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A Cost-Effectiveness Analysis of Antenatal Influenza Vaccination among HIV-Infected and HIV-Uninfected Pregnant Women in South Africa

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Abstract

Background: Pregnant women and infants are at increased risk of severe disease from influenza. Antenatal influenza vaccination is safe and can reduce the risk of illness for women and their infants. We evaluated for South Africa the health effects of antenatal influenza vaccination among pregnant women and their infants aged <6 months old and assessed its cost-effectiveness.

Methods: We constructed a decision tree model to simulate the population of pregnant women and infants aged <6 months in South Africa using TreeAge Pro Suite 2015. The model evaluated

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the change in societal costs and outcomes associated with a vaccination campaign that prioritized HIV-infected over HIV-uninfected pregnant women compared with no vaccination. We also examined the impacts of a campaign without prioritization. Upper and lower 90% uncertainty intervals (90% UI) were generated using probabilistic sensitivity analysis on 10,000 Monte Carlo simulations. The cost-effectiveness threshold was set to the 2015 per capita gross domestic product of South Africa, US$5,724.

Results: Antenatal vaccination with prioritization averted 9,070 (90% UI: 7,407–11,217) total cases of influenza among pregnant women and infants, including 411 (90% UI: 305–546) hospitalizations and 30 (90% UI: 22–40) deaths. This corresponds to an averted fraction of 13.5% (90% UI: 9.0%–20.5%). Vaccinating without prioritization averted 7,801 (90% UI: 6,465–9,527) cases of influenza, including 335 (90% UI: 254–440) hospitalizations and 24 (90% UI: 18–31) deaths. This corresponds to an averted fraction of 11.6% (90% UI: 7.8%–17.4%). Vaccinating the cohort of pregnant women with prioritization had societal cost of $4,689 (90% UI: $3,128–$7,294) per Quality Adjusted Life Year (QALY) gained while vaccinating without prioritization had a cost of $5,924 (90% UI: $3,992–$9,056) per QALY.

Conclusions: Antenatal influenza vaccination campaigns in South Africa would reduce the impact of influenza and could be cost-effective.

Keywords

Influenza; vaccine; pregnant; maternal; cost effectiveness; infant

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Influenza is an important cause of illness among pregnant women and their infants aged <6 months, and pregnant women and infants are at increased risk of severe outcomes [1]. Influenza vaccination is safe for pregnant women [2, 3], and observational studies [4] and randomized controlled trials (RCT) in Bangladesh, South Africa, Mali, and Nepal have demonstrated the efficacy of antenatal vaccination against influenza illness among pregnant women or their infants aged <6 months [5–8]. In the RCTs, vaccine efficacy estimates against laboratory-confirmed influenza ranged from 50% to 70% among healthy pregnant women and 30% to 63% among their infants aged <6 months. In addition, the results from the South African trial indicated that vaccine efficacy estimates were similar for HIV-infected (point estimate: 58%, 95% confidence interval [CI]: 0.2%–82%) and HIV-uninfected (point estimate: 50%, 95% CI: 15%–71%) pregnant women. Efficacy was significant for infants born to HIV-uninfected pregnant women (point estimate: 49%, 95% CI: 12%–70%) while it was non-significant for infants born to HIV-infected pregnant women (point estimate: 27%, 95% CI: −132%–77%) [5]. Because of the vaccine's safety and the benefit to both pregnant women and their infants, the World Health Organization (WHO) released a position paper in 2012 stating that pregnant women should have the highest priority for seasonal influenza vaccination in countries considering the initiation or expansion of influenza immunization programs [9].

South Africa is a middle-income country with a prevalence of HIV-infection among pregnant women of 23% in 2016 [10]. Annual influenza epidemics can start as early as April or as late as July and typically peak from June to August [11]. During 1999–2009, the estimated annual burden of influenza-associated respiratory deaths was 6.8/100,000

among pregnant women and 22/100,000 among children aged <1 year [12, 13]. These rates varied significantly by HIV status [12, 13]. The influenza-associated mortality rate among HIV-infected pregnant women was 74.9/100,000 while it was 1.5/100,000 among HIV-uninfected pregnant women and the authors estimated that 90% of seasonal influenza–associated deaths in pregnancy occurred among HIV-infected women [13].

The South African Department of Health initiated its first national influenza vaccination campaign where pregnant women were targeted in 2010 [14]. However, an evaluation of the impact of this decision on the health and economic outcomes of pregnant women and their infants is needed to justify the investment in influenza vaccine and better inform policy decisions, including whether antenatal influenza vaccination should be prioritized for HIV-infected pregnant women. Therefore, in this study, we estimated how many cases, hospitalizations, and deaths are averted among pregnant women and their infants aged <6 months through antenatal influenza vaccination and whether it is a cost-effective intervention.

Material and methods

We used a decision tree model to simulate a cohort of pregnant women and infants aged <6 months in South Africa using TreeAge Pro Suite 2015 (TreeAge Software, Williamstown, MA). Figure 1A displays the overall simplified decision-tree model structure for pregnant women and Figure 1B displays the model for their infants. The number of pregnant women to include in the cohort was based on the monthly recorded number of live births in South Africa in 2016, thus accounting for the seasonality of births [15]. We assumed pregnancies lasted 40 weeks from conception date. Women were included if their pregnancy or the infant's first six months of life overlapped with at least 10% of the influenza positive tests that were identified during either the 2012, 2013, or 2014 South African influenza season. Supplemental Figure 1 shows an example of this calculation for pregnant women for selected conception weeks using data from the 2013 influenza season in South Africa. The full cohorts covered 84 conception weeks and included 1.52 million pregnant women.

We simulated an influenza vaccination campaign based on the timing of the 2017 South African influenza campaign (unpublished data, National Department of Health, Republic of South Africa). In these scenarios, about 265,000 doses of influenza vaccine were administered annually to pregnant women, which roughly represented a doubling of the typical number of influenza doses administered to pregnant women each season in South Africa [16]. Vaccination began the third week of March and ended the last week of July, to coincide with the seasonal influenza peak in winter. Five percent of available vaccine was administered in March, 10% in April, 60% in May, 20% in June, and 5% in July. We evaluated two different vaccination scenarios against the baseline of no antenatal vaccination in South Africa. In the first scenario, we simulated a hypothetical campaign that targeted influenza vaccination to HIV-infected pregnant women (with prioritization). In this scenario, we vaccinated 70% of HIV-infected women and 41% of HIV-uninfected women who were pregnant during the period of vaccination. We chose these percentages to administer the same number of doses in the scenario without prioritization. In the second scenario, we simulated a campaign that vaccinated HIV-infected and HIV-uninfected pregnant women at

equal rates (without prioritization). In this scenario, we vaccinated 50% of both HIV-infected and HIV-uninfected women who were pregnant during the period of vaccination. The goal of the prioritization scenario was for HIV+ pregnant women to receive proportionally more of the influenza vaccine than they represent among the population of pregnant women (and therefore have higher coverage) while the goal of the no prioritization scenario was for a proportional allocation of influenza vaccine among HIV+ and HIV- pregnant women.

