to half the LLD (2.3 and 4.6, respectively).

Statistical Methods

Participants were considered infected with vaccine if they had a vaccine virus identified by culture or qPCR in a nasal wash up to 28 days after vaccine receipt and/or a ≥4-fold increase in serum RSV-PRNT$_{60}$ and/or anti-RSV F IgG antibodies between prior to and 56 days after vaccination. The kinetics of viral shedding and proportions of participants infected by study vaccine were summarized by vaccine and HIV exposure status. To account for serum antibody titers below the LLD, a linear regression model for censored data was fit to compare antibody titers by HIV exposure status prior to and 56 days after vaccination [26]. All models were adjusted for age, sex, and the RSV vaccine received; models of antibody titers from 56 days after vaccination were also adjusted for the antibody titer prior to vaccination. Exposure to wild-type RSV during the RSV surveillance period was evaluated through the identification of symptomatic (RSV detected by culture or qPCR in a nasal wash performed as part of an illness visit) or asymptomatic (≥4-fold increase in serum antibody titers as measured by RSV-PRNT$_{60}$ or anti-RSV F IgG ELISA between prior to and after the RSV surveillance period) infection. A significance level of 5% was used to highlight results, with no adjustments made for multiple testing. Analyses were conducted in SAS version 9.4 software.

RESULTS

Participant Characteristics

Of the 160 children randomized to receive an RSV vaccine across the 6 trials, 4 were excluded from these analyses, including 2 children who did not receive a vaccine and 2 children who received a vaccine but did not have subsequent study visits. Among the 156 children comprising the analysis population, 90 (58%) were HUU and 66 (42%) were HEU. Baseline characteristics of the analysis population are shown in Table 1 (overall) and Supplementary Table 3 (by study). Median (interquartile range [IQR]) age at enrollment was 11 (7–15) months among HUU children and 11 (8–15) months among HEU children. Lower percentages of HUU children were male (52% vs 62%), Black or African American (20% vs 47%), and Hispanic or Latino (39% vs 48%) compared to HEU children. Participant accrual by study, year, site, and HIV exposure status is shown in Supplementary Table 2.

Table 1. Participant Characteristics by Human Immunodeficiency Virus Exposure Status

Characteristic	Overall (n = 156)	HUU (n = 90)	HEU (n = 66)
Age, mo, median (IQR)	11 (7–15)	11 (7–15)	11 (8–15)
Sex			
Female	68 (44)	43 (48)	25 (38)
Male	88 (56)	47 (52)	41 (62)
Race			
Black or African American	49 (31)	18 (20)	31 (47)
White	82 (53)	56 (62)	26 (39)
Other	17 (11)	11 (12)	6 (9)
Unknown	8 (5)	5 (6)	3 (5)
Ethnicity			
Hispanic or Latino	67 (43)	35 (39)	32 (48)
Not Hispanic or Latino	87 (56)	54 (60)	33 (50)
Unknown	2 (1)	1 (1)	1 (2)
Vaccine candidate (study)			
cps2 (P1114)	34 (22)	18 (20)	16 (24)
ΔM2-2 (IMPAACT 2000)	20 (13)	12 (13)	8 (12)
ΔM2-2/1030s (IMPAACT 2011)	20 (13)	6 (7)	14 (21)
cp ΔM2-2 (IMPAACT 2012)	11 (7)	8 (9)	3 (5)
D46/NS2 (IMPAACT 2013)	21 (13)	12 (13)	9 (14)
ΔNS2 (IMPAACT 2018)	25 (16)	17 (19)	8 (12)
276 (IMPAACT 2018)	25 (16)	17 (19)	8 (12)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: HEU, human immunodeficiency virus–exposed, uninfected; HUU, human immunodeficiency virus–unexposed, uninfected; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trials; IQR, interquartile range.

