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THE COST-EFFECTIVENESS OF INFLUENZA VACCINATION OF PREGNANT WOMEN IN THE SOUTH AFRICAN PUBLIC HEALTHCARE SETTING

by

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Declaration

I, Trudy D. Leong, student number u14272907 hereby declare that this dissertation, "*The cost-effectiveness of influenza vaccination of pregnant women in the South African public healthcare setting,*" is submitted in accordance with the requirements for the Master of Science in Clinical Epidemiology degree at University of Pretoria, is my own original work and has not previously been submitted to any other institution of higher learning. All sources cited or quoted in this research paper are indicated and acknowledged with a comprehensive list of references.

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Trudy D. Leong

9 November 2016

Dedication

I dedicate this research to the South African citizens, who are dependent on the public sector in accessing healthcare and to Almighty God, who provided me the perseverance to complete this analysis.

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I would like to express my sincere gratitude to the following people:

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- Last, but not the least –my family and friends for their patience and enduring support.

Abstract

Background: International analyses suggest that routine maternal vaccination with seasonal trivalent influenza vaccine is cost-effective, but few studies have been done in middle- to low- income countries.

Method: A decision-tree analysis was modelled for the South African public healthcare setting over one year from a payer's perspective. Direct medical costs and consequences were obtained from published literature. Incremental cost effectiveness ratios (ICERs) and univariate sensitivity analyses were then measured. Discounting was excluded due to the seasonality of influenza, limiting the time horizon to a one year period.

Findings: The model predicted that to avert influenza-associated hospitalisations amongst pregnant women and their infants less than six months of age, vaccination of pregnant women was not cost-effective. This was irrespective of whether the universal vaccination or HIV-targeted approach was used.

A base model simulating 100% vaccine uptake predicted that seasonal vaccination of 100,000 pregnant women results in an estimated net cost of R69,118,114.05 per neonatal influenza-associated hospitalisation averted. Similarly, the model suggested that vaccinating 100,000 pregnant women would cost R1,197,779.79 per maternal hospitalisation averted.

Univariate sensitivity analyses reinforced that influenza vaccination of pregnant women was not cost-effective, except when lower incidence of maternal influenza-associated hospitalisations associated with antenatal influenza vaccination were

simulated where the targeted approach became dominant. The latter analysis predicted savings of R770,530.86 per maternal influenza-associated hospitalisation averted.

Interpretation: The ICERs suggest that influenza vaccination amongst pregnant women is not cost-effective in the South African public healthcare sector compared to no vaccination, with respect to averting influenza-associated hospitalisations amongst pregnant women and their infants less than six months of age. However, these estimates should be re-evaluated, pending vaccine effectiveness studies of higher methodological quality for low- and middle- income countries and using cost inputs relevant to South African public healthcare setting. This analysis may provide preliminary information regarding the upscaling of influenza vaccination amongst pregnant women as a priority in the constraints of a limited healthcare budget and careful consideration is required regarding vaccine mobilisation amongst pregnant women.

Key terms: seasonal influenza, vaccination, pregnant, hospitalisation, neonate, South Africa

List of abbreviations

AIDS	Autoimmune deficiency syndrome
ADR	Adverse drug reaction
CAD	Canadian dollar
CI	Confidence interval
CPI	Consumer price index
CRP	C-reactive protein
DALY	Disability adjusted life year
EML	Essential medicine list
GAVI	Global Alliance for Vaccines and Immunization
GBD	Global Burden of Disease
GBS	Guillain-Barre syndrome
GDP	Gross domestic profit
GP	General practitioner
HIV	Human immunodeficiency virus
HTA	Health technology assessment
HUE	HIV uninfected exposed
HUU	HIV unexposed uninfected
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
LBW	Low birth weight
LRTI	Lower respiratory tract infection
LYG	Life year gained
MTCT	Mother to child transmission (HIV)
NHLS	National Health Laboratory Service
NDoH	National Department of Health
NNV	Number needed to vaccinate
NP	Nurse practitioner
OR	Odds ratio

QALY	Quality adjusted life year
RCT	Randomised controlled trial
RR	Risk ratio
SAGE	Strategic Advisory Group of Experts
SGA	Small for gestational age
STG	Standard treatment guideline
TB	Tuberculosis
TIV	Trivalent influenza vaccine
UK	United Kingdom
UPFS	Uniform patient fee schedule
USA	United States of America
USD	United States dollar
VAC	Vaccinated
WHO	World Health Organisation
ZAR	South African rand

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1. CHAPTER ONE: INTRODUCTION

1.1 INFLUENZA

Seasonal influenza is an acute viral infection that commonly manifests as upper and/or lower respiratory tract symptoms with fever, headache, myalgia, and weakness. In temperate climates, like South Africa, disease occurs seasonally in the winter months with high rates of transmission through coughing, sneezing or exposure with contaminated surfaces. There are 3 types (A, B and C). Influenza type A is further divided into subtypes based on two proteins, haemagglutinin (H) and neuraminidase (N) found on the surface of the virus. Currently, there are 2 main circulating strains of influenza B viruses: B/Yamagata and B/Victoria. Influenza type A and B viruses circulate and cause seasonal influenza outbreaks and epidemics, whilst type C is less common. Influenza viruses evolve continually requiring public health measures of annual vaccination that includes the current circulating influenza A(H1N1) and A(H3N2) and one or two influenza B viruses (in a trivalent or quadrivalent vaccine, respectively).(1)

Influenza vaccines provide moderate protection against virologically confirmed influenza, but protection is greatly reduced or absent in some seasons.[2]This implies that the circulating serotype for that season would require matching to the strain of the vaccine, although previous exposure could provide a degree of immunogenicity.[3]

1.2 EPIDEMIOLOGY

Epidemiological data demonstrate increased mortality and morbidity associated with flu pandemics amongst pregnant women, as early as 1919.[4]This was similarly confirmed in the 1957 Asian influenza A (H2N2)[5]pandemic and 2009 Hong Kong influenza A (H1N1) pandemic (Hong Kong)[6].

Mortality data for 2013 lists influenza and pneumonia amongst the top 10 underlying causes of death in South Africa[7]. Of note is that tuberculosis was ranked the leading underlying natural cause of death for the period 2011 to 2013, whilst influenza and pneumonia was listed as the second leading cause, the latter grouping based on ICD10 codes J09-J18.

1.3 INFLUENZA VACCINATION

Preventing severe disease in pregnant women (who are at highest risk for severe sequelae of influenza) and secondary protection of infants < 6 months of age through routine trivalent influenza vaccination (TIV) has been recommended by the WHO Strategic Advisory Group of Experts.[8]Trivalent influenza vaccine is an inactivated vaccine that contains two viral A strains and one B strain and is safe in pregnancy and in children ≥ 6 months of age. As not everyone is at risk for severe influenza-associated disease, and due to limited availability of the vaccine, the South African National Department of Health's Immunisation Guide for 2016 recommends priority groups for seasonal influenza vaccination. Not everyone can be vaccinated against influenza. Pregnant women, irrespective of stage of pregnancy, are included amongst these priority groups.[9]

1.4 BUDGETS

Healthcare budgets are limited and economic evaluation studies assist in informing cost-effective expenditure of healthcare resources.Thus, making choices or determining priorities will be an activity that will take place at all levels of public funded healthcare, especially during periods of global economic pressures where rationing may be warranted. Healthcare decision-making mostly involved political negotiation and historical allocation patterns. However, efficiently assessing opportunity costs will result in better use of healthcare funds and a more sustainable healthcare system. Using health technology assessments(HTAs) may be one method for priority setting.[10]An HTA is "the systematic evaluation of a medical or health technology for evidence of its safety, efficacy, effectiveness, cost, cost-effectiveness, and ethical and legal implications, both in absolute terms and in comparison with other competing technologies".[11] Thus, economic modelling to determine cost-effectiveness is included as a component of the development of HTA.[12]

1.5 MOTIVATION FOR THE STUDY

A number of cost-effectiveness analyses have been done internationally for prenatal influenza vaccine strategies.[13–16]However, to date, there are no published cost-effectiveness analyses for South Africa. Furthermore, with South Africa's quadruple burden of disease poses additional challenges in terms of allocation of limited resources, a mind shift to focus on preventative (i.e. vaccination) medicine rather than curative treatment of communicable diseases (HIV/AIDs and TB),

maternal and child health conditions, non-communicable and injury-related disorders[17], would take priority from a public healthcare perspective.

1.6 AIM OF THE STUDY

The aim of this cost-effectiveness evaluation is to determine whether influenza vaccination of pregnant women in the South African context is cost-effective.

1.7 OBJECTIVES OF THE STUDY

Toestimate the incremental cost-effective ratios (ICERs) of maternel immunisation, by determining the effect of the intervention in both thepregnant woman and her newborn infant in thefollowing contexts:

- Universal prenatal influenza vaccination compared to placebo.
- Targeted influenza vaccination of pregnant HIV-infected mothers compared to placebo.

1.8 ETHICS APPROVAL

The study will promote the advocacy for immunization of pregnant women against influenza. Data used in this economic evaluation is published in the public domain and therefore there was no contravention of confidentiality. The study was evaluated and approved by the Academic Advisory Committee and Ethics Committee (Ethics Reference No.: 490/2015). (Refer to Annexure A: Ethics

approval letter). The student and supervisor declare that there are no conflicts of interest.

1.9 FUNDING OF THE STUDY

No external funding was sourced for the study. The study was self-funded.

1.10 DATA COLLECTION

Data were obtained from peer reviewed published literature, sourced through literature searches.

1.11 DATA ANALYSIS

This cost-effectiveness evaluation compared the cost-effectiveness of targeted prenatal influenza vaccination of HIV-infected pregnant women, universal vaccination of all pregnant women and a no vaccination approach, using a decision tree analytic model construct similar to that described by Skedgel et al. (2011).[15]The probabilistic model mapped the different clinical pathways of both the pregnant women and their newborn over time, with each pathway representing one possible sequence of events. The models did not represent events that recur over time.[18]

2. CHAPTER 2: LITERATURE REVIEW

2.1 INFLUENZA IN PREGNANT WOMEN AND THEIR NEWBORN

Epidemiological data from seasonal influenza episodes and influenza pandemics demonstrate increased mortality and morbidity associated with flu pandemics amongst pregnant women, compared to the general population.[4–6]The World Health Organization (WHO) defines severe acute respiratory infection as a sudden onset of fever of > 38°C) or reported fever, cough or sore throat, and shortness of breath or difficulty breathing.[1]However, it is assumed that the increased morbidity and mortality in pregnant is probably due to physiological changes during pregnancy. Furthermore, low quality evidence published in peer review literature suggests that the increased risk in pregnancy occurs mostly in the third trimester and 4 weeks postpartum.[19]

The effect of maternal influenza on the fetus is not well documented in the published literature.[20]However, antenatal immunization with TIV may confer protection to the newborn via transplacentally-acquired antibodies against influenza.[21–25]Furthermore, influenza vaccines are currently not licensed for children < 6 months of age, as their immune response has been shown to be variable.[26]

2.2 LOCAL EPIDEMIOLOGY DATA

The mid-year 2015 population estimates from Statistics South Africa for live births was reported to be 1,250,782 per annum.[7]Thus, it was considered reasonable to use a cohort of 100,000 pregnant women in this decision analytic model. More

importantly, due to South Africa's quadruple burden of disease, co-morbid HIV needs to be factored into many decisions. The overall prevalence of HIV amongst pregnant women who presented at public sector ante-natal clinics was estimated to be 29.7% in 2013 as per the 2013 National Antenatal Sentinel HIV Prevalence Survey[27]; whilst the most recent transmission rates reported from the National Department of Health for mother to child (MTCT) was estimated to be 1.5%.[28]

2.3 CLINICAL BENEFITS OF MATERNAL INFLUENZA VACCINATION

2.3.1 Mortality associated with influenza infection

Historically (1919)[4] and globally[5,6]influenza has been associated with high morbidity and mortality amongst pregnant women and their neonates. From April to June 2009, 13% of total influenza A (H1N1) deaths were reported in pregnant women in the USA.[29]During the H1N1 pandemic of April to October 2009, pregnancy was reported as the second most frequent underlying conditions of fatal cases.[30]Previously, a meta-analysis done in 2013 showed a non-significant association of HIV-infection and influenza-associated mortality (seasonal and pandemic). In addition, the meta-analysis suggested that women less than four weeks postpartum and women in third trimester of pregnancy had an increased risk of mortality (1.22, 1.01-1.48, I^2=0%).[19]

However, a subsequent epidemiological study (for the period of 1999 to 2009) conducted in South Africa showed an association and reported a higher burden of seasonal and pandemic influenza-associated mortality for HIV compared to HIV-uninfected pregnant women with a relative risk 2.8, 95% CI 1.7 to 3.9. The age-

standardized relative risk of mortality for pregnant compared to the non-pregnant was 3.9, 95% CI 2.9 to 5.2, for HIV-uninfected, whilst for the HIV-infected, 4.1, 95% CI 3.6 to 4.5. Of note is that this mortality risk grouped influenza diagnosis with pneumonia, presumably because influenza may progress to pneumonia. The relative risk adjusted for age and HIV status for pregnant versus non-pregnant women was likewise reported as a statistically significant relative risk of 2.9; 95% CI 1.8 to 4.0.[31]

Tempia et al., 2015[31]further reported that the respiratory deaths among both pregnant and non-pregnant women were seasonal, peaking between May and August (winter season). In addition, pandemic influenza A (H1N1) pdm09 resulted in a second peak of mortality in 2009. The HIV epidemic and management of HIV follows the pattern of mortality rates, increasing from 1999 to 2004 where there was an increased HIV prevalence and decreasing thereafter after the progressive rollout of triple antiretroviral therapy. This differs from data from countries of low HIV prevalence where HIV-infected patients were more likely to be hospitalised for influenza, but rates of death were comparable amongst the HIV-infected and HIV-uninfected.[32,33]

Available data from four surveillance sites (for the period 2009 to 2013) suggested a higher mortality rate associated with lower respiratory tract infections for HIV infected and HIV exposed infants less than six months of age compared to HIV unexposed and uninfected (ORs2.1; 95% CI 1.1 to 3.8 and 12.2; 95% CI 1.7 to infinity, respectively).[34]However, the rates of “in" and "out" of influenza-associated mortality of neonates were not differentiated in this study and the social determinants of access to healthcare may possibly have affected the results. In addition, lower

respiratory infections included respiratory infections caused by the respiratory syncytial virus, human Meta pneumovirus as well as the influenza virus.[34]Sufficientlyrobust evidence for the reduction of neonatal death associated with maternal influenza vaccination is lacking. There are a paucity of local epidemiological data for perinatal deaths as a result of not vaccinating pregnant women for seasonal influenza. Although overall perinatal death rates in the general population can be sourced from local perinatal reports, perinatal deaths are seldom included in health economic predication models.

