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 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 10000 Monte Carlo simulations. The cost-effectiveness threshold was set to the 2015 per capita gross domestic product of South Africa, US$5724.
Results: Antenatal vaccination with prioritization averted 9070 (90% UI: 7407–11217) 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 7801 (90% UI: 6465–9527) 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 $4689 (90% UI: $3128–$7294) per Quality Adjusted Life Year (QALY) gained while vaccinating without prioritization had a cost of $5924 (90% UI: $3992–$9056) per QALY.
Conclusions: Antenatal influenza vaccination campaigns in South Africa would reduce the impact of influenza and could be cost-effective.

1. Introduction

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

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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 to 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 6.8/100000 among pregnant women and 22/100000 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 74.9/100000 while it was 1.5/100000 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.

2. 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). Fig. 1A displays the overall simplified decision-tree model structure for pregnant women and Fig. 1B displays the model for their infants. The number of pregnant women to include in the cohort was based
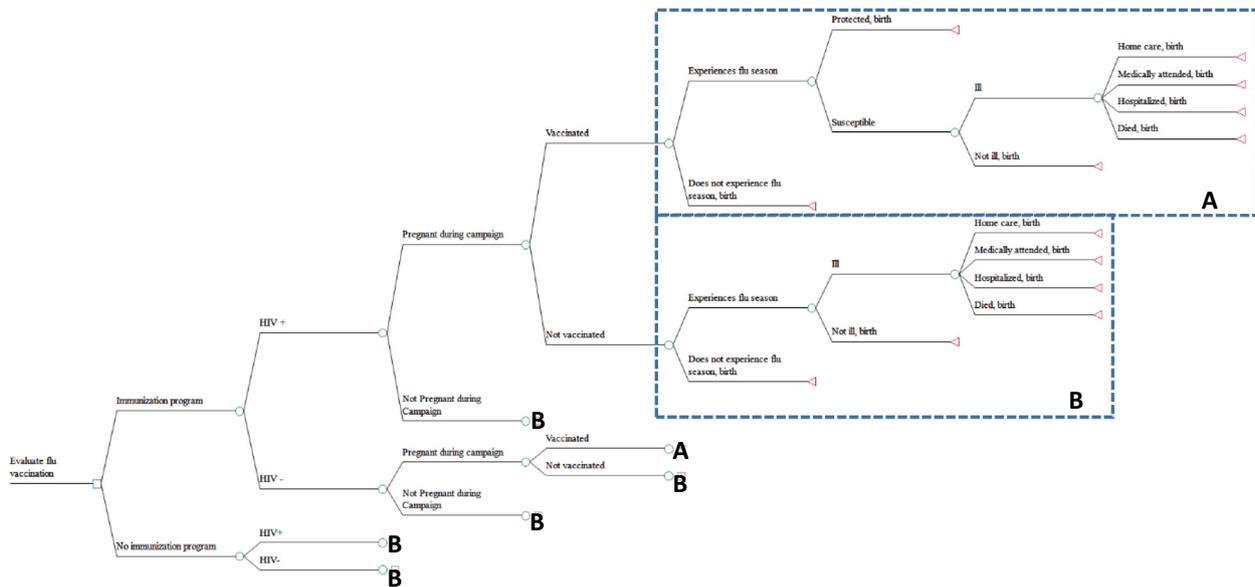

