Original Investigation

Duration of Infant Protection Against Influenza Illness Conferred by Maternal Immunization

Secondary Analysis of a Randomized Clinical Trial

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IMPORTANCE Influenza immunization of women during pregnancy protects the young infants against influenza illness. The duration of this protection remains unclear.

OBJECTIVE To evaluate the duration of infant protection conferred by maternal immunization and its association with transplacental antibody transfer.

DESIGN, SETTING, AND PARTICIPANTS Infants born to women who participated in a randomized, double-blind, placebo-controlled clinical trial in 2011 and 2012 on the safety, immunogenicity, and efficacy of trivalent inactivated influenza vaccine (IIV3) during pregnancy were followed up during the first 6 months of life for polymerase chain reaction (PCR)–confirmed influenza illness. In a secondary analysis of a subset of infants, hemagglutination inhibition (HAI) antibodies were measured. The study was performed at a single center in South Africa. The secondary analysis was performed in October 2014.

EXPOSURE Maternal immunization for influenza.

MAIN OUTCOMES AND MEASURES The vaccine's efficacy against PCR-confirmed influenza illness and the percentage of infants with HAI titers of 1:40 or more by age group.

RESULTS There were 1026 infants (47.2% female) born to IIV3 recipients and 1023 infants (47.3% female) born to placebo recipients who were included in the analysis of the vaccine's efficacy. The vaccine's efficacy against PCR-confirmed influenza illness was highest among infants 8 weeks of age or younger at 85.6% (95% CI, 38.3%-98.4%) and decreased with increasing age to 25.5% (95% CI, −67.9% to 67.8%) among infants 8 to 16 weeks of age and to 30.3% (95% CI, −154.9% to 82.6%) among infants 16 to 24 weeks of age. Similarly, in the IIV3 group, the percentage of infants with HAI titers of 1:40 or more to the influenza vaccine strains decreased from more than 56% in the first week of life to less than 40% at 16 weeks of age and less than 10.0% at 24 weeks of age.

CONCLUSIONS AND RELEVANCE Maternal immunization conferred protection against infection in the infants for a limited period during early life. The lack of protection beyond 8 weeks of age correlated with a decrease in maternally derived antibodies.

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Editorial

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The incidence of influenza illness among infants is high and is associated with a substantial increase in outpatient visits and hospitalizations during the influenza season,[1,2] especially among infants younger than 6 months of age.[2-4] There are also concomitantly high rates of influenza-related deaths in this age group.[5,6] While active annual influenza vaccination is the most efficient mode for the prevention of influenza, current vaccines are poorly immunogenic and not licensed for use for infants younger than 6 months of age. Alternative strategies to prevent influenza illness in young infants include passive protection or cocooning through vaccination of pregnant women and other household members.[7]

We recently reported that immunization with trivalent inactivated influenza vaccine (IIV3) of pregnant women uninfected with the human immunodeficiency virus (HIV) was safe and immunogenic and partially protected the women and their infants with a vaccine efficacy of 50% and 49%, respectively, against polymerase chain reaction (PCR)–confirmed influenza illness during a 24-week follow-up period after delivery.[8] The exact duration of the protection for the infants, however, was never assessed and is generally described during the overall follow-up period (often the first 6 months of life).[8,9]

Furthermore, we also described the kinetics of the transplacentally acquired hemagglutination inhibition (HAI) antibodies in the infants of vaccinated women and determined that the half-life of HAI antibodies in the infants was 43 to 45 days.[10] In this secondary analysis, we report on the secondary and exploratory objectives of the study, which were to determine the percentage of infants born to vaccinated mothers and the percentage of infants born to unvaccinated mothers, both with seroprotective titers from birth to 24 weeks of age, and to evaluate the protection conferred to the infant by maternal immunization stratified by age group.

Key Points

Question For infants, what is the duration of protection against influenza illness conferred by maternal immunization?

Findings Infants born to women who participated in a randomized clinical trial of trivalent inactivated influenza vaccine during pregnancy were followed up to determine the vaccine's efficacy against influenza illness and the infants' antibody levels during the first 6 months of life. The vaccine's efficacy was highest among infants 8 weeks of age or younger, and the percentage of infants with seroprotective titers decreased from birth to 6 months.

