Effectiveness of Influenza Vaccination of Pregnant Women for Prevention of Maternal and Early Infant Influenza-Associated Hospitalizations in South Africa: A Prospective Test-Negative Study

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Background. Influenza vaccination during pregnancy reduces influenza-associated illness in the women and their infants, but effectiveness estimates against influenza-associated hospitalization are limited and lacking from settings with high human immunodeficiency virus (HIV) infection prevalence. We assessed the effect of maternal vaccination in HIV-uninfected women and women with HIV in preventing influenza-associated hospitalizations in infants and the women.

Methods. During 2015–2018, influenza vaccination campaigns targeting pregnant women were augmented at selected antenatal clinics; these were coupled with prospective hospital-based surveillance for acute respiratory or febrile illness in infants aged <6 months and cardiorespiratory illness among pregnant or postpartum women. Vaccine effectiveness (VE) was assessed using a test-negative case-control study.

Results. Overall, 71 influenza-positive and 371 influenza-negative infants were included in the analysis; mothers of 26.8% of influenza-positive infants were vaccinated during pregnancy compared with 35.6% of influenza-negative infants, corresponding to an adjusted VE (aVE) of 29.0% (95% confidence interval [CI], −33.6% to 62.3%). When limited to vaccine-matched strains, aVE was 65.2% (95% CI, 11.7%–86.3%). For maternal hospitalizations, 56 influenza-positive and 345 influenza-negative women were included in the analysis, with 28.6% of influenza-positive women being vaccinated compared with 38.3% of influenza-negatives, for an aVE of 46.9% (95% CI, −2.8% to 72.5%). Analysis restricted to HIV-uninfected women resulted in 82.8% (95% CI, 40.7%–95.0%) aVE. No significant aVE (=32.5% [95% CI, −208.7% to 43.1%]) was detected among women with HIV.

Conclusions. Influenza vaccination during pregnancy prevented influenza-associated hospitalizations in young infants when infected with vaccine strains and among HIV-uninfected women.

Keywords. influenza; pregnancy; vaccine.

Randomized controlled trials (RCTs) performed in low- and middle-income countries (LMICs) have demonstrated that the efficacy of seasonal influenza vaccination during pregnancy is 50%–70% in preventing mild to moderately severe laboratory-confirmed influenza-associated illness in pregnant women [1, 2]. After vaccination, maternal antibodies cross the placenta and may offer protection to the infant during the first months of life. Therefore, an additional benefit of maternal vaccination has been the protection of the young infants. Maternal vaccination to protect young infants is pertinent since there is no influenza vaccine approved for use in infants aged <6 months. A meta-analysis of 4 RCTs in pregnant women revealed a combined vaccine efficacy of 36% (95% confidence interval [CI], 22%–48%) against laboratory-confirmed influenza-associated illness in infants aged <6 months [1–5]. Vaccine efficacy was higher if the analyses were restricted to the first 8 weeks (86%) or 4 months (68%) of life [2, 6].
Vaccination was also documented at the discretion of the attend-
women attending those clinics to at least 50% [2]. Active surveillance was conducted among infants aged <6 months by vaccinating pregnant women in reducing the risk of poly-
merase chain reaction (PCR)–confirmed influenza-associated hospitaliza-
tion, hemagglutination inhibition, and H1-hemagglutinin stalk domain antibodies following vaccination compared with those without human immunodeficiency virus (HIV) [7–9], the overall vaccine efficacy against influenza-associated illness was similar in both groups (57.7% and 50.4%, respectively) [1]. The study in WLWH was not powered to detect vaccine efficacy in the HIV-exposed infants; nevertheless, similar influenza attack rates were detected in infants born to WLWH in the vaccinated (5.0%) or placebo (6.8%) groups. Attack rates were lower in infants of HIV-uninfected placebo recipients (3.6%) [1].