2.3.2 Severe influenza-associated respiratory infection requiring hospitalisation, laboratory-confirmed influenza and influenza-like illness

A global review of pandemic influenza infection in high risk groups reported a higher risk of hospitalisation in pregnancy, reported as a median of 6.8 (n=10 countries) compared to the risk of death (unadjusted relative risk of death of 1.9; n=11 countries) amongst pregnant versus non-pregnant women.[35]In high income countries, Canada,[36]Australia, New Zealand[37] and the United States,[29]rates of influenza-associated hospitalisation and ICU admission were also shown to be higher among pregnant women than compared to the general population. Additional observational data demonstrates that pregnant women have increased rates of influenza-associated hospitalisation compared to non-pregnant women.[38,39] Similarly, another systematic review showed that pregnant women were at higher risk for hospital admission (4.43, 95% CI 1.24 to 15.81, I2=0%, n=3).[19]

A subsequent Cochrane review (2014) of observational data of moderate methodological quality showed that to prevent influenza-like illness in pregnant

women, the number needed to vaccinate (NNV) was 92 (95% CI 63 to 201) and NNV for laboratory-confirmed influenza in newborns of vaccinated women was 27 (95% CI 18 to 185). The prevention of hospitalisation amongst vaccinated compared to unvaccinated healthy adults was reported to be statistically non-significant RR 0.96; 95% CI 0.85 to 1.08. As the 95% CI crosses 1.00 (the point of null effect), and therefore, the rate of hospitalisation amongst vaccinated and non-vaccinated pregnant women were considered to be similar.[40]

Vaccine efficacy studies have been conducted in low- and middle income countries that showed a reduction of laboratory confirmed influenza in pregnant women and their newborns less than six months of age. A RCT in Bangladesh showed a 36% (95% CI 4 to 57) reduction in febrile respiratory illness and a 63% (95% CI 5 to 85) reduction in laboratory-confirmed influenza amongst the vaccinated pregnant women's infants. However, the comparator to TIV was pneumococcal vaccine, contributing to effect bias.[41]The RCT done in South Africa[42]showed that prenatal influenza vaccination was associated with a reduction in laboratory-confirmed influenza among women (HIV uninfected or HIV infected) and their neonates less than six months of age. However, the study was not powered to show a clear difference between the vaccine and placebo groups in terms of adverse pregnancy outcomes (preterm or low birth weight), influenza-like illness, hospitalisations or adverse events of mothers and their newborn. A more recent study conducted in Mali showed an overall vaccine efficacy rate (against first episodes of laboratory confirmed influenza) of 33.1%; 95% CI 3.7 to 53.9 amongst the newborn of vaccinated pregnant women. This was robust during the first 4 months of follow-up

(67.9%; 95% CI 35.1 to 85.3) but diminished during the fifth month (57.3%; 95% CI 30·6 to 74·4).[43]

A local epidemiological study investigating the incidence of influenza-associated lower respiratory infection (LRTI) showed that at four local South African sentinel surveillance sites, for the period of 35 months (i.e. February 2009 to December 2011), the incidence of LRTI was higher amongst the HIV-infected compared to the HIV uninfected, with elevated rates of hospitalisation, prolonged hospitalisation and increased risk of in-hospital death.[44]A non-statistically significant difference in severe influenza-associated ICU admission amongst HIV versus HIV-uninfected adults was reported. However, this study enrolled few pregnant women.

Observational studies have also shown that maternal immunisation reduces the rates of influenza like illness and influenza hospitalisations among infants up to 6 months of age.[45–47]A similar trend was seen in a local epidemiological study[3434]that differentiated between HIV uninfected exposed (HUE), HIV-infected and HIV uninfected unexposed (HUU) infants less than 6 months of age. The incidence rate ratio of LRTI-associated hospitalisations between the HUE verse HUU, and the HIV-infected versus HUE groups were 3.9 (95% CI 1.6 to 8.0) and 1.2 (95% CI 0.8 to 1.8), respectively.

Most evidence for transferred infant protection against influenza has been done in studies of maternal influenza vaccination in the 2nd and 3rd trimesters.[41,48] However, for pragmatic purposes, WHO recommends vaccination at any time in pregnancy before and during the influenza season, as influenza vaccines has been found to be

safe and immunogenic during pregnancy. Immunogenic response of flu vaccines has been thought to persist for a year and the annual seasonal change in the circulating influenza strains contributes to this.[8]

2.3.3 Out-patient visits

There are no available local data on outpatient visits to healthcare facilities for symptomatic relief of maternal influenza. However, various economic analyses have been published in the medical literature that derived probabilities for outpatient influenza-associated visits from a variety of sources.

From a societal perspective, Beigi et al.[13] assumed that four hours of lost productivity and wages would occur if pregnant women required an outpatient visit for influenza. However, the economic model assumed that if this visit was part of the prenatal schedule no loss would be incurred. Roberts et al.[49] sourced the probabilities for ambulatory care medical visits for influenza from the published literature (0.554; 95% CI 0.1 to 0.6), whilst Myers et al.[50] derived the model inputs for seasonal Influenza-attributable outpatient visits from population based studies[38,39,46]and other economic analysies,[13,49]further assumed to follow the same temporal distribution as the Center for Disease Control and Prevention's surveillance data (0.65; 95% CI 0.49 to 0,81).[51,52]Jit et al.[14] extracted the incidence of outpatient consultations for maternal influenza from an anonymised database with information from approximately 70 sentinel practices in England and Wales (the Royal College of General Practitioners (RCGP) Weekly Returns Service,[53]triangulated with the General Practice Research Database and population based study (0.5; 95% CI 0.37 to 0.63).[54]Skedgelet al.[15]derived the baseline event rate of a physician visit for influenza in the pregnant

woman from a population based study[38]that extracted data from administrative databases in Nova Scotia for the period 1990 to 2003 (0.21; 95% CI 0.24 to 0.24). A more recent cost-effective analysis[16]sourced the probabilities for an outpatient visit given influenza infection in the mother (0.559; 95% CI 0.313 to 0.625) and infant (0.547; 95% CI 0.455 to 0.551) from a disease burden study.[55]

2.3.4 Side-effects associated with vaccination

There is increasing evidence supporting the safety of influenza vaccination during pregnancy. Side effects are considered to be mild and self-limited to reactogenicity.[56] There is also currently no available evidence of teratogenicity associated with maternal influenza vaccination with inactivated vaccines.[57]

2.3.5 Guillain-Barre syndrome associated with vaccination

Guillain-Barre syndrome is a very rare, but serious and life-threatening side-effect and even more rare subsequent to vaccination.[58]A non-statistical borderline significant risk has been shown of 1.45 (95% CI 1.05 to 1.99) and 1.7 (95% CI 1.0 to 2.8; p=0.04) by Juurlink (2006)[59] and Lasky (1998),[60] respectively. Precise risk is difficult to predict, but epidemiological evidence for GBS associated with influenza vaccination has been reported to be 1 to 2 per million influenza vaccinations.[58]

2.3.6 Preterm and small for gestational age births

Data regarding the protective effect of maternal influenza vaccination on preterm and small for gestational age (SGA) births is not very robust, as although the evidence is

mostly sourced from observational studies, a RCT showed a non-significant benefit associated with maternal influenza vaccination in terms of preterm and SGA births. Generally, RCTs are accepted as the gold standard for the generation of evidence-based medicine, so as to minimise bias.[61]The systematic review by Steinhoff et al., 2014[62] reviewed 1 RCT and 7 observational studies of a mix of vaccination for seasonal and pandemic flu, showed an unadjusted OR of 0.78; 95% CI 0.74 to 0.82 for preterm births and 0.83; 95% CI 0.79 to 0.87, for SGA births. Of note, is that in this systematic review, the two largest observational studies (performed in Canada and Sweden) produced ORs that were either statistically non-significant or had borderline significance and that overall the results of the various studies reviewed was very heterogeneous. Furthermore, the RCT[63]showed non-statistically significant benefits of maternal flu vaccination in terms of neonatal outcomes of preterm, SGA and LBW births. The latter RCT was underpowered and effect bias may have occurred with pneumococcal vaccine as the control.

Similarly a retrospective cohort analysis of surveillance data from the Georgia Pregnancy Risk Assessment Monitoring System (n=4168) showed a 69% lower odds of SGA newborns and 82% lower odds of preterms amongst vaccinated versus unvaccinated women. However, this only occurred during the period of widespread influenza activity (Adjusted OR 0.31; 95% CI 013 to 0.75; p = 0.009 and 0.28; 95% CI 0.11 to 0.74; p=0.01, for unvaccinated and vaccinated pregnant women respectively), and during the putative influenza season (Oct to May) where an unadjusted OR 0.60 (95% CI 0.41 to 0.89); p=0.01 and adjusted OR 0.60 (0.38 to 0.94); p=0.02 was reported.[64]Furthermore, a retrospective cohort analysis (n=12 223) showed that although there was a lower odds for preterm births and SGA amongst women

vaccinated for seasonal influenza, there was no risk reduction in terms of birth weight (RR 0.81; 95% CI 0.54 to 1.23; p= 0.321) but a possible protective effect on prematurity (RR 0.76; 95% CI 0.61 to 0.94; p=0.01).[65]

Most of these studies were conducted in high-income countries. However, recently a RCT performed locally, in South Africa (2014),[42]and a low income country, Mali (2016)[43], showed an absence of a reduction in small gestational age births associated with maternal influenza vaccination. The authors of the Mali study noted that the exclusion of high-risk pregnant women and the inclusion of women in late pregnancy may have contributed to differences in birth weight not being detected between the vaccinated and unvaccinated groups.

2.3.7 Stillbirth, miscarriage and congenital abnormalities

A systematic review and meta-analysis of observational studies by Luteijnet al.[66]showed that maternal influenza infection acquired in the first trimester was associated with higher risk for non-chromosomal congenital anomalies. However, the outcomes of congenital anomalies may have been confounded by factors such as maternal fever, other immune response(s) to influenza infection or the nutritional status of the pregnant woman. A more recent meta-analysis of observational studies showed that influenza vaccination was associated with a lower likelihood of stillbirth (RR 0.73, 95% CI 0.55 to 0.96) but the risk reduction for miscarriage (spontaneous abortion) was reported as not significant (RR 0.91, 95% CI 0.68-1.22).[67]

2.4 COST ANALYSES

Cost analysis studies of influenza vaccination have been studied mostly in World Bank defined high income temperate countries, with a few reported from middle-income countries. No studies have been performed in low-income countries and there are limited analyses investigating cost-effectiveness for routine seasonal influenza amongst pregnant women. However, these studies reported a wide range of cost-effectiveness ratios of savings of $10,000/outcome in 13 studies, $10,000 to $50,000 in 13 studies, and ≥$50,000 in 3 studies. This reflects the heterogeneity of the studies in terms of methodologies, study settings and study contexts.[68]

Studies performed in the USA indicated that influenza immunisation demonstrated cost-savings. Roberts et al.'s (2006) cost-effectiveness analysis[49]from a societal perspective showed that universal influenza vaccination of pregnant women relative to support care alone was cost-saving. Vaccinating 100% of pregnant women would result in cost-savings of approximately $50 per woman and a net-gain of approximately 45 quality-adjusted hours. A later study[13] compared routine vaccination of pregnant women compared to no vaccination using a cost-effectiveness decision analytic model incorporating epidemic and pandemic influenza characteristics. The incremental cost-effectiveness ratios (ICERs) showed that from both societal and payer perspectives vaccination, the dominant strategy was when the prevalence of influenza ≥ 7.5% and influenza-attributable mortality was ≥ 1.05%, and the ICERs increased incrementally as the prevalence and/or seriousness of the outbreak increased. A 2-dose vaccination approach was reported to be highly cost-effective with ICER ≤ USD6,787.77 per quality-adjusted life year, when compared to the cost-effective threshold ICER of ≤ USD50,000.00 per quality-adjusted life year.

A Canadian incremental economic evaluation[15]compared the cost and consequences of universal antenatal influenza vaccination or targeted vaccination of pregnant women with one or more co-morbidities to placebo from the payer's perspective, using a decision tree analysis. When administered by primary healthcare clinic or during a routine prenatal visit to a family physician, targeted vaccination was economically dominant relative to no vaccination (ICER CAD39,942 per quality-adjusted life year gained (QALY)), whilst universal vaccination of pregnant women was shown to be strongly cost-effective, (ICER ≤ CAD40,000, with a net cost-saving of <CAD10 per pregnant woman). However, one additional family physician visit increased the ICERs to CAD62,796 and CAD150,000 of both the targeted and universal strategies, respectively.

A cost analysis performed in England and Wales[14]showed that maternal influenza vaccination during the influenza season (September to December) and during the second and third trimester was cost-saving, ICER, £23,000 per QALY; 95% CI £10,000 to £140,000, with the assumption that infants are partially protected through their mothers. The ICER increased to £28,000 per QALY (95% CI £13,000 to£200,000) if infants were assumed not to be protected. As it is unlikely that vaccine protection would extend into a second season due to the variation in circulating viral strains, the ICER of £15,000 per QALY gained (95% CI £6,000 to £93,000) needs to contemplated with caution.

Cost savings were likewise reported in a recent study by Xu *et al.* (2016).[16] Data for three influenza seasons in the USA was used to develop a decision-analytic model

determining the cost-effectiveness of prenatal seasonal influenza vaccination from a societal perspective. Model parameters included 52.2% vaccine coverage and estimated vaccine effectiveness of 73% and 63% amongst pregnant women and their infants less than 6 months of age, respectively. Compared to placebo, the ICER showed cost-savings of USD250,689/QALY for the 2011–2012 influenza season data. This season had a lower attack rate compared to the other two seasons (2010-2011 and 2012-2013).[16]

Cost-effectiveness analyses were also performed to determine whether increasing vaccine coverage was cost-effective in Belgium, where pregnant women are considered a priority risk group for seasonal influenza vaccination. Increasing vaccine coverage was predicted to be cost-effective (median € 6616/QALY gained; [€ 4097–€10,345]) if there were no additional vaccine administration costs. The impact of vaccination on neonatal outcomes was shown to strongly influence cost-effectiveness. However, the authors cautioned that vaccine efficacy and case-fatality ratios were key factors of uncertainty.[69]

Timing of seasonal influenza was shown to affect the effectiveness of seasonal influenza vaccination in pregnancy in a cost-effectiveness analysis. The incremental cost-effectiveness of seasonal vaccination in pregnancy was predicted to be USD70,089/QALY. Benefits for infants were mostly realised when pregnant women were vaccinated early in the influenza season; whilst vaccination of women in early pregnancy was shown to be beneficial for mothers but not their infants.[50]

Limited healthcare budget requires efficient spending and economic evaluation studies are required as evidence for cost-effective use of these health resources. Although cost-effectiveness analyses pertaining to influenza vaccination in pregnant women has been published for a number of countries, there are no published analyses for South Africa. Furthermore, the recent recommendation of WHO SAGE[8] to promote influenza vaccination, prioritising the pregnant women to protect the mother and infant adds further constraint on South Africa's healthcare budget. South Africa has a quadruple burden of disease (communicable diseases with the HIV/AIDS epidemic and TB; perinatal and maternal disorders, injury-related disorders and an increasing burden of non-communicable diseases). Thus, evidence-based decision making is required to ensure rational, effective and efficient use of scarce resources. This would not only require adequate local epidemiological data, but moreover, local economic evaluations in order to make explicit decisions, promote public spending accountability and thus improve population health benefits.[70]

2.5 DECISION ANALYSIS

Decision-making in healthcare is complex, particularly with allocation of limited budget resources.[71]To produce benefits to a specific patient population's health, resources are consumed. Multiple factors needs to be considered, including the burden of disease evidence, safety aspects, affordability and patients' values.[70,72]Under conditions of uncertainty, a systematic and transparent approach is required to determine trade-offs between competing interventions or strategies.[73] Decision analysis modelling and cost-effectiveness analysis are simulated, mathematical disease-state tools that evaluates the consequences and costs of a

particular decision.[74,75]This approach minimises decisions informed by personal experiences, often subject to much bias.[70,71]Derived from game theory in the 1920s[75], decision analysis has increasingly been applied to economic questions in the healthcare environment.[76]

A detailed stepwise approach in conducting a decision analysis is described below:

1) Defining the research question (including the perspective and the base case i.e. patient population and ultimate objective of the analysis);

2) Specifying all decision alternatives;

3) Describe outcomes of each decision alternatives;

4) Defining time horizon;

5) Mapping out clinical pathways for each decision to the relevant outcomes, including chance events;

6) Quantifying uncertainty: Populate the probabilities and respective costs of each chance outcome;

7) Quantifying values: Populate outcomes and respective costs;

8) Calculating the expected value of each decision alternative; and

9) Conducting sensitivity analyses to verify the base model.[71]

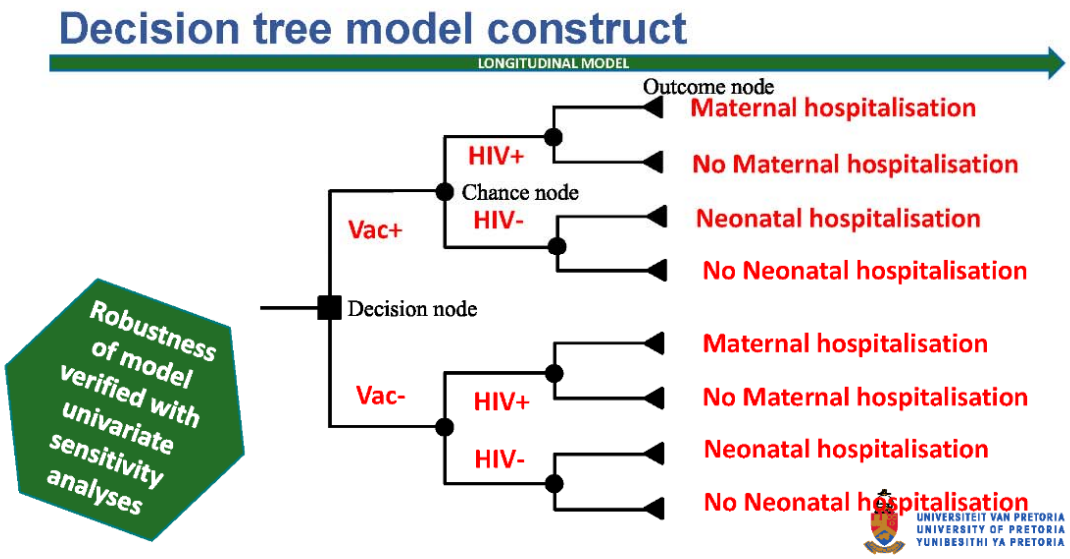
Expected value is defined as “on average” occurrences, if the decision was implemented repeatedly.[72]

