ORIGINAL ARTICLE

Influenza Vaccination of Pregnant Women and Protection of Their Infants

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ABSTRACT

BACKGROUND

There are limited data on the efficacy of vaccination against confirmed influenza in pregnant women with and those without human immunodeficiency virus (HIV) infection and protection of their infants.

METHODS

We conducted two double-blind, randomized, placebo-controlled trials of trivalent inactivated influenza vaccine (IIV3) in South Africa during 2011 in pregnant women infected with HIV and during 2011 and 2012 in pregnant women who were not infected. The immunogenicity, safety, and efficacy of IIV3 in pregnant women and their infants were evaluated until 24 weeks after birth. Immune responses were measured with a hemagglutination inhibition (HAI) assay, and influenza was diagnosed by means of reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays of respiratory samples.

RESULTS

The study cohorts included 2116 pregnant women who were not infected with HIV and 194 pregnant women who were infected with HIV. At 1 month after vaccination, seroconversion rates and the proportion of participants with HAI titers of 1:40 or more were higher among IIV3 recipients than among placebo recipients in both cohorts. Newborns of IIV3 recipients also had higher HAI titers than newborns of placebo recipients. The attack rate for RT-PCR–confirmed influenza among both HIV-uninfected placebo recipients and their infants was 3.6%. The attack rates among HIV-uninfected IIV3 recipients and their infants were 1.8% and 1.9%, respectively, and the respective vaccine-efficacy rates were 50.4% (95% confidence interval [CI], 14.5 to 71.2) and 48.8% (95% CI, 11.6 to 70.4). Among HIV-infected women, the attack rate for placebo recipients was 17.0% and the rate for IIV3 recipients was 7.0%; the vaccine-efficacy rate for these IIV3 recipients was 57.7% (95% CI, 0.2 to 82.1).

CONCLUSIONS

Influenza vaccine was immunogenic in HIV-uninfected and HIV-infected pregnant women and provided partial protection against confirmed influenza in both groups of women and in infants who were not exposed to HIV. (Funded by the Bill and Melinda Gates Foundation and others; ClinicalTrials.gov numbers, NCT01306669 and NCT01306682.)

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Pregnant women are designated as a priority group for seasonal influenza vaccination by the World Health Organization (WHO)[1] because of their heightened susceptibility to severe influenza from the second trimester to the early postpartum period.[2,3] Since pregnancy is associated with immunomodulation, including the attenuation of cell-mediated immune responses,[4] the efficacy of inactivated influenza vaccine (IIV) in pregnant women may differ from its efficacy in healthy nonpregnant women and in men.[5] This difference in vaccine efficacy could be further accentuated in pregnant women infected with the human immunodeficiency virus (HIV), who are at heightened risk for severe influenza illness[6-8] because of HIV-related immunosuppression.[9-14]

Reduced attack rates for all-cause febrile respiratory illness among women vaccinated against influenza during pregnancy were observed during the 1957 Asian influenza pandemic in the United States and in a later randomized, controlled trial in Bangladesh.[15,16] A recent case–control study in the United States also reported that pregnant women with influenza confirmed by means of reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay (hereafter referred to as confirmed influenza) were 44 to 53% less likely to have been vaccinated with trivalent IIV (IIV3) than controls who did not have influenza.[17] To our knowledge, no published randomized, controlled trial has assessed the efficacy of IIV in preventing confirmed influenza in pregnant women with HIV infection and those without HIV infection.[18,19]

The vaccination of pregnant women may also confer partial protection against confirmed influenza in their infants, as reported in the Bangladeshi trial (in which infants whose mothers had been vaccinated with IIV3 were 63% less likely to have influenza [confirmed by means of enzyme-linked immunosorbent assay]).[16] However, observational studies have had conflicting results with regard to the efficacy of IIV3 vaccination during pregnancy in protecting infants against all-cause respiratory illness.[20-23] The protection of infants 6 months of age or younger against influenza is a public health priority. These infants are at high risk for influenza-associated hospitalization, and their immune responses to IIV vaccination are poor.[24-26] We conducted two studies, one involving pregnant women without HIV infection and the other involving pregnant women with HIV infection, to evaluate the safety, immunogenicity, and efficacy of IIV3 in these women and in their infants until 24 weeks post partum.

Methods

Study Design, Objectives, and Oversight

The two studies were randomized, double-blind, placebo-controlled trials conducted in Soweto, South Africa, where antenatal HIV testing is routine. The enrollment of HIV-uninfected pregnant women was initiated at four antenatal clinics before the onset of the 2011 influenza season (March 3 through August 4) and the 2012 season (March 6 through July 2). Members of the HIV-infected cohort were enrolled at the same facilities (March 3 through June 2, 2011). Eligibility criteria for both cohorts included an age of 18 to 38 years, an estimated gestation of 20 to 36 weeks, and the ability to understand and comply with planned study procedures. (The methods used to determine gestational age and the exclusion criteria are provided in the Supplementary Appendix, which is available with the full text of this article, along with the original and final protocols, at NEJM.org.) All HIV-infected mother–infant dyads in 2011 and a subset of HIV-uninfected dyads were included in a nested immunogenicity study that was performed during each year of the trial. The primary objectives for the cohort of women without HIV infection were to evaluate the efficacy of IIV3 vaccination during pregnancy in protecting their infants against confirmed influenza through 24 weeks of age and to compare seroconversion rates between IIV3 recipients and placebo recipients 1 month after vaccination. Secondary objectives included measuring vaccine efficacy against confirmed influenza in all women until 24 weeks post partum. In the HIV-infected cohort, an additional primary objective was to evaluate the immunogenicity of IIV3 in the women. Secondary objectives for this cohort included measuring vaccine efficacy against confirmed influenza in the women and their infants until 24 weeks post partum. Additional secondary objectives for both cohorts are listed in the Supplementary Appendix.