The main outcomes of the study were estimates of the number of influenza-associated outcomes averted by a vaccination campaign and its cost-effectiveness. The incremental cost-effectiveness ratio (ICER) of antenatal influenza immunization was calculated by dividing the difference in the net costs of the vaccination campaign with or without prioritization by the difference in the Quality Adjusted Life Years (QALYs) between the two scenarios. The threshold for cost-effectiveness was set to the 2015 per-capita gross domestic product of South Africa, US$5724, which was based on WHO CHOICE guidelines to be considered very cost-effective [17, 18]. We used a societal perspective for all calculations and a time horizon of one year.

Uncertainty and sensitivity analysis

Point estimates based on the median value and upper and lower 90% uncertainty intervals (UIs) and the cost-effectiveness plane were generated using probabilistic sensitivity analysis on 10,000 Monte Carlo simulations that varied all the parameters across their ranges shown in Table 1. To investigate the effect of changes in our model inputs on the averted hospitalization burden or the incremental cost-effective ratio, we preformed one-way sensitivity analysis for all parameters with ranges. Additionally, we estimated the impact of varying influenza vaccination coverage among HIV-infected and HIV-uninfected on the averted burden.

Model Inputs

Timing: Because of the variable timing of pregnancies, the influenza season, and seasonal influenza vaccination campaign, each pregnancy and infancy period experiences a different chance of influenza vaccination and risk of influenza disease. For example, because the vaccine campaign is timed to begin before the start of the influenza season, women who are pregnant during the period when the majority of influenza vaccine is administered will have a different risk of influenza than those not pregnant during that period [19]. To account for this in the model, we first added branches to the maternal and infant decision trees to account for the chance of being pregnant (or in utero for infants) during the vaccination campaign and the chance for being pregnant during the campaign and experiencing the influenza season while pregnant (or less than six months for infants).

We calculated the first of these branches (the proportion of the cohort that was both pregnant/in utero during the vaccination campaign) by stratifying the cohort by pregnancy start week and calculating the proportion of vaccine administered during each pregnancy period or period in utero (based on the 2017 South African influenza campaign described above). Supplemental Figure 2 shows an example of this calculation for pregnant women for selected conception weeks. We calculated the second of these branches (the proportion

that were pregnant during the campaign at risk of influenza) by stratifying the cohort by pregnancy start week and dividing the number of influenza positive specimens identified during the pregnancy or infancy period by the total number of influenza positive specimens from the entire season [20]. Supplemental Figure 1 shows an example of this approach. We then multiplied the proportion of vaccine administered by the proportion of influenza positives identified for each of the pregnancy start weeks for pregnant women and infants in the cohort to create a vaccination value weighted by influenza risk. We then summed the weighted vaccine values for every week in each cohort and divided those values by the sum of the proportion of administered vaccine over the cohorts. We then calculated the proportion of the cohort that was not pregnant/in utero during the campaign but exposed to influenza using the same procedure as described above but using the inverse proportion of vaccine administered for each pregnancy start week. We used influenza virus surveillance data for South Africa from the 2012–2014 influenza seasons. Virus detections peaked between June and August and were used to create ranges for these values [20].

Attack rates: The estimates for the seasonal attack rate were based on the placebo arm of the randomized controlled trial of antenatal influenza vaccination conducted in South Africa in 2011 and 2012 [5]. These values from this study represent the symptomatic attack rate of pregnant women and infants that met the influenza-like illness criteria for the study, were ascertained under active surveillance, and were reverse-transcription-polymerase-chain-reaction (RT-PCR) positive for influenza. This value may not have included symptomatic cases that did not meet the case definition, and serologic results indicate higher infection rates among pregnant women [21].

Care seeking: The care-seeking proportion for pregnant women was based on the 2003 DHS survey that indicated 51% of women aged 15–49 years reported they have major problems in accessing health care for themselves when they are sick and a household survey conducted in South Africa indicating that around 52% of respondents with severe pneumonia were admitted to a hospital [22, 23]. The care-seeking proportion for HIV-infected pregnant women was adjusted upwards according to a study that found HIV-infected individuals were around 3 times more likely to seek care for an acute illness with a licensed medical provider [24]. The care-seeking proportion for infants were based on the 2003 DHS survey and the household survey described above that indicated around 53% of infants <6 months of age with cough accompanied by fast breathing were taken to a health facility or provider [22, 23].

Hospitalizations and deaths: No direct estimates of the case hospitalization or fatality ratio of influenza for pregnant women or infants in South Africa were available. Instead, we calculated estimates of the number of hospitalizations and deaths occurring among pregnant women and infants based on previously published work [12, 13, 25, 26]. The numbers of hospitalizations among HIV-infected and HIV-uninfected pregnant women were based on estimates of influenza-associated severe acute respiratory illness (SARI) with symptom duration of ≤10 days for the HIV-infected and HIV-uninfected 25–44-year-old age group respectively; estimates were adjusted upwards by 2.4 to account for the increased hospitalization risk associated with pregnancy [25, 27]. Calculations for infants were based

on HIV-uninfected estimates of severe respiratory illness hospitalizations for the <6 month old age group [26]. The numbers of deaths were based on excess influenza-associated all-cause mortality estimates for HIV-infected and HIV-uninfected pregnant women from the 1999–2009 seasons while calculations for infants were based on to all-respiratory mortality estimates for HIV-uninfected <1-year-olds from the 1999–2009 seasons [12, 13].

Vaccine Effectiveness: Estimates of seasonal influenza vaccine effectiveness were based on a randomized controlled trial of antenatal influenza vaccination conducted among HIV-uninfected and HIV-infected pregnant women and their infants in South Africa in 2011 and 2012 [5]. The clinical trial estimated vaccine efficacy against mild influenza-associated laboratory-confirmed illness. Here we assumed that vaccine effectiveness against illness, outpatient visits, hospitalizations, and deaths would be equal to the vaccine efficacy found in this study [4]. We also assumed that the vaccine would not be effective until 2 weeks after administration [4]. We assumed no impact of influenza vaccination on birth outcomes (e.g. preterm birth, small-for-gestational-age, or fetal death) because a recent systematic review found that studies were limited in quality and had inconsistent results [28].