Vaccine Infectivity

Higher infectivity of live-attenuated virus vaccines may enhance immunogenicity as a result of vaccine virus replication. Seventy-six (84%) HUU and 63 (95%) HEU study participants met the definition of having been infected by vaccine virus. Vaccine virus shedding during the 28 days after vaccination is summarized by HIV exposure status in Figure 1 (overall analysis population) and Supplementary Table 4 (by study). Peak vaccine virus titers were determined for each participant independent of study day. Among 115 (74%) children with at least 1 positive culture, the median (IQR) peak vaccine virus titer by immunoplaque assay was 3.4 (2.6–4.2) $\log_{10}$ PFU/mL in HUU children and 3.1 (2.4–3.6) $\log_{10}$ PFU/mL in HEU children. Vaccine shedding was detectable in nasal washes by immunoplaque assay for a median duration (IQR) of 6 (3–8) days among 66 HUU and 6 (4–8) days among 49 HEU children. Among 131 (84%) children from whom vaccine virus was detected by qPCR, the median (IQR) peak qPCR values were 5.8 (4.4–6.4) $\log_{10}$ copies/mL in HUU children and 5.1 (3.9–5.9) $\log_{10}$ copies/mL in HEU children. When determined using qPCR, viral shedding was detected for a median (IQR) of 10 (8–12) days among 71 HUU children and 8 (3.5–11.5) days among 60 HEU children.