2.6 DECISION TREES

The decision analysis process is diagrammatically presented as decision trees. See Figure 1 for schematic representation of a decision tree. A decision node, represented by a square is the point in time when a choice is made between two

alternatives. Circles are chance nodes that are points in a decision where there is a probability that one of either events may occur. The sum of probabilities for all branches originating from a chance node will always equal one. To calculate the expected value of each decision alternative, the value of each outcome is multiplied by its respective probability. The branches are then "folded back", whereby the results are then added to the previous chance node or quantified probability. The decision with the higher expected value would be preferred.[71]

Figure 1: Schematic presentation of a decision tree



2.6.1 Parameters inputs for decision trees

2.6.1.1 Decision

The first part in developing the basis of the decision tree model is problem structuring to identify the research question.[73,77]The decision is formulated using discrete or continuous variables, though the simpler attribute of a decision in the analysis of healthcare decisions is to use discrete variables, e.g. yes or no.[76] Represented by squares in a decision tree model, decision nodes identify points where a choice between alternatives can be made and is under control of the decision-maker.[75]The perspective of the analysis and the study population are likewise identified.[73]

2.6.1.2 Consequences and probability of consequences

Once the clinical question has been established, the uncertain variables require evaluation (i.e. consequences or outcomes of each decision; as well as the probability of each consequence. Uncertain variables are identified through extensive literature searches. Standard hierarchies of data quality should apply to the retrieved evidence which is mostly ranked in the following order for robustness: meta-analysis of randomised controlled trial > randomised controlled trials > smaller randomised controlled trials > cohort studies > case-controlled studies > case series or case studies > descriptive studies, guidelines, expert opinion. Evidence is preferably sourced from high level of evidence such as meta-analyses or randomised controlled trials.[78]However, observational studies, guidelines and expert opinions may be required if the former sources are not available. The decision, probabilities, consequences and effect sizes are organized in the tree graph.[73,75,76]As per Petiti the

probabilities represented by circular chance nodes are “events that are mutually exclusive and jointly exhaustive”.[76]

Effects and effect sizes are best sourced from available evidence through an extensive literature search, preferably meta-analyses or randomised controlled trials.[73]Common measures of health effectiveness includes Quality Adjusted Life Years (QALYs),[79]Disability Adjusted Life Years (DALYs) lives saved, years of life saved, disease cases prevented and cost.[80]Outcomes or consequences are represented by triangular end nodes (also known as leaf nodes), displayed at the terminal point of a branch of a decision tree. Each branch depicts a specific clinical pathway that a patient can follow.[81] Effectiveness measures are probably moregeneralisable to the general population than efficacy measures obtained from RCTs. Thus, caution should be exercised when extrapolating efficacy estimates from RCTs to ensure it is representative of the real-world population. A typical example is that most vaccine efficacy RCTs do not factor in the uptake of vaccines, but should be included as an important component in decision analysis modelling.[79]Furthermore, in decision tree simulations, outcomes cannot be combined and should be considered separately; a significant limitation in decision-making. QALYs and DALYs are discounted at an average 3% per annum rate, determined by the time horizon of the model as the current utility of life is valued over future quality or disability, respectively.

Clinical inputs sourced from literature may also present as a relative risk, odds or odds ratio, risk difference, survival curve, mean, standardised mean difference etc. However, these estimates require to be converted to probabilities for use in the

decision tree model. Crude probability values may be processed manually using a mathematical formula or a data analysis and statistical software, if sufficient data have been reported in the literature to enable conversion to probabilities. Mathematical formulas to derive probabilities include:

- Relative Risk = probability in exposed/ probability in unexposed
- Odds = probability / (1-probability)
- Risk difference = probability exposed - probability in unexposed.

When using StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP., by selecting the option to convert OR or RR to a probability.

Another factor to consider is that the literature-sourced probability should fit into the time horizon of the model. Where relevant, probabilities may need to be transformed to a relevant time frame using mathematical calculations: Probability = 1 - $exp^{(-rt)}$ and Rate = -ln(1-p)/t; where p represents probability, t=time and r=rate.[76]

2.6.1.3 Costs

"Resource use" was one of the factors that was reported to frequently influence decision-makers' views on vaccines, as reported in a systematic review.[82]Other frequent decision-making factors included the importance of illness or problem, vaccine characteristics and feasibility of vaccination programmes. However, social acceptability, values and preferences were seldom considered. Monetary costs for each competing decision can be sourced from published literature or other local sources. Reliable hospital costs has been reported to be limited in developing

countries.[83]Therefore, to conduct a cost-effectiveness analysis in the South African context would require the majority of costs to be obtained from international cost-effectiveness studies. It is important to adjust costs to a single currency and year using the Consumer Price Index[84] to ensure comparative evaluation. In addition, costs should be discounted as required by three percent per year, dependant on the time horizon of the decision analysis framework.[75] Resources such as verified online currency converter tools can assist. An example is the OANDA average currency converter tool. OANDA is a technology-driven, financial services corporation with membership with six regulators (United States, Canada, Europe, Asia-Pacific and Australia).[85]

2.6.1.3.1 Time horizon, inflation and discounting

Cost-effectiveness results are sensitive to the time horizon of the analysis, and therefore the total period over which the intervention is effective should be considered.[86]As influenza has a seasonal distribution over the temperate South African setting, with circulating influenza strains changing over seasons the time period of one year would be appropriate for the decision analytic model. Costs that are distributed over time should be discounted and inflated accordingly.[76] Discounting benefits implies that an effect measured in the present is of more value if measured in the future.[87] Discounting is calculated per annum and the standard discount rate used is 3%, as per the World Bank Disease Control Priorities study and the GBD project, as well as the United States Panel on Cost-Effectiveness in Health and Medicine.[88] Cost-effectiveness models to predict cost-effectiveness of seasonal influenza vaccination need not include discounting, as influenza vaccination is seasonal. However, prices and costs extrapolated from previously published peer-

reviewed literature require to be adjusted for inflation to real prices that would be relevant for the base year of the cost-effectiveness model. Inflation relates to the concept of the “time value of money” and is mostly due to economic development over time. Therefore, inflation adjustments are mostly based on the Consumer Price Index in the specific setting where the economic analysis is modelled (e.g. South Africa).[89]

2.6.1.3.2 Vaccine supply and administration costs

Costs for the supply and administration of TIV were shown to be heterogeneous across cost-effectiveness studies.[14–16]However, as the local price for the direct costs of the administration of vaccines is available for the public sector in South Africa, it would be better to calculate the local costs. The price for the influenza vaccine and surgical sundries are sourced from the contract circulars (tenders) that are published on the National Department of Health’s website.[90]The Uniform Patient Fee Schedule,[91]a simple charging approach for public sector hospitals that utilises “grouped fees” rather than “itemised billing”[89]is a source for the facility and professional fees for services rendered. These services include not only out-patient administration of an influenza vaccine by a nurse practitioner, but also in-patient influenza-associated hospitalisation for a pregnant woman or her newborn.

Influenza vaccines arethermolabile and require to be kept at constant temperatures between 2°C and 8°C to retain efficacy. Effective cold chain management (defined as network of refrigerators, cold stores, freezers and cold boxes organised and maintained so that vaccines are kept at the right temperature to remain potent during vaccine transportation, storage and distribution from factory to the point of use) is

thus required.[92]Costs for cold chain management vary widely between developed and developing countries, as reported in the World Health Organisation's "Historical Analysis of the Comprehensive Multi-Year Plans in GAVI-Eligible countries (2004-2015)".[93]However, this report grouped South Africa together with other African countries in the WHO African region, and may possibly result in an over-estimation of costs as South Africa has better infrastructure than most other African countries.

Vaccine wastage costs require to be factored into the analysis, with most vaccine cost-effectiveness studies using a vaccine wastage rate of 10%.[94] This estimate reccomended by the World Health Organisation for liquid vaccines supplied in single or two-dose vials is 5%, oral polio vaccine is 10% and vaccines requiring reconstitution is 25%.[92]

2.6.1.3.3 Hospitalisation costs

No validated hospital unit cost estimates for influenza-associated hospitalisation for either the neonate (less than six months of age) or for the pregnant women in the South African context, could be sourced from the published peer-review literature. Therefore, costs require to be extrapolated from other cost analyses, as appropriate. Costs were very heterogeneous across the various cost-effectiveness studies for influenza-associated hospitalisation of the neonate.[13,16,95,96]However, direct cost studies are published in the literature. A study by Keren et al.[97] estimated the direct medical costs for influenza-related hospitalisations for the age group 0 to 5 months to be a median of USD9148 (Interquartile range USD3898 to USD7083). However, direct costs for influenza-associated hospitalisation for pregnant women was sourced from the cost-effectiveness analysis evaluated by Beigi et al.[13]

2.6.1.3.4 Preterm birth costs

Beigi et al. described the costs of preterm births from a third payer perspective, sourced from the Institute of Medicine of the National Academies 2006 report on the causes, consequences, and prevention of preterm births.[13]

2.6.1.3.5 Guillain-Barre Syndrome costs

The annual cost for the management of Guillain-Barre syndrome (GBS) was derived from the Canadian cost-effectiveness study conducted by Skedgel et al.[15]The source of the value of CAD135,464 was the Nova Scotia Consumer Price Index for Health and Personal Care of 2006. The management plan for this life-threatening condition likely includes intensive care admission to manage respiratory failure, inpatient rehabilitation, occupational, recreational and speech therapy, immunosuppressive therapy as well as prevention of thromboembolism due to long-term paralysis associated with GBS.

2.6.1.3.6 Out-patient consultation costs

The costs for outpatient consultations for the symptomatic relief of influenza is best derived from the South African Primary Healthcare Standard Treatment Guidelines and Essential Medicines list (2014 edition)[98] that provides guidance for the management of outpatient maternal and neonatal influenza. This costs management in the local South African context. The prices for medicines were sourced from the current contract circulars (tenders)[90] for public sector and the tariffs for an out-patient

consultation with a general practitioner, nursing practitioner or specialist physician were sourced from the Uniform Patient Fee Schedule (UPFS).[91]Important to note that the UPFS tariffs are a fee schedule for public sector healthcare that replaces historic itemised billing with a grouped fee approach. It was initially based on the Board of Healthcare Funders Scale of Benefits and is updated annually by the National Department of Health. The UPFS tariff considers different levels of care and is based on health service activity.

2.6.1.3.7 Cost of HIV diagnostic tests

For the diagnosis of HIV in the pregnant woman and the neonate, costs could be sourced from the UPFS and National Health Laboratory Service (NHLS) price list for public sector, and inflated as required. However, as the routine testing for HIV of the pregnant women is included in the prenatal schedule, this was not considered to be relevant.

2.6.1.3.8 Perspective

The perspective of the economic analysis or model will determine the costs that need to be factored into the model. The perspective also determines the choice of health benefits for the model. Perspectives includes a societal perspective where all costs and outcomes are evaluated, whilst a patient's perspective analyses a new health intervention/programme's impact on the patient's out of pocket expenses, travel, waiting time and loss of productivity. Other perspectives includes a third party payer (e.g. private medical scheme) or a health care provider (e.g. hospital).[76]

2.7 DECISION TREE ANALYSIS

When all the constituents of the model has been sourced and inputted into the model (i.e. probabilities, outcomes and costs) the decision tree can be analysed to determine the best strategy. Over fitting of a decision tree may occur (i.e. the decision tree is complex and bushy). However, pruning of the tree may be required to reduce the size and complexity of the tree, thereby improving predictive accuracy.[99]

2.7.1 Folding back decision trees

Folding back of the branches is a process of calculating the expected value (or payoff) of each outcome by multiplying values by the respective probabilities to obtain a net value of that branch. The result of each event is added up sequentially starting from the endpoint (outcome) to the root node (decision). The expected value of the various branches originating from a root node is then compared. The expected value or payoff, is therefore the weighted average net value for each outcome.[76]A number of decision analysis modelling software programmes are available, mostly as a plug-in to the Microsoft Excel programme.

2.8 INCREMENTAL COST-EFFECTIVENESS RATIO (ICER)

The ICER, which is the ratio of the difference between the costs to the difference in total effects of the two different health strategies is calculated to determine the cost-effectiveness of the proposed strategy compared to a standard.[76] The formula is presented as follows:

$$\textbf{ICER} = \frac{Cost_1 - Cost_0}{Effect_1 - Effect_0}$$

$Cost_1$ = cost of intervention

$Cost_0$ = cost of control

$Effect_1$ = effect in intervention group

$Effect_0$ = effect in control group

2.8.1 Cost-effectiveness threshold

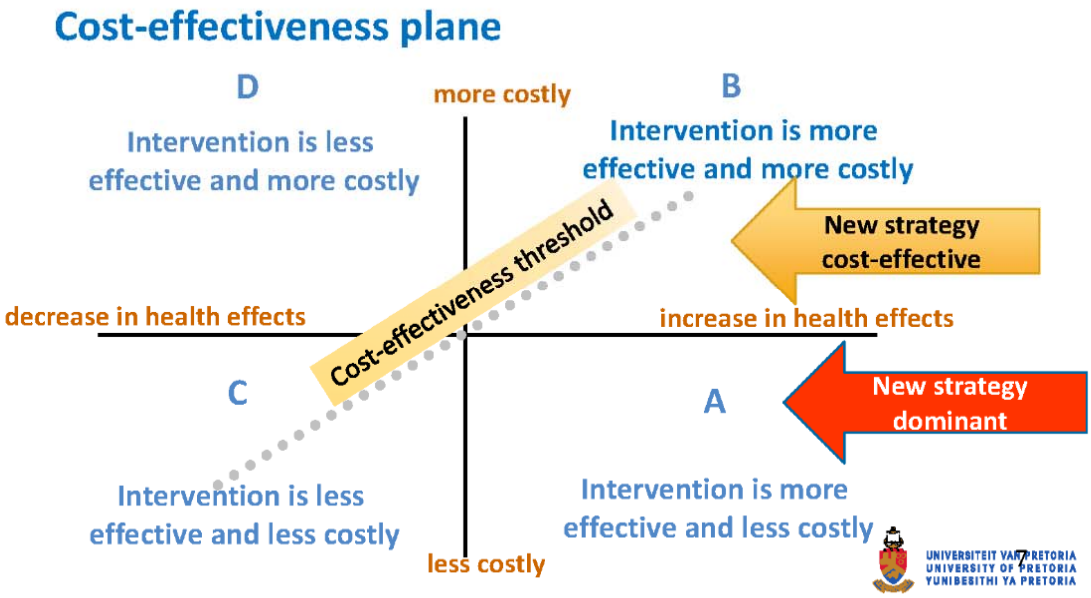
Deciding whether a strategy is cost-effective requires the establishment of a threshold. The WHO Commission on Macroeconomics and Health recommends that a health strategy or intervention is considered to be cost-effective if the threshold value is less than three times the gross domestic product (GDP) per capita and highly cost-effective, if less than one times the GDP per capita.[100] There is minimal consensus on the value of the threshold value and speculation has been reported to cause much criticism as there is much debate on the value of health.[101] The thresholds differs in the USA, UK and The Netherlands as USD50,000 per QALY, £30,000 per QALY and €20,000 per life year gained (LYG), respectively.[102] Theoretically the cost-effectiveness threshold can be set on the uniform standard i.e. the GDP per capita approach. However, in real-world situations it is set by budget constraints and the willingness to pay for a unit of effect. A recent WHO report (2015) states that the uniform standard GDP per capita threshold, used globally to determine cost-effectiveness, is easily attainable.[103]Thresholds may lead to excessive health-expenditure and disregards the resources constraints of limited budgets.[104,105]Ideally, estimates of costs and effectiveness should be interpreted within the relevant context. This should consider the local disease burden and budget

allocation. The development of league tables for specific country settings, ranking healthcare strategies and interventions according to ICERs may assist decision-making. Essentially, progress towards consensus regarding this possible new framework for determining cost-effectiveness of various interventions or strategies is required to improve on the standard GDP per capita approach, which will benefit low- to middle- income countries.[102]