The studies were approved by the Human Research Ethics Committee of the University of the Witwatersrand and were conducted in accor-

dance with Good Clinical Practice guidelines. Written informed consent was obtained from all participants. All the authors vouch for the fidelity of this report to the protocols and the completeness of the data and analyses. The funders did not participate in the conduct of the study, data collection, analyses of the data, or the writing of the manuscript.

RANDOMIZATION AND STUDY TREATMENT

Participants were randomly assigned in a 1:1 ratio to receive IIV3 or placebo. Randomization was performed by the study statistician with the use of computer-generated assignments. With the exception of the statistician and the pharmacist, study personnel were unaware of the group assignments, as were the study participants.

Influenza vaccine (Vaxigrip, lot number G05831 in 2011 and H7221-2 in 2012; Sanofi Pasteur) was purchased by the study team. The vaccine contained 15 μg each of A/California/7/2009 (A/[H1N1]pdm09), A/Victoria/210/2009 (A/H3N2), and a B/Brisbane/60/2008–like virus (B/Victoria), as recommended by WHO for the Southern Hemisphere in 2011 and 2012.[27,28] The study pharmacist used a 2-ml syringe to draw 0.5 ml of vaccine for the women receiving IIV3 and 0.5 ml of sterile 0.9% normal saline solution for the women receiving placebo. The two preparations were macroscopically indistinguishable. The vaccines were administered into the deltoid muscle by study staff.

SEROLOGIC EFFICACY AND IMMUNOGENICITY

In 2011 and 2012, all mothers and infants in the HIV-infected cohort and a nested group of 180 HIV-uninfected mother–infant dyads were enrolled in an intensive safety and immunogenicity study. The timing of blood-sample collection and processing, the method used for antibody testing (hemagglutination inhibition [HAI]), and the standard criteria used to qualify HAI results as seroconversion and as seroprotective or seronegative titers are provided in the Supplementary Appendix.

VACCINE EFFICACY

Active surveillance for influenza-like illness (as defined in the protocols) was conducted through weekly contact with participants (see the Supplementary Appendix for details). Women and infants identified as having influenza-like illness, and those unexpectedly presenting with or hospitalized for any respiratory illness, were tested for influenza virus by means of an RT-PCR assay. The laboratory methods used for sample collection, influenza-virus identification, and genotyping are detailed in the Supplementary Appendix.

SAFETY

Women enrolled in the nested immunogenicity subsets were provided with diary cards on which to document possible local and systemic reactions to vaccination for 1 week. Digital thermometers were provided to measure oral temperature in women and axillary temperature in infants after vaccination and during illness. Serious adverse events were recorded and graded throughout the study period with the use of an established system.[29]

STATISTICAL ANALYSIS

In the HIV-uninfected cohort, the sample size was based on the primary outcome of vaccine efficacy in the infants. The sample size for the HIV-uninfected cohort was outcome-driven. We aimed at identifying at least 27 cases of confirmed illness caused by influenza virus in infants up to 24 weeks of age in order to detect a 70% reduction in confirmed influenza among the infants, with 80% power. The sample size required for the HIV-infected cohort was 180 participants, which provided 90% power to detect a difference of at least 67% in rates of seroconversion to individual vaccine strains between IIV3 recipients and placebo recipients.

The immunogenicity analyses included comparisons of geometric mean titers between study groups and of the increase in titers from baseline to 1 month after vaccination. We performed a two-sided, two-sample t-test and calculated the corresponding 95% confidence intervals for the titers, using logarithmic transformation for all values. Post-vaccination analyses of immune response were adjusted for baseline HAI titers and between-group differences in baseline characteristics. The proportions of participants in each group who underwent seroconversion and the proportions of participants who had local or systemic reactions were compared by means of chi-square or Fischer's exact tests. Vaccine efficacy was calculated with the use of the formula $(1–I_L)/I_p$, where I_L is the case incidence rate in the vaccinated group and I_p is the case incidence rate in the placebo group; 95% confidence intervals were calculated and between-group differences were

tested. Estimates of vaccine efficacy were adjusted for differences in maternal age and status with respect to antiretroviral treatment at enrollment, which were prevalent in the HIV-infected cohort. For vaccine efficacy end points, data were censored after the first episode of a specific clinical outcome. Between-group differences in the time to a first episode of confirmed influenza were compared in survival analyses by means of the log-rank test.

The intention-to-treat analyses included maternal outcomes from receipt of vaccine or placebo to 175 days after birth and infant outcomes from birth to 175 days of age. The per-protocol analyses included maternal outcomes that occurred 14 or more days after receipt of vaccine or placebo; per-protocol analyses of outcomes for infants were limited to those born at least 28 days after their mother's vaccination, those whose gestational age at birth was at least 37 weeks, or those who had a birth weight of at least 2500 g. The per-protocol immunogenicity analysis was limited to women from whom a blood sample was obtained 28 to 35 days after vaccination and to infants from whom a blood sample was obtained within 7 days after birth and who had a gestational age of at least 37 weeks at birth or a birth weight of at least 2500 g. An exploratory analysis was performed with the use of extended windows for obtaining blood samples after vaccination (28 to 42 days) and after delivery (up to 14 days).

Study data were collected and managed with the use of Research Electronic Data Capture (REDCap), version 5.9.13.[30] All statistical analyses were conducted with the use of Stata software, version 12.1. All P values were two-sided, and a value of 0.05 or less was considered to indicate statistical significance.