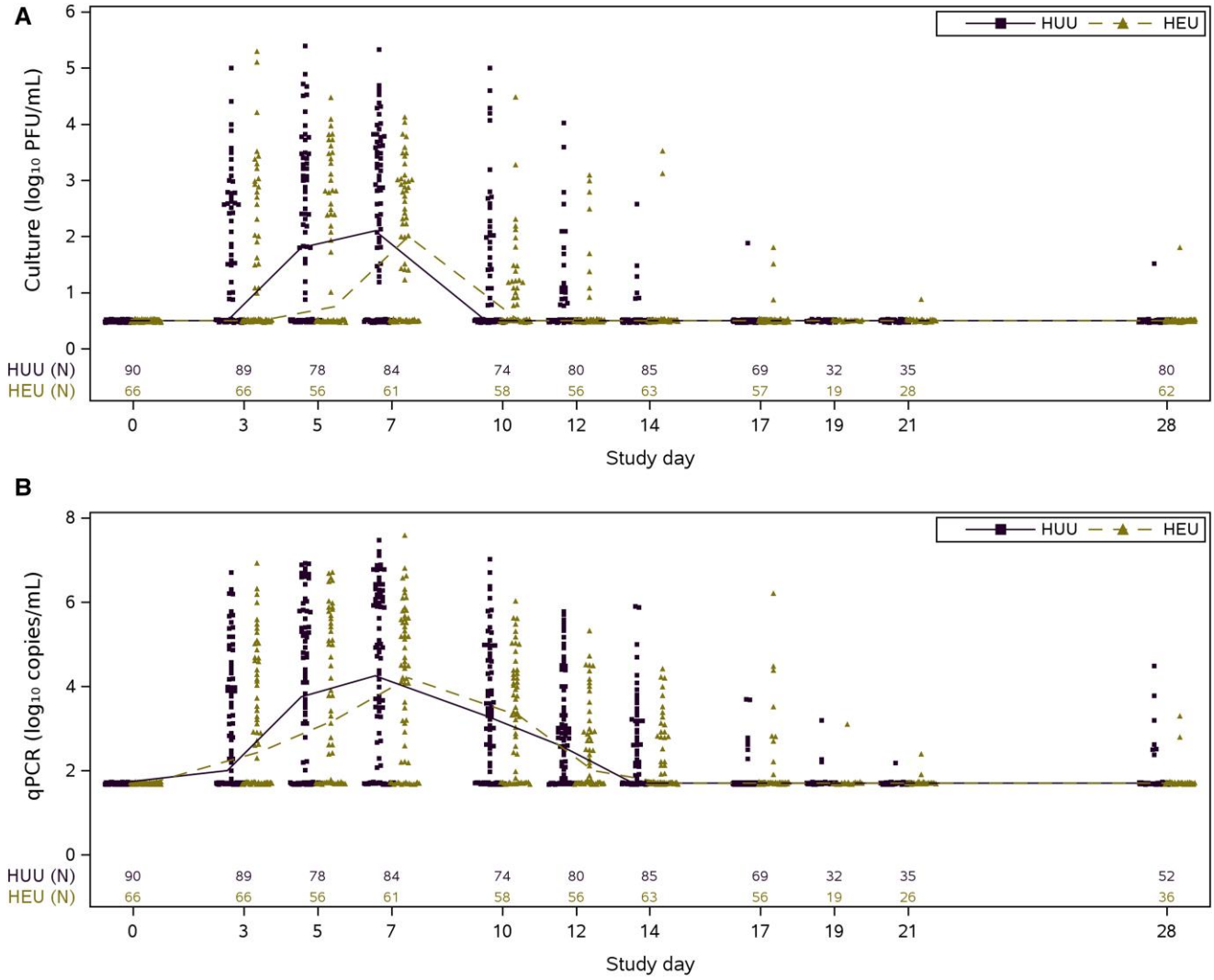

Figure 1. Kinetics of vaccine virus shedding in nasal wash specimens, by human immunodeficiency virus (HIV) exposure status. Dot plots depict vaccine virus titers in nasal washes collected from HIV-unexposed, uninfected (HUU) and HIV-exposed, uninfected (HEU) study participants during the 28 days after intranasal vaccination. Each point represents a vaccine virus titer measurement by immunoplaque assay (culture, *A*) or quantitative polymerase chain reaction (qPCR, *B*) from a single participant for nasal wash samples collected at indicated timepoints (with windows of ± 1 day). Lines depict the median virus shedding at each timepoint, including samples in which shedding was not identified, and are shown by HIV exposure status. Negative cultures and qPCR measurements were assigned values equal to the lower limits of detection for these assays (0.5 $\log_{10}$ plaque-forming units [PFU]/mL and 1.7 $\log_{10}$ copies/mL, respectively). Horizontal jittering was applied to data points to show the large number of participants with values below the limit of detection. Only 2 studies (P1114 and IMPAACT 2000) measured viral shedding on days 19 and 21.

Vaccine Immunogenicity

RSV serum antibody titers measured prior to and 56 days after vaccination are shown by HIV exposure status in the overall analysis population and by study in Figure 2. Lower percentages of HUU children than HEU children had serum RSV-PRNT$_{60}$ (62% vs 88%) and anti-RSV F IgG antibodies (19% vs 30%) prior to vaccination that were below the LLD (Supplementary Table 5). Specifically, HUU children had baseline RSV-PRNT$_{60}$ titers (expressed on the reciprocal $\log_2$ scale) that were, on average, 0.72 (95% confidence interval [CI], .30–1.13) higher than those observed among HEU children adjusting for age, sex, and vaccine candidate (Table 2). Similarly, in adjusted analyses, baseline anti-RSV F IgG titers were, on average, 1.13 (95% CI, .36–1.90) higher among HUU children than among HEU children. In contrast, serum antibody titers after vaccination were generally lower among HUU children than among HEU children. At 56 days after vaccination, serum RSV-PRNT$_{60}$ (adjusted mean difference: −0.55 [95% CI, −1.03 to −.07]) and anti-RSV F IgG (adjusted mean difference: −0.82 [95% CI, −1.51 to −.14]) titers were lower for HUU children compared to HEU children adjusting for age, sex, vaccine candidate, and the antibody titer prior to vaccination (Table 2). HUU children generally had smaller increases in both serum RSV-PRNT$_{60}$ and anti-RSV F IgG antibodies after vaccination