Fig. 1A. Decision tree to estimate the impact of influenza vaccination among pregnant women and their infants.
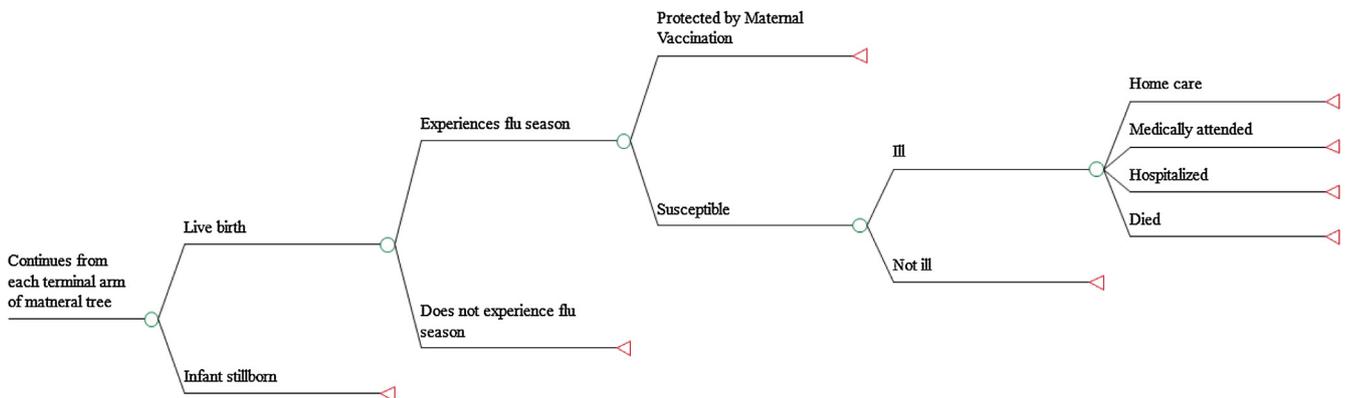

Fig. 1B. Infant subtree to estimate the impact of influenza vaccination among pregnant women and their infants.

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 Fig. 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 26000 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, using the no vaccine scenario as the baseline. The threshold for cost-effectiveness was set to the 2015 per-capita gross domestic product of South Africa, US$5724, which was based

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				
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]

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.

2.1. 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 10000 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.

2.2. Model inputs

2.2.1. 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 Fig. 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 Fig. 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].

2.2.2. 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].

2.2.3. 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].

2.2.4. 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].

2.2.5. 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].

2.2.6. 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.

2.2.7. 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].

2.2.8. 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 preg-

nant 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].

3. Results

In the base case scenario with no vaccination, influenza infection among pregnant women resulted in 48320 (90% UI: 39622–58550) total illnesses, including 1700 (90% UI: 1271–2259) hospitalizations and 126 (90% UI: 94–165) deaths (Table 2). Influenza infection among infants resulted in 19014 (90% UI: 15038–23839) illnesses, including 1343 (90% UI: 1023–1734) 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 7640 (90% UI: 6243–9410) 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 6372 (90% UI: 5268–7768) 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 1431 (90% UI: 1164–1808) 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 1429 (90% UI: 1197–1760) 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 $4689 (90% UI: $3128–$7294), 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 $5924 (90% UI: $3992–$9056), and the median point estimate was nearly considered cost-effective (Table 4).

3.1. Sensitivity analysis

Fig. 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. Fig. 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 Fig. 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 Fig. 3 displays the estimated averted burden of antenatal influenza vaccination in South Africa for pregnant women and infants, varied by vaccine coverage among

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)	48320 (39622–58550)	30890 (24669–38294)	1700 (1271–2259)	126 (94–165)
HIV-Infected Prioritization	40680 (33380–49140)	25736 (20579–31803)	1390 (1045–1845)	102 (76–133)
No Prioritization	41948 (34354–50782)	26753 (21355–33159)	1466 (1097–1948)	109 (81–142)
Infants				
No Vaccination (Baseline)	19014 (15038–23839)	9639 (7432–12381)	1343 (1023–1734)	80 (60–103)
HIV-Infected Prioritization	17583 (13874–22031)	8910 (6850–11427)	1241 (944–1602)	74 (56–95)
No Prioritization	17585 (13841–22079)	8909 (6833–11462)	1241 (943–1605)	74 (56–96)
Combined				
No Vaccination (Baseline)	67334 (54660–82388)	40528 (32101–50675)	3043 (2294–3993)	206 (154–268)
HIV-Infected Prioritization	58264 (47254–71171)	34646 (27429–43229)	2708 (2041–3550)	176 (132–229)
No Prioritization	59533 (48195–72861)	35662 (28188–50675)	2707 (2040–3553)	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	264430	7640 (6243–9410)	15.8 (10.7–23.7)	5153 (4090–6491)	310 (226–414)	24 (18–32)
No Prioritization	264430	6372 (5268–7768)	13.2 (9.0–19.6)	4137 (3313–5134)	233 (173–311)	18 (13–23)
Infants						
HIV-Infected Prioritization		1431 (1164–1808)	7.5 (4.9–12.0)	729 (582–954)	102 (79–132)	6 (5–8)
No Prioritization		1429 (1197–1760)	7.5 (5.0–11.7)	730 (599–918)	102 (81–129)	6 (5–8)
Combined						
HIV-Infected Prioritization	264430	9070 (7407–11217)	13.5 (9.0–20.5)	5882 (4672–7445)	411 (305–546)	30 (22–40)
No Prioritization	264430	7801 (6465–9527)	11.6 (7.8–17.4)	4866 (3913–6053)	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)	6664 (4445–10515)
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)	9240 (6187–14445)
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 to −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 to −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)	4689 (3128–7294)
No Prioritization	1.89457 (1.89372–1.89529)	0.00035 (0.00027–0.00045)	3.95 (3.20–4.89)	2.07 (1.78–2.4)	5924 (3992–9056)