The low incidence of influenza-associated hospitalization within each influenza season poses a challenge to demonstrate the effectiveness of influenza vaccination against severe disease. Nonetheless, a few observational studies, mainly from Europe and the United States (US), have reported a 45%–92% reduction of laboratory-confirmed influenza-associated hospitalizations in infants aged <6 months by vaccinating pregnant women [3, 10–15]. Furthermore, a multicountry study conducted in Australia, Canada, Israel, and the US reported a vaccine effectiveness (VE) of 40% (95% CI, 12%–59%) against influenza-associated hospitalizations in pregnant women from 2010 to 2016 [16].

Understanding the effect of influenza vaccination on severe influenza outcomes in infants and during pregnancy in LMICs, including among WLWH and their infants, will help to delineate the potential benefit of the maternal immunization programs in these countries. We conducted a prospective test-negative study over 4 consecutive influenza seasons. The primary objective was to evaluate the effectiveness of influenza vaccination of pregnant women in reducing the risk of polymerase chain reaction (PCR)–confirmed influenza-associated hospitalization in their infants during the first 6 months of life, and to estimate VE in pregnant or postpartum women.

METHODS

From 2015 to 2018, once the inactivated influenza vaccine (IIV) formulated for the Southern Hemisphere was available in South Africa, we provided additional IIV doses to selected antenatal clinics in 2 South African cities (Johannesburg and Cape Town), aiming to increase vaccination coverage of pregnant women attending those clinics to at least 50% [17]. Study staff based at the clinics compiled vaccination registers of the women attending the clinics during the period that IIV was available. Vaccination was also documented at the discretion of the attend-
ing nurse on the individual maternal antenatal cards. Prospective active surveillance was conducted among infants aged <6 months hospitalized for acute respiratory or febrile illness (ARI/FI), from when IIV was available to the end of each calendar year, at 4 hospitals in the 2 cities; and among pregnant women and women within 42 days postdelivery hospitalized for cardiorespiratory illness in 6 hospitals during the influenza seasons. More details on study design and population are shown in the Supplementary Material. Enrolled participants had respirato-
ry swabs collected and tested by real-time PCR for influenza as previously described [1, 18]. Influenza A–positive samples were subtyped as A(H1N1)pdm09 or A(H3N2). All A(H1N1) pdm09 viruses were considered to be vaccine-matched as they belonged to the 6B lineage with antigenic characteristics similar to vaccine strains; for A(H3N2) each year we compared the dominant lineage circulating in South Africa with the vaccine lineage and considered them matched or unmatched (Supplementary Table 1) [19–23]. Influenza B–positive samples were typed as Victoria or Yamagata lineages and compared with the vaccine lineages (Supplementary Table 1).

Influenza Vaccination

During the study period, only trivalent IIV formulations were available. The virus strains contained in the vaccines recom-

From the previous RCTs, only a South African trial assessed vac-
cine immunogenicity and efficacy among pregnant women living with human immunodeficiency virus (WLWH) and their infants [1]. In that study, despite WLWH having lower levels of neutraliza-
tion, hemagglutination inhibition, and H1-hemagglutinin stalk domain antibodies following vaccination compared with those without human immunodeficiency virus (HIV) [7–9], the overall vaccine efficacy against influenza-associated illness was similar in both groups (57.7% and 50.4%, respectively) [1]. The study in WLWH was not powered to detect vaccine efficacy in the HIV-exposed infants; nevertheless, similar influenza attack rates were detected in infants born to WLWH in the vaccinated (5.0%) or placebo (6.8%) groups. Attack rates were lower in infants of HIV-uninfected placebo recipients (3.6%) [1].