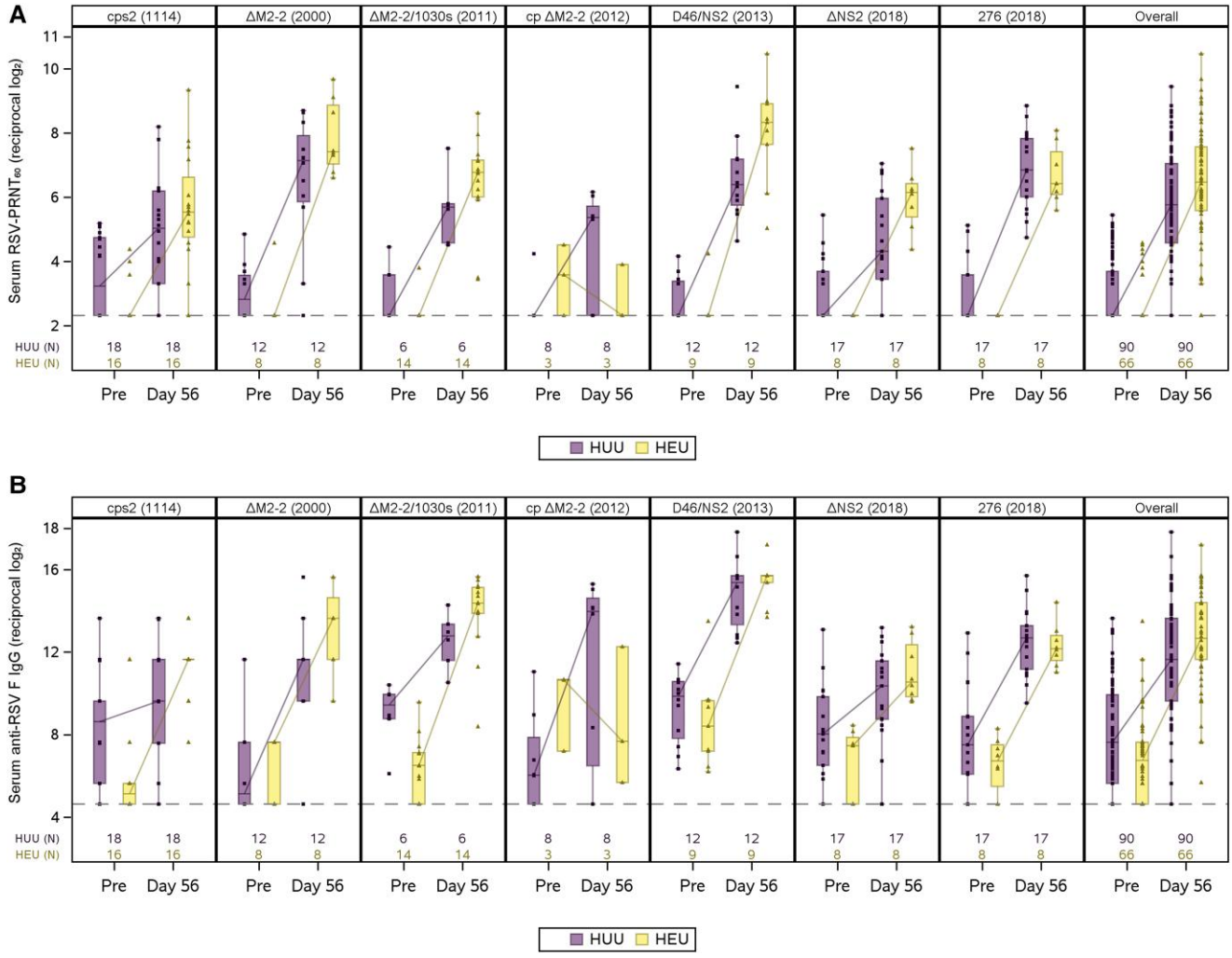

Figure 2. Serum respiratory syncytial virus (RSV) antibodies before and after vaccination, by human immunodeficiency virus (HIV) exposure status. Box and whisker plots depict antibody titers by RSV 60% plaque reduction neutralization assay (*A*) and anti-RSV F immunoglobulin G enzyme-linked immunosorbent assay (*B*), prior to ("Pre") and 56 days after vaccination ("Day 56") by HIV exposure status and study. Vaccine candidates (abbreviated) and IMPAACT study numbers (in brackets) are indicated above each plot. Antibody titers are shown on the reciprocal $\log_2$ scale. Values below the lower limits of detection for these assays are indicated by dashed lines. Median values prior to and after vaccination are joined by lines. Abbreviations: HEU, human immunodeficiency virus–exposed, uninfected; HUU, human immunodeficiency virus–unexposed, uninfected; IgG, immunoglobulin G; RSV-PRNT$_{60}$, serum respiratory syncytial virus 60% plaque reduction neutralizing titers.