Meaning Maternal immunization conferred protection against infection to the infants for a limited period during early life that correlated with a decrease in maternally derived antibodies.

Methods

Study Design

Details of the study have been published elsewhere.[8] In brief, we conducted a randomized, double-blind, placebo-controlled clinical trial of IIV3 for HIV-uninfected pregnant women in Soweto, South Africa.[8] This involved 2 cohorts of HIV-uninfected pregnant women in their second/third trimester who were enrolled prior to the onset of the influenza seasons in 2011 (n = 1060) and 2012 (n = 1056). A subset of these women and their babies were included in the immunogenicity substudy; these participants were recruited from when enrollment started until the desirable sample size was reached. Women and their infants were followed up to 24 weeks post partum. The present report describes results from the infants born to the mothers enrolled in the study. The study used the influenza vaccine recommended by the World Health Organization for the southern hemisphere for both the 2011 and 2012 influenza seasons (A/California/7/2009 [A/H1N1pdm09], A/Victoria/210/2009 [H3N2], and B/Brisbane/60/2008-like virus [B/Victoria lineage]; Vaxigrip; Sanofi Pasteur)[11,12] and sterile 0.9% normal saline solution as placebo.

Ethical Considerations

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand, registered at ClinicalTrial.gov, and conducted in accordance with Good Clinical Practice guidelines. Mothers provided written informed consent for themselves and their infants.

Sample Collection and Testing

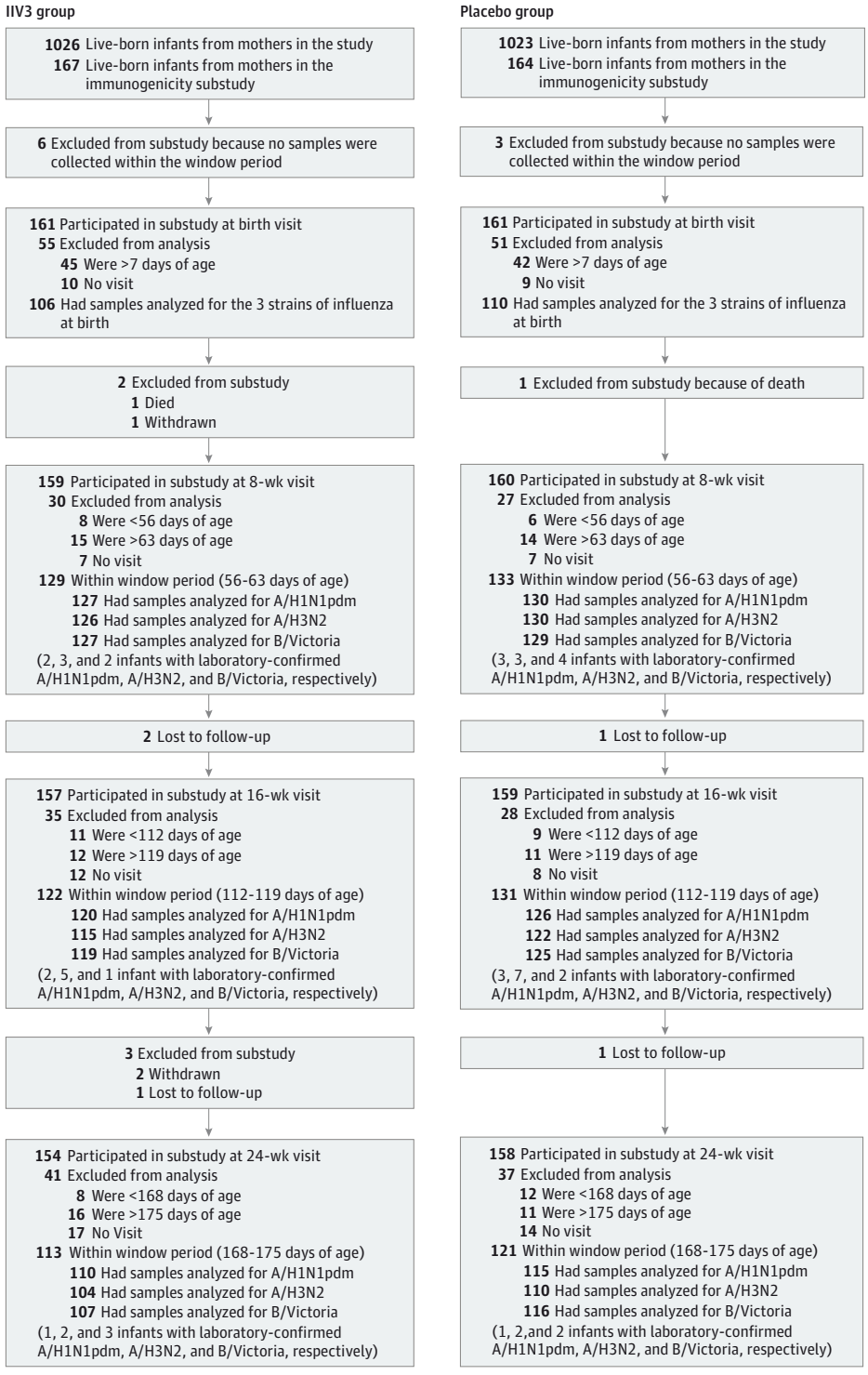
Blood samples were obtained from infants within 7 days of birth and at 8 weeks of age (56-63 days), 16 weeks of age (111-119 days), and 24 weeks of age (168-175 days). The HAI assays were performed as previously described.[13] The percentage of infants with HAI titers of 1:40 or more (putative correlate of protection) was calculated.