RESULTS

BASELINE CHARACTERISTICS OF THE STUDY PARTICIPANTS

We enrolled 2116 black African pregnant women who were not infected with HIV; 1062 were randomly assigned to the group vaccinated with IIV3 and 1054 to the group that received placebo. There were 1026 live infants born to IIV3 recipients and 1023 live infants born to placebo recipients (Fig. S1 in the Supplementary Appendix). The mean maternal age at enrollment was 26.2 years, and the mean gestational age was 26.8 weeks (Table 1). We enrolled 194 pregnant women who were infected with HIV; 100 were randomly assigned to the group vaccinated with IIV3 and 94 to the placebo group (Fig. S2 in the Supplementary Appendix). The mean maternal age at enrollment was 28.2 years, and the mean gestational age was 27.3 weeks (Table 2). The baseline median CD4+ T-cell count in the HIV-infected women was 393.5 cells per cubic millimeter; 12.6% of the women (24 of 190) had counts of less than 200 cells per cubic millimeter. The median level of plasma HIV-1 RNA was 1067 copies per milliliter; 23.0% of the women (43 of 187) had undetectable levels of HIV-1 RNA. There were 100 live births in the group vaccinated with IIV3 and 88 live births in the placebo group among the 183 HIV-infected women who remained in the study until delivery.

IMMUNOGENICITY OF THE VACCINE

HIV-Uninfected Cohort

Of the 376 participants in the immunogenicity subset, 142 IIV3 recipients and 148 placebo recipients were included in the per-protocol analysis of immunogenicity (Fig. S3 and Table S1 in the Supplementary Appendix). Post-vaccination geometric mean titers increased from baseline by a factor of 6 to 10 in IIV3 recipients and were significantly higher for all three vaccine strains, as compared with titers in placebo recipients (Table 3). Seroconversion rates for strains A(H1N1) pdm09, A(H3N2), and B(Victoria) among IIV3 recipients were 72.5%, 64.8%, and 92.3%, respectively; rates among placebo recipients were 8.1%, 2.7%, and 2.0%, respectively ($P<0.001$ for all comparisons). A greater proportion of IIV3 recipients had seroprotective HAI titers after vaccination, as compared with placebo recipients (Table 3).

Newborns of IIV3 recipients had higher HAI geometric mean titers for all vaccine strains than did newborns of placebo recipients and were also more likely to have an HAI titer of 1:40 or higher for A/(H1N1)pdm09 (81.1% vs. 34.0%), A(H3N2) (60.0% vs. 17.5%), and B(Victoria) (82.1% vs. 43.7%) ($P<0.001$ for all comparisons) (Table 3). The ratios of HAI titers in newborns to maternal titers were 0.7 to 1.0 for the three vaccine strains and were similar between study groups, with the exception of higher ratios for B/Victoria in the placebo group (Table 3). Similar findings were observed in the immunogenicity analyses when the window for obtaining blood samples was extended (Tables S2 and S3 in the Supplementary Appendix).

Table 1. Baseline Characteristics of HIV-Uninfected Pregnant Women, Fetal Outcomes, and Newborn Characteristics.*

Characteristic or Outcome	Overall	IIV3	Placebo
Women			
Total no. of women	2116	1062	1054
Mean age — yr	26.2±5.3	26.4±5.3	25.9±5.3
Body-mass index†			
Median	27.6	28.0	27.4
Interquartile range	24.3–31.9	24.6–32.1	24.1–31.6
Mean gestational age at enrollment — wk	26.8±4.4	26.7±4.4	26.9±4.4
Gravidity			
Median	2.0	2.0	2.0
Interquartile range	0.0–3.0	0.0–3.0	0.0–3.0
Parity			
Median	1.0	1.0	1.0
Interquartile range	0.0–1.0	0.0–1.0	0.0–1.0
Fetuses and newborns			
Total no. of known outcomes	2081	1044	1037
Miscarriage, gestational age <28 wk — no. (%)‡	8 (0.4)	3 (0.3)§	5 (0.5)
Stillbirth, gestational age ≥28 wk — no. (%)‡	24 (1.2)	15 (1.4)	9 (0.9)
Live birth — no. (%)	2049 (98.5)	1026 (98.3)	1023 (98.7)
Twin birth — no. (%)	110 (5.3)	60 (5.7)	50 (4.8)
Type of delivery — no. (%)			
Normal vaginal delivery	1393 (66.9)	700 (67.0)	693 (66.8)
Cesarian section	656 (31.5)	326 (31.2)	330 (31.8)
Preterm birth, gestational age <37 wk — no. (%)¶	204 (10.0)	108 (10.5)	96 (9.4)
Overall birth weight — kg¶‖**			
Median	3.1	3.1	3.1
Range	0.5–4.8	0.5–4.6	0.7–4.8
Birth weight of infants born during influenza season — kg¶**††			
Median	3.1	3.1	3.1
Range	0.4–4.8	0.6–4.6	0.4–4.8
Birth weight of <2500 g — no. (%)¶‖**	255 (12.5)	133 (13.0)	122 (12.0)
Death after delivery — no. (%)¶‡‡	22 (1.1)	12 (1.2)	10 (1.0)
Admission to neonatal nursery — no. (%)¶	142 (6.9)	71 (6.9)	71 (6.9)

* Plus–minus values are means ±SD. HIV denotes human immunodeficiency virus, and IIV3 trivalent inactivated influenza vaccine.
† The calculations for body-mass index (the weight in kilograms divided by the square of the height in meters) were based on 796 women in the IIV3 group and 789 women in the placebo group.
‡ Details on miscarriages and stillbirths are provided in Table S9 in the Supplementary Appendix.
§ This number includes one medically assisted termination of pregnancy.
¶ Numbers and percentages are based on live births.
‖ Numbers are based on 1024 observations in the IIV3 group and 1021 observations in the placebo group.
** No significant difference in birth weight between the study groups was observed, even when weight was stratified according to sex.
†† Numbers are based on 857 observations in the IIV3 group and 874 observations in the placebo group.
‡‡ Further details on newborn deaths are provided in Table S10 in the Supplementary Appendix.