than HEU children in both the overall analysis population and by study (Supplementary Figure 1). Overall, lower percentages of HUU children than HEU children had ≥4-fold increases in serum RSV-PRNT$_{60}$ (67% vs 88%) and anti-RSV F IgG antibodies (70% vs 89%) between prior to and 56 days after vaccination. Similar results were obtained when analyses were limited to children with serum RSV-PRNT$_{60}$ or anti-RSV F IgG antibodies below the LLD prior to vaccination (Supplementary Table 6).

Differences in vaccine-elicited antibody responses were also observed based on serum antibody titers prior to vaccination irrespective of HIV exposure status. Compared to children with detectable antibody titers at baseline, a higher percentage of children with undetectable titers had a ≥4-fold increase in serum RSV-PRNT$_{60}$ (89% vs 41%) and anti-RSV F IgG (95% vs 73%) between prior to and 56 days after vaccination.

RSV Detections and Antibody Titers During the RSV Surveillance Period

The prevalence of symptomatic or asymptomatic wild-type RSV infection during the RSV surveillance period is summarized in Supplementary Table 7. Among children with complete data during the surveillance period, 25 of 60 (42%) HEU children and 32 of 86 (37%) HUU children had evidence of wild-type RSV infection. The prevalence of wild-type RSV infection was lower among children who had ≥4-fold increases in serum RSV-PRNT$_{60}$ (30% vs 65%) or anti-RSV F IgG antibodies (32% vs 65%) between prior to and 56 days after

Table 2. Serum Respiratory Syncytial Virus Antibodies Prior to and 56 Days After Vaccination by Human Immunodeficiency Virus Exposure Status

Timepoint	HUU (n = 90) Median (IQR)	HEU (n = 66) Median (IQR)[a]	Mean (95% CI) Difference in Antibody Titers (HUU – HEU)[b]	*P* Value
Prevaccination				
RSV-PRNT$_{60}$	<LLD (<LLD, 3.7)	<LLD (<LLD, <LLD)	0.72 (.30–1.13)	<.001
Anti-RSV F IgG	7.6 (5.6–9.9)	6.8 (<LLD–7.6)	1.13 (.36–1.90)	.004
Day 56				
RSV-PRNT$_{60}$	5.8 (4.6–7.1)	6.5 (5.6–7.6)	−0.55 (−1.03 to −.07)	.026
Anti-RSV F IgG	11.6 (9.6–13.6)	12.7 (11.6–14.4)	−0.82 (−1.51 to −.14)	.018

Anti-RSV F IgG determined by enzyme-linked immunosorbent assay (ELISA).

Abbreviations: Anti-RSV F IgG, serum immunoglobulin G antibodies to the RSV F glycoprotein; CI, confidence interval; HEU, human immunodeficiency virus–exposed, uninfected; HUU, human immunodeficiency virus–unexposed, uninfected; IQR, interquartile range; LLD, lower limit of detection; RSV, respiratory syncytial virus; RSV-PRNT$_{60}$, serum respiratory syncytial virus 60% plaque reduction neutralizing titers.

[a]The LLD was 1:10 for the RSV-PRNT$_{60}$ assay and 1:50 for the anti-RSV F IgG ELISA (antibody titers were analyzed on the reciprocal $\log_2$ scale).