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VE was calculated as 1 – odds ratio [ratio of odds of vaccination among cases to the odds of vaccination among controls] × 100% using logistic regression. Both VE estimates were adjusted for HIV infection (maternal analysis) or HIV exposure (infant analysis) and any other variables that were significantly associated with the exposure (vaccination) or the outcome (influenza infection) on univariate analysis. Other potential confounder variables were evaluated by assessing if they altered the VE estimates; however, none changed the adjusted VE by >10% and thus were not included in the final model. A variable was created to define influenza season timing at hospital admission by dividing each influenza season into early, middle, and late season tertiles of equal duration; for the infant analysis, an “outside of season” period was also considered. The South African influenza seasons were defined using data from the influenza sentinel surveillance from the National Institute for Communicable Diseases [24]. Descriptive statistics were used to characterize cases and controls and the proportion of women who received IIV.

### Table 1. Characteristics of Hospitalized Infants Born to Mothers With Known Influenza Vaccination Status Who Tested Influenza Polymerase Chain Reaction Positive and Randomly Selected Control Infants Testing Influenza Negative—South Africa, 2015–2018

| Characteristic                                      | Influenza-Positive Cases (n = 71) | Influenza-Negative Controls (n = 371) | P Value |
|-----------------------------------------------------|-----------------------------------|--------------------------------------|---------|
| **Age at admission**                                |                                   |                                      |         |
| Mean age, d (SD)                                    | 66.2 (38.4)                       | 46.2 (37.2)                          | <.001   |
| <3 mo                                               | 54 (76.1)                         | 316 (85.2)                           | .057    |
| 3–5 mo                                              | 17 (23.9)                         | 55 (14.8)                            |         |
| **HIV exposure**                                    |                                   |                                      |         |
| Exposed                                             | 16/70 (22.9)                      | 67 (18.1)                            | .35     |
| Unexposed                                           | 54/70 (77.1)                      | 304 (81.9)                           |         |
| **Sex**                                             |                                   |                                      |         |
| Male                                                | 41 (57.8)                         | 206 (55.5)                           | .73     |
| Female                                              | 30 (42.3)                         | 165 (44.5)                           |         |
| **Race**                                            |                                   |                                      |         |
| Black African                                       | 50 (70.4)                         | 269 (72.5)                           | .94     |
| South African Coloured                              | 19 (26.8)                         | 89 (24.0)                            |         |
| White                                               | 1 (1.4)                           | 8 (2.2)                              |         |
| Asian                                               | 1 (1.4)                           | 5 (1.4)                              |         |
| **Term (≥37 wk gestation) or normal birthweight (≥2500 g)** |                                   |                                      |         |
| Yes                                                 | 57 (80.3)                         | 318 (85.7)                           | .24     |
| No                                                  | 14 (19.7)                         | 53 (14.3)                            |         |
| **Ever breastfed**                                  |                                   |                                      |         |
| Yes                                                 | 54/69 (78.3)                      | 301/364 (82.7)                       | .38     |
| No                                                  | 15/69 (21.7)                      | 63/364 (17.3)                        |         |
| **Study site**                                       |                                   |                                      |         |
| Chris Hani Baragwanath Academic Hospital, Johannesburg | 26 (36.6)                         | 159 (42.9)                           | .74     |
| Rahima Moosa Mother and Child Hospital, Johannesburg  | 17 (23.9)                         | 77 (20.8)                            |         |
| Red Cross Hospital, Cape Town                        | 26 (36.6)                         | 121 (32.6)                           |         |
| Mitchell’s Plain Hospital, Cape Town                 | 2 (2.8)                           | 14 (3.8)                             |         |
| Antenatal clinic attended supplemented with vaccine  |                                   |                                      |         |
| Yes                                                 | 42/64 (65.6)                      | 214/348 (61.5)                       | .53     |
| No                                                  | 22/64 (34.4)                      | 134/348 (38.5)                       |         |
| **Year of enrollment**                              |                                   |                                      |         |
| 2015                                                | 12 (16.9)                         | 49 (13.2)                            | .58     |
| 2016                                                | 24 (33.8)                         | 111 (29.9)                           |         |
| 2017                                                | 14 (19.7)                         | 98 (26.4)                            |         |
| 2018                                                | 21 (29.6)                         | 113 (30.5)                           |         |
| **Period of influenza season**                      |                                   |                                      |         |
| Early                                               | 14 (19.7)                         | 66 (17.8)                            | .46     |
| Middle                                              | 20 (28.2)                         | 118 (31.8)                           |         |
| Late                                                | 28 (39.4)                         | 129 (34.8)                           |         |
| Outside                                             | 9 (12.7)                          | 58 (15.8)                            |         |
| **Influenza vaccination during pregnancy (>13 d before delivery)** |                                   |                                      | .15     |
| Yes                                                 | 19 (26.8)                         | 132 (35.6)                           |         |
| No                                                  | 52 (73.2)                         | 239 (64.4)                           |         |