[1] Upper and lower 90% uncertainty intervals.
[2] In 2016 U.S. dollars and includes costs related to influenza-associated illness and vaccination.
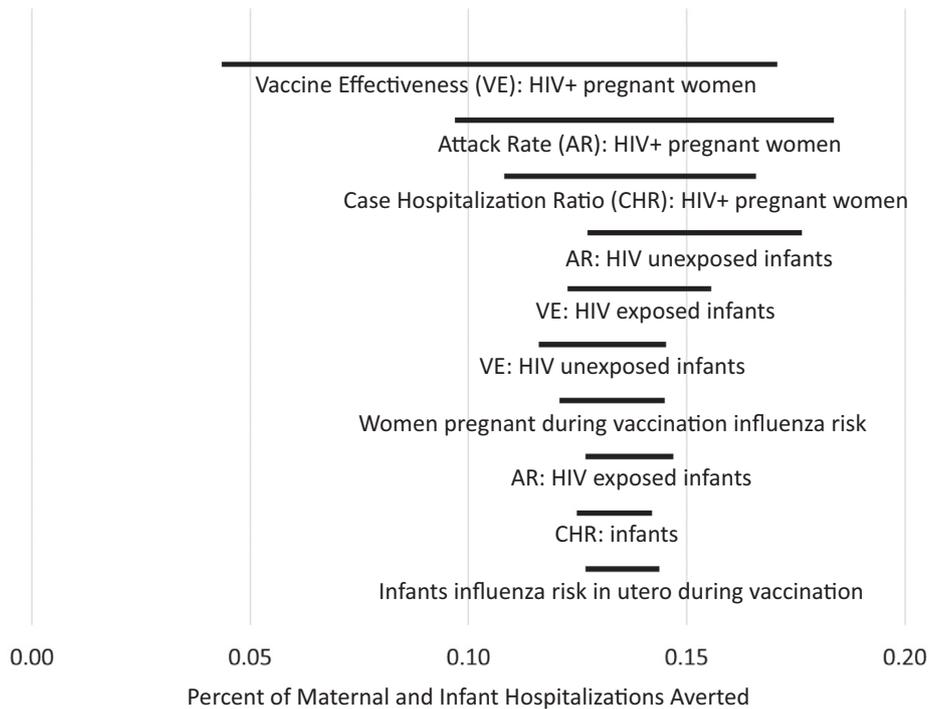
Fig. 2. Tornado diagram of one-way sensitivity analyses of the 10 most influential model parameters on the burden of maternal and infant hospitalizations averted by antenatal influenza vaccination with HIV-infected prioritization.
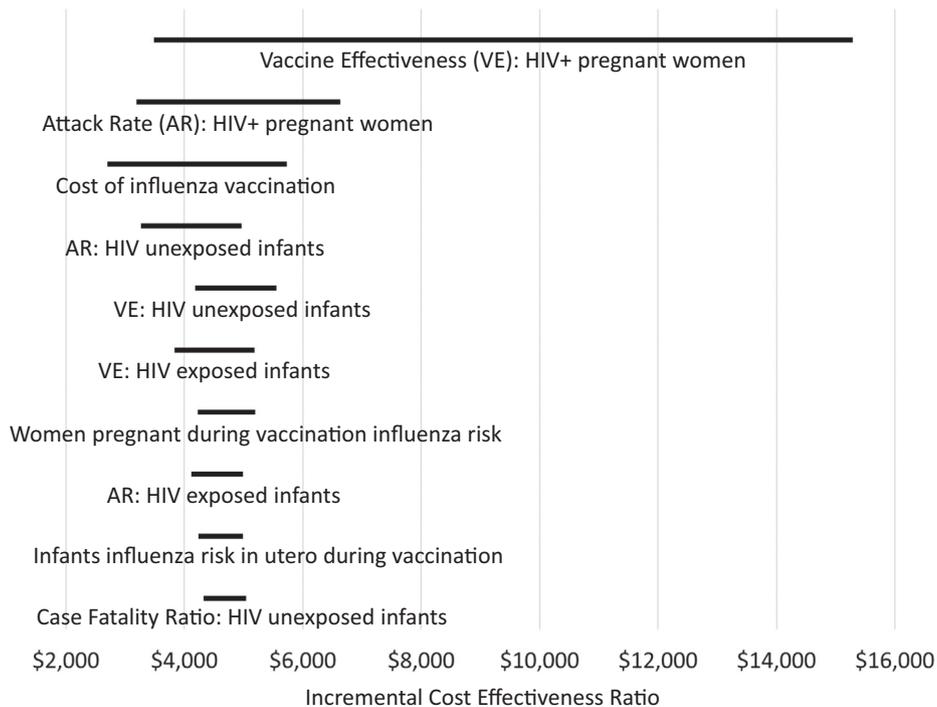