[b]Differences in antibody titers on the reciprocal $\log_2$ scale between HUU and HEU children were estimated using censored linear regression models adjusted for age, sex, vaccine candidate, and prevaccination antibody titer (day 56 estimates only).

vaccination, compared with children who had <4-fold increases in these antibodies with vaccination. Fourteen (10%) children, including 7 (12%) HEU and 7 (8%) HUU, had RSV detected by culture or qPCR from a nasal wash obtained during an illness visit. An additional 43 participants had evidence of wild-type RSV infection during the RSV surveillance period on the basis of a ≥4-fold increase in serum RSV-PRNT$_{60}$ (n = 38) or anti-RSV F IgG antibodies (n = 42). The distribution of changes in serum antibody titers during the RSV surveillance period is shown in Figure 3. The distributions were bimodal, with 1 peak centered around an antibody increase of 5 on the reciprocal $\log_2$ scale, corresponding to a 32-fold increase in antibody titers, and a larger peak centered around no change in antibody titer. These peaks correspond with those in the distributions of changes in antibody titers observed among participants who did or did not have RSV detected at an illness visit during the RSV surveillance period. Distributions of antibody changes were generally similar among HUU and HEU children.

DISCUSSION

Analyzing pooled data from clinical trials of 7 live-attenuated RSV vaccine candidates conducted among children with serum RSV-neutralizing titers of <1:40 demonstrated that these vaccines had high infectivity and immunogenicity among HEU children. Compared to HUU children, HEU children had lower RSV serum antibody titers prior to vaccination but mounted robust humoral immune responses to vaccination. Taken together, these results suggest that HIV exposure is unlikely to substantively affect the immunogenicity of live-attenuated RSV vaccines among young children.

Children were eligible for these trials if they had a RSV-neutralizing serum antibody titer <1:40 at screening. Within this study population, considered RSV-seronegative per the study protocols, serum RSV antibodies prior to vaccination were lower among HEU children than among HUU children. In particular, HEU children had lower baseline titers of RSV-neutralizing antibodies and IgG antibodies to the RSV F glycoprotein compared to HUU children, with higher percentages of HEU children having undetectable titers of these antibodies than HUU children. Prior studies demonstrated that HEU newborns acquire lower titers of maternal antibodies to several common bacterial and viral pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae* type B (Hib), and RSV [12–14, 27–29]. The available data suggest that this may relate both to lower pathogen-specific serum antibody titers among pregnant women with HIV and impaired transplacental transfer of antibodies to their newborns [13, 14, 28–30]. In a study conducted among 316 mother–newborn dyads in Botswana, lower placental transfer of RSV antibodies to newborns was observed from women with HIV, although maternal viral suppression was associated with more effective antibody transfer to HEU infants [14]. Similarly, among 240 mother–newborn dyads in South Africa, HEU infants had lower RSV serum antibody titers than HUU infants; maternal hypergammaglobulinemia was more common in women living with HIV than in women without HIV (90% vs 10%) and was associated with lower RSV antibody transfer [13].

Most, but not all, prior studies reported that HEU children have similar or superior humoral immune responses to vaccination than HUU children [12, 31–34]. Jones and colleagues demonstrated that HEU children developed comparable vaccine-elicited antibody titers to pertussis and Hib and higher antibody titers to *S pneumoniae* and pertussis than HUU children despite having lower titers of antibodies to these pathogens at birth [12]. Similarly, a meta-analysis of 27 studies that evaluated the immunogenicity of live-attenuated measles vaccines reported similar quantitative antibody responses among HUU and HEU children [33]. In contrast, Abramczuk and colleagues reported that HEU children were more likely to be nonresponders to hepatitis B vaccine and developed lower antibody titers to tetanus toxoid than HUU children [34]. In the current