Illness costs: Costs for the acute care of influenza-associated non-medically attended cases and outpatient visits were obtained from a study describing the direct and indirect costs of lower respiratory tract infections among South African children [29]. This study measured the direct medical costs of outpatient visits among children with lower respiratory tract infection as well as indirect costs like work-loss, transportation, traditional healing, and out-of-pocket medication costs. These values were obtained using a micro-costing approach and by interviewing family members of patients with acute lower respiratory tract infection [29]. Because there were no direct estimates of the costs for influenza–associated non-medically attended or outpatient illness for pregnant women, we used the estimated costs for infants.

Costs for influenza-associated hospitalizations for pregnant women and infants were obtained from a study that estimated the direct and indirect costs of hospitalized SARI patients of all ages (Centre for Respiratory Diseases and Meningitis, unpublished data). This study estimated the cost of hospital admission using the cost per patient day equivalent approach and by interviewing caregivers of patients with SARI. Because no estimates for the medical costs of influenza-associated deaths were available, we assumed the costs to be 49% of the cost of influenza-associated hospitalizations since 51% of all-age respiratory deaths occurred outside of the hospital in South Africa [30]. Costs associated with long-term sequelae or from lifetime lost productivity due to death were not included. Costs in South African Rands or estimated in previous years were converted to 2016 US dollars using the South Africa all-items Consumer Price Index [31] and the average monthly South African Rand to US dollar exchange rate in 2016.

Vaccination costs: Because the percentage of pregnant women who visit an antenatal clinic at least once during their pregnancy is high in South Africa (95%), we assumed influenza vaccination would take place during an antenatal clinic visit and there would be no additional patient travel or time costs for vaccine administration [22]. Because 65% of women make their first antenatal care visit after their first trimester, we assumed vaccinations would only be given in the second and third trimesters of pregnancy [22].

The costs for influenza vaccination were obtained from a review of influenza vaccine price data among WHO European Member states [32]. The campaign and administration cost was assumed to be two times the vaccine purchase cost based on the estimated costs of immunization in 117 low- and lower-middle-income countries [33]. Vaccine purchase costs were increased by 10% to account for wastage [11].

Utilities: No direct estimates of influenza-associated QALY losses are available for influenza-associated illness in South Africa, so QALY estimates were based on the duration of influenza illness and health utility data from the United States and the United Kingdom [34–38]. The baseline QALY values were assumed to be 0.82 for HIV-infected pregnant woman, 0.92 for HIV-uninfected pregnant woman, and 1.0 for infants (regardless of the HIV status of the mother) [36, 39]. Daily QALY losses were calculated by multiplying the baseline QALY value by 0.35 (0.19–0.51) for medically and non-medically attended illness and 0.50 (0.37–0.62) for hospitalized influenza [34–36]. Influenza illnesses were assumed to last 3.6 days for non-medically attended illness, 4.0 days for medically attended illness, and 7 days for hospitalized illness [34–36]. To determine the number of QALYs lost per death, we assumed a median age of 27 for both HIV-uninfected and HIV-infected pregnant women, and further life expectancies of 43 years for HIV-uninfected pregnant women and 34 years for HIV-infected pregnant women [15, 40, 41]. We assumed a life expectancy of 60 years for infants [40]. Future life years were discounted at a rate of 3%. Because major side effects from influenza vaccination are very rare in the general population and among pregnant women, we did not account for them in cost or utilities calculations [2, 3].

Results

In the base case scenario with no vaccination, influenza infection among pregnant women resulted in 48,320 (90% UI: 39,622–58,550) total illnesses, including 1,700 (90% UI: 1,271–2,259) hospitalizations and 126 (90% UI: 94–165) deaths (Table 2). Influenza infection among infants resulted in 19,014 (90% UI: 15,038–23,839) illnesses, including 1,343 (90% UI: 1,023–1,734) hospitalizations and 80 (90% UI: 60–103) deaths (Table 2).

Prioritization of vaccination by HIV status affected the number of health outcomes averted among pregnant women. Vaccinating with prioritization averted 7,640 (90% UI: 6,243–9,410) total cases of illnesses, including 310 (90% UI: 226–414) hospitalizations and 24 (90% UI: 18–32) deaths; this corresponds to an averted fraction of 15.8% (90% UI: 10.7%–23.7%). Vaccinating without prioritization averted 6,372 (90% UI: 5,268–7,768) total cases of illness, including 233 (90% UI: 173–311) hospitalizations and 18 (90% UI: 13–23) deaths; this corresponds to an averted fraction of 13.2% (90% UI: 9.0%–19.6%) (Table 3).

However, among infants, prioritization did not affect the number of health outcomes averted. Antenatal influenza vaccination with prioritization averted 1,431 (90% UI: 1,164–1,808) total cases of infant illnesses, including 102 (90% UI: 79–132) hospitalizations and six (90% UI: 5–8) infant deaths; this corresponds to an averted fraction of 7.5% (90% UI: 4.9%–12.0%). Antenatal influenza vaccination without prioritization averted 1,429 (90% UI: 1,197–1,760) cases of infant illness, including 102 (90% UI: 81–129) hospitalizations and

6 (90% UI: 5–8) infant deaths; this corresponds to an averted fraction of 7.5% (90% UI: 5.0%–11.7%) (Table 3).

Vaccination under either prioritization scheme was not cost-saving, but it was potentially cost-effective. Antenatal influenza vaccination with HIV-infected prioritization resulted in an ICER of $4,689 (90% UI: $3,128–$7,294), and the median value was considered cost-effective using our pre-defined threshold (US$5724). The strategy where influenza vaccination was not prioritized to HIV-infected pregnant women resulted in an ICER of $5,924 (90% UI: $3,992–$9,056), and the median point estimate was nearly considered cost-effective (Table 4).

Sensitivity Analysis

Figure 2 displays the results of the one-way sensitivity analyses of the 10 most influential model parameters on the burden of maternal and infant hospitalizations averted by antenatal influenza vaccination with HIV-infected prioritization in a tornado diagram. The top three parameters that affected the averted hospitalization burden were vaccine effectiveness, disease incidence, and severity of influenza illness among HIV-infected pregnant women. Figure 3 displays the results of one-way sensitivity analyses of the 10 most influential model parameters on maternal and infant ICER for antenatal influenza vaccination with HIV-infected prioritization compared to no vaccination in a tornado diagram. Similar to the sensitivity analysis findings presented in Figure 2, the top two parameters with the greatest effect on the ICER were vaccine effectiveness and disease incidence among HIV-infected pregnant women. The third most influential parameter was the cost of the influenza vaccine. Supplemental Figure 3 displays the estimated averted burden of antenatal influenza vaccination in South Africa for pregnant women and infants, varied by vaccine coverage among HIV-infected and HIV-uninfected pregnant women. As coverage among HIV-infected pregnant women increased by 5% increments from the left to the right, the averted influenza burden among pregnant women increased by approximately 0.7%, while the averted burden among infants remains relatively flat.