Fig. 3. Tornado diagram of one-way sensitivity analyses on the effect of range of the 10 most influential model parameters on the maternal and infant Incremental Cost Effectiveness Ratio (ICER) for antenatal influenza vaccination with HIV-infected prioritization.

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.

Fig. 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 $4000 while over 90% of vaccination with prioritization simulations and 70% of vaccination without prioritization simulations were cost-effective at a threshold of $7000.
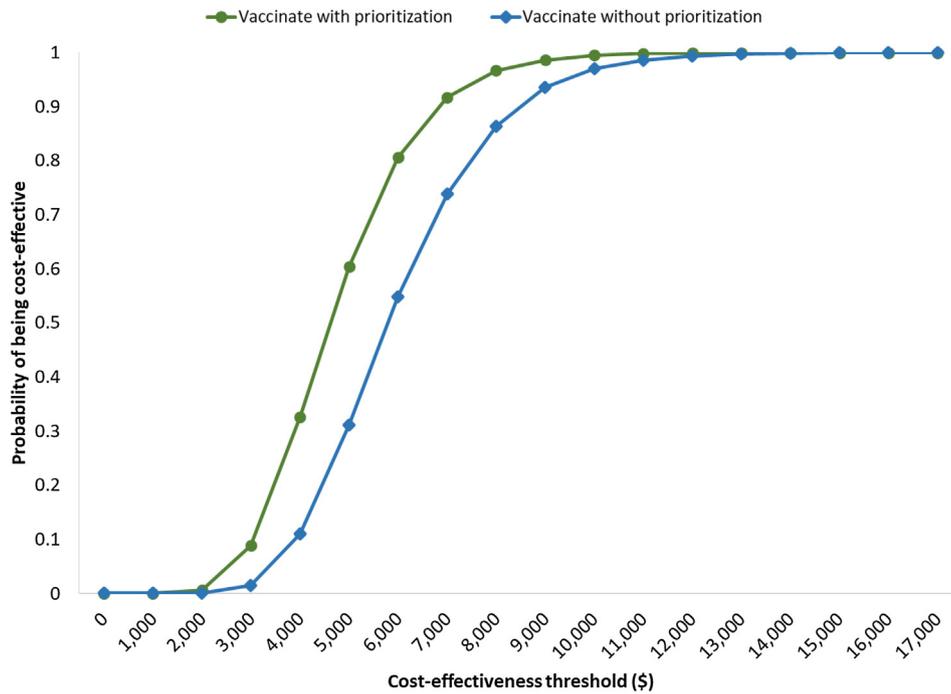
Fig. 4. Cost-effectiveness acceptability curve for antenatal influenza vaccination with and without HIV-infected prioritization compared to no vaccine.