Active surveillance for respiratory illness was performed through weekly contact with study participants. Infants with suspected influenza-like illness, as well as those presenting with or hospitalized for any respiratory illness, underwent a procedure to obtain nasopharyngeal aspirate samples. These samples were placed in viral transport medium and tested with a qualitative 2-step real-time reverse transcriptase-PCR assay. Primers and probe sets targeted either the matrix gene or the hemagglutinin gene designed for the universal detection of type A and B influenza viruses, respectively. All influenza A viruses were further subtyped as either H1 or H3, and the influenza B viruses as B/Victoria (homotypic vaccine strain) or B/Yamagata.[14]

Statistical Analysis

All analyses of study outcomes were performed under the principle of intention to treat, meaning that infants born less than 28 days after their mothers had been vaccinated and preterm infants (ie, <37 weeks of gestational age at birth or a birth weight of <2500 g) were included in the analyses. The immunogenicity analysis included all infants who had blood samples that were obtained within the protocol-defined time periods at each particular time point. Infants who had an episode of PCR-confirmed influenza illness or serological evidence of influenza (ie, ≥4-fold increase in HAI titers between birth and any

Figure 1. Flow Diagram Representing the Number of Infants Analyzed at the Different Immunogenicity Visits



Participants were excluded from the analysis for the relevant strain from the current visit onward. A laboratory-confirmed episode of influenza illness (confirmed by serology or polymerase chain reaction) occurred in the interval between the previous visit and the current visit. IIV3 indicates trivalent inactivated influenza vaccine.

of the subsequent visits) during the follow-up period were excluded from the immunogenicity analyses of the putative strain after the diagnosis of infection. **Figure 1** shows the number of infants who contributed data at each study visit. All the infants born to mothers enrolled in the study were included in the efficacy analyses. The vaccine efficacy was estimated as 1 minus the incidence rate ratio of PCR-confirmed influenza illness in the IIV3 group and placebo group. Incidence rates were calculated as density incidence using Poisson regression and person-time as the denominator. Time-to-event data were right