Figure 4 displays the cost-effectiveness acceptability plane for antenatal influenza vaccination with HIV-infected prioritization and antenatal influenza vaccination without prioritization compared to no vaccination when compared to no vaccination. About 30% of vaccination with prioritization simulations and 10% of vaccination without prioritization simulations were considered cost effective at a threshold value of $4,000 while over 90% of vaccination with prioritization simulations and 70% of vaccination without prioritization simulations were cost-effective at a threshold of $7,000.

Timing Analysis

The results of the timing analysis indicate that 35% of the period when women were pregnant overlapped with the influenza vaccination campaign and 48–49% of the period when women were pregnant overlapped with influenza activity (Supplemental Figure 4). Fifty-eight to 73% of pregnancies overlapping with the campaign were at risk of influenza while 35–43% of pregnancies not overlapping with the campaign were at risk of influenza. For infants, 31–32% of the period when infants were aged <6 months overlapped with

influenza activity (Supplemental Figure 5). Twenty-seven to 42% of infants were in utero during the campaign and at risk from influenza while 26–33% were not in utero during the campaign but at risk from influenza.

Discussion

Influenza is an important cause of illness and death in South Africa, and pregnant women and infants are at increased risk of severe disease [12, 13]. We estimate that an antenatal influenza vaccination campaign that vaccinated approximately 265,000 pregnant women in South Africa, roughly a doubling of the current number of pregnant women vaccinated, could reduce the total number of influenza-associated illnesses in pregnant women and infants by 9,000, including reductions in the number of hospitalizations by 400 and the number of deaths by 30. The greatest impact would come from reductions in maternal influenza illness rather than reductions in infant illness. The decision to prioritize vaccination of pregnant women by HIV status affected the number of health outcomes averted, and in scenarios where HIV-infected mothers are prioritized, the number of health outcomes averted was higher and the incremental costs were lower when compared to scenarios without prioritization. While we did not find influenza vaccination to be cost saving, vaccination with prioritization was cost-effective and vaccination without prioritization was nearly cost-effective using a threshold value of the per capita GDP in South Africa. We also found that accounting for the timing of the influenza vaccination campaign influenced the number of outcomes averted by the vaccination campaign.

In 2012, the World Health Organization recommended that countries considering the initiation or expansion of influenza immunization programs place pregnant women at the highest priority for seasonal influenza vaccination. However, the evidence for the averted influenza burden and the cost-effectiveness of this recommendation was limited for low- and middle- income countries (LMICs). This study found that a vaccination campaign that prioritizes HIV-infected pregnant women and distributes around 265,000 doses could avert ~14% of the influenza burden among pregnant women and infants, suggesting that antenatal influenza vaccination could reduce the burden of influenza in South Africa. This conclusion is similar to a recent analysis from South Africa indicating that vaccination of pregnant women against influenza had among the lowest costs per hospital day averted and year of life saved among the risk groups analyzed [42].

However, antenatal influenza vaccination does not avert the influenza burden among pregnant women and infants evenly. The vaccination campaign considered in this analysis averted around 16% of influenza-associated health outcomes among pregnant women but only 8% of the health outcomes among infants. The reasons for the greater reduction in influenza burden among pregnant women compared to infants are at least twofold. First, the vaccine effectiveness considered in this analysis was lower for infants (27% for HIV-exposed infants and 49% for HIV-unexposed infants) than for pregnant women (58% for HIV-infected pregnant women and 50% for HIV-uninfected pregnant women). Second, the impact of the timing of the vaccine campaign relative to the influenza season affected the results for infants more than pregnant women. In this study, around 60 and 70% of pregnant women who were pregnant during the campaign were at risk for influenza but only

around 25 and 40% of infants whose mothers were vaccinated were at risk for influenza. In addition, many of the infants who are most at risk of influenza were born before the seasonal influenza vaccination campaign began. Campaigns with the goal of reducing the burden of influenza-associated health outcomes among infants in temperate countries should consider how quickly the vaccination campaign could begin after the vaccine becomes available in order to increase the overlap between vaccination opportunity and influenza risk in the infant population.

This study found that influenza vaccination with prioritization was cost-effective according to a predefined threshold of the per capita GDP of South Africa, and these findings were robust to variable values of the threshold. This result is similar to the majority of previous studies that estimate the cost-effectiveness of influenza vaccination during pregnancy [36, 43–50]. Of the nine studies identified, four reported cost-savings, three were considered to be cost-effective based on their threshold values, and two reported positive cost-effectiveness findings but did not explicitly state a threshold value for cost-effectiveness. Reasons for the different conclusions among the studies and this study are likely related to many factors, including the varied epidemiological, healthcare utilization, cost, and vaccine effectiveness assumptions used in the analyses.

However, this study differs from many of the previous studies in two important ways. First, almost all of the previous studies were conducted in high-income countries where healthcare access, utilization, and costs are often greater but the burden of severe influenza (e.g. hospitalization and deaths) is often lower. Only one cost-effectiveness analysis of antenatal influenza vaccination was found from a low-income country, which was conducted in Mali and found a cost-effectiveness ratio of $857/disability-adjusted-life-year gained [50]. The second major difference was the use of a method to account for the timing of the pregnancy or infancy period, the risk of influenza, and the opportunity for vaccination. Most of the other studies did not account for timing issues, potentially overestimating the cost effectiveness of maternal vaccination. In one study that did, the authors found that 60% of the pregnant women who were vaccinated were still pregnant during the peak of influenza season (and thus were still at risk of influenza), which is similar to the proportion found in this study [44].

This study found that the prioritization of antenatal influenza vaccination among HIV-infected women resulted in a greater reduction of influenza-associated health outcomes among pregnant women at lower incremental costs than vaccination programs that did not prioritize by HIV status. However, the absolute difference between the averted burdens for the two prioritization schemes was small, had overlapping uncertainty intervals, and was fully attributable to greater reductions in illness among pregnant women and not infants (Table 3). While HIV-infected pregnant women have effectively been targeted in South Africa to prevent the transmission of HIV from mother to child [51], the cost and feasibility of prioritizing of influenza vaccine as well as the achievable coverage among HIV-infected pregnant women should be considered when designing influenza vaccination campaigns and estimating their expected impact on the influenza disease burden. Prioritization programs will need to be able to identify HIV-infected pregnant women during their antenatal visits for vaccination, achieve high vaccine acceptance, and ensure they are not increasing the risk

of stigma, introducing ethical issues, or reducing the overall coverage of pregnant women by targeting HIV-infected pregnant women for vaccination. In addition, this study found that the vaccine effectiveness, disease incidence, the severity of influenza illness among HIV-infected pregnant women, and the cost of the influenza vaccine most affected the results. All of these factors (except the cost of the vaccine) can vary significantly from season-to-season because circulating influenza viruses change, potentially leading to the different conclusions about the benefits of prioritizing HIV-infected pregnant women or antenatal influenza vaccination. For example, the U.S. CDC estimates that the seasonal attack rate can vary fourfold, the numbers of influenza-associated hospitalizations and deaths can vary fivefold, and the vaccine effectiveness can vary between 10 and 60% between each influenza season [52, 53]. Similar levels of variability in these inputs were included in this study.