HIV-Infected Cohort

The demographic characteristics of HIV-infected women included in the per-protocol analysis of immunogenicity (Fig. S2 in the Supplementary Appendix) are shown in Table S4 in the Supplementary Appendix. The receipt of IIV3 resulted in increases in geometric mean titers of antibodies to A/(H1N1)pdm09, A/H3N2, and B/Victoria by factors of 2.9, 2.4, and 3.2, respectively, and seroconversion rates of 42.9%, 35.7%, and 40.0%, respectively. Furthermore, as compared with placebo recipients, a higher proportion of IIV3 recipients had seroprotective HAI titers after vaccination (Table S5 in the Supplementary Appendix).

The newborns of IIV3 recipients had higher HAI geometric mean titers than did the newborns of placebo recipients. The ratio of geometric mean HAI titers ranged between 0.7 and 1.4; ratios were higher in the placebo group for A/(H1N1) pdm09 (P=0.05) and A/H3N2 (P=0.01). In the IIV3 group, the proportion of newborns with an HAI titer of 1:40 or higher was 60.7% for A/(H1N1) pdm09, 42.9% for A/H3N2, and 78.6% for B/Victoria; titers for all three strains were higher than those in the placebo group (Table S5 in the Supplementary Appendix). Similar findings were observed in the immunogenicity analyses when extended windows for obtaining blood samples were used (Tables S6 and S7 in Supplementary Appendix).

VACCINE EFFICACY

HIV-Uninfected Cohort

The attack rates for confirmed influenza among placebo recipients and IIV3 recipients were 3.6% and 1.8%, respectively, indicating a vaccine efficacy of 50.4% (95% confidence interval [CI], 14.5 to 71.2) (Table 4 and Fig. 1). The vaccine efficacy was similar when determined according to the vaccine strain (46.1%; 95% CI, 6.4 to 69.0). For the 2 years of the study, the predominant strain of influenza virus circulating among placebo recipients was A/H3N2 (57.9%), for which an exploratory analysis identified a vaccine efficacy of 57.5% (95% CI, 7.6 to 80.4).

The attack rate was lower among infants whose mothers were IIV3 recipients (1.9%) than among those whose mothers were placebo recipients (3.6%), indicating a vaccine efficacy of 48.8% (95% CI, 11.6 to 70.4) (Table 4 and Fig. 1). The predominant strains causing illness in the 38 infants of placebo recipients were A/H3N2 (14 infants [37%]), B/Victoria (11 [29%]), and B/Yamagata (12 [32%]). Among infants with confirmed influenza, the numbers infected with the influenza virus strain carried by their mothers were as follows: 1 of 19 infants in the IIV3 group (5.3%) and 11 of 37 in the placebo group (29.7%, P=0.04). The vaccine efficacy estimates in the per-protocol analysis were similar to the estimates in the intention-to-treat analysis for the women and their infants (Table S8 in the Supplementary Appendix).

HIV-Infected Cohort

In the cohort of HIV-infected mothers, the attack rate was lower among IIV3 recipients than among placebo recipients (7.0% vs. 17.0%), indicating an adjusted vaccine efficacy of 57.7% (95% CI, 0.2 to 82.1) (Table 4 and Fig. 1). The attack rates were 5.0% and 6.8% among infants of IIV3 recipients and infants of placebo recipients, respectively (vaccine efficacy, 26.7%; P=0.60) (Table 4 and Fig. 1). In 6 of 11 infants of HIV-infected mothers with confirmed influenza (55%), including 2 infants whose mothers received IIV3, the mothers were infected with the same strain as their infants. Estimates of vaccine efficacy among HIV-infected women and their infants were similar in the per-protocol and intention-to-treat analyses (Table S8 in the Supplementary Appendix).

SAFETY

The details of solicited local and systemic reactions in the HIV-uninfected cohort and the HIV-infected cohort are shown in Tables S9 and S10 in the Supplementary Appendix. Injection-site reactions (mainly mild to moderate) were more frequent among IIV3 recipients than among placebo recipients in both cohorts, but there were no other significant differences in solicited reactions between the two study groups in either cohort. Data on serious adverse events in both cohorts, including infant and maternal deaths and hospitalizations, are shown in Tables S11 to S23 in the Supplementary Appendix. There were no significant between-group differences with regard to rates of miscarriage, stillbirth, or premature birth or birth weight in the HIV-uninfected cohort (Table 1, and Table S11 in the Supplementary Appendix) and in the HIV-infected cohort (Table 2). The findings were similar in an analy-

Table 2. Baseline Characteristics of HIV-Infected Pregnant Women, Fetal Outcomes, and Newborn Characteristics.*

Characteristic or Outcome	Overall	IIV3	Placebo
Women			
Total no. of women	194	100	94
Mean age — yr	28.2±5.1	27.2±4.9†	29.2±5.1†
Mean body-mass index‡	28.7±5.3	29.2±5.0	28.3±5.7
Mean gestational age at enrollment — wk	27.3±3.8	27.6±3.9	26.9±3.7
Gravidity			
Median	2.0	2.0	2.0
Interquartile range	2.0–3.0	2.0–3.0	2.0–3.0
Parity			
Median	1.0	1.0	1.0
Interquartile range	1.0–2.0	1.0–2.0	1.0–2.0
HAART — no. (%)			
At enrollment	60 (30.9)	22 (22.0)†	38 (40.4)†
At delivery	77 (39.7)	33 (33.0)	44 (46.8)
ART for prevention of mother-to-child HIV transmission — no. (%)			
At enrollment	86 (44.3)	54 (54.0)†	32 (34.0)†
At delivery	87 (44.9)	52 (52.0)§	35 (37.2)§
CD4+ T-lymphocyte count — cells/mm^3			
At enrollment¶			
Median	393.5	410.0	379.0
Interquartile range	271.0–557.0	284.0–572.0	245.0–550.0
At post-vaccination visit‖			
Median	399.5	371.0	409.0
Interquartile range	265.0–499.0	255.0–499.0	274.0–500.0
At delivery**			
Median	446.5	441.0	508.0
Interquartile range	330.0–599.00	303.0–549.0	346.0–673.0
HIV-1 viral load — copies/ml			
At enrollment††			
Median	1067.0	1679.0	399.0
Interquartile range	61.0–13,923.0	118.5–15,906.5	39.0–9990.0
At post-vaccination visit‡‡			
Median	620.0	812.0§	292.5§
Interquartile range	39.0–8278.0	130.0–13,221.0	39.0–3056.0
At delivery§§			
Median	265.0	222.0	356.0
Interquartile range	54.0–2040.0	64.0–2262.0	39.0–1880.0
Fetuses and newborns			
Total no. of live-born infants	188	100	88
Twin birth — no. (%)	10 (5.3)	6 (6.0)	4 (4.5)
Type of delivery — no. (%)			
Normal vaginal	111 (59.0)	58 (58.0)	53 (60.2)
Cesarian section	77 (41.0)	42 (42.0)	35 (39.8)
Preterm birth, gestational age <37 wk — no. (%)	26 (13.8)	13 (13.0)	13 (14.8)