Values are presented as No. (%) unless stated otherwise. The number of participants with available information is indicated (no./No.) if different from the total number of participants. Abbreviations: HIV, human immunodeficiency virus; SD, standard deviation.
**Table 2. Effectiveness of Influenza Vaccine Administered in Pregnancy Against Influenza-Confirmed Hospitalization in Infants <6 Months of Age—South Africa, 2015–2018**

| Characteristic | Influenza Positive, No. Vaccinated/Total No. | Influenza Negative, No. Vaccinated/Total No. | Unadjusted VE, % (95% CI) | Adjusted VE, % (95% CI)* |
|---------------|---------------------------------------------|---------------------------------------------|---------------------------|--------------------------|
| All infants   |                                             |                                             |                           |                          |
| Overall       | 19/71                                       | 132/371                                     | 33.8 (−16.6 to 62.5)      | 29.0 (−33.6 to 62.3)     |
| Born at term  | 16/57                                       | 122/318                                     | 37.3 (−16.6 to 66.3)      | 38.4 (−23.5 to 69.3)     |
| Admitted to hospital at <3 mo of age | 14/54                                       | 120/316                                     | 42.8 (−9.5 to 70.1)       | 42.8 (−17.0 to 72.0)     |
| Vaccine-matched strains | 7/43                                        | 132/371                                     | 64.8 (18.7–84.8)          | 65.2 (11.7–86.3)         |
| Born at term  | 6/35                                        | 122/318                                     | 69.8 (17.6–86.6)          | 69.3 (15.1–88.9)         |
| Admitted to hospital at <3 mo of age | 6/36                                        | 120/316                                     | 70.6 (19.2–86.8)          | 70.6 (21.0–89.1)         |
| HIV unexposed |                                             |                                             |                           |                          |
| Overall       | 15/54                                       | 111/304                                     | 33.1 (−26.8 to 64.7)      | 24.1 (−55.1 to 62.8)     |
| Born at term  | 12/41                                       | 104/267                                     | 35.1 (−32.7 to 68.3)      | 34.6 (−45.9 to 70.6)     |
| Admitted to hospital at <3 mo of age | 10/39                                       | 100/259                                     | 45.2 (−17.4 to 74.4)      | 43.8 (−29.3 to 75.6)     |
| Vaccine-matched strains | 6/31                                        | 111/304                                     | 58.3 (−4.8 to 83.4)       | 50.6 (−39.6 to 82.5)     |
| Born at term  | 5/23                                        | 104/267                                     | 56.5 (−20.8 to 84.3)      | 55.8 (−35.2 to 85.6)     |
| Admitted to hospital at <3 mo of age | 5/26                                        | 100/259                                     | 62.1 (−3.6 to 86.2)       | 62.2 (−10.7 to 87.1)     |
| HIV exposed   |                                             |                                             |                           |                          |
| Overall       | 4/16                                        | 21/67                                       | 27.0 (−153.3 to 78.9)     | 28.7 (−226.4 to 84.4)    |
| Born at term  | 4/15                                        | 18/51                                       | 33.3 (−139.9 to 81.5)     | 58.5 (−125.6 to 92.4)    |
| Admitted to hospital at <3 mo of age | 4/14                                        | 20/67                                       | 26.0 (−168.4 to 79.4)     | 26.7 (−232.5 to 83.0)    |
| Vaccine-matched strains | 1/11                                        | 21/67                                       | 78.1 (−82.4 to 97.4)      | 87.9 (−48.5 to 99.0)     |
| Born at term  | 1/11                                        | 18/51                                       | 81.7 (−54.9 to 97.8)      | 96.1 (10.0–99.8)         |
| Admitted to hospital at <3 mo of age | 1/9                                         | 20/67                                       | 76.9 (−98.3 to 97.3)      | 86.9 (−61.7 to 98.9)     |