This study is subject to a number of limitations. First, even though we identified a number of South Africa-specific studies to include in this analysis (especially compared to the number that could be included for other low- and middle-income countries), a number of the model inputs, including influenza-associated QALY losses and the costs of maternal influenza were taken from studies that were either not specific to South Africa or the population in question. In addition, for some of the inputs (e.g. the case fatality and hospitalization ratios), the information to inform the parameter estimate and distribution was limited, leading to the use of the triangle distribution. Second, side effects associated with influenza vaccination were not included in cost or QALY estimates. Major vaccine adverse events are rare and the cost or QALY impacts of the minor side effects associated with influenza vaccination (e.g. sore arm) should be minimal [2, 3]. Third, because the evidence from previous literature is mixed, this study did not include any benefit of influenza vaccination for pregnancy outcomes (e.g. small for gestational age, preterm births), possibly underestimating the impact of vaccination on the health benefits and cost averted if influenza vaccination is associated with improved pregnancy outcomes [8, 28]. Fourth, this study did not assume any benefit of vaccination to women whose pregnancies did not result in a live birth, to women once they had given birth, or for additional influenza seasons. Extending the benefits of vaccination to these groups could increase the benefits of influenza vaccination. Fifth, because a national program in South Africa has reduced early mother to child transmission of HIV to 3.5%, this study did not account for mother-to-child transmission of HIV or the increased rates of influenza hospitalization and death in HIV-infected infants [12, 26, 54]. Sixth, the estimates for the seasonal attack rate are based on the symptomatic attack rate of pregnant women and infants that met the influenza-like illness criteria in a randomized controlled trial, were ascertained, and were RT-PCR positive for influenza [5]. This value may not have included symptomatic cases that did not meet the case definition, and serologic results indicate higher influenza infection rates among pregnant women [21]. Finally, the results of this study are specific to South Africa and may not be generalizable to other countries due to differences in influenza epidemiology and healthcare utilization and cost.

Antenatal influenza immunization has the potential to reduce influenza-associated outcomes among pregnant women and their infants aged <6 months. This study found that vaccinating 265,000 pregnant women in South Africa would reduce the influenza burden between 12–14% and would likely be cost-effective, especially if influenza vaccination was prioritized

for HIV-infected pregnant women. To have the greatest impact, it is necessary to consider the goals of the campaign and the timing of vaccination, which is highly dependent on the vaccine production and availability schedule, to maximize the impact on pregnant women or infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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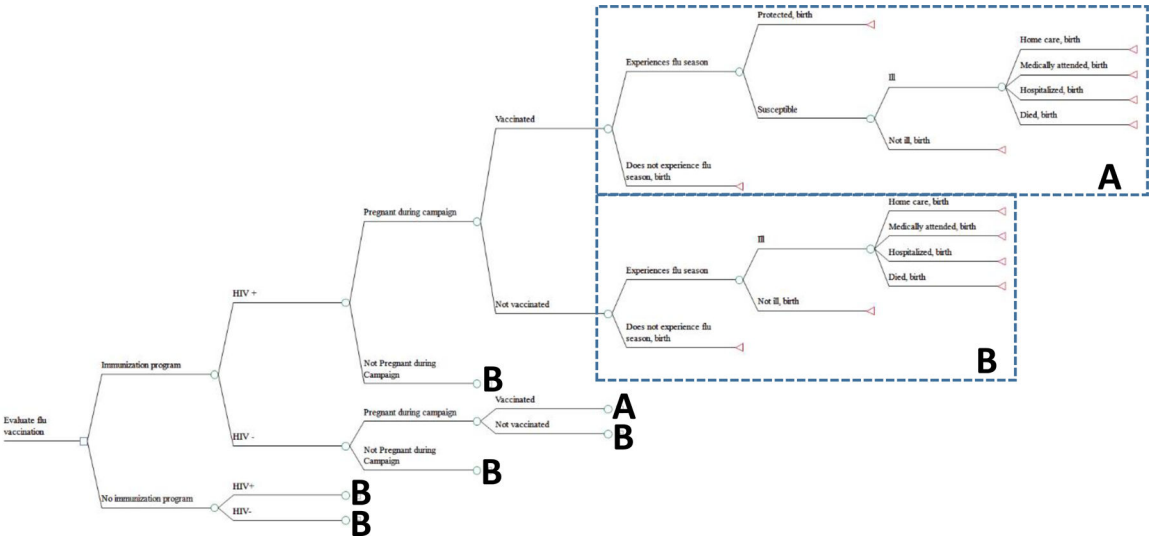

Figure 1A.

Decision tree to estimate the impact of influenza vaccination among pregnant women and their infants.

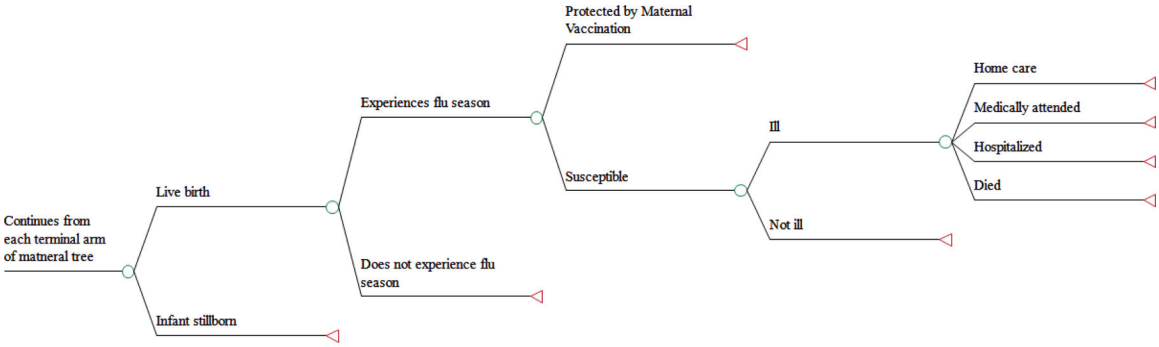

Figure 1B.