Table 2. (Continued.)

Characteristic or Outcome	Overall	IIV3	Placebo
Overall birth weight — kg¶¶			
Median	3.0	2.9	3.0
Range	0.8–4.3	0.8–4.3	1.9–4.0
Birth weight of infants born during influenza season — kg‖‖			
Median	3.0	3.0	3.0
Range	0.8–4.3	0.8–4.3	1.9–4.1
Birth weight of <2500 g — no. (%)¶¶	29 (15.6)	14 (14.1)	15 (17.2)
Death after delivery — no. (%)***	4 (2.1)	2 (2.0)	2 (2.3)
Admission to neonatal nursery — no. (%)	9 (4.8)	6 (6.0)	3 (3.4)

* Plus–minus values are means ± SD. ART denotes antiretroviral therapy, and HAART highly active antiretroviral therapy.
† P<0.01.
‡ Data are based on 81 observations in the IIV3 group and 74 observations in the placebo group.
§ P<0.05.
¶ Numbers are based on 97 observations in the IIV3 group and 93 observations in the placebo group.
‖ Numbers are based on 78 observations in the IIV3 group and 68 observations in the placebo group.
** Numbers are based on 77 observations in the IIV3 group and 69 observations in the placebo group.
†† Numbers are based on 96 observations in the IIV3 group and 91 observations in the placebo group.
‡‡ Numbers are based on 77 observations in the IIV3 group and 64 observations in the placebo group.
§§ Numbers are based on 72 observations in the IIV3 group and 65 observations in the placebo group.
¶¶ Numbers and percentages are based on 99 observations in the IIV3 group and 87 observations in the placebo group.
‖‖ Numbers are based on 88 observations in the IIV3 group and 80 observations in the placebo group.
*** Further details on newborn deaths are provided in Table S17 in the Supplementary Appendix.

sis stratified according to sex and an analysis limited to births that occurred during the influenza season.

DISCUSSION

The trials of IIV3 efficacy in HIV-infected and HIV-uninfected pregnant women showed a reduction in confirmed cases of influenza in both cohorts. Furthermore, we observed protection against confirmed influenza among infants of IIV3 recipients who were not exposed to HIV, with a similar trend observed in infants exposed to HIV. IIV3 was found to be safe, and the vaccine was immunogenic in HIV-uninfected women and HIV-infected women, supporting the current WHO recommendations for influenza vaccination during pregnancy.[19]

The vaccine efficacy against confirmed influenza in infants who were not exposed to HIV (45.6%; 95% CI, 2.4 to 69.7) was similar to that reported in Bangladesh (63%; 95% CI, 5 to 85).[16] However, direct comparisons with the results of the Bangladesh study are limited because of differences in the assays used for viral detection. In addition, influenza virus circulation in Bangladesh is prolonged and perennial, limiting the generalizability of the Bangladesh study to temperate regions with more discrete influenza seasons, such as South Africa.[16] The effectiveness of IIV3 vaccination in protecting the infants of pregnant women not infected with HIV is further corroborated by case–control studies in the United States among American Indians (in which most cases were diagnosed through serologic testing) and by a study of influenza-associated hospitalization in a large urban hospital (in which the diagnosis was confirmed through fluorescent antibody testing).[20,22]

It has been proposed that higher HAI titers may be required to provide protection against influenza in children; in adults, an HAI titer of 1:40 or higher is associated with 50% protection.[31,32,33] Nevertheless, in our study the proportion of HIV-unexposed newborns in the IIV3 group with HAI titers of 1:40 or higher (60 to 82%) suggests that this threshold may be associated with approximately 50% protection against confirmed influenza in such infants. Further studies and analyses are warranted to establish a serocorrelate for the protection of HAI antibodies acquired through the placenta. Another way in which the

vaccination of pregnant women may protect their infants against influenza involves prevention of the transmission of the virus to the infant by reducing the mother's risk of influenza illness. This is corroborated in part by our study, in which concurrent confirmed influenza infection by homotypic strains occurred more frequently in HIV-unexposed infants of placebo recipients than in HIV-unexposed infants of IIV3 recipients; infections with homotypic strains also occurred concurrently in 54.5% of the mothers of HIV-exposed infants with confirmed influenza illness.