2.8.2 Cost-effectiveness plane

Cost-effectiveness can be illustrated graphically using a tool, the cost-effectiveness plane. The x axis represents the incremental effectiveness relative to the incremental costs of a health strategy or intervention, represented on the y axis. The left-hand side of the graph describes decreased effectiveness, whilst the higher up the y axis, the increase in costs.[100]See Figure 2 which depicts the four quadrant graph of a cost-effectiveness plane. The different quadrants graphically represent the strategies according to their effectiveness and cost relative to a control. ICERs in quadrants A and C have negative values, with A showing that the new treatment strategy is dominant (being more effective and cost-saving) compared to the comparative treatment strategy. In quadrant C, the ICER suggests that the control or comparator dominates the new treatment and there is no value in implementing the new treatment. ICERS in quadrants B and D are cost-effective, if it appears below the predetermined cost-effectiveness threshold (as discussed in section 2.8.1 Cost-effectiveness threshold). This will assist decision-makers with regards to health policy decisions through to individual patient case management, by comparing the ICER with the willingness to pay for the new healthcare strategy.[103]

Figure 2: The cost-effectiveness plane



2.9 SENSITIVITY ANALYSIS

To handle uncertainty, the analysis can examine what the impact would be if the values of important variables are altered using probabilistic sensitivity analyses.[106]These analyses serve as an alternative to confidence intervals to verify the robustness of the base-case decision tree model. An input parameter (including probability and cost variables) is extended to acceptable extremes (often determined by the 95% confidence interval of the underlying clinical data) while other input parameters are kept constant. Univariate, bivariate or multivariate sensitivity analyses

are often reported, dependant on the number of variables that are allowed to fluctuate at a time.[76]

2.10 USES OF ANALYTIC DECISION TREE MODELS

These analyses are often used when randomized clinical trials reports inadequate data to inform pharmacoeconomic analysis, and decision makers need to determine the most cost-effective healthcare strategy. Other reasons include if underlying effectiveness evidence only report surrogate outcomes, there is no direct comparative data comparing two health strategies or if routine clinical care effectiveness requires to be predicted from randomised controlled trial efficacy data. Then extrapolation of clinical data and appropriate assumptions would need to made, provided for in decision tree simulations.

2.11 OTHER COST-EFFECTIVENESS ANALYSIS METHODOLOGIES

Other cost-effectiveness analysis methodologies include Markov models. Markov models are more suitable than decision trees to analyse complex decision problems that involve repetitive events, where patients transition from one finite “Markov” state to another and when probabilities and utilities (or other outcome measures) are time dependant. Various Markov models include Monte Carlo simulations or Markov-cycle trees. However, these methodologies have not been described in detail, as it is not relevant to this research project.[107]

3. CHAPTER 3: METHODS

3.1 INTRODUCTION

Available evidence supports seasonal influenza vaccination in pregnant women, specifically from the second trimester,[108] and priority immunisation of pregnant women during pandemics.[40] However, for the purpose of this evaluation, only seasonal influenza vaccination in pregnant women was evaluated.

3.2 COHORT

A cohort of 100,000 pregnant women was considered practical for this decision analytic model as the estimated live births per year since 2000 has been consistently over 1,000,000.[109] The model assumed that over a period of one year pregnant women entered the model.

3.3 PERSPECTIVE

Costs and consequences of routine maternal influenza vaccination in both the pregnant women and their neonates were modeled in Excel using PrecisionTree® software (Palisade; Newfield, New York), from a payer's perspective.

3.4 TIME HORIZON, DISCOUNTING

Discounting of costs and consequences were not performed as the model followed the clinical course of pregnant women and their neonates longitudinally over one

year time horizon (single flu season). Timing of vaccination during the flu vaccine and the respective effects was not considered in the baseline model. Events were likewise assumed to occur at a constant rate throughout the model and pregnancies were assumed to correlate to the number of live births estimated in South Africa for 2015 i.e. approximately 1,000,000.[109]The influenza vaccine was also assumed to match the circulating seasonal influenza strains.

3.5 EVENT RATES

A literature review of EBSCOhost, AfricaWide Information, CINAHL and MEDLINE was performed to extrapolate relevant clinical inputs for the baseline model, using the terms “influenza vaccination", "pregnancy" and "HIV/AIDS" for the period 20130101 to 20160802. Seventeen studies were retrieved and three published articles were considered relevant to the South African public health setting.

3.5.1 Vaccine effectiveness studies

A South African vaccine efficacy study showed that routine prenatal influenza vaccination averts laboratory confirmed influenza in the pregnant women and infants less than 6 months of age.[42] Similarly shown in studies performed in Bangladesh[41]and Mali.[43] For purposes of this analysis, it was assumed that laboratory confirmed prenatal influenza may result in either hospitalisation, an outpatient visit or be a self-limiting condition, dependent on the severity of influenza infection. The risk of laboratory confirmed influenza in HIV-uninfected pregnant woman borders on statistical significance (1.8; 95% CI 1.1 to 2.8).[42]

3.5.2 Maternal influenza-associated hospitalisation

A systematic review reported not statistically significant maternal influenza-associated hospitalisation (RR 0.96; 95% CI 0.85 to 1.08).[40]Thus, available local data was sourced. A local epidemiological reported incidence rates for influenza hospitalisations for the period 2009 to 2011.[44]However, the study did not differentiate between gender or pregnant and non-pregnant women. As there is a paucity of local data pertaining to maternal hospitalisation associated with influenza, available data from international CEA studies were sourced. A more recent CEA study reported the rate of neonatal hospitalisation rate specifically due to confirmed influenza infection as 2.4% (95% CI 0.4 to 3.6%) derived from studies performed in the USA. The model furthermore assumes that the probability of maternal influenza-associated hospitalisation is similar amongst HIV-infected and HIV-uninfected pregnant women. Cohen et al., 2013[44] showed a non-statistical difference in severe influenza-associated acute respiratory infection-ICU admission amongst HIV compared to HIV-uninfected adults.

3.5.3 Neonatal influenza-associated hospitalisation

The parameter for the rate of neonatal influenza-associated hospitalisation required extrapolation from international studies, due to limited local data. An observational prospective cohort study showed that seasonal influenza vaccination of pregnant women resulted in hospitalisation of 17%ofnewborn infants less than six months of age for influenza-like illness.[47]However, the recent CEA by Xu et al. reported a neonatal hospitalisation rate of 2.8% (95% CI 1.4 to 3.1%), which appears more probable as it was comparable to the reported rate of maternal influenza-associated

hospitalisations (2.4%; 95% CI 0.4 to 3.6%). Influenza (in infants less than six months of age) is probably mostly transmitted from mothers to their neonates.[16] Furthermore, there is a paucity of robust data determining the risk of hospitalisation of newborn infants born to HIV-infected mothers. Local epidemiological data[34]showed a non-significant difference of LRTI-associated hospitalisations between HIV uninfected, HIV uninfected exposed compared to HIV infected infants less than six months of age. Therefore, the model assumed that the risk of influenza-associated hospitalisation amongst infants less than six months of age were comparable amongst HIV-infected and HIV-uninfected neonates.

3.5.4 Outpatient consultations

There is no available data to determine the incidence rate of outpatient visits to either primary or secondary healthcare facilities for symptomatic relief of maternal and neonatal influenza. Thus, data was sourced from other cost-effectiveness studies. The probabilities from the most recently published study by Xu et al.[16] was inputted into the model, triangulated with similar results reported in two previous studies.[14,49]The South African Primary Healthcare Standard Treatment Guidelines and Essential Medicines list, 2014 version[98], guided management of outpatient maternal and neonatal influenza. The Standard Treatment Guideline recommendation is described in Figure3: Primary Healthcare Standard Treatment Guideline for the management of influenza.

Figure 3: Primary Healthcare Standard Treatment Guideline for the management of influenza

17.3.1 INFLUENZA

J11.1

DESCRIPTION

Influenza is a self-limiting viral condition that may last up to 14 days. It presents with headache, muscular pain and fever, and begins to clear within 7 days.
Malnourished children, the elderly and debilitated patients are at greater risk of developing complications.

CAUTION
Malaria, measles, and HIV seroconversion may present with flu-like symptoms.

Complications
Secondary bacterial infections, including:
» pneumonia secondary to influenza » sinusitis
» otitis media

GENERAL MEASURES

» Bed rest if feverish.
» Ensure adequate hydration.
» Advise patient to return to clinic if earache, tenderness or pain over sinuses develops and/or cough or fever persists for longer than a week.

MEDICINE TREATMENT

Note: Antibiotics are of no value for the treatment of influenza.

Pain and fever with distress:
Children
• Paracetamol, oral, 10–15 mg/kg/dose 4–6 hourly when required. See dosing table, pg 22.7.

Adults
• Paracetamol, oral, 1 g 6 hourly when required.

Infants
• Sodium chloride 0.9%, instilled into each nostril.

REFERRAL

Severe complications.

Source: South African National Department of Health Primary Health Care Standard Treatment Guidelines and Essential Medicine List, 2014 edition. Available at: www.health.gov.za

3.5.5 Preterm and small for gestational age births

Assumptions that pregnant women hospitalised for influenza-associated respiratory tract infections would be at risk of preterm births and that neonates less than 6

months of age with laboratory confirmed influenza required in patient treatment were included in the initial model. However, outcomes of small gestational age and preterm deaths in the South African[42] and Mali[43] studies were reported as not statistically significant. Although, it is noted that additional analysis of the Mali study is still forthcoming, to determine clinically relevant outcomes; whilst an additional South African study is currently underway to investigate the association of prenatal influenza vaccination with amongst other outcomes, preterm births and hospitalisations. Thus, these parameters were not included in the decision analytic model.

3.5.6 Adverse drug reactions

Side effects of reactogenicity are reported to be mild and self-limiting; whilst available evidence on teratogenicity is limited. As life-threatening, but rare, Guillain-Barre syndrome (GBS) adverse drug reactions associated with influenza vaccines has been reported, this side-effect was included in the model as a borderline significant risk, RR of 1.45 (95% CI 1.05 to 1.99) and 1.7 (95% CI 1.0 to 2.8) by Juurlink, 2006[59] and Lasky, 1998[60]respectively. GBS is expensive to manage.

3.5.7 HIV-infection

Despite the influence of HIV status on influenza outcomes being unclear.[32]South African surveillance data showed a higher risk of severe illnesses related to influenza amongst HIV-infected persons.[44]Overall HIV prevalence amongst pregnant women was estimated to be 29.7%[27](The National Antenatal Sentinel HIV prevalence Survey, South Africa, 2013, National Department of Health. https://www.health-

e.org.za/wp-content/uploads/2016/03/Dept-Health-HIV-High-Res-7102015.pdf) and mother to child transmission rates, 1.5%.[28]:National Department of Health. Programme data on file)

3.5.8 Vaccine uptake

The base model assumed a 100% uptake of seasonal TIV amongst the cohort of pregnant women. However, a systematic review showed that vaccination uptake ranged from 1.7% to 88.4%. Contributory factors included the lack of awareness of the high risk of influenza during pregnancy and the complications of influenza on both mother and the fetus. In addition, the perception that influenza vaccination are associated with harms and the negative media coverage regarding this further impacts influenza vaccine uptake.[110]

3.5.9 Other assumptions

Multiple pregnancies or TIV administration prior to pregnancy were not accounted for in this model. Seasonal variability of the influenza strains precluded effects of herd immunity and longitudinal simulation assumed that pregnant women and their neonates only had one negative influenza-associated outcome. In addition, the model assumed that incidence rates of vaccine associated GBS events, preterm births and hospitalisations (maternal and neonatal) of the HIV-infected were similar to those in HIV-uninfected cohorts (due to paucity of evidence amongst the HIV-infected prenatal women). This may have the potential of underestimating ICERs for the targeted annual seasonal influenza vaccination of prenatal HIV-infected pregnant women. Refer to Table 1: Model parameters for the Decision Tree Analysis.

Table 1: Model parameters for the base decision analytic model

Probabilities	Universal influenza vaccination	Targeted vaccination (HIV-infected pregnant women)	References
Seasonal flu vaccine uptake	1	1	[110]
HIV prevalence in pregnant women		0.297	[27]
Guillain-Barre Syndrome	0.0000017	0.0000017	[58]
Laboratory confirmed influenza (Maternal)	0.018	0.07	[42]
Maternal influenza-associated hospitalisation	0.0916	0.178	[16]
Preterm births	0.24	0.24	[16]
Outpatient/clinic visit - maternal flu	0.559	0.559	[16]
Laboratory confirmed influenza (Infant)	0.019	0.05	[42]
Neonatal influenza-associated hospitalisation	0.39	0.39	[16]
Outpatient visit (Neonate)	0.547	0.547	[16]
MTCT rate		0.015	[28]
Costs			
Vaccine administration	R 608.77	608.77	[90–93]
Maternal HIV test	R 118.68	118.68	NHLS*
Guillain-Barre Syndrome	R 1,750,488.81	R 1,750,488.81	[15]
Maternal influenza-associated hospitalisation	R 65,087.32	R 65,087.32	[111]
Preterm birth	R 620,278.22	R 620,278.22	[16]
Outpatient/clinic visit - maternal flu	R 229.75	R 229.75	[90,91,98]
Neonatal HIV test	R 105.44	R 105.44	NHLS*
Neonate influenza-associated hospitalisation	R 156,038.27	R 156,038.27	[97]
Neonatal outpatient visit	R 240.67	R 240.67	[90,91,98]
Full term birth	R 6,318.00	R 6,318.00	[91]

*National Health Laboratory Services (NHLS) public sector price list, 2015 inflated to 2016 prices.

3.6 COSTS

The lack of validated unit medical costs in the South African public care setting necessitated costs to be sourced from international high income cost-effectiveness studies which may not truly reflect the local context.

International currency (as reflected in relevant studies) was converted to South African currency using Oanda average exchange rate for period 1 January 2016 to 17 August 2016 and was inflated using the Consumer Price Index [Statistics South Africa [Internet]. Consumer Price Index publications, 2010 to 2016.[Cited August 2016] http://www.statssa.gov.za/. Discounting was not included in the model, as influenza vaccination is seasonal. Refer to Table 1 for the model costs for the base decision analytic model.

3.6.1 Administration of vaccine

The baseline case cost-effectiveness model assumed that the administration of influenza vaccine will require an additional outpatient consultation with a nurse prescriber. However, sensitivity analyses will determine if administering seasonal TIV as part of the prenatal schedule, or by a general practitioner would influence the cost-effectiveness of the various vaccination approaches (i.e. universal influenza vaccination of all pregnant women or targeted approach of only HIV-infected pregnant women).

The costs for the supply and administration of TIV were heterogeneous across cost-effectiveness studies.[15,16,43]Thus, local costs were calculated from current public sector tenders[90] and the Uniform Patient Fee Schedule[91]. Cold chain operational

costs were obtained from World Health Organisation's "Historical Analysis of the Comprehensive Multi-Year Plans in GAVI-Eligible countries (2004-2015)".[93]However, for the WHO African region, there may be a possible over-estimation of costs as South Africa has better infrastructure than most other African countries. Refer to Table 2 for a breakdown of the costs for the administration of influenza vaccines for the different modes of delivery.