3.2. 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 Fig. 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 Fig. 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.

4. 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 265000 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 9000, 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 265000 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 265000 pregnant women in South Africa would reduce the influenza burden between 12 and 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.

Disclaimer

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.09.059.

References

[1] Fell DB, Azziz-Baumgartner E, Baker MG, Batra M, Beaute J, Beutels P, et al. Influenza epidemiology and immunization during pregnancy: final report of a World Health Organization working group. Vaccine 2017;35:5738–50.

[2] Keller-Stanislawski B, Englund JA, Kang G, Mangtani P, Neuzil K, Nohynek H, et al. Safety of immunization during pregnancy: a review of the evidence of selected inactivated and live attenuated vaccines. Vaccine 2014;32(52):7057–64.

[3] Sukumaran L, McCarthy NL, Kharbanda EO, Weintraub ES, Vazquez-Benitez G, McNeil MM, et al. Safety of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis and influenza vaccinations in pregnancy. Obstet Gynecol 2015;126:1069–74.

[4] Thompson MG, Kwong JC, Regan AK, Katz MA, Drews SJ, Azziz-Baumgartner E, et al. Influenza vaccine effectiveness in preventing influenza-associated hospitalizations during pregnancy: a multi-country retrospective test negative design study, 2010–2016. Clin Infect Dis 2018.

[5] Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, et al. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 2014;371:918–31.

[6] Tapia MD, Sow SO, Tamboura B, Teguete I, Pasetti MF, Kodio M, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. Lancet Infect Dis 2016.

[7] Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. N Engl J Med 2008;359:1555–64.

[8] Steinhoff MC, Katz J, Englund JA, Khatry SK, Shrestha L, Kuypers J, et al. Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial. Lancet Infect Dis 2017;17:981–9.

[9] World Health Organization. Vaccines against influenza WHO position paper - November 2012. Wkly Epidemiol Rec 2012;87:461–76.

[10] Johnson LF, May MT, Dorrington RE, Cornell M, Boulle A, Egger M, et al. Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: a mathematical modelling study. PLoS Med 2017;14:e1002468.

[11] The Centre for Respiratory Diseases and Meningitis, National Institute for Communicable Diseases, National Health Laboratory Service, South African National Department of Health. Healthcare Workers Handbook on Influenza; 2016.

[12] Tempia S, Walaza S, Viboud C, Cohen AL, Madhi SA, Venter M, et al. Mortality associated with seasonal and pandemic influenza and respiratory syncytial virus among children <5 years of age in a high HIV prevalence setting–South Africa, 1998–2009. Clin Infect Dis 2014;58:1241–9.

[13] Tempia S, Walaza S, Cohen AL, von Mollendorf C, Moyes J, McAnerney JM, et al. Mortality associated with seasonal and pandemic influenza among pregnant and nonpregnant women of childbearing age in a High-HIV-prevalence setting-South Africa, 1999–2009. Clin Infect Dis 2015;61:1063–70.

[14] South Africa National Department of Health. National Influenza Policy and Strategic Plan: 2017 to 2021. Pretoria, South Africa; 2017.

[15] Statistics South Africa. Recorded Live Births, 2014; 2015.

[16] Ramkrishna W. Trends in influenza vaccine coverage of high risk groups in South Africa (2011–2015), prior to influenza policy implementation. Options IX for the Control of Influenza. Chicago, IL; 2016.

[17] The World Bank. GDP per capita (current US$) | Data; 2017.

[18] World Health Organization. WHO | Table: Threshold values for intervention cost-effectiveness by Region. WHO: World Health Organization; 2014.