Unlike the study in Bangladesh, in which rates of clinical febrile respiratory illness were reduced by 29% and 36% in infants and mothers, respectively,[16] our study did not show any reduction in the less specific outcomes of clinical influenza-like illness or respiratory illness in either infants or mothers. The use of pneumococcal polysaccharide vaccine as the comparator for the control group in the Bangladeshi study, as well as the use of different case definitions, may have contributed to the discrepant findings in the two studies. Observational studies in the United States have also shown that maternal influenza vaccination was not effective in protecting infants against all-cause respiratory illness, indicating the lack of specificity of such end points for the evaluation of influenza vaccine efficacy in infants.[21,23]

The vaccine efficacy against confirmed influenza among HIV-uninfected women in our study (per-protocol analysis, 54.4%; 95% CI, 19.5 to 74.2) was similar to that reported in an observational study of vaccination against monovalent A/(H1N1)pdm09 in pregnant Norwegian women (70%; 95% CI, 66 to 75)[33] and in a more recent case–control study in the United States (44 to 53%).[17] The vaccine efficacy against confirmed influenza in HIV-infected pregnant women in our study (per-protocol analysis, 70.6%) was similar to that reported in a trial of IIV3 in South African HIV-infected men and women during the 2008 influenza epidemic (75.5%).[34] The efficacy of the vaccine in our study was also similar to that reported in a meta-analysis of HIV-infected adults in high-income countries (66%; 95% CI, 36 to 82).[35] Notably, the attack rate among HIV-infected placebo recipients in our study (17.0%) was greater than that observed among HIV-uninfected placebo recipients (3.6%), a finding that highlights the greater susceptibility of HIV-infected persons to influenza, even when the HIV infection is managed with antiretroviral treatment.

Extrapolation of the potential effect of influenza vaccination in pregnancy solely on the basis of HAI immune responses may be affected by pregnancy-inducing immune tolerance, which could influence vaccine effectiveness.[4,5,36] The availability of immunogenicity and efficacy data in our nested immunogenicity study helped to address this question. The proportions of HIV-uninfected IIV3 recipients with seroprotective HAI titers for A/(H1N1)pdm09, A/H3N2, and B/Victoria were 93.3%, 78.0%, and 96.0%, respectively, with corresponding overall vaccine efficacy against confirmed influenza of 54.4%. These findings suggest that the threshold of 1:40 or higher was predictive of an anticipated vaccine efficacy of 50%, as proposed for healthy adults.[31] Theoretically, the rate of naturally acquired immunity among placebo recipients (20 to 45%) could have decreased the true efficacy of the vaccine, a consideration that would not be required in an immunologically naive placebo group of women not infected with influenza.

Among IIV3 recipients in the HIV-infected cohort, HAI titers of 1:40 or higher were observed for A/H3N2 and A/(H1N1)pdm09 (48.6% and 68.6%, respectively). Consequently, the HAI titer of 1:40 or higher, as a relative serocorrelate of protection, would have paradoxically underestimated vaccine efficacy against confirmed influenza among the HIV-infected women (reported as 70.6%). This observation is consistent with findings from our previous study involving HIV-infected adults.[34] Among the HIV-infected cohort, IIV3 did not affect the plasma HIV-1 viral load, minimizing concern about the possibility of an increased risk of vertical transmission of HIV in vaccinees.[37,38]

One of the limitations of our study is the fact that it was conducted at a single center; the generalizability of the findings needs to be corroborated. Furthermore, the timing of enrollment was contingent on the commercial availability of IIV3. Although we initiated enrollment within 1 week after vaccine availability, vaccination extended into the influenza season, with some births occurring after the influenza season. The difference in duration of exposure to the influenza virus between the women and their infants limited our ability to make a direct comparison of the attack

Table 3. Immune Responses to IIV3 Vaccine in HIV-Uninfected Pregnant Women and Transplacental Transfer of Antibodies to Newborns.*

Measure	A(H1N1)pdm09			A/H3N2			B/Victoria		
	IIV3	Placebo	P Value†	IIV3	Placebo	P Value†	IIV3	Placebo	P Value†
Mothers									
Total no. of mothers	142	148		142	148		142	148	
Geometric mean HAI titer (95% CI)									
Before vaccination	30.7 (25.5–37.0)	27.2 (21.8–34.0)	0.41	14.6 (124–17.0)	14.0 (11.8–16.6)	0.74	17.6 (15.6–19.9)	15.4 (13.4–17.7)	0.15
After vaccination	213.4 (175.7–259.2)	29.1 (23.0–36.8)	<0.001	87.8 (70.5–109.2)	16.0 (13.3–19.1)	<0.001	175.5 (148.7–207.3)	16.9 (14.6–19.6)	<0.001
P value‡	<0.001	0.30		<0.001	0.005		<0.001	0.05	
Factor increase in geometric mean HAI titer (95% CI)	6.9 (5.6–8.6)	1.1 (0.9–1.2)	<0.001	6.0 (4.9–7.4)	1.1 (1.0–1.2)	<0.001	10.0 (8.4–11.8)	1.1 (1.0–1.2)	<0.001
HAI titer ≥1:40 — no. (%); (95% CI)									
Before vaccination	73 (51.4); (42.9–59.9)	66 (44.6); (36.4–53.0)	0.73	33 (23.2); (16.6–31.1)	37 (25.0); (18.3–32.8)	0.25	29 (20.4); (14.1–27.7)	30 (20.3); (14.1–28.0)	0.97
After vaccination	133 (93.7); (88.3–97.1)	71 (47.8); (40.4–57.0)	<0.001	112 (78.9); (71.2–85.3)	40 (27.0); (20.1–35.0)	<0.001	138 (97.2); (92.9–99.2)	43 (29.1); (21.9–37.1)	<0.001
P value‡	0.006	0.37		0.001	0.43		<0.001	<0.001	
Seroconversion 1 mo after vaccination — no. (%); (95% CI)	103 (72.5); (64.4–79.7)	12 (8.1); (4.3–13.7)	<0.001	92 (64.8); (56.3–72.6)	4 (2.7); (0.7–6.8)	<0.001	131 (92.3); (86.6–96.1)	3 (2.0); (0.4–5.8)	<0.001
Newborns									
Total no. of newborns	95	103		95	103		95	103	
Geometric mean HAI titer at ≤7 days of age (95% CI)	93.3 (71.1–122.4)	17.2 (13.8–22.7)	<0.001	41.8 (31.6–55.3)	12.7 (10.6–15.1)	<0.001	80.6 (64.9–100.1)	21.4 (17.8–25.7)	<0.001
Ratio of newborn to maternal HAI titer (95% CI)§	0.7 (0.6–0.8)	0.7 (0.6–0.8)	0.78	0.7 (0.6–0.9)	0.7 (0.6–0.8)	0.49	0.8 (0.7.–0.9)	1.0 (0.9–1.2)	0.04
HAI titer ≥1:40 at <7 days of age — no. (%); (95% CI)¶	77 (81.1); (71.7–88.4)	35 (34.0); (24.9–44.0)	<0.001	57 (60.0); (49.4–69.9)	18 (17.5); (10.7–26.2)	<0.001	78 (82.1); (72.9–89.2)	45 (43.7); (33.9–53.8)	<0.001