Table 2: Cost for the administration of influenza vaccine

Mode of delivery	Nurse prescriber	Pre-natal schedule	General practitioner	Reference(s)
Breakdown of costs				
Prefilled influenza vaccine	R 60.69	R 60.69	R 60.69	HP10-2014BIO[90]
Disposable gloves	R 0.45	R 0.45	R 0.45	HM05-2013SG[90]
Medication fee (facility fee)	R 50.00	R 50.00	R 50.00	UPFS 2016 Tariffs[91]
Outpatient consultation	R 54.00	-	R 93.00	UPFS 2016 Tariffs[91]
Outpatient facility fee (level 1)	R 84.00	R 84.00	R 84.00	UPFS 2016 Tariffs[91]
Cold chain operational costs	R 316.39	R 316.39	R 316.39	[93]
Vaccine wastage costs	10%	10%	10%	[92,93]
TOTAL COST	***R 608.77***	***R 470.77***	***R 647.77***	

3.6.2 Vaccine wastage

Vaccine wastage was estimated to be 10% in the base model, the most commonly assumed wastage rate used in most cost-effectiveness studies.[92,93]However, uncertainty around this variable would be evaluated through sensitivity analyses.

3.6.3 Influenza-associated hospitalisation costs

There is a lack of robust local epidemiological data that could verify the length of hospital stay for seasonal influenza-associated hospitalisation of the pregnant women and her newborn infant less than six months of age in the HIV-uninfected and HIV-infected patient groups. As this analysis investigates the cost-effectiveness of maternal influenza from the perspective of the National Department of Health, the payer, direct costs are essentially required. Thus, for hospitalisation in the pregnant

women costs were obtained from a direct cost analysis by Zhang et al.[111]Hospitalisation costs for infants less than six months of age, data from a direct cost study was sourced that estimated the direct medical costs for influenza-related hospitalizations for the age group 0 to 5 months, reported as a median of $9148 (Interquartile range $3898 to $7083).[97]The costs sourced from these studies were inflated to 2016 prices, using the Consumer Price Index. It is noted that most of the cost-effectiveness studies published in peer reviewed literature included indirect cost (i.e. cost of lost wages;[13,49]cost of productivity loss;[16] travel costs to a healthcare facility.[16,49]

3.6.4 Outpatient costs

The South African Primary Healthcare Standard Treatment Guidelines and Essential Medicines list, 2014 version[98], guided management of outpatient maternal and neonatal influenza. Direct costs for medication and outpatient consultations at the various facilities were sourced from the contract circulars and Uniform patient fee schedule. Refer to Table 3 for a breakdown of the costs for outpatient consultations for neonatal and maternal influenza.

Table 3: Costs for outpatient consultation for maternal and neonatal influenza

	General practitioner	Nurse prescriber	Specialist	Reference(s)
A: Maternal influenza				
Medicine (paracetamol)	R 2.755	R 2.755	R 2.755	HP09-2016SD[90]
Medication fee (facility fee)	R 50.00	R 50.00	R 50.00	UPFS 2016 Tariffs[91]
Outpatient consultation	R 93.00	R 54.00	R 216.00	UPFS 2016 Tariffs[91]
Outpatient facility fee (level 1)	R 84.00	R 84.00	R 84.00	UPFS 2016 Tariffs[91]
TOTAL COST	***R 229.755***	***R 190.755***	***R 352.755***	
B: Neonatal influenza				
Medicine (paracetamol syrup, 100 ml + sodium chloride 0.9% as nasal drops)	R 13.666	R 13.666	R 13.666	HP12-2014LQ[90] HP11-2014LVP/01[90]
Medication fee (facility fee)	R 50.00	R 50.00	R 50.00	UPFS 2016 Tariffs[91]

Outpatient consultation	R 93.00	R 54.00	R 216.00	UPFS 2016 Tariffs[91]
Outpatient facility fee (level 1)	R 84.00	R 84.00	R 84.00	UPFS 2016 Tariffs[91]
TOTAL COST	***R 240.666***	***R 201.666***	***R 363.666***	

3.6.5 Guillain-Barre syndrome (GBS)

The costs for GBS was obtained from the cost-effectiveness study by Skedgel et al.[15]The costs were inflated to 2016 prices and converted to South African rands, accordingly.

3.7 DECISION TREE MODEL

The decision tree models were constructed in Excel (Microsoft; Redmond, Washington) using Palisade Decision Tools (Palisade; Newfield, New York). The models estimated the direct medical costs averted due to influenza-associated hospitalisation for both mother and their infants aged less than six months of age due to vaccination, and the overall cost-effectiveness of vaccination for the various outcomes using either a universal or HIV-targeted vaccination approach.

3.7.1 Over fitting and pruning of initial decision tree

An initial decision tree was developed that describe various outcomes of the decision to vaccinate or not. This included outpatient consultations and hospitalisations of the pregnant women and her infant less than six months of age, pre-term births as well as maternal and neonatal mortality death. Mapping out the clinical pathways for each decision to the relevant outcomes, including chance events resulted in over fitting of the decision tree may occur (i.e. the decision tree was complex and bushy). (Refer to Annexure B: Initial decision tree model). Therefore, the tree was pruned to reduce

size and complexity in order to improve predictive accuracy. Pruning was based on relevant outcomes for seasonal influenza vaccination with supporting clinical evidence relevant to the South African setting. The outcomes selected were a reduction in laboratory confirmed influenza[41–43]that was assumed to translate into influenza-associated hospitalisations or outpatient consultation averted in the pregnant mother and her infant less than six months of age.

This economic analysis was based on effects and not common measures of health effectiveness such as utilities and thus, different patient-relevant clinical outcome parameters were expressed in different units. Therefore, two analytic decision tree models were developed, to reduce neonatal influenza-associated hospitalisations (Refer to Annexure C: Decision tree model for averting neonatal influenza-associated hospitalisations) and maternal influenza-associated hospitalisations (Refer to Annexure D: Decision tree model for averting maternal influenza-associated hospitalisations).

3.7.2 Decision tree model: Maternal influenza associated hospitalisations averted

The first model evaluated the cost-effectiveness of vaccination in reducing the risk of influenza-associated hospitalisations.A hypothetical cohort of 100,000 pregnant women was evaluated during a single influenza season. The rate and risk of developing influenza events were assumed to be constant throughout the models time horizon of one year. As infants were assumed to acquire passive immunity through transplacental transfer of maternal antibodies if a pregnant woman was vaccinated with TIV, infant population (less than six months of age) were also

included in the analysis. Each pregnant woman that entered the model had an option of being vaccinated against influenza. She may have co-morbid HIV infection. On vaccination there may be a probability of developing adverse drug reactions, of which GBS is the most costly to manage. Based on efficacy data, each women then has the probability of developing laboratory confirmed influenza either requiring hospitalisation for serious acute respiratory infections; or an outpatient consultation for symptomatic management(Annexure D: Decision tree model for averting maternal influenza-associated hospitalisations).

3.7.3 Decision tree model: Neonatal influenza associated hospitalisations averted

The second model predicted the cost-effectiveness of seasonal influenza vaccination in reducing resultant neonatal hospitalisations. A hypothetical cohort of 100,000 pregnant women entered the model. The clinical pathway included the probability of prenatal HIV co-infection and mother to child transmission of HIV infection. Infants (less than six months of age) were assumed to acquire passive immunity through transplacental transfer of maternal antibodies if a pregnant woman was vaccinated with TIV and the probability of these infants developing laboratory confirmed influenza from vaccine effectiveness studies were translated into either neonatal influenza-associated hospitalisation or an outpatient consultation. (Annexure C: Decision tree model for averting neonatal influenza-associated hospitalisations).

The value for each cost and probability variable is then inputted and branches folded back to measure the expected value along each clinical pathway. ICERs are then measured to determine whether seasonal influenza vaccination of pregnant women

(either universally or HIV-targeted) is cost-effective using the WHO criteria for cost-effectiveness threshold of one times the GDP per capita of South Africa.

3.8 SENSITIVITY ANALYSIS

Univariate probabilistic sensitivity analyses was performed to determine the impact of altering the value of key parameters (whether epidemiological, clinical probability or cost variables) Uptake of influenza vaccination was systematically varied from 0.017 to 0.884 as reported in a systematic review by Yuen et al.[110]The base-case scenario assumed that influenza vaccinations were administered by a nurse prescriber. However, sensitivity analyses explored alternative modes of delivery (part of the prenatal schedule, not requiring an additional consultation; or an outpatient general practitioner consultation). Vaccine wastage was likewise varied from 5% to 25% to simulate operational issues with cold chain management specifically in rural areas.[94]Probability distributions for variables were mostly determined by the 95% confidence intervals for point estimates in the related studies. Ranges for other variables were either obtained from other cost-effectiveness studies or determined using a 10% variance around the parameter described in the base-case model. Refer to Table 4 for a list of variables that were varied in the sensitivity analyses.

Table 4: Model parameters varied for the sensitivity analyses

VARIABLE	BASE VALUE	LOWER VALUE	UPPER VALUE	REFERENCE(S)
Seasonal influenza uptake	1	0.017	0.884	[110]
Vaccine wastage	10%	5%	25%	[94]
HIV prevalence amongst vaccinated pregnant women	0.015	0.1	0.4	[27]
Guillain-Barre Syndrome adverse drug reaction	0.0000017	0.000001	0.0000028	[58]
Pregnant women (probabilities)				
Laboratory confirmed influenza of HIV-uninfected, vaccinated pregnant women	0.07	0.029	0.139	[42]
Laboratory confirmed	0.07	0.029	0.139	[42]

influenza of HIV-infected, vaccinated pregnant women				
Laboratory confirmed influenza of HIV-uninfected, unvaccinated pregnant women	0.036	0.026	0.049	[42]
Laboratory confirmed influenza of HIV-uninfected, unvaccinated pregnant women	0.018	0.011	0.028	[42]
Laboratory confirmed influenza of HIV-infected, vaccinated pregnant women	0.092	0.007	0.127	[42]
Maternal influenza-associated hospitalisation	0.178	0.151	0.209	[16]
Outpatient consultation for maternal influenza	0.559	0.313	0.625	[16]
Neonates (probabilities)				
Laboratory confirmed influenza of HIV-infected neonates of vaccinated women	0.05	0.016	0.113	[42]
Laboratory confirmed influenza of HIV-uninfected neonates of vaccinated women	0.019	0.011	0.029	[42]
Laboratory confirmed influenza of HIV-infected neonates of unvaccinated women	0.068	0.025	0.143	[42]
Laboratory confirmed influenza of HIV-uninfected neonates of unvaccinated women	0.036	0.026	0.05	[42]
Neonatal influenza-associated hospitalisation	0.028	0.014	0.031	[16]
Outpatient consultation for neonatal influenza	0.547	0.455	0.551	[16]
Costs				
Cost of administering influenza vaccination	R608.77	R407.77	R647.77	Refer to Table 2
Cost of maternal influenza-associated hospitalisation	R65,087.00	R58,579.00	R71,596.00	[111]
Cost of neonatal influenza-associated hospitalisation	R156,038.00	R140,434.00	R171,642.00	[97]
Cost of managing Guillain-Barre Syndrome	R1,750,488.81	R1,575,439.92	R1,925,537.69	± 10% deviation
Cost of outpatient consultation for maternal influenza	R229.755	R190.755	R352.755	Refer to Table 3
Cost of outpatient consultation for neonatal influenza	R240.666	R201.666	R363.666	Refer to Table 3

4. CHAPTER 4: RESULTS

The aim of the research question was divided into two key objectives to address the context of the local South African population that lists HIV as part of the country's quadruple burden of disease. The findings noted during this research, are detailed below.

4.1 Cost-effectiveness results

4.1.1 Influenza-associated hospitalisations in infants less than six months

From a payer's perspective, the base-case model predicted that routine seasonal vaccination of pregnant women (subject to base-case assumptions) is not cost-effective relative to non-vaccination. One hundred thousand prenatal vaccinations predicted an ICER of R 69,118,114.05/neonatal influenza-associated hospitalisation averted which is more than three times the current South African GDP per capita of R 340,800. Similarly, the model suggested that targeted vaccination of 100,00 HIV-infected pregnant women was not cost-effective by the no-vaccination approach for preventing influenza related hospitalisations amongst the newborn less than 6 months of age (ICER of -R 159,134,365.50/neonatal hospitalisation averted). Despite the costs of a neonatal hospitalisation being relatively high which includes diagnostic workup (i.e. chest X-ray evaluation, respiratory distress management including oxygen saturation tests, laboratory testing e.g. CRP monitoring), hospital bed days with possible referral to ICU, medical management, personnel and facility resources; the latter ICER should be interpreted with caution as the underlying clinical data in the HIV-infected cohort was of low methodological quality.

See Table 5: Base-model incremental cost-effectiveness ratios (ICERs) for various vaccination strategies. (Refer to Annexure C: Decision tree model for averting neonatal influenza-associated hospitalisations).

4.1.2 Maternal influenza-associated hospitalisation

Similarly, both universal seasonal influenza vaccination as well as the HIV-targeted approach of vaccinating 100 000 pregnant woman was shown to be not cost-effective, projecting ICERs of R 1,197,779.79 and 854,053.42/ maternal influenza-associated hospitalisation averted, respectively) compared to not vaccinating with influenza vaccines. See Table 5: Base-model incremental cost-effectiveness ratios (ICERs) for various vaccination strategies. (Refer to Annexure D: Decision tree model for averting maternal influenza-associated hospitalisations).

Table 5: Base-model net incremental cost-effectiveness ratios (ICERs) for various vaccination strategies

UNIVERSAL VACCINATION STRATEGY (100 000 PREGNANT WOMEN)				
Effect	**Incremental cost**	**Incremental effectiveness** (hospitalisationavert ed)	**ICER**	
Neonatal hospitalisation	R 547,893,000.00	-8	-R 69,118,114.05	not cost-effective
Maternal hospitalisation	R 121,754,000.00	-102	-R 1,197,779.79	not cost-effective
HIV-TARGETED VACCINATION STRATEGY (100 000 PREGNANT WOMEN)				
Effect	**Incremental cost**	**Incremental effectiveness** (hospitalisationavert ed)	**ICER**	
Neonatal hospitalisation	R 962,061,680.00	-6	-R 159,134,365.50	not cost-effective
Maternal hospitalisation	R 60,877,000.00	-71	-R 854,053.42	not cost-effective

*Strategy is not cost-effective compared to not vaccinating, as the ICER is more than three times the current South African GDP of R 340,800.

4.2 Sensitivity analyses

4.2.1 Key variables

Univariate probabilistic sensitivity analyses tested the impacted of altering key variables including mode of delivery, vaccine uptake and vaccine wastage. The base-case model assumed that influenza vaccination of all pregnant women required an additional nurse practitioner consultation. Sensitivity analysis considered other modes of administration either as part of the routine prenatal schedule or requiring an additional general practitioner visit at a primary healthcare facility and showed that universal influenza vaccination would still not be cost-effective for the outcomes of averting both neonatal and maternal influenza-associated hospitalisations, irrespective of the vaccine approach (i.e. universal or targeted HIV-approach).

The base-case scenario assumed 100% vaccine uptake and predicted that all strategies were shown to be not cost-effective when compared to not vaccinating. Estimates for the sensitivity analysis was derived from a systematic review[109]that reported that vaccination uptake ranged from 1.7% to 88.4%. For averting neonatal influenza-associated hospitalisations, at both these vaccine uptake rates, the universal strategy became dominant (saving of R 558,985,493.45 and R 5,001,945.43/neonatal influenza-associated hospitalisation averted). However, the targeted approach of vaccinating HIV-infected pregnant women was not cost-effective when the vaccine uptake rate was amended to 88.4% (cost of R 94,326,742.15/neonatal influenza-associated hospitalisation averted) but became dominant at the lower uptake rate of 1.7% (saving of R 390,054,373.76/neonatal influenza-associated hospitalisation averted). For the outcome of averting

maternal hospitalisation, the lowest value for vaccine uptake, 1.7%, produced ICERs of R 3,115,644.44 and R 2,188,324.71 per neonatal influenza-associated hospitalisation averted for both the universal and targeted vaccine strategies; whilst the uptake rate of 88.4% predicted that both strategies would not be cost-effective. This reinforces that vaccination of pregnant women (either universally or via a targeted approach of the HIV-infected) is not cost-effective.

Similarly, by systematically varying the amount of vaccine wastage (range of 5% to 25%) predicted that all strategies would not be cost-effective. (Refer to Annexure E: Simulations and calculations for sensitivity analysis of key variables: mode of delivery, vaccine uptake and vaccine wastage).

For detailed information of the results of the sensitivity analyses, refer to Table 7: Results of the sensitivity analysis for averting influenza-associated hospitalisations among infants less than 6 months of age and Table 8: Results of the sensitivity analysis for averting influenza-associated hospitalisations among pregnant women.