Values in bold denote significant vaccine effectiveness estimates. Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; VE, vaccine effectiveness.

*Vaccine effectiveness overall adjusted for year of study, hospital, period of influenza season when hospitalization occurred, age at hospitalization, antenatal clinic attended by the mother being supplemented with vaccine (yes or no), born at term (yes or no), and HIV exposure status.

In the primary infant analysis, VE was estimated for hospitalizations associated with any PCR-confirmed influenza illness from birth until 6 months of age. Subgroup analyses were conducted by HIV infection status of the mother (ie, HIV exposure), restricted to infants born at term (defined as infants born at ≥37 weeks’ gestation or with a birthweight ≥2500 g) or to infants admitted at <3 months of age. For the maternal analysis, VE was estimated for hospitalizations occurring during the influenza seasons associated with any PCR-confirmed influenza illness at any stage during pregnancy and up until 42 days postpartum; subgroup analyses were conducted by HIV infection status. Both infant and maternal analyses were also done to estimate VE limited to viruses matched with the vaccine strains for each year. Odds ratios were considered statistically significant when the 95% CIs did not overlap 1.0. Analyses were performed with Stata software, version 13.1 (StataCorp, College Station, Texas).

**Patient Consent Statement**

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M140826) and University of Cape Town (835/2014) and conducted in accordance with Good Clinical Practice guidelines. The Centers for Disease Control and Prevention Institutional Review Board (IRB) relied on the local IRB review (#6746, 45 Code of Federal Regulations [CFR] part 46; 21 CFR part 56). Written informed consent was obtained from the infants’ legal guardian or the hospitalized women.

**RESULTS**

Each year, the vaccination of pregnant women started as soon as IIV was available in the country. The timing of vaccine availability was 22 April–31 July 2015; 4 April–16 August 2016; 3 April–16 August 2017; and 13 March–29 June 2018.

**Infant Analyses**

Overall, 3484 infants aged <6 months born to women eligible to have received IIV during pregnancy and who were born at least 14 days after vaccines were available were hospitalized with ARI/FI at the participating hospitals and enrolled in the study. All the infants were tested by PCR for influenza virus, of whom 83 (2.4%) had a positive result. Maternal vaccination status was unavailable for 3 of the 83 (3.6%) infants and, for another 9 (10.8%), their mothers were vaccinated <14 days before delivery. Among all the influenza-negative infants enrolled, 421 were randomly selected, of whom 25 (5.9%) were excluded because maternal vaccination status was unavailable and 25 because their mothers were vaccinated <14 days before delivery. Accordingly, 71 influenza-positive and 371 influenza-
negative infants were included in the analysis (Supplementary Figure 1).

Infant cases were older than controls (mean age, 66.2 vs 46.2 days; \( P < .001 \)), whereas all other demographic characteristics were similar between the 2 groups (Table 1).

Overall, 151 (34.3%) infants were born to vaccinated mothers, and 291 (65.7%) were born to unvaccinated mothers. Infants born to vaccinated mothers compared with unvaccinated mothers, were younger at hospital admission, and a higher percentage were born at term. Furthermore, a higher percentage of vaccinated mothers attended antenatal care at the clinics where vaccines were supplied by the study. Other significant differences between the vaccinated and unvaccinated group were year of enrollment and timing during the influenza season that hospitalization occurred (Supplementary Table 2).