* HAI denotes hemagglutination inhibition.
† These P values are for the comparison of the IIV3 and placebo groups.
‡ These P values are for the comparison of values within a group before and after vaccination.
§ The ratio of the newborn HAI titer to the maternal HAI titer was based on 93 observations in the IIV3 group and 102 observations in the placebo group.
¶ P values were adjusted for the mean number of days from maternal vaccination to birth.

Table 4. Efficacy of IIV3 Vaccination in Mothers and Infants until 24 Weeks after Birth, Intention-to-Treat Population.*

Efficacy End Point	HIV-Uninfected Cohort				HIV-Infected Cohort			
	IIV3 (N=1026)	Placebo (N=1023)	Vaccine Efficacy	P Value	IIV3 (N=100)	Placebo (N=88)	Vaccine Efficacy	P Value
Infants								
RT-PCR–confirmed influenza — no. (%); (95% CI)								
With inclusion of B/Yamagata	19 (1.9); (1.1 to 2.9)†	37 (3.6); (2.6 to 5.0)†‡	48.8 (11.6 to 70.4)	0.01	5 (5.0); (1.6 to 11.3)§	6 (6.8); (2.5 to 14.3)§	26.7 (–132.0 to 76.8)	0.60
With exclusion of B/Yamagata	13 (1.3); (0.7 to 2.2)	25 (2.4); (1.6 to 3.6)	48.2 (–0.8 to 73.3)	0.05	4 (4.0); (1.1 to 9.9)	3 (3.4); (0.7 to 9.6)	14.8 (–270.4 to 80.4)	0.57
Influenza-like illness — no. (%); (95% CI)	595 (58.0); (54.9 to 61.0)	584 (57.1); (54.0 to 60.1)	–1.6 (–9.4 to 5.7)	0.68	66 (66.0); (55.8 to 75.2)	57 (64.8); (53.9 to 74.7)	–1.9 (–25.5 to 17.3)	0.86
Any respiratory illness — no. (%); (95% CI)	706 (68.8); (65.9 to 71.6)	697 (68.1); (65.2 to 71.0)	–1.0 (–7.1 to 4.8)	0.74	76 (76.0); (66.4 to 84.0)	70 (79.5); (69.6 to 87.4)	4.5 (–11.3 to 18.0)	0.56
	IIV3 (N=1062)	Placebo (N=1054)	Vaccine Efficacy	P Value	IIV3 (N=100)	Placebo (N=94)	Vaccine Efficacy	P Value
Women								
RT-PCR confirmed influenza — no. (%)								
With inclusion of B/Yamagata	19 (1.8); (1.1 to 2.8)¶	38 (3.6); (2.6 to 4.9)¶	50.4 (14.5 to 71.2)	0.010	7 (7.0); (2.9 to 13.9)‖	16 (17.0); (10.1 to 26.2)‖	57.7 (0.2 to 82.1)	0.05
With exclusion of B/Yamagata	19 (1.8); (1.1 to 2.8)	35 (3.3); (2.3 to 4.6)	46.1 (6.4 to 69.0)	0.03	7 (7.0); (2.9 to 13.9)	13 (13.8); 7.6 to 22.5	48.2 (–27.0 to 78.8)	0.15
Influenza-like illness — no. (%)	175 (16.5); (14.3 to 18.8)	181 (17.2); (14.9 to 19.6)	4.0 (–16.0 to 20.6)	0.67	24 (24.0); (16.0 to 33.6)	27 (28.7); (19.9 to 39.0)	–0.07 (–63.7 to 38.8)	0.99
Any respiratory illness — no. (%)	674 (63.5); (60.5 to 66.4)	687 (65.2); (62.2 to 68.1)	2.6 (–3.7 to 8.6)	0.41	72 (72.0); (62.1 to 80.5)	73 (77.7); (67.9 to 85.6)	5.2 (–12.2 to 19.8)	0.54

* Vaccine efficacy in HIV-infected women was adjusted for maternal age and status with respect to antiretroviral treatment at enrollment. RT-PCR denotes reverse-transcriptase–polymerase-chain-reaction.

† Among HIV-unexposed infants of IIV3 recipients and placebo recipients, there were 0 and 1 cases of infection with A/(H1N1)pdm09, 7 and 14 cases of infection with A/H3N2, 6 and 11 cases of infection with B/Victoria, and 6 and 12 cases of infection with B/Yamagata, respectively.

‡ One baby born to a placebo recipient had a single influenza episode during which both A/(H1N1)pdm09 and A/H3N2 were detected.

§ Among HIV-exposed infants of IIV3 recipients and placebo recipients, infection with A/(H1N1)pdm09 occurred in 2 and 0 infants, respectively, infection with A/H3N2 occurred in 2 infants in each group, infection with B/Victoria occurred in 0 and 1 infants, respectively, and infection with B/Yamagata occurred in 1 and 3 infants, respectively.

¶ Among HIV-uninfected IIV3 recipients and placebo recipients, there were 5 and 6 cases of influenza virus strain A/(H1N1)pdm09, 10 and 22 cases of A/H3N2, 4 and 7 cases of B/Victoria, and 0 and 3 cases of B/Yamagata, respectively.