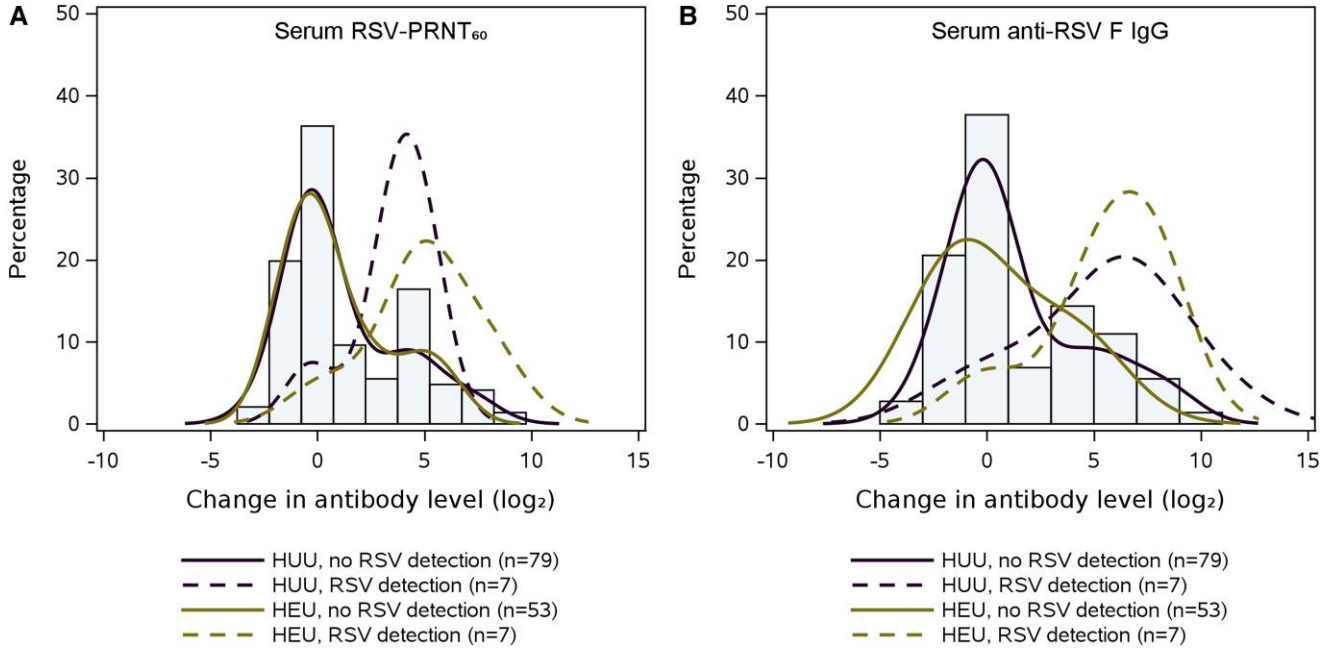

Figure 3. Distribution of changes in serum respiratory syncytial virus (RSV) antibodies during the surveillance period. Changes were calculated as the antibody titer after the RSV surveillance period minus the antibody titer prior to the surveillance period analyzed on the reciprocal $\log_2$ scale. Each bar represents the percentage of all children who experienced a given change in serum antibody titers during the RSV surveillance period as measured by RSV 60% plaque reduction neutralization assay (*A*) or anti-RSV F immunoglobulin G enzyme-linked immunosorbent assay (*B*). Density lines are shown by human immunodeficiency virus exposure status and whether RSV was detected in a nasal wash specimen. Abbreviations: anti-RSV F IgG, serum immunoglobulin G antibodies to the RSV F glycoprotein, as determined by enzyme-linked immunosorbent assay; HEU, human immunodeficiency virus–exposed, uninfected; HUU, human immunodeficiency virus–unexposed, uninfected; RSV, respiratory syncytial virus; RSV-$PRNT_{60}$, serum respiratory syncytial virus 60% plaque reduction neutralizing titers.

study, the intranasally administered live-attenuated RSV vaccines tended to be more immunogenic among HEU children than HUU children in the absence of differences in vaccine infectivity and the magnitude or duration of vaccine shedding.