[19] Savitz DA, Fell DB, Ortiz JR, Bhat N. Does influenza vaccination improve pregnancy outcome? Methodological issues and research needs. Vaccine 2015;33(47):6430–5.

[20] World Health Organization. WHO | FluNet. WHO: World Health Organization; 2017.

[21] Madhi SA, Nunes MC, Weinberg A, Kuwanda L, Hugo A, Jones S, et al. Contribution of serologic assays in the evaluation of influenza virus infection rates and vaccine efficacy in pregnant women: report from randomized controlled trials. Clin Infect Dis 2017;64:1773–9.

[22] Department of Health/South Africa, Medical Research Council/South Africa, ORC Macro. South Africa Demographic and Health Survey 2003. Pretoria, South Africa: Department of Health/South Africa; 2007.

[23] Murray J, Cohen A, Walaza S, Groome M, Madhi S, Variava E, et al. Determining the provincial and national burden of influenza-associated severe acute respiratory illness in South Africa using a rapid assessment methodology. PLoS ONE 2015;10:e0132078.

[24] Kai-Lun Wong K, von Mollendorf C, Martinson N, Norris S, Tempia S, Walaza S, et al. Healthcare utilization for common infectious disease syndromes in Soweto and Klerksdorp, South Africa. Pan Afr Med J. 2018;30.

[25] Tempia S, Walaza S, Moyes J, Cohen AL, von Mollendorf C, McMorrow ML, et al. The effects of the attributable fraction and the duration of symptoms on burden estimates of influenza-associated respiratory illnesses in a high HIV prevalence setting, South Africa, 2013–2015. Influenza Other Respir Viruses 2018;12:360–73.

[26] McMorrow ML, Tempia S, Walaza S, Treurnicht FK, Moyes J, Cohen AL, et al. The role of HIV in influenza- and respiratory syncytial virus-associated hospitalizations in South African children, 2011–2016. Clin Infect Dis 2018.

[27] Mertz D, Geraci J, Winkup J, Gessner BD, Ortiz JR, Loeb M. Pregnancy as a risk factor for severe outcomes from influenza virus infection: a systematic review and meta-analysis of observational studies. Vaccine 2017;35:521–8.

[28] Fell DB, Bhutta ZA, Hutcheon JA, Karron RA, Knight M, Kramer MS, et al. Report of the WHO technical consultation on the effect of maternal influenza and influenza vaccination on the developing fetus: Montreal, Canada, September 30-October 1, 2015. Vaccine 2017;35:2279–87.

[29] Sinha A, Kim S, Ginsberg G, Franklin H, Kohberger R, Strutton D, et al. Economic burden of acute lower respiratory tract infection in South African children. Paediatrics Int Child Health 2012;32:65–73.

[30] Cohen C, Walaza S, Treurnicht FK, McMorrow M, Madhi SA, McAnerney JM, et al. In- and out-of-hospital mortality associated with seasonal and pandemic influenza and respiratory syncytial virus in South Africa, 2009–2013. Clin Infect Dis 2018;66:95–103.

[31] Statistics South Africa. Consumer Price Index data from January 2008 Publication Number P0141; 2018.

[32] World Health Organization Regional Office for Europe. Review of vaccine price data; 2015.

[33] Wolfson LJ, Gasse F, Lee-Martin SP, Lydon P, Magan A, Tibouti A, et al. Estimating the costs of achieving the WHO-UNICEF Global Immunization Vision and Strategy, 2006–2015. Bull World Health Organ 2008;86:27–39.

[34] Bilcke J, Coenen S, Beutels P. Influenza-like-illness and clinically diagnosed flu: disease burden, costs and quality of life for patients seeking ambulatory care or no professional care at all. PLoS ONE 2014;9:e102634.

[35] Baguelin M, Hoek AJ, Jit M, Flasche S, White PJ, Edmunds WJ. Vaccination against pandemic influenza A/H1N1v in England: a real-time economic evaluation. Vaccine 2010;28:2370–84.