‖ Among HIV-infected IIV3 recipients and placebo recipients, there were 6 and 8 cases of influenza virus strain A/(H1N1)pdm09, 1 and 4 cases of A/H3N2, 0 and 1 case of B/Victoria, and 0 and 3 cases of B/Yamagata, respectively.

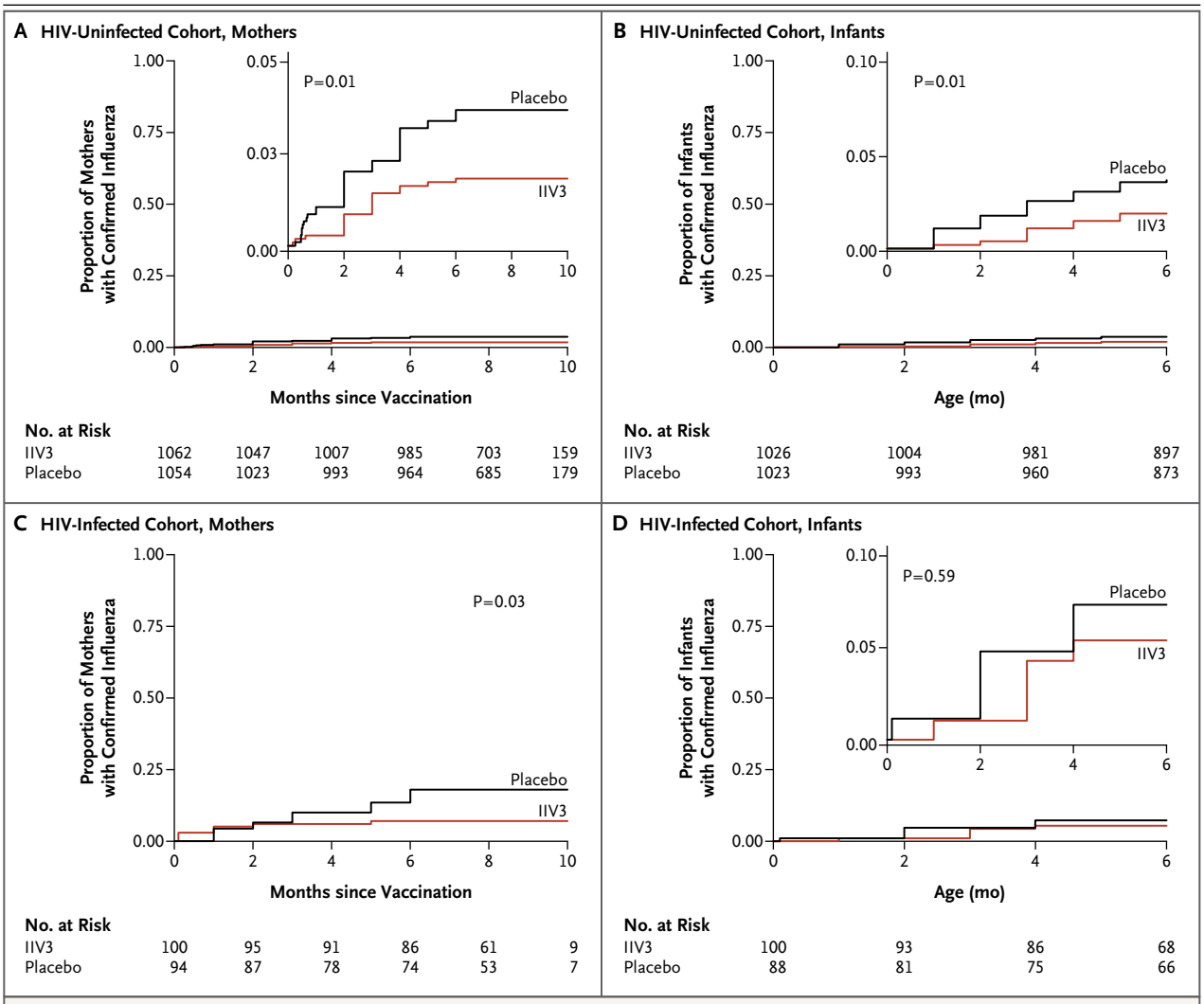

Figure 1. Kaplan–Meier Estimates of Percentages of Confirmed Cases of Influenza According to Cohort and Study Group.

Confirmed influenza was defined as influenza diagnosed by means of reverse-transcriptase–polymerase-chain-reaction assay. The insets show the same data on an expanded y axis. HIV denotes human immunodeficiency virus, and IIV3 trivalent inactivated influenza vaccine.

rates between them and between these infants and those in the Bangladeshi study, for whom exposure was probably more prolonged.[16,39] Another limitation of our study is the fact that the evaluation of vaccine efficacy among HIV-infected women was a secondary objective; nevertheless, its efficacy in these women was indicated by the high attack rate in the placebo group. However, the study lacked power to evaluate vaccine efficacy among the infants of HIV-infected women, for whom the point estimate was similar to that for HIV-uninfected infants in the per-protocol analysis. Although 23% of the HIV-infected and uninfected immunogenicity cohorts were outside the protocol-defined windows for obtaining post-vaccination blood samples, the results were similar to those included in the exploratory immunogenicity analysis with an expanded window. An inadvertent occurrence in the study was the difference in HIV disease characteristics between the placebo group and the IIV3 group, including the fact that placebo recipients were more likely to be receiving highly active antiretroviral therapy. However, this factor would

have biased the results in the direction of a reduced risk of influenza in the placebo group.[7] In addition, in HIV-infected women, the lower HAI titers among placebo recipients as compared with IIV3 recipients could have been due to differences in HIV disease stage between the groups.

In conclusion, these data show that IIV3 vaccination in pregnant HIV-uninfected and HIV-infected African women was immunogenic and provided protection against confirmed influenza. The vaccination was also effective in HIV-unexposed infants up until 24 weeks after birth.

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APPENDIX

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