4.2.2 Tornado graph

Parameters that were tested for their impact on the model over specific ranges as listed in Table 5: Parameters tested for the sensitivity analyses. The parameter estimates conformed to evidence-based medicine principles, wherever possible. Univariate or one way deterministic sensitivity analysis was reported as a tornado graph developed in Excel using PrecisionTree® software (Palisade; Newfield, New York) shown in Figure 4: Tornado graph, ranking variables that impacted the

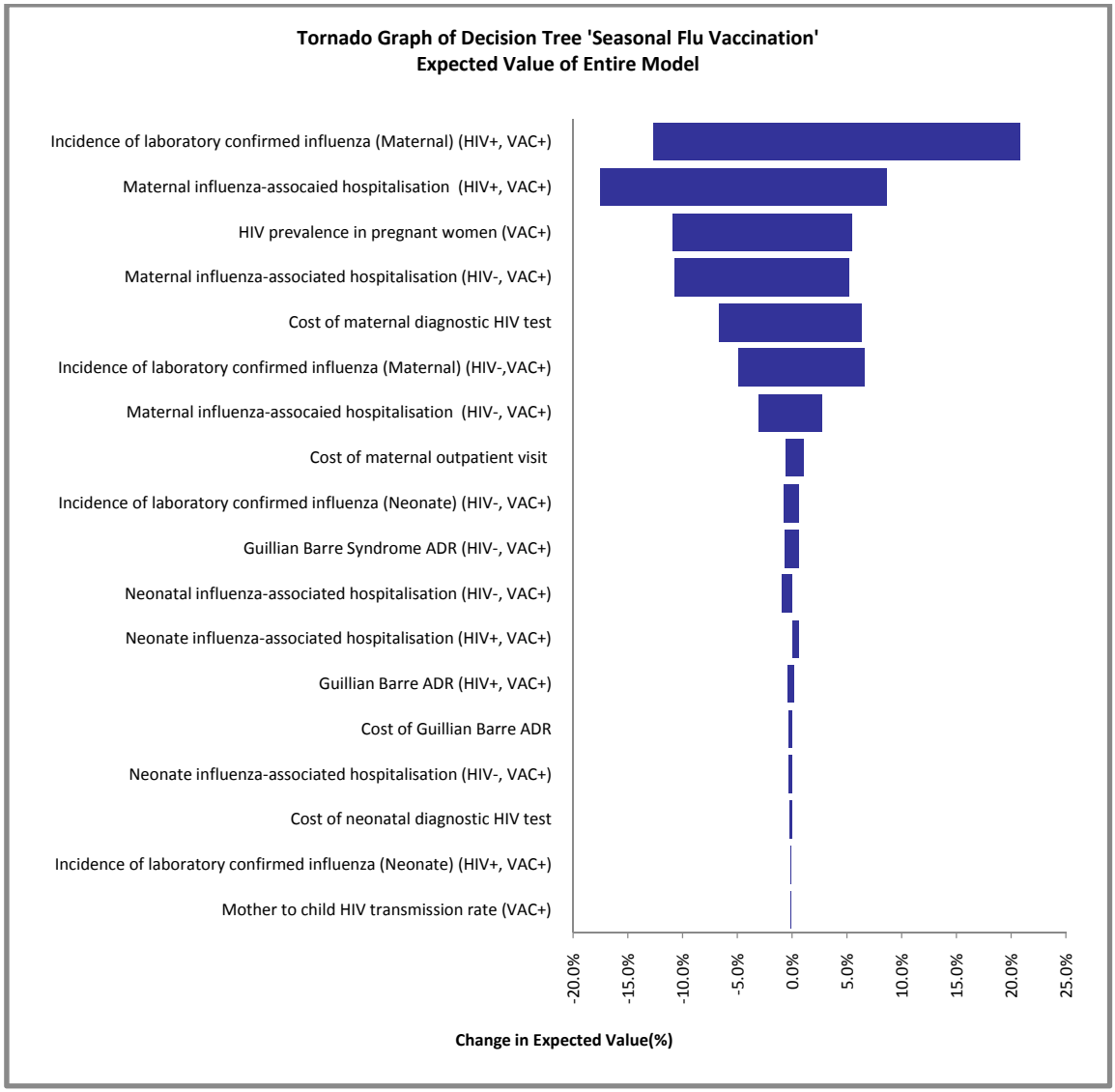
decision tree model. The horizontal axis displayed the expected outcome values and the vertical axis listed the parameters, represented by horizontal bars that depict the estimated outcome range for specific parameters. The longest bar is ranked at the top which describes the parameter with the widest uncertainty, and the other bars are arranged in decreasing order of cost or probability (or descending order of length).

Table 6: Parameters used in the sensitivity analyses

Parameter	Base case estimate	Lower case estimate	Upper case estimate	Reference
Probabilities				
Seasonal influenza vaccine uptake	100%	1.7%	88.4%	[110]
Vaccine wastage	10%	5%	25%	[94]
Incidence of Guillain-Barre adverse drug reaction (VAC+)	0.0000017	0.000001	0.0000028	[58]
Laboratory confirmed influenza in pregnant women - HIV+, VAC+ - HIV+, VAC- - HIV+, VAC- - HIV-, VAC-	 0.07 0.018 0.036 0.017	 0.029 0.011 0.026 0.011	 0.139 0.028 0.049 0.028	[42]
Laboratory confirmed influenza in infants less than 6 months of age - HIV+, VAC+ - HIV-, VAC+ - HIV+, VAC- - HIV-, VAC-	 0.05 0.019 0.068 0.036	 0.016 0.011 0.02 0.61	 0.113 0.028 0.821 0.94	[42]
Influenza associated hospitalisation of pregnant women (HIV+/-, VAC+/-)	0.024	0.313	0.625	[16]
Influenza associated hospitalisation of infants less than 6 months of age (HIV+/-, VAC+/-)	0.028	0.014	0.031	[16]
Outpatient visits for influenza in pregnant women (HIV+/-, VAC+/-)	0.559	0.313	0.625	[16]
Outpatient visits for neonatal influenza (HIV+/-, VAC+/-)	0.547	0.455	0.551	[16]
HIV prevalence in pregnant women (VAC+/-)	0.297	0.017	0.884	[27]
Mother to child transmission of HIV	0.015	0.1	0.4	[28]
Cost (ZAR)				
Cost of vaccine administration	608.77	407.77	647.77	[90–93]
Cost of Guillain-Barre adverse drug reaction	1,750,488.81	1,575,439.92	1,925,537.69	[15]
Cost of influenza-associated hospitalisation of pregnant woman	65,087.32	58,578.59	71,596.06	[111]
Cost of influenza-associated hospitalisation of infant less than 6 months of age	156,038.27	140,434.45	171,642.10	[97]
Cost of outpatient visit for maternal influenza	229.75	190.75	352.75	[90,91,98]
Cost of outpatient visit for neonatal influenza	240.67	201.67	363.67	[90,91,98]
Cost of maternal HIV diagnostic test	118.68	106.81	130.55	± 10% deviation
Cost of neonatal HIV diagnostic test	105.44	94.89	115.98	± 10% deviation

Key: HIV+=HIV-infected pregnant women; HIV-=HIV-uninfected pregnant women; VAC+=Influenza vaccinated pregnant women; VAC-= Pregnant women not vaccinated with influenza vaccine

Figure 4: Tornado graph ranking variables that impacted the decision tree model



Univariate one way sensitivity analysis, using Palisade Decision Tools (Palisade; Newfield, New York), showed that parameters that most affected cost-effectiveness of TIV were: a) Incidence of laboratory confirmed influenza amongst HIV-infected pregnant women who were vaccinated; b) Incidence of influenza-associated hospitalisation of HIV-infected, vaccinated pregnant women; c) HIV prevalence amongst vaccinated pregnant women; d) Incidence of influenza-associated hospitalisation of HIV-infected, vaccinated pregnant women; e)Cost of maternal diagnostic HIV test; f) Incidence of laboratory confirmed influenza

amongst HIV-uninfected, vaccinated pregnant women (Refer to Figure 4: Tornado graph, ranking variables that impacted the decision tree model). When these six parameters with the most uncertainty were tested over an acceptable range, it showed that both the universal vaccination strategy and the HIV-targeted strategy were generally not cost-effective compared to not vaccinating, for the outcomes of averting infant and maternal influenza-associated hospitalisations. Except when the incidence of influenza-associated hospitalisation of HIV-infected, vaccinated and HIV-uninfected, vaccinated pregnant women were changed. (Refer to Annexure F: Simulations and calculations for sensitivity analysis of tornado graph parameters).

Table 7: Results of the sensitivity analysis for averting influenza-associated hospitalisations among infants less than 6 months of age

UNIVERSAL VACCINATION (100000 PREGNANT WOMEN)				
	Parameter value (95% CI)	**ICER/Infant hospitalisation averted**		
Parameter	**Base (Lower to higher)**	**Base case**	**Lower case**	**Higher case**
Seasonal influenza uptake	1 (0.017 to 0.884)	-R 69,118,114.05	R 558,985,493.45*	R 5,001,945.43*
Mode of delivery: NP(Prenatal schedule to GP)	R608.77 (R407.77 to R647.77)	-R 69,118,114.05	- R 53,449,963.95	-R 73,546,069.51
Vaccine wastage	10% (5% to 25%)	-R 69,118,114.05	- R 66,689,323.71	-R 76,407,664.12
Laboratory confirmed influenza of HIV-infected , vaccinated pregnant women	0.07 (0.029 to 0.139)	-R 69,118,114.05	- R 70,849,497.32	- R 80,454,168.39
Incidence of influenza-associated hospitalisation of HIV-infected, vaccinated pregnant women	0.024(0.0.0004 to 0.036)	-R 69,118,114.05	- R 30,362,509.49	- R 88,824,353.66
HIV prevalence amongst vaccinated pregnant women	0.015 (0.1 to 0.4)	-R 69,118,114.05	- R 69,942,499.92	- R 71,323,714.23
Incidence of influenza-associated hospitalisation of HIV-uninfected, vaccinated pregnant women	0.024 (0.0.0004 to 0.036)	-R 69,118,114.05	- R 49,740,311,77	- R 78,971,233.85
Cost of maternal HIV diagnostic test	R 118.68 (106.81 to 130.55)	-R 69,118,114.05	-R 69,118,114.05	-R 69,118,114.05
Laboratory confirmed influenza of HIV-uninfected , vaccinated pregnant women	0.018 (0.011 to 0.028)	-R 69,118,114.05	-R 69,118,114.05	-R 69,118,114.05
HIV-TARGETED VACCINATION (100000 PREGNANT WOMEN)				
Parameter	**Parameter value**	**Base case ICER**	**Lower case ICER**	**Higher case ICER**
Seasonal influenza uptake	1 (0.017 to 0.884)	-R 159,134,365.50	R 390,054,373.76*	-R 94,326,742.15
Mode of delivery: NP(Prenatal schedule to GP)	R608.77 (R407.77 to R647.77)	-R 159,134,365.50	-R 145,438,439.61	-R 163,004,953.25
Vaccine wastage	10% (5% to 25%)	-R 159,134,365.50	-R 157,011,298.49	-R 165,506,345.39
Laboratory confirmed influenza of HIV-infected , vaccinated pregnant women	0.07 (0.029 to 0.139)	-R 159,134,365.50	- R 143,393,045.22	- R 195,196,387.84
Incidence of influenza-associated hospitalisation of HIV-infected, vaccinated pregnant women	0.024(0.0.0004 to 0.036)	-R 159,134,365.50	- R 108,318,485.76	- R 184,972,948.41
HIV prevalence amongst vaccinated pregnant women	0.015 (0.1 to 0.4)	-R 159,134,365.50	- R 153,436,083.17	- R 171,494,560.20
Incidence of influenza-associated hospitalisation of HIV-uninfected, vaccinated pregnant women	0.024 (0.0.0004 to 0.036)	-R 159,134,365.50	-R 159,134,365.50	-R 159,134,365.50
Cost of maternal HIV diagnostic test	R 118.68 (106.81 to 130.55)	-R 159,134,365.50	-R 159,076,052.11	-R 159,192,678.88
Laboratory confirmed influenza of HIV-uninfected , vaccinated pregnant women	0.018 (0.011 to 0.028)	-R 159,134,365.50	-R 159,134,365.50	-R 159,134,365.50

* ICER shows that strategy is dominant compared to no vaccination, where there is a saving per hospitalisation averted.

Table 8: Results of the sensitivity analysis for averting influenza-associated hospitalisations among pregnant women

UNIVERSAL VACCINATION (100000 PREGNANT WOMEN)				
	Parameter value	**ICER/Maternal hospitalisation averted**		
Parameter	**Base (Lower to higher)**	**Base case**	**Lower case**	**Higher case**
Seasonal influenza uptake	1 (0.017 to 0.884)	-R 1,197,779.79	R 3,115,644.44*	-R 688,769.40
Mode of delivery: GP (NP to Specialist)**	R608.77 (R407.77 to R647.77)	-R 1,197,779.79	-R 926,259.16	-R 1,274,513.88
Vaccine wastage	10% (5% to 25%)	-R 1,197,779.79	-R 1,155,690.16	-R 1,324,103.78
Laboratory confirmed influenza of HIV-infected , vaccinated pregnant women	0.07 (0.029 to 0.139)	-R 1,197,779.79	-R 930,311.19	-R 2,320,599.27
Incidence of influenza-associated hospitalisation of HIV-infected, vaccinated pregnant women	0.092 (0.007 to 0.127)	-R 1,197,779.79	R 211,341.11*	-R 2,605,660.35
HIV prevalence amongst vaccinated pregnant women	0.015 (0.1 to 0.4)	-R 1,197,779.79	-R 964,500.46	-R 1,371,175.28
Incidence of influenza-associated hospitalisation of HIV-uninfected, vaccinated pregnant women	0.024 (0.0.0004 to 0.036)	-R 1,197,779.79	R 242,196.93*	-R 2,311,442.45
Cost of maternal HIV diagnostic test	R 118.68 (106.81 to 130.55)	-R 1,197,779.79	-R 1,197,779.79	-R 1,197,779.79
Laboratory confirmed influenza of HIV-uninfected , vaccinated pregnant women	0.018 (0.011 to 0.028)	-R 1,197,779.79	-R 1,073,099.55	-R 1,436,154.87
HIV-TARGETED VACCINATION (100000 PREGNANT WOMEN)				
Parameter	**Parameter value**	**Base case ICER**	**Lower case ICER**	**Higher case ICER**
Seasonal influenza uptake	1 (0.017 to 0.884)	-R 854,053.42	R 2,188,324.71*	-R 495,034.23
Mode of delivery: GP (NP to Specialist)**	R608.77 (R407.77 to R647.77)	-R 854,053.42	-R 660,450.95	-R 908,767.16
Vaccine wastage	10% (5% to 25%)	-R 854,053.42	-R 824,042.23	-R 944,126.26
Laboratory confirmed influenza of HIV-infected , vaccinated pregnant women	0.07 (0.029 to 0.139)	-R 854,053.42	-R 605,712.15	-R 2,754,993.30
Incidence of influenza-associated hospitalisation of HIV-infected, vaccinated pregnant women	0.024(0.0.0004 to 0.036)	-R 854,053.42	R 770,530.86*	-R 2,999,684.93
HIV prevalence amongst vaccinated pregnant women	0.015 (0.1 to 0.4)	-R 854,053.42	-R 560,847.21	-R 1,150,497.86
Incidence of influenza-associated hospitalisation of HIV-uninfected, vaccinated pregnant women	0.024 (0.0.0004 to 0.036)	-R 854,053.42	-R 854,053.42	-R 854,053.42
Cost of maternal HIV diagnostic test	R 118.68 (106.81 to 130.55)	-R 854,053.42	-R 854,053.42	-R 854,053.42
Laboratory confirmed influenza of HIV-uninfected , vaccinated pregnant women	0.018 (0.011 to 0.028)	-R 854,053.42	-R 854,053.42	-R 854,053.42

* ICER shows that strategy is dominant s compared to no vaccination, where there is a saving per hospitalisation averted.