Table 1. Infant Characteristics and Time Points of Scheduled Visits

Variable	Infants, No. (%)	
	From IIV3 Recipient	From Placebo Recipient
Full cohort, No.	1026	1023
Female sex[a]	484 (47.2)	484 (47.3)
Born at <37 wk of gestation	108 (10.5)	96 (9.4)
Birth weight, mean (SD),[b] kg	3.0 (0.5)	3.1 (0.5)
Low-birth-weight newborns[b]	133 (13.0)	122 (12.0)
Time from vaccination to birth, mean (SD), d	81.5 (35.3)	80.6 (35.4)
Follow-up period, median (IQR), d	172 (168-175)	172 (168-175)
Immunogenicity cohort, No.	161	161
Female sex	62 (38.5)	75 (46.6)
Born at <37 wk of gestation	17 (10.6)	16 (10.0)
Birth weight, median (range), kg	3.1 (0.5)	3.1 (0.5)
Low-birth-weight newborns	18 (11.2)	25 (15.5)
Time from vaccination to birth, mean (SD), d	76.7 (36.3)	81.7 (37.9)
Follow-up period, median (IQR), d	169 (168-171)	168 (168-170)
Age,[c] median (IQR), d		
At first antibody measure	5 (4-6) [106]	5 (4-6) [110]
At 8-wk antibody measure	56 (56-57) [129]	56 (56-57) [133]
At 16-wk antibody measure	112 (112-114) [122]	112 (112-114) [131]
At 24-wk antibody measure	168 (168-170) [113]	168 (168-169) [121]

Abbreviations: IIV3, trivalent inactivated influenza vaccine; IQR, interquartile range.

[a] Missing data for 1 infant in the IIV3 group.

[b] Missing data for 2 infants in the IIV3 group and 2 infants in the placebo group.

[c] Only participants who had their scheduled visits within the study window periods were included in the immunogenicity analyses. The number of infants evaluated at each immunogenicity visit is provided in brackets.

censored after the first episode of PCR-confirmed influenza illness or at study termination (maximum 175 days of age). Percentages were compared using the χ^2 test or the Fisher exact test, and demographic continuous variables were compared using the *t* test or the Mann-Whitney test. $P < .05$ was considered to be statistically significant. Study data were collected and managed using Research Electronic Data Capture.[15] Analyses were performed using Stata version 12.1 (StataCorp). The South African influenza seasons were defined using the National Institute for Communicable Diseases surveillance data.[16]