Infant subtree to estimate the impact of influenza vaccination among pregnant women and their infants.

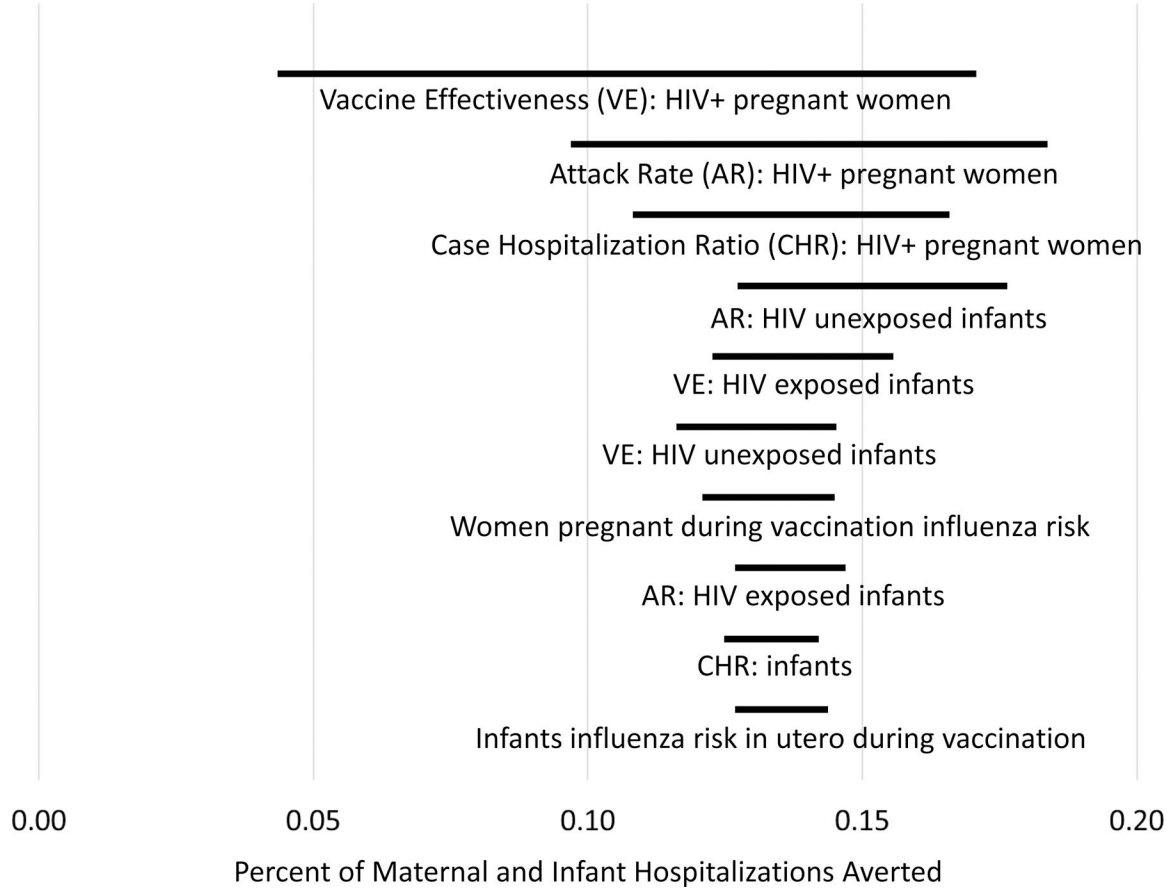

Figure 2.
Tornado diagram of one-way sensitivity analyses of the 10 most influential model parameters on the burden of maternal and infant hospitalizations averted by antenatal influenza vaccination with HIV-infected prioritization.

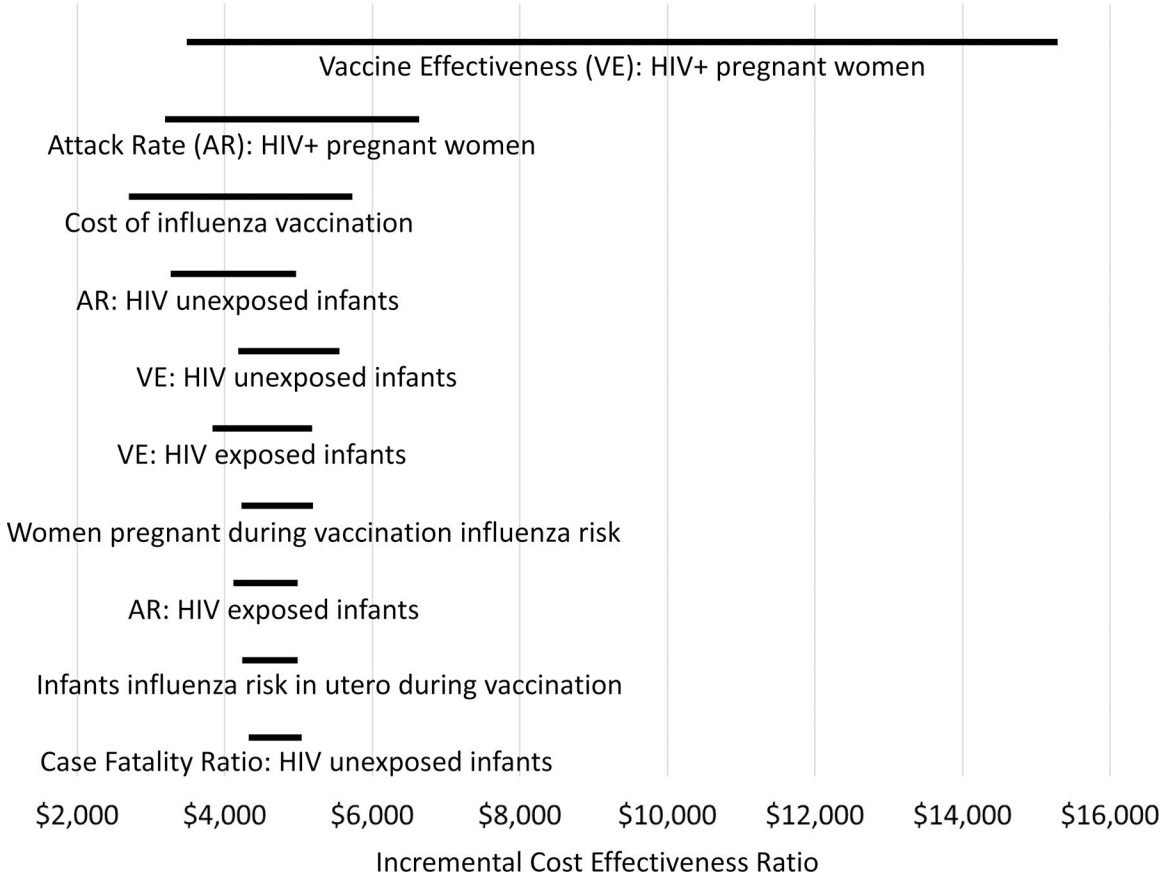

Figure 3.