Univariate sensitivity analyses of variables identified in the tornado graph to have the most effect on predicted ICERs reinforced that influenza vaccination of pregnant women (either routinely or using a targeted approach of only vaccinating HIV-infected women) was not cost-effective. (The sensitivity analyses results are shown in Tables 7 and 8). Exceptions were simulations using lower rates of maternal influenza-associated hospitalisations amongst both HIV-infected and HIV-uninfected vaccinated pregnant women in the universal vaccination strategy; savings of R 211,341.11 and R 242,196.93 per maternal influenza-associated hospitalisation averted, respectively. Similarly, the targeted approach became dominant when a lower incidence rate of influenza-associated hospitalisations amongst HIV-infected vaccinated pregnant women was modelled, predicting a saving of R 770,530.86/maternal influenza-associated hospitalisation averted. The model predicts that increased effectiveness of influenza vaccination in reducing maternal-influenza associated hospitalisations will result in savings for averting hospitalisation cases.

The sensitivity analyses shows that the cost-effectiveness model for the various vaccination strategies is robust; when variable values were changed to plausible lower and upper estimate values. The only assumptions that affected the cost-ineffectiveness of the vaccination strategies with respect to averting influenza-associated hospitalisations in the pregnant women was a lower incidence of influenza-associated hospitalisations amongst HIV-infected and HIV-uninfected vaccinated pregnant women in the universal approach; and amongst HIV-infected vaccinated pregnant women in the HIV-targeted strategy.

5. DISCUSSION

This analysis, from a health system payer perspective, clearly demonstrates that universal influenza vaccination of pregnant women, as well as the HIV-targeted strategy is not cost-effective, compared to not vaccinating for averting influenza-associated hospitalisations amongst infants less than six months of age and maternal influenza-associated hospitalisations. Conversely, international cost-effectiveness analyses showed that TIV resulted in a decrease in influenza-related costs from a payer's perspective;[14,15] and from a societal perspective.[13,16,49]

Only when the incidence rate of maternal influenza-associated hospitalisation associated with vaccination was reduced from 0.092 to 0.007 amongst HIV-infected pregnant women; and from 0.024 to 0.0004 amongst the HIV-uninfected, did the model predict that the universal approach was economically dominant over not vaccinating, in terms of averting maternal influenza-associated hospitalisations. Furthermore, the ICER was only from a cost of R 854,053.42 to a saving of R 770,530.86 per maternal influenza-associated hospitalisation averted when compared to not vaccinating, when lowering maternal influenza-associated hospitalisation amongst the HIV-infected pregnant women in the univariate sensitivity analysis for the targeted HIV-approach. Further sensitivity analyses of the remaining variables as determined by the tornado graph indicated the robustness of the base-model regarding uncertainties. Conversely, the analysis by Skedgel *et al.*[15]suggested that a targeted vaccination strategy in pregnant women, with at least one co-morbidity may be economically dominant.

It should be noted that a serious limitation in this evaluation is the uncertainty regarding the estimation of probabilities and costs, because of the paucity of robust data regarding influenza amongst pregnant women, and particularly amongst HIV-infected pregnant women, especially in the South African context. Measures for the HIV-targeted strategy was sourced from local underpowered studies, whilst costs were sourced from studies from high-income countries.[13,15,97]

Cost-effectiveness of TIV for reducing hospitalisation in both the pregnant women and her newborn infant was evaluated in this analysis. However, natural service delivery units of outcome were used in this analysis, rather than the cost per QALY. This was considered to be reasonable as the study was performed from a payer's perspective. Although quality of life estimation has its limitations (as qualitative phenomenon including personal, cultural and psychological beliefs vary amongst persons and particularly amongst pregnant women where cultural valuations of quality of life due to illness or hospitalisationperceptions regarding influenza vaccination may vary), the international standard is to measure cost per QALY or cost/DALY in cost-effectiveness analyses. Cultural perceptions and values may be one of the factors that could contribute to vaccine uptake as indicated by the systematic review by Yuen et al. (1.7% to 88.4%).[110]

Sensitivity analysis testing the uncertainty of vaccine uptake confirmed robustness of the model as most simulations were comparable to the base-case model, predicting that the vaccination strategies for averting hospitalisations amongst infants less than six months of age and antenatal influenza-associated hospitalisations were not cost-effective. The only exception was when the

universal and targeted strategies became dominant when the incidence of maternal influenza-associated hospitalisation was lowered.

An assumption in this analysis was that pregnant women and their infants with laboratory confirmed influenza would require influenza-associated hospitalisations, the rates of which were sourced from epidemiological studies and other international studies.[16,31,34,44,47] The cost of neonatal hospitalisation was sourced from an international direct cost study[97] and are known to be relatively high[13,16,97] as it includes chest X-ray evaluation, respiratory distress management including oxygen saturation tests and mechanical ventilation, laboratory testing, hospital bed days with possible referral to ICU, medical management, personnel (probably medical specialists) and facility resources. The incidence rates of hospitalisations for pregnant women was extrapolated from a recent cost-effectiveness study,[16]with an assumption that rates were similar in both the HIV-infected and HIV-uninfected cohorts.

Jit et al.[14] reported less optimistic results compared to the evaluation done by Beigi et al.[13], as the timing of vaccination due to the seasonality of influenza was taken into consideration. Timing of vaccination was not factored into this model, as it was assumed that vaccine effectiveness would be the same irrespective of when vaccines are administered during the influenza season, disregarding the possibility that a pregnant woman may not be timeously vaccinated and thus have insufficient protection in an influenza season. However, this analysis did consider passive immunity acquired by infants when the pregnant woman is vaccinated for seasonal influenza.[41,45]

Univariate sensitivity analysis on mode of administration of the influenza vaccine did not affect the ICERs predicted in the base-case model. (Refer to Table 7: Results of the sensitivity analysis for averting influenza-associated hospitalisations among infants less than 6 months of age and Table 8: Results of the sensitivity analysis for averting influenza-associated hospitalisations among pregnant women). Furthermore, testing the model for uncertainty regarding vaccine wastage showed comparability of the ICERs between the base-case model and the lower and higher estimate value simulations. Similarly, this was shown when simulations for variables with the most uncertainty, as depicted by the tornado graph, were performed.

However, the lower value of the parameters: influenza-associated hospitalisations of the HIV-infected and HIV-uninfected, vaccinated pregnant women, predicted that the universal vaccine strategy would be dominant (ICERs of R 211,341.11 and R 242,196.93, respectively), when a cohort of 100000 pregnant women were vaccinated for seasonal influenza to avert maternal influenza-associated hospitalisations. Likewise, the targeted approach showed a saving of R 770,530.86 per maternal influenza-associated hospitalisation averted, with a lower incidence of hospitalisations amongst the HIV-infected. It is important to note that a key assumption was that the vaccine matched the circulating influenza virus strain that may not actually be the situation.

Although there are no confirmed fetal risks associated with vaccination of the pregnant woman with inactivated TIV[112–114]uptake has been reported to be generally poor. Awareness and education of pregnant women and healthcare

workers is required to alter perceptions. Needless to say, a recent study suggests that serial annual seasonal influenza vaccination may increase the risk of influenza compared to the unvaccinated.[115]Further research is required to verify these recent findings.

Despite decision analytic models being important research tools that assists decision-making in a global environment where healthcare costs are spiralling, limitations need to be acknowledged. The model is dependent on the quality of the data that is sourced from published peer reviewed literature. In addition, the research question needs to be well defined, preferably according to the PICO principle, carefully considering the effects of the decision. Specific outcomes of averted influenza-associated hospitalisations amongst pregnant women and their infants (less than six months of age) due to vaccination of pregnant women were used, as opposed to a generic measure of disease burden such as QALYs of DALYs. This resulted in two decision tree models for the different outcomes implying that the two clinical settings are separate and distinct scenarios which may not be the case in clinical practice. QALYs and DALYs further enable evaluations to be performed from a societal perspective. However, as the model was simulated from a payer's perspective, the effects and effect sizes used in this analysis were considered to be acceptable.

A serious limitation of this model was the uncertainty regarding costs and clinical effects of vaccinating pregnant women. There is a paucity of good quality evidence in the South African context (or from low- to middle income countries) and lack of available patient-oriented evidence regarding the absolute effect of vaccination on

hospitalisations, preterm births, small for gestational age births, morbidity and mortality requires the results of this evaluation to be interpreted with caution.

Costs were sourced from studies performed in high income countries that may not necessarily be generalisable to the local setting. Unit costs from South African public healthcare sector studies would probably be more meaningful, as well as the creation of local league tables to assist with distribution of limited resources to determine whether additional large-scale strategies can be sustained by the healthcare.

Other limitations including vaccine mismatch to the circulating strains, timing of vaccination, assumption that cases of laboratory-confirmed influenza would require hospitalisation, hospitalisation rates for HIV-infected assumed to be the same as for the HIV-uninfected has already been described. In addition, the model assumed that incidence rates of vaccine associated GBS events, preterm births of the HIV-infected pregnant women and maternal and neonatal influenza-associated hospitalisations were similar to those in the HIV-uninfected cohorts, due to paucity of evidence. This could have resulted in under prediction of ICERs for the targeted annual seasonal influenza vaccination of prenatal HIV-infected pregnant women. Furthermore, the longitudinal nature of decision tree models follows the model cohort through clinical pathways once, without the opportunity of re-entering the model at any point in the tree, assuming that a pregnant women and her infant would only require a single hospitalisation in an influenza season. A Markov model allows for recurring events, where patients can transition from one “state” another within the model.[107]

In addition, it should be noted that this analysis evaluates whether a vaccination program (where 100,000 pregnant women are vaccinated) is cost-effective, using the WHO parameter of less than three times the GDP.

6. IMPLICATIONS FOR POLICY

Preliminary findings based on available clinical evidence relevant to the South African setting suggest that vaccination of pregnant women is not cost-effective.

6.1 Universal influenza vaccination of pregnant women

Overall, the impact of this evaluation shows that routine antenatal influenza vaccination is not cost-effective in South Africa and careful consideration is required of the upscaling of influenza vaccination amongst pregnant women as a priority in the constraints of a limited healthcare budget. However, a significant limitation was the paucity of local randomised controlled trial data showing vaccine effectiveness (i.e. clinical outcomes such as decreased hospitalisations, morbidity and mortality). Although the South African study[42]showed that prenatal influenza vaccination was associated with a reduction in laboratory-confirmed influenza among women (HIV uninfected or HIV infected) and their neonates less than six months of age; the study was statistically underpowered to detect a difference between vaccinating and not vaccinating of pregnant women pertaining to improved clinical outcomes. Although, currently a South African study is underway as well as further analysis of the Mali vaccine effectiveness study to evaluate clinical outcomes such as adverse pregnancy outcomes (preterm or low birth weight), influenza-like illness and hospitalisations. This will provide much needed evidence to provide more meaningful economic predictions.

6.2 Targeted influenza vaccination of HIV-infected pregnant women

This evaluation suggests that at a lower rate of maternal influenza-associated hospitalisation, the HIV-targeted strategy is the most cost-effective to avert maternal influenza-associated hospitalisations. However, uncertainty of the probability and cost estimates due to limited evidence in the HIV-infected cohort cautions interpretation of the results of the decision analytic model.

6.3 Further research

Additional studies investigating patient-oriented outcomes as opposed to disease-oriented outcomes[116]are required to determine vaccine efficacy in terms of measuring clinical benefit to patients (e.g. prevention of preterm births, influenza-associated hospitalisations, etc.), rather than surrogate outcomes (such as laboratory confirmed influenza) in order to inform decision-makers on policy of vaccine mobilisation amongst pregnant women in the local South African context.

Standardised unit costs for the South African public healthcare setting could assist in systematising cost analyses and possibly facilitate the development of South African league tables, going forward.

It is established that globally, influenza vaccine uptake is a major limitation amongst pregnant women due to perceived harms associated with influenza vaccination. Studies to determine the attitudes of South African pregnant women and healthcare workers towards seasonal influenza vaccination of pregnant women, with respective education programmes are advocated.

7. CONCLUSION

Decision analytic modelling is less time consuming and less expensive than traditional research techniques, with no direct patient risk. Cost-effectiveness gains are increasingly contributing to decision making. This evaluation predicts that universal influenza vaccination of pregnant women in the South African public healthcare setting is not cost-effective, even if a HIV-targeted approach is used. However, this analysis was based on clinical model inputs that were either extrapolated from international studies or based on local studies that measured surrogate outcomes. This analysis provides inadequate information for upscaling of influenza vaccination amongst pregnant women as a priority. However, suggests that further research is required to evaluate vaccine effectiveness measured by appropriate clinical outcomes and cost inputs relevant to the South African public healthcare setting. And, lastly budget impact analyses and the development of league tables will assist decision making regarding affordability in the South African context with constrained healthcare resources.

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.
- FWA 00002567, Approved dd 22 May 2002 and Expires 20 Oct 2016.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 22/04/2017.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

26/11/2015

Approval Certificate
New Application

Ethics Reference No.: 490/2015

Title: The cost-effectiveness of influenza vaccination of pregnant women in the South African public healthcare setting

Dear Trudy Leong

The **New Application** as supported by documents specified in your cover letter dated 26/10/2015 for your research received on the 26/10/2015, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 25/11/2015.

Please note the following about your ethics approval:
- Ethics Approval is valid for 1 year.
- Please remember to use your protocol number (**490/2015**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:
- The ethics approval is conditional on the receipt of 6 monthly written Progress Reports, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

*** Kindly collect your original signed approval certificate from our offices, Faculty of Health Sciences, Research Ethics Committee, H W Snyman South Building, Room 2.33 / 2.34.*

Dr R Sommers; MBChB; MMed (Int); MPharMed.
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2015 (Department of Health).