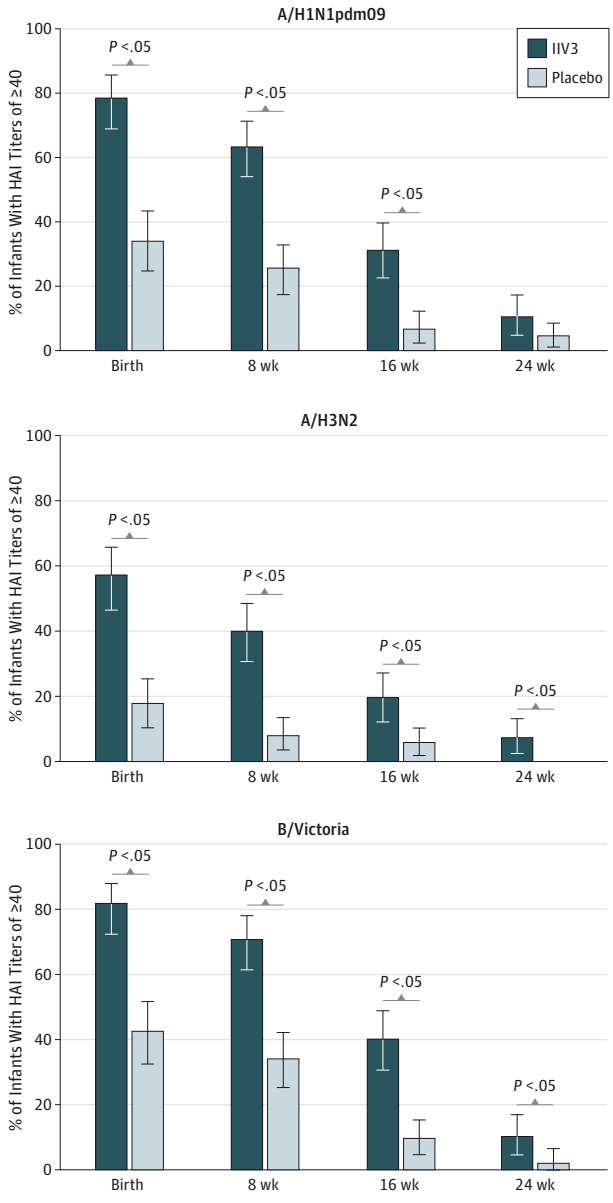
Results

Of 2049 infants included in the vaccine efficacy analysis, 1026 were born to mothers who received IIV3 during pregnancy, and 1023 were born to mothers who received to placebo during pregnancy (**Table 1**). Infants were born at a mean of 81.0 days (range, 1-175 days) after maternal vaccination and were monitored for influenza illness for a median of 172 days of life (interquartile range, 168-175 days). The baseline demographic characteristics and follow-up times were similar between infants in the IIV3 group and infants in the placebo group. An immunogenicity substudy enrolled 331 infants, including 9 (6 born to IIV3 recipients) who did not have any samples collected within the study's window periods and were excluded from the analysis. The 161 evaluable infants born to IIV3 recipients had similar characteristics and follow-up times as the 161 infants born to placebo recipients (Table 1). Infants in the immunogenicity substudy had characteristics similar to those of the entire cohort, except for a lower percentage of girls in the substudy (41.7% vs 48.3%; $P = .03$) and a shorter follow-up (168 vs 174 days; $P < .001$) (eTable in the Supplement).

The percentages of infants born to IIV3 recipients with HAI titers of 1:40 or more at birth was 78.3% for the A/H1N1pdm09 strain, 56.6% for the A/H3N2 strain, and 81.1% for the B/Victoria stain; and these percentages were significantly higher than those of infants born to placebo recipients (33.6% for the A/H1N1pdm09 strain, 17.3% for the A/H3N2 strain, and 41.8% for the B/Victoria strain; $P < .001$ for all comparisons) (**Figure 2**). The percentage of infants with HAI titers of 1:40 or more decreased in both groups during the first 24 weeks of age. At 16 weeks of age, 39.5%, 19.1%, and 40% of infants born to IIV3 recipients had HAI titers of 1:40 or more for the A/H1N1pdm09 strain, the A/H3N2 strain, and the B/Victoria strain, respectively, and at 24 weeks of age, the percentages were further reduced to 10.0%, 6.7%, and 9.4%, respectively. Corresponding percentages of infants with HAI titers of 1:40 or more in the placebo group were 5% to 9% at 16 weeks ($P \le .001$ for all comparisons) and 3.5% ($P = .06$), 0% ($P = .01$), and 1.7% ($P = .02$), respectively, at 24 weeks (Figure 2).

Thirty-seven infants born to placebo recipients and 19 infants born to IIV3 recipients experienced 1 episode of PCR-confirmed influenza illness during the study follow-up period[8] (**Table 2**). Of the 37 infants born to placebo recipients, 14 were 8 weeks of age or younger, 16 were between 8 and 16 weeks of age, and 7 were between 16 and 24 weeks of age; of

Figure 2. Percentage of Infants With Hemagglutination Inhibition Titers of 1:40 or More at the Different Study Time Points



The error bars indicate 95% CIs. HAI, indicates hemagglutination inhibition; IIV3, trivalent inactivated influenza vaccine.

the 19 infants born to IIV3 recipients, 2 were 8 weeks of age or younger, 12 were between 8 and 16 weeks of age, and 5 were between 16 and 24 weeks of age. The vaccine efficacy (against PCR-confirmed influenza illness) was highest when limited to outcomes occurring among infants 8 weeks of age or younger (85.6% [95% CI, 38.3%-98.4%]). The estimated vaccine efficacy) gradually decreased with increasing age, including a vaccine efficacy of 53.9% (95% CI, 10.4%-77.4%) for infants 16 weeks of age or younger and 49.5% (95% CI, 9.9%-72.6%) for infants 24 weeks of age or younger. No protective effect of IIV3 was detected if the analysis was restricted to infants between 8 and 16 weeks of age (vaccine efficacy, 25.5% [95% CI, −67.9% to 67.8%]) or between 16 and 24 weeks of age (vaccine efficacy, 30.3% [95% CI, −154.9% to 82.6%]). Restricting the outcomes to those that occurred during the influenza season yielded similar vaccine efficacy estimates (Table 2).