Tornado diagram of one-way sensitivity analyses on the effect of range of the 10 most influential model parameters on the maternal and infant Incremental Cost Effectiveness Ratio (ICER) for antenatal influenza vaccination with HIV-infected prioritization.

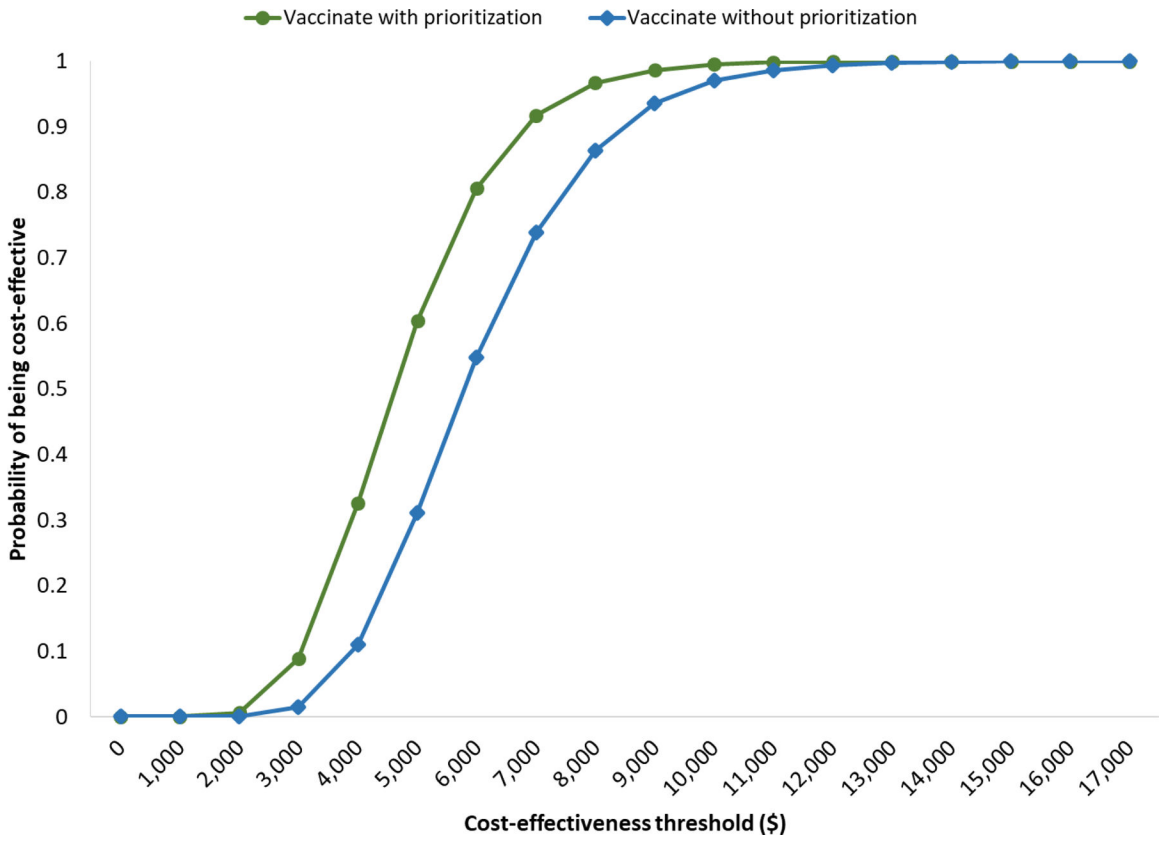

Figure 4.

Cost-effectiveness acceptability curve for antenatal influenza vaccination with and without HIV-infected prioritization compared to no vaccine.

Table 1.

Model inputs and their sources for measuring cost-effectiveness of antenatal influenza immunization in South Africa.

Input	HIV-infected value (range)	HIV-uninfected value (range)	Distribution	Reference
Burden of Influenza				
Pregnant women				
Prevalence of HIV in 2016	**0.225**		**Not varied**	[10]
Pregnant women at risk for influenza	**0.483 (0.479–0.486)**		**Triangle**	Described in timing section
Symptomatic attack rate	**0.17 (0.10–0.26)**	**0.036 (0.026–0.049)**	**Beta**	[5]
Proportion seeking outpatient care	**0.74 (0.68–0.83)**	**0.47 (0.40–0.60)**	**Triangle**	[22, 23]
Case hospitalization ratio	**0.048 (0.037–0.69)**	**0.013 (0.013–0.015)**	**Triangle**	[25, 27]
Case fatality ratio	**0.0041 (0.0042–0.0044)**	**0.00042 (0.00039–0.00043)**	**Triangle**	[13]
Infants (The HIV-infected value for infants denotes HIV-exposed uninfected infants while the HIV-uninfected value denotes HIV-unexposed uninfected infants)				
Infant mortality	**0.033**		**Not varied**	[55]
Proportion of infants at risk for influenza	**0.312 (0.311–0.316)**		**Triangle**	Described in timing section
Symptomatic attack rate	**0.068 (0.025–0.143)**	**0.036 (0.026–0.050)**	**Beta**	[5]
Proportion seeking outpatient care	**0.524 (0.40–0.60)**		**Triangle**	[22, 23]
Case Hospitalization Ratio	**0.074 (0.052–0.086)**		**Triangle**	[26]
Case Fatality Ratio	**0.0044 (0.0031–0.0051)**		**Triangle**	[12]
Cost (in 2016 USD)				
Pregnant women and infants				
Influenza case cared for at home	**0.18 (0.15–0.21)**		**Lognormal**	[29]
Influenza-associated outpatient visit	**8.11 (6.35–9.31)**		**Lognormal**	
Influenza-associated hospitalization	**798.74 (652.35–945.12)**		**Lognormal**	A. Cohen, unpublished
Influenza-associated death	**341.74 (319.65–463.11)**		**Lognormal**	
Vaccine				
Cost of influenza vaccine	**4.55 (2.73–5.13)**		**Lognormal**	[32]
Vaccination administration cost	**2X vaccine cost**		**Not varied**	[33]
QALYs				
Pregnant women				
QALYs lost for home-care influenza	**0.0028 (0.0015–0.0041)**	**0.0032 (0.0017–0.0046)**	**Triangle**	[34–38]
QALYs lost for outpatient influenza	**0.0031 (0.0017–0.0046)**	**0.0035 (0.0019–0.0051)**	**Triangle**	[34–38]
QALYs lost for hospitalization	**0.0079 (0.0058–0.0098)**	**0.0088 (0.0065–0.0011)**	**Triangle**	[34–38]
QALYs lost for death (discounted)	**17.6 years**	**22.2 years**	**Not varied**	[15, 40, 41]
Infants				