Across study seasons and sites, 26.8% (19/71) of mothers of the infant cases were vaccinated during pregnancy compared with 35.6% (132/371) of the control infants, yielding an adjusted VE (aVE) of 29.0% (95% CI, −3.3% to 62.3%). Similar non-significant aVE point estimates were obtained when restricting the analysis to infants <3 months old or to infants born at term. When only vaccine-matched strains across the different years were included in the analysis (ie, excluding 4 influenza B un-subtyped cases, 18 influenza B/Victoria, and 6 influenza B/Yamagata), aVE was 65.2% (95% CI, 11.7%–86.3%), with similar VE in infants <3 months old or born at term (Table 2).

Among HIV-unexposed infants, the maternal vaccination coverage was 27.8% in the cases and 36.8% in controls, corresponding to an aVE of 24.1% (95% CI, −55.1% to 62.8%). Only 16 PCR-confirmed influenza virus infections were detected among HIV-exposed infants and 25% of their mothers were vaccinated compared to 31.4% of mothers from control infants, for an aVE of 28.7% (95% CI, −226.4% to 84.4%). Similar VE point estimates were obtained in both HIV exposure–stratified groups restricting the analyses to infants <3 months old or born at term. For only vaccine-matched strains, the aVE was 50.6% (95% CI, −39.6% to 82.5%) among HIV-unexposed infants and 87.9% (95% CI, −48.5% to 99.0%) for HIV-exposed infants (Table 2).

**Maternal Analyses**

During the study period, 415 pregnant or postpartum women eligible to have received IIV during pregnancy were hospitalized during the influenza seasons at least 14 days after IIV was available. Fifty-nine (14.2%) PCR-confirmed influenza cases were detected, among whom vaccination status was unavailable for 3 (5.1%). Among the 356 influenza-negative controls, 3 (0.8%) had unknown vaccination status, 1 (0.3%) was vaccinated but date was missing, and 7 (2.0%) received vaccine <14 days before hospitalization. Therefore, 56 cases and 345 controls were included in the maternal analysis (Supplementary Figure 2). Cases and controls had similar characteristics (Table 3). Overall, 148 (36.9%) women received IIV before admission; vaccinated and unvaccinated women differed by admitting hospital, pregnancy trimester at admission, and year of hospitalization (Supplementary Table 3).

Overall, 28.6% of the cases were vaccinated compared with 38.3% of the controls, for an aVE of 46.9% (95% CI, −2.8% to 72.5%). When analysis was stratified by HIV infection status, HIV-uninfected women had a vaccination coverage of 10.7% among cases and 40.3% among controls, resulting in an aVE of 82.8% (95% CI, 40.7%–95.0%). In WLWH, vaccination coverage was 46.4% and 35.8% among cases and controls, respectively (aVE, −32.5% [95% CI, −208.7% to 43.1%]). Similar results were obtained when restricted to vaccine-matched strains (Table 4).

**Circulating Strains**

The percentage of influenza strains detected among study participants matched to the annual vaccines’ formulations varied from 38.7% in 2018, when 2 distinct peaks of A(H1N1)pdm09 and influenza B/Victoria (vaccine mismatch) were detected in the country, to 93% in 2016 when there was a good match between influenza B and A(H3N2) co-circulating strains and the vaccine strains (Table 5).

**DISCUSSION**

In our study covering 4 consecutive influenza seasons, influenza vaccination during pregnancy had an estimated effectiveness of 65% against influenza-associated hospital admissions in young infants, although VE was only demonstrated against influenza viruses considered to be vaccine matches. Overall, 84% of all enrolled infants were aged <3 months at hospital admission, and therefore the VE point estimates were similar considering all ages or restricting to infants aged <3 months. In a stratified analysis by HIV exposure status, although the VE point estimates for vaccine-matched strains were 58% for HIV-unexposed infants and 78% for HIV-exposed infants, these were nonsignificant, due to the small number of cases that only provided power of 48% and 27%, respectively.