Seventeen infants in the immunogenicity substudy had an episode of PCR-confirmed influenza illness (7 born to IIV3 recipients and 10 born to placebo recipients). Of these 17 infants, 7 had an episode in which the B/Yamagata strain was detected (2 from the IIV3 group), 5 had an episode in which the A/H3N2 strain was detected (2 from the IIV3 group), 4 had an episode in which the B/Victoria strain was detected (3 from the IIV3 group), and 1 from the placebo group had an episode in which t he A/H1N1pdm09 and A/H3N2 strains were simultaneously detected. All 5 infants infected with a homotypic vaccine strain born to IIV3 recipients were between 8 and 16 weeks of age and had a blood sample obtained for determination of HAI titer immediately preceding the influenza episode at an average of 34.6 days (range, 7-56 days). Of the 5 infants in the placebo group infected with a homotypic vaccine strain, 1 was 45 days of age, 2 were between 8 and 16 weeks of age, and 2 were between 16 and 24 weeks of age, and blood samples were available for determination of HAI titer at a mean 27.6 days (range, 15-38 days) before the influenza episode. **Table 3** shows that the HAI titers at the immunogenicity visits preceding the episode of PCR-confirmed influenza illness were 1:40 or more in 3 cases (2 in the IIV3 group and 1 in the placebo group) and less than 1:40 in the remaining 8 cases of infection (3 in the IIV3 group and 5 in the placebo group).

Discussion

We and others have previously demonstrated that the administration of IIV3 during pregnancy confers protection against symptomatic influenza infection to the infants of the vaccinated mothers[8,9]; here we show that the duration of this protection is likely to be limited to the first 8 weeks of age. Several potential mechanisms of protection have been proposed, such as maternal immunization against influenza providing indirect protection of the infant by preventing transmission of influenza virus from the mother to the baby, maternal antibody-mediated protection through transplacental transfer, or maternal antibody-mediated protection through breast milk.[10,17,18] Our study suggests that the most likely mechanism of protection of the infants is through the transplacental transfer of maternal antibodies.[10,19,20]

The concentration of maternally acquired antibodies decreased rapidly in the infants, and by 16 weeks of age, less than 40% of the infants born to IIV3 recipients had HAI titers of 1:40 or more for any of the vaccine strains, mimicking the reduction in vaccine efficacy. Although the HAI titer threshold of 1:40 is generally recognized as corresponding to a 50% reduction in the risk of influenza illness in adults, this may be too low to confer adequate protection in children, and it was estimated that a more appropriate titer for 50% protection in children

Table 2. Incidence Rates of PCR-Confirmed Influenza Illness and Vaccine Efficacy by Age Group

PCR-Confirmed Influenza	IIV3 Group			Placebo Group			Vaccine Efficacy (95% CI)	*P* Value
	Infants, No.	Person-Time, mo	Incidence Rate (95% CI)[a]	Infants, No.	Person-Time, mo	Incidence Rate (95% CI)[a]		
Overall								
≤8 wk	2	2083.7	1.0 (0.2-3.8)	14	2066.4	6.8 (4.0-11.4)	85.8 (38.3-98.4)	.01
>8-16 wk	12	1818.0	6.6 (3.7-11.6)	16	1806.5	8.9 (5.4-14.5)	25.5 (−67.9 to 67.8)	.44
>16-24 wk	5	1670.5	3.0 (1.2-7.2)	7	1628.8	4.3 (2.0-9.0)	30.4 (−154.9 to 82.6)	.54
≤16 wk	14	3898.0	3.6 (2.1-6.1)	30	3847.2	7.8 (5.5-11.2)	53.9 (10.4-77.4)	.02
≤24 wk	19	5568.4	3.4 (2.2-5.3)	37	5476.1	6.8 (4.9-9.3)	49.5 (9.9-72.6)	.02
During influenza season								
≤8 wk	2	1697.8	1.2 (0.15-4.3)	14	1697.8	8.2 (4.5-13.8)	85.4 (36.5-98.4)	.01
≤16 wk	14	2538.2	5.5 (3.0-9.2)	30	2534.1	11.8 (8.0-16.9)	53.4 (9.4-77.2)	.02
≤24 wk	19	2766.1	6.9 (4.1-10.7)	36	2755.1	13.1 (9.2-18.0)	47.4 (5.9-71.5)	.02