Input	HIV-infected value (range)	HIV-uninfected value (range)	Distribution	Reference
QALYs lost for home-care influenza	**0.0035 (0.0019–0.0050)**		**Triangle**	[34–38]
QALYs lost for outpatient influenza	**0.00384 (0.0021–0.0056)**		**Triangle**	[34–38]
QALYs lost for hospitalization	**0.0096 (0.0071–0.012)**		**Triangle**	[34–38]
QALYs lost for death (discounted)	**27.9 years**		**Triangle**	[40]
Vaccine				
Pregnant women				
Effectiveness	**0.577 (0.002–0.821)**	**0.504 (0.145–0.712)**	**Beta**	[5]
Infants				
Effectiveness	**0.267 (0–0.768)**	**0.488 (0.116–0.704)**	**Beta**	[5]

Table 2.

Estimated number of outcomes for HIV-infected prioritization, no HIV-infected prioritization, and no vaccination (baseline) antenatal influenza immunization strategies in South Africa

Scenario	Cases (90% UI[1])	Outpatient (90% UI)	Hospitalization (90% UI)	Deaths (90% UI)
Pregnant Women				
No Vaccination (Baseline)	48,320 (39,622–58,550)	30,890 (24,669–38,294)	1,700 (1,271–2,259)	126 (94–165)
HIV-Infected Prioritization	40,680 (33,380–49,140)	25,736 (20,579–31,803)	1390 (1,045–1,845)	102 (76–133)
No Prioritization	41,948 (34,354–50,782)	26,753 (21,355–33,159)	1,466 (1,097–1,948)	109 (81–142)
Infants				
No Vaccination (Baseline)	19,014 (15,038–23,839)	9,639 (7,432–12,381)	1,343 (1,023–1,734)	80 (60–103)
HIV-Infected Prioritization	17,583 (13,874–22,031)	8,910 (6,850–11,427)	1,241 (944–1,602)	74 (56–95)
No Prioritization	17,585 (13,841–22,079)	8,909 (6,833–11,462)	1,241 (943–1,605)	74 (56–96)
Combined				
No Vaccination (Baseline)	67,334 (54,660–82,388)	40,528 (32,101–50,675)	3,043 (2,294–3,993)	206 (154–268)
HIV-Infected Prioritization	58,264 (47,254–71,171)	34,646 (27,429–43,229)	2,708 (2,041–3,550)	176 (132–229)
No Prioritization	59,533 (48,195–72,861)	35,662 (28,188–50,675)	2,707 (2,040–3,553)	183 (137–237)

[1] Upper and lower 90% uncertainty intervals

Table 3.

Number vaccinated and estimated averted burden of influenza-associated illness for HIV-infected prioritization, no HIV-infected prioritization compared with no vaccination (baseline) in South Africa

Scenario	Vaccinated	Averted Number of Cases (90% UI[1])	% Averted (90% UI)	Averted Number of Outpatient Visits (90% UI)	Averted Number of Hospitalizations (90% UI)	Averted Number of Deaths (90% UI)
Pregnant Women						
HIV-Infected Prioritization	264,430	7,640 (6,243–9,410)	15.8 (10.7–23.7)	5,153 (4,090–6,491)	310 (226–414)	24 (18–32)
No Prioritization	264,430	6,372 (5,268–7,768)	13.2 (9.0–19.6)	4,137 (3,313–5,134)	233 (173–311)	18 (13–23)
Infants						
HIV-Infected Prioritization		1,431 (1,164–1,808)	7.5 (4.9–12.0)	729 (582–954)	102 (79–132)	6 (5–8)
No Prioritization		1,429 (1,197–1,760)	7.5 (5.0–11.7)	730 (599–918)	102 (81–129)	6 (5–8)
Combined						
HIV-Infected Prioritization	264,430	9,070 (7,407–11,217)	13.5 (9.0–20.5)	5,882 (4,672–7,445)	411 (305–546)	30 (22–40)
No Prioritization	264,430	7,801 (6,465–9,527)	11.6 (7.8–17.4)	4,866 (3,913–6,053)	335 (254–440)	24 (18–31)

[1] Upper and lower 90% uncertainty intervals

Table 4.

Estimated quality-adjusted life year and cost (in US dollars) per member of the pregnant women and infants aged 0–5 months cohort in the no vaccination (baseline), HIV-infected prioritization, and no HIV-prioritization scenarios, South Africa.

Scenario	QALYs per member (90% UI[1])	Incremental QALYs gained (compared to baseline) (90% UI)	Cost[2] per member ($USD) (90% UI)	Incremental Cost ($USD) (90% UI)	ICER ($USD) (90% UI)
Pregnant Women					
No Vaccination (Baseline)	0.89584 (0.89536–0.89625)		1.09 (0.82–1.44)		
HIV-Infected Prioritization	0.89615 (0.89576–0.89648)	0.00031 (0.00023–0.0004)	3.17 (2.61–3.86)	2.08 (1.79–2.42)	6,664 (4,445–10,515)
No Prioritization	0.89607 (0.89565–0.89642)	0.00023 (0.00017–0.0003)	3.22 (2.65–3.92)	2.13 (1.83–2.48)	9,240 (6,187–14,445)
Infants					
No Vaccination (Baseline)	0.99838 (0.99791–0.99877)		0.80 (0.6–1.05)		
HIV-Infected Prioritization	0.99850 (0.99807–0.99886)	0.00012 (0.00009–0.00016)	0.74 (0.55–0.97)	−0.06 (−0.05–−0.08)	Cost savings
No Prioritization	0.99850 (0.99806–0.99887)	0.00012 (0.0001–0.00016)	0.74 (0.55–0.97)	−0.06 (−0.05–−0.08)	Cost savings
Combined					
No Vaccination (Baseline)	1.89422 (1.89326–1.89502)		1.88 (1.41–2.49)		
HIV-Infected Prioritization	1.89466 (1.89383–1.89535)	0.00044 (0.00032–0.00056)	3.91 (3.16–4.83)	2.02 (1.74–2.34)	4,689 (3,128–7,294)
No Prioritization	1.89457 (1.89372–1.89529)	0.00035 (0.00027–0.00045)	3.95 (3.2–4.89)	2.07 (1.78–2.4)	5,924 (3,992–9,056)

[1] Upper and lower 90% uncertainty intervals

[2] In 2016 U.S. dollars and includes costs related to influenza-associated illness and vaccination