During the study period, surveillance was also performed for influenza-associated hospitalizations among women. Among HIV-uninfected women, high VE estimates were detected either for all influenza (82%) and for vaccine-matched strains only (85%). In this study, maternal influenza vaccination did not demonstrate effectiveness against hospitalization in WLWH.

In previous RCTs over 2 influenza seasons in South Africa, the efficacy of influenza vaccination during pregnancy against any PCR-confirmed influenza illness was similar among HIV-uninfected women (50.4% [95% CI, 14.5%–71.2%]) and WLWH (57.7% [95% CI, 2.0%–82.1%]), notwithstanding WLWH having lower humoral immune responses following
The efficacy of influenza vaccination against confirmed influenza illness was also 75.5% (95% CI, 9.2%–95.6%) among nonpregnant South African adults with HIV. We are not aware of any study reporting on the efficacy of influenza vaccination specifically against influenza-associated hospitalization among people with HIV. Residual confounding inherent to observational studies may, however, explain the differences in the current results with the RCTs. Throughout the entire study, both influenza A and B viruses circulated in South Africa. Genetic data showed that during the study period, most of the circulating A(H1N1)pdm09 viruses were similar to the ones included in the seasonal vaccines.
For A(H3N2), using national sequencing information, for each study year but 2015, there was good concordance between the circulating and vaccine viruses. In 2015 the lineage 3C.3a was included in the vaccine, but circulating strains were in the 3C.2a lineage and therefore the A(H3N2) cases in 2015 were considered not similar to vaccine viruses. For the influenza B lineages, the viruses identified in study participants during 2017 and 2018 were not of the same lineage that was contained in the trivalent vaccine. It has been suggested that trivalent IIV offers cross-protection against nonvaccine B lineages [26, 27]; in our study, however, where most of the influenza B vaccine-unmatched viruses were detected in the infants, a protective effect in the infants was only detected for vaccine matches. This result is different from the vaccine efficacy among HIV-unexposed infants in the South African RCT, which was similar either including all PCR-confirmed influenza episodes (48.8% [95% CI, 11.6%–70.4%]) or excluding the 17 cases of nonvaccine B lineage (48.2% [95% CI, −8.8% to 73.3%]) [1]. Our VE of 65% among the infants is in line with previous reports from Europe and the US where estimates of 45%–92% were reported [3, 10–15]. A study from England that measured the effectiveness of maternal influenza vaccination in preventing influenza-associated hospitalizations in infants aged <6 months over 2 consecutive seasons of 2013–2014 (dominated by A[H1N1]pdm09) and 2014–2015 (dominated by a drifted A[H3N2] strain) reported an overall VE of 64% (95% CI, 5%–87%) in 2013–2014 and 50% (95% CI, 8%–73%) in 2014–2015, with a similar estimate for 2014–2015 (58% [95% CI, 7%–81%]) if restricted to infants infected with the dominant drifted A(H3N2) strain [15].
Our VE estimates among HIV-uninfected women are higher than previously reported in a study across 4 countries from 2010 to 2016 (40% [95% CI, 12%–59%]), although in that study only 16% of all hospitalized women were vaccinated [16].
From 2015 to 2018, our study supplemented the national influenza vaccination program at selected antenatal clinics aiming at increasing vaccination rates to at least 50%. Although the vaccination campaigns were very successful and >75% of the women who received care at the selected clinics were vaccinated during the campaigns [17], the vaccination coverage among the hospitalized study participants, many of whom sought antenatal care at clinics which did not have supplemental vaccine supply, was <36%. This low vaccination coverage impacted the power of our analyses and might be the result of several factors. First, although analyses were restricted to those who were eligible to have received IIV during pregnancy, it is possible that not all participants had antenatal visits during the period that vaccines were available, even though our campaigns lasted for 3–4 months, and South African national estimates for 2016 revealed that 76% of pregnant women attended ≥4 antenatal care visits and that 47% of women had their first visit during the first pregnancy trimester [28]. Second, not all
women attended antenatal care at clinics supplemented with study vaccine and, as shown in Supplementary Table 2, only 18% of the women attending other clinics were vaccinated. Third, although the vaccination campaigns aimed to deliver vaccines before the start of the influenza season, the actual timing of vaccination was determined by the availability of vaccines at the selected clinics, and as previously reported across the study years, approximately only 52% of the vaccines were administered prior to the start of the influenza seasons [17]. Vaccination campaigns aimed at reducing the burden of influenza-associated illness, especially among infants, need to consider how quickly vaccination can be implemented once vaccines are available to maximize the overlap between vaccination opportunity and the risk of influenza infection in the population.