Abbreviations: IIV3, trivalent inactivated influenza vaccine; PCR, polymerase chain reaction.

[a] Incidence rates calculated as number of cases per 1000 child-months, using person-time between birth and event or end of study.

Table 3. Data on Antibody Titers in Infants in the Immunogenicity Substudy Who Developed a PCR-Confirmed Influenza Illness

Treatment Group, Case No.	Age at Influenza Detection, d	Strain(s) of Influenza Virus	Age Immediately Preceding Collection of Blood Sample, d	HAI Titer
IIV3				
1	67	A/H3N2	59	1:160
2	81	A/H3N2	28	1:10
3	105	B/Victoria	56	1:5
4	112	B/Victoria	56	1:10
5	119	B/Victoria	112	1:40
Placebo				
6	45	A/H1N1pdm09; A/H3N2	7	1:20; 1:80
7	72	A/H3N2	57	1:20
8	82	A/H3N2	58	1:10
9	142	A/H3N2	118	1:5
10	151	B/Victoria	114	1:5

Abbreviations: HAI, hemagglutination inhibition; IIV3, trivalent inactivated influenza vaccine; PCR, polymerase chain reaction.

older than 6 months of age might be 1:110.[21,22] However, because the threshold of maternally acquired HAI antibodies as a predictor of protection against influenza in young infants is unknown, we used the 1:40 threshold as guidance, anticipating that a higher threshold would predict an even shorter time of protection.

The fact that lower levels of HAI antibodies are associated with reduced protection was also observed in the primary analysis of our IIV3 trials in which both HIV-infected and HIV-uninfected pregnant women participated. In the primary analysis, we showed that HIV-exposed infants had significantly lower HAI titers than HIV-unexposed infants throughout the first 6 months of life and a higher incidence of influenza compared with infants born to uninfected mothers. Although the studies were not powered to show efficacy in the HIV-exposed infants, in the intention-to-treat analysis, we did not detect any indication that maternal immunization may prevent disease in HIV-exposed infants.[8,10]

The amount of maternal antibodies transferred to the infant is influenced by the interval between immunization and delivery.[23,24] We have previously shown that a higher transplacental antibody transfer was achieved with a longer interval between vaccination and delivery, which suggests that a prolonged cumulative transfer of antibodies leads to higher quantity of antibodies at birth compared with a shorter period during maximal transplacental transfer.[10] Our study finds that, to achieve better infant protection, vaccination during pregnancy should not be delayed until the third trimester.

The main limitation of this study is that the same IIV3 formulation was used in both study years. It would be important to confirm these results in other seasons and in different populations.

Conclusions

Estimating the period that infants can be protected through maternal vaccination has important implications, especially since currently there is no influenza vaccine licensed for use in infants younger than 6 months of age. To enhance the concentration of the antibodies transferred transplacentally and decrease the period of vulnerability to disease in young infants, there is the need to find more immunogenic vaccines for pregnant women. Alternatively, more immunogenic vaccines that can generate a protective immune response in infants, beginning at 8 weeks of age, need to be identified. Importantly, whereas protection conferred by vaccination is likely to be mediated by both antibodies and cellular-immune responses in vaccine recipients, passive protection of infants is almost exclusively mediated by antibodies.

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Author Contributions: Dr Nunes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Nunes, Cutland, Jones, Simões, Weinberg, Madhi.
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Drafting of the manuscript: Nunes.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Nunes.
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