[36] Xu J, Zhou F, Reed C, Chaves SS, Messonnier M, Kim IK. Cost-effectiveness of seasonal inactivated influenza vaccination among pregnant women. Vaccine 2016;34(27):3149–55.

[37] Prosser LA, Payne K, Rusinak D, Shi P, Uyeki T, Messonnier M. Valuing health across the lifespan: health state preferences for seasonal influenza illnesses in patients of different ages. Value Health 2011;14:135–43.

[38] Chow MY, Yin JK, Heron L, Morrow A, Dierig A, Booy R, et al. The impact of influenza-like illness in young children on their parents: a quality of life survey. Qual Life Res 2014;23:1651–60.

[39] Tengs TO, Lin TH. A meta-analysis of utility estimates for HIV/AIDS. Med Decis Making 2002;22:475–81.

[40] Knoema. Global Health Observatory, 2015. @knoema; 2017.

[41] Johnson LF, Mossong J, Dorrington RE, Schomaker M, Hoffmann CJ, Keiser O, et al. Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. PLoS Med 2013;10:e1001418.

[42] McMorrow ML, Tempia S, Walaza S, Treurnicht FK, Ramkrishna W, Azziz-Baumgartner E, et al. Prioritization of risk groups for influenza vaccination in resource limited settings - A case study from South Africa. Vaccine 2019;37:25–33.

[43] Beigi RH, Wiringa AE, Bailey RR, Assi TM, Lee BY. Economic value of seasonal and pandemic influenza vaccination during pregnancy. Clin Infect Dis 2009;49:1784–92.

[44] Myers ER, Misurski DA, Swamy GK. Influence of timing of seasonal influenza vaccination on effectiveness and cost-effectiveness in pregnancy. Am J Obstet Gynecol 2011;204:S128–40.

[45] Roberts S, Hollier LM, Sheffield J, Laibl V, Wendel Jr GD. Cost-effectiveness of universal influenza vaccination in a pregnant population. Obstet Gynecol 2006;107:1323–9.

[46] Blommaert A, Bilcke J, Vandendijck Y, Hanquet G, Hens N, Beutels P. Cost-effectiveness of seasonal influenza vaccination in pregnant women, health care workers and persons with underlying illnesses in Belgium. Vaccine 2014;32:6075–83.

[47] Jit M, Cromer D, Baguelin M, Stowe J, Andrews N, Miller E. The cost-effectiveness of vaccinating pregnant women against seasonal influenza in England and Wales. Vaccine 2010;29:115–22.

[48] Skedgel C, Langley JM, MacDonald NE, Scott J, McNeil S. An incremental economic evaluation of targeted and universal influenza vaccination in pregnant women. Can J Public Health 2011;102:445–50.

[49] Ding Y, Zangwill KM, Hay JW, Allred NJ, Yeh SH. Cost-benefit analysis of in-hospital influenza vaccination of postpartum women. Obstet Gynecol 2012;119:306–14.

[50] Orenstein EW, Orenstein LA, Diarra K, Djiteye M, Sidibe D, Haidara FC, et al. Cost-effectiveness of maternal influenza immunization in Bamako, Mali: a decision analysis. PLoS ONE 2017;12:e0171499.

[51] Pillay Y, Mametja D, Mbengashe T, Makakole-Nene S, Banda M, Gqwaru N, et al. Joint Review of HIV, TB and PMTCT programmes in South Africa October 2013 main report. Pretoria: National Department of Health; 2014.

[52] Centers for Disease Control and Prevention. Disease Burden of Influenza | Seasonal Influenza (Flu) | CDC; 2016.

[53] Centers for Disease Control and Prevention. Seasonal Influenza Vaccine Effectiveness, 2004–2018 | Health Professionals | Seasonal Influenza (Flu); 2019.

[54] Goga AE, Dinh T-H, Jackson DJ, Lombard C, Delaney KP, Puren A, et al. First population-level effectiveness evaluation of a national programme to prevent HIV transmission from mother to child, South Africa. J Epidemiol Community Health 2014.

[55] United Nations Inter-agency Group for Child Mortality Estimation. Levels & Trends in Child Mortality Report 2014; 2014.