Limitations of our study include that the vaccination coverage among study participants was lower than initially anticipated, leading to a decrease in the power of the analyses. We tried to systematically document the vaccination status of the women attending the antenatal clinics selected for vaccine supplementation, and in the analyses, women were considered vaccinated only if written evidence was available; however, women could have been vaccinated and if this information was not recorded in their antenatal cards or in the study registries, they would be misclassified as unvaccinated. This misclassification would likely have been nondifferential, which would potentially result in an underestimation of the VE. Since written informed consent was required for participation, not every eligible patient was included in the study; however, differences in participation should have been similar according to influenza infection and vaccination status. Overall, as this is an observational study, there could be residual confounding that we were unable to account for. A further limitation is that we were unable to investigate VE in WLWH stratified by their degree of immunosuppression, as these data were not available.

Our study provides additional evidence for the benefit of maternal influenza vaccination to prevent severe disease in infants and among HIV-uninfected women. The effectiveness in WLWH may depend on the degree of immunosuppression, but we were unable to assess that, and further studies are needed.

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 copypedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes
Acknowledgments. The authors thank the study participants, as well as the clinic, laboratory, and data teams of the Vaccines and Infectious Diseases Analytics Research Unit of the University of the Witwatersrand (Wits-VIDA) and the National Institute for Communicable Diseases. The authors also acknowledge the expert advice provided by the study scientific advisory committee members: Haroon Saloojee, Danuta Skowronska, Gaston de Serres, Jennifer Verani, and Joseph Bresee.

Disclaimer. The funders had no role in the design, analysis, or interpretation of data.

Financial support. This work was supported by the National Institute for Communicable Diseases of the National Health Laboratory Service; the US Centers for Disease Control and Prevention (CDC) (cooperative agreement number 5U51IP000155); and the Bill and Melinda Gates Foundation (BMGF) (grant number OPP1118349). There was also partial support from the Department of Science and Technology and National Research Foundation: South African Research Chair Initiative in Vaccine Preventable Diseases, and the South African Medical Research Council: Wits-VIDA Research Unit.

Potential conflicts of interest. M. C. N. reports grants to institution from BMGF, the European and Developing Countries Clinical Trials Partnership (EDCTP), Pfizer, AstraZeneca, and Sanofi, and personal honoraria received from Pfizer and Sanofi, unrelated to the manuscript. S. A. M. reports grants to institution from BMGF, the South African Medical Research Council, Novavax, Pfizer, Gritstone (PATH), Providence, Johnson & Johnson, AstraZeneca, EDCTP, GSK, and Minervax, and personal honoraria received from BMGF unrelated to the manuscript. C. C. reports grants to institution from Sanofi, Advanced Vaccine Initiative, and the CDC, and payment of travel costs from Parexel. H. J. Z. reports grants to institution from BMGF, the South African Medical Research Council, Novavax, Pfizer, AstraZeneca, MSD, and EDCTP. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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