The interference of passively acquired antibodies with serum antibody responses to live vaccines has been recognized for >50 years. Some of the first data to demonstrate this phenomenon were from studies of infants receiving live-attenuated measles vaccine in which the persistence of maternal measles antibodies was implicated in the failure of some infants to develop appropriate vaccine-elicited humoral immune responses [35, 36]. Subsequent studies reported that preexisting maternal antibodies can also interfere with serum antibody responses to inactivated vaccines, while demonstrating that this effect varies based on the vaccine antigen for both live and inactivated vaccines. Preexisting antibodies were demonstrated to interfere with the development of serum antibodies following live-attenuated rubella vaccine among children 15 months of age [37], whereas this was not observed with live-attenuated mumps vaccine among infants 6, 9, or 12 months of age [38]. Similarly, preexisting maternal antibodies interfered to a greater extent with the serum antibody responses to inactivated vaccines for tetanus (8, 12, and 16 weeks of age) and pneumococcus (8 and 16 weeks of age) than for Hib (8, 12, and 16 weeks of age) [39], while maternal antibody interference was observed for whole-cell but not acellular pertussis vaccines administered at 2, 4, and 6 months of age [40]. Among the children 6 to <25 months of age with serum RSV 60% plaque neutralizing titers of <1:40 at screening included in this study, the proportion with a ≥4-fold rise in antibody titers following vaccination was lower among participants with detectable antibody titers prior to vaccination compared to those with undetectable prevaccination antibodies. The lower RSV antibody titers at baseline among HEU children likely contribute to their higher RSV antibody titers after vaccination; however, HEU children had higher antibody titers 56 days after vaccination even after adjustment for the antibody titer prior to vaccination. This difference in vaccine-elicited antibody titers by HIV exposure status was also observed in analyses limited to children with undetectable serum antibodies prior to vaccination. Taken together, these data suggest that factors in addition to the titers of maternally derived antibodies at the time of vaccination contribute to the superior quantitative serum antibody responses of HEU children to intranasal, live-attenuated vaccines.

In a prior post hoc analysis of combined results from several phase 1 studies of live-attenuated RSV vaccines, including some studies included in the present analysis, a ≥4-fold rise in serum RSV-neutralizing antibodies following intranasal vaccination

was identified as a potential predictor of vaccine efficacy [41]. This analysis also suggested that a ≥4-fold rise in serum RSV-neutralizing antibodies could be considered both a direct mediator of protection and a marker for priming of other protective immune responses, such as systemic and mucosal T-cell responses or mucosal antibody responses following live-attenuated RSV vaccination [41]. Consistent with this prior study, a lower proportion of children who had a ≥4-fold rise in serum RSV-neutralizing antibodies with vaccination had evidence of wild-type RSV infection during the surveillance period than children who had less robust vaccine responses in the current analysis of data from clinical trials of 7 RSV vaccine candidates. Further analyses of the mucosal and T-cell responses following intranasal vaccination with live-attenuated RSV vaccines in the presence of residual maternal or passive RSV antibodies would be needed to elucidate the ability of live-attenuated RSV vaccines to prime active immune responses in the presence of preexisting RSV antibodies.

This study has several limitations. First, although analyses were adjusted for the vaccine received, data were pooled from clinical trials of 7 RSV vaccine candidates that had varied infectivity and immunogenicity. Additionally, data were unavailable for sociodemographic factors other than age and sex that have the potential to affect immune responses to vaccination. Nasal washes were collected only on specific days after vaccination, with minor differences in the days of sample collection across studies. Thus, data on the duration of vaccine shedding should be interpreted with caution. Although HEU children had quantitatively stronger antibody responses to live-attenuated RSV vaccines compared to HUU children, these trials were not powered to evaluate if these differences in vaccine immunogenicity correlate with improved protection from RSV infection or severe disease. Finally, these studies did not evaluate or compare mucosal and T-cell immune responses among HUU and HEU children following intranasal vaccination with live-attenuated RSV vaccines.

In conclusion, pooled analyses of clinical trials data for 7 live-attenuated RSV vaccine candidates suggest that these vaccines are highly immunogenic in HEU children. Given their increased morbidity and mortality during early childhood from RSV-ALRI and other infections, HEU children should be prioritized for vaccination as the RSV vaccines currently under development become available.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. P. L. C. and U. J. B. are named as inventors on patents for live-attenuated RSV vaccines, with royalties paid to the NIH by Sanofi Pasteur. M. S. K. reports consulting or advisory board fees from Merck & Co, Inc, and Invivyd. All other authors report no potential conflicts.

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