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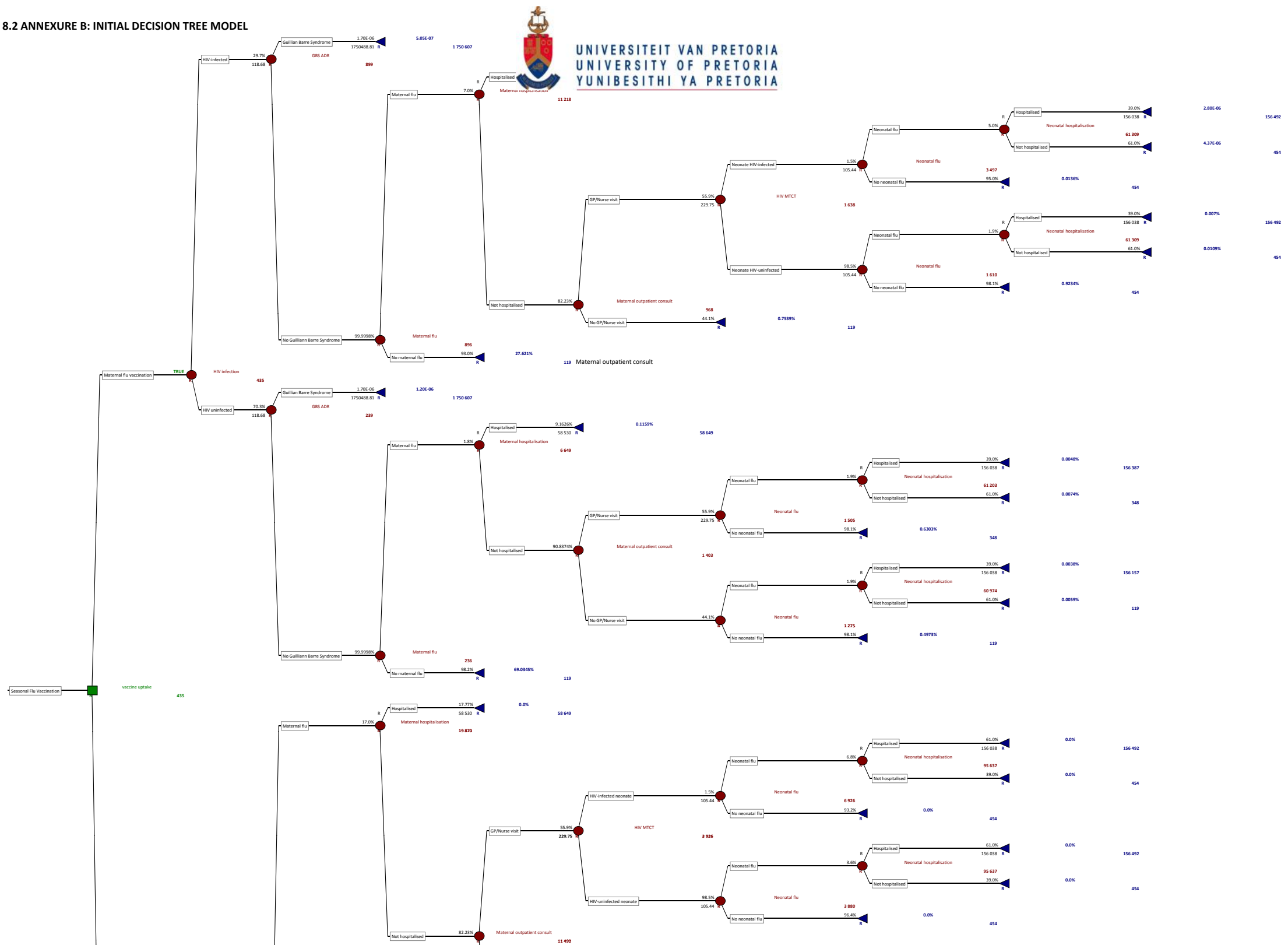
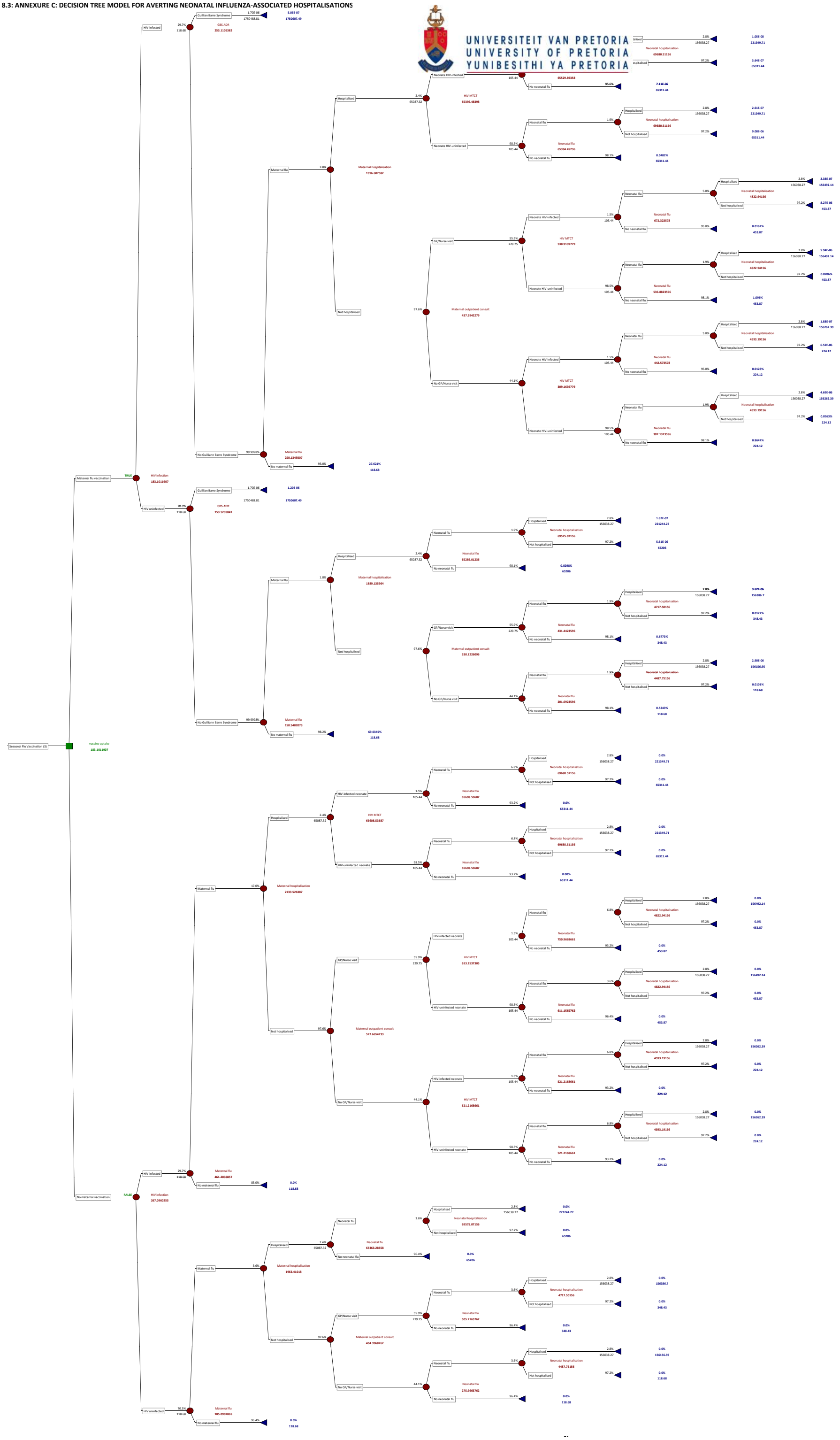
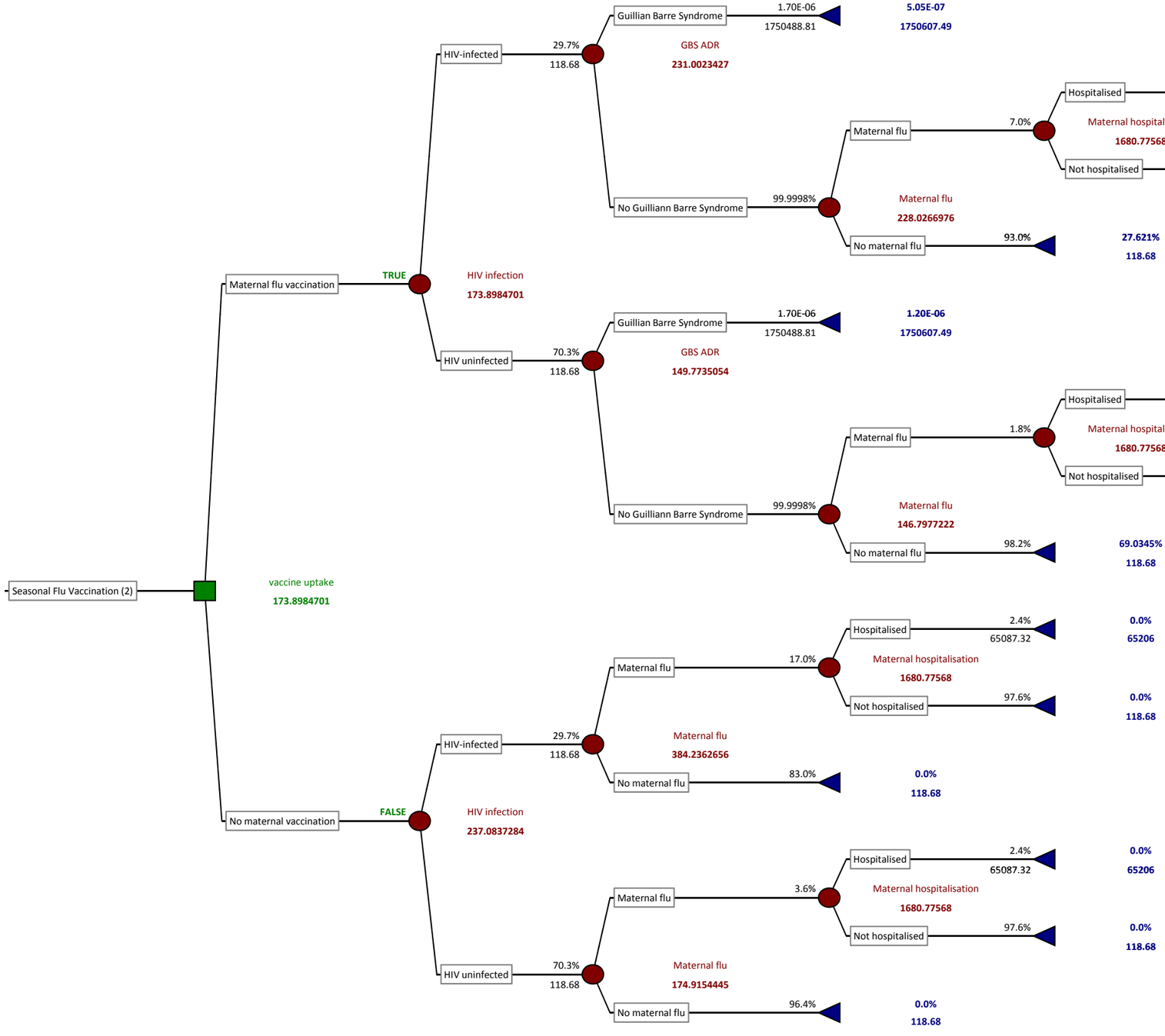
8.2 ANNEXURE B: INITIAL DECISION TREE MODEL



8.3: ANNEXURE C: DECISION TREE MODEL FOR AVERTING NEONATAL INFLUENZA-ASSOCIATED HOSPITALISATIONS



8.4. ANNEXURE D: DECISION TREE MODEL FOR AVERTING MATERNAL INFLUENZA ASSOCIATED HOSPITALISATIONS



	PROBABILITIES	COSTS
HIV+/VACC+	0.000498959	2206.11364
	0.000303695	2254.29772
VACC +	0.000802655	4460.41136
HIV+/VACC-	0.00121176	1597.34364
	0.000607392	1645.52772
VACC -	0.001819152	3242.87136

8.5 APPENDIX E: i) Sensitivity analysis: Different modes of administration

NEONATAL HOSPITALISATION: ALL WOMEN			BASE MODEL: Nurse practitioner (R608.77)						
ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)	prenatal schedule (R470.77)	ICER (100000)	general practitioner (R647.77)	ICER (100000)
VACC+	1.80629E-05	R 50 650.26	2	R 5 065 025 571.00		R 4 940 825 571.00		R 5 100 125 571.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00		R 4 517 132 571.00		R 4 517 132 571.00	
Difference			-8	R 547 893 000.00	-R 69 118 114.05	R 423 693 000.00	-R 53 449 963.95	R 582 993 000.00	-R 73 546 069.51
NEONATAL HOSPITALISATION: HIV WOMEN			BASE MODEL: Nurse practitioner						
HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)	prenatal schedule	ICER (100000)	general practitioner	ICER (100000)
VACC+	1.13309E-05	R 33 775.91	1	R 3 377 590 898.00		R 3 294 790 898.00		R 3 400 990 898.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00		R 2 415 529 218.00		R 2 415 529 218.00	
Difference			-6	R 962 061 680.00	-R 159 134 365.50	R 879 261 680.00	R -145 438 439.61	R 985 461 680.00	-R 163 004 953.25
MATERNAL HOSPITALISATION: ALL WOMEN			BASE MODEL: Nurse practitioner						
ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)	prenatal schedule	ICER (100000)	general practitioner	ICER (100000)
VACC+	0.000802655	R 4 460.41	80	R 446 041 136.00		R 418 441 136.00		R 453 841 136.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00		R 324 287 136.00		R 324 287 136.00	
Difference			-102	R 121 754 000.00	-R 1 197 779.79	R 94 154 000.00	-R 926 259.16	R 129 554 000.00	-R 1 274 513.88
MATERNAL HOSPITALISATION: HIV WOMEN			BASE MODEL: Nurse practitioner						
HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)	prenatal schedule	ICER (100000)	general practitioner	ICER (100000)
VACC+	0.000498959	R 2 206.11	50	R 220 611 364.00		R 206 811 364.00		R 224 511 364.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00		R 159 734 364.00		R 159 734 364.00	
Difference			-71	R 60 877 000.00	-R 854 053.42	R 47 077 000.00	-R 660 450.95	R 64 777 000.00	-R 908 767.16

ICER (Vaccinate vs No Vaccine)

[is equal to ((Avg cost V+)-(Avg cost V-)) / ((Avg Effect V+)-(Avg Effect V-))]:

8.5 APPENDIX E: ii) Sensitivity analysis: Different percentage uptake of maternal influenza vaccination

NEONATAL HOSPITALISATION: ALL WOMEN			100% UPTAKE		1.7% UPTAKE		88.4% UPTAKE	
ALL	Probability	ZAR	100000 women vaccinated	ICER (100000)		ICER (100000)		ICER (100000)
VACC+	1.80629E-05	R 50 650.26	2	R 5 065 025 571.00		R 86 105 434.71		R 4 477 482 604.76	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00		R 4 517 132 571.00		R 4 517 132 571.00	
Difference			-8	R 547 893 000.00	-R 69 118 114.05	-R 4 431 027 136.29	R 558 985 493.45	-R 39 649 966.24	R 5 001 945.43

NEONATAL HOSPITALISATION: HIV WOMEN			100% UPTAKE		1.7% UPTAKE		88.4% UPTAKE	
HIV	Probability	ZAR	100000 women vaccinated	ICER (100000)		ICER (100000)		ICER (100000)
VACC+	1.13309E-05	R 33 775.91	1	R 3 377 590 898.00		R 57 419 045.27		R 2 985 790 353.83	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00		R 2 415 529 218.00		R 2 415 529 218.00	
Difference			-6	R 962 061 680.00	-R 159 134 365.50	-R 2 358 110 172.73	R 390 054 373.76	R 570 261 135.83	-R 94 326 742.15

MATERNAL HOSPITALISATION: ALL WOMEN			100% UPTAKE		1.7% UPTAKE		88.4% UPTAKE	
ALL	Probability	ZAR	100000 women vaccinated	ICER (100000)		ICER (100000)		ICER (100000)
VACC+	0.000802655	R 4 460.41	80	R 446 041 136.00		R 7 582 699.31		R 394 300 364.22	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00		R 324 287 136.00		R 324 287 136.00	
Difference			-102	R 121 754 000.00	-R 1 197 779.79	-R 316 704 436.69	R 3 115 644.44	R 70 013 228.22	-R 688 769.40

MATERNAL HOSPITALISATION: HIV WOMEN			100% UPTAKE		1.7% UPTAKE		88.4% UPTAKE	
HIV	Probability	ZAR	100000 women vaccinated	ICER (100000)		ICER (100000)		ICER (100000)
VACC+	0.000498959	R 2 206.11	50	R 220 611 364.00		R 3 750 393.19		R 195 020 445.78	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00		R 159 734 364.00		R 159 734 364.00	
Difference			-71	R 60 877 000.00	-R 854 053.42	-R 155 983 970.81	R 2 188 324.71	R 35 286 081.78	-R 495 034.23

ICER (Vaccinate vs No Vaccine)

[is equal to ((Avg cost V+)-(Avg cost V-)) / ((Avg Effect V+)-(Avg Effect V-))]:

8.5 APPENDIX E: iii)Sensitivity analysis: Different percentage of influenza vaccine wastage

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)	5% wastage	ICER (10000)	25% wastage	ICER (100000)
VACC+	1.80629E-05	R 50 650.26	2	R 5 065 025 571.00		R 5 045 772 771.00		R 5 122 809 171.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00		R 4 517 132 571.00		R 4 517 132 571.00	
Difference			-8	R 547 893 000.00	-R 69 118 114.05	R 528 640 200.00	-R 66 689 323.71	R 605 676 600.00	-R 76 407 664.12

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)	5% wastage	ICER (10000)	25% wastage	ICER (100000)
VACC+	1.13309E-05	R 33 775.91	1	R 3 377 590 898.00		R 3 364 755 698.00		R 3 416 113 298.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00		R 2 415 529 218.00		R 2 415 529 218.00	
Difference			-6	R 962 061 680.00	-R 159 134 365.50	R 949 226 480.00	-R 157 011 298.49	R 1 000 584 080.00	-R 165 506 345.39

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)	5% wastage	ICER (10000)	25% wastage	ICER (100000)
VACC+	0.000802655	R 4 460.41	80	R 446 041 136.00		R 441 762 736.00		R 458 881 936.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00		R 324 287 136.00		R 324 287 136.00	
Difference			-102	R 121 754 000.00	-R 1 197 779.79	R 117 475 600.00	-R 1 155 690.16	R 134 594 800.00	-R 1 324 103.78

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)	5% wastage	ICER (10000)	25% wastage	ICER (100000)
VACC+	0.000498959	R 2 206.11	50	R 220 611 364.00		R 218 472 164.00		R 227 031 764.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00		R 159 734 364.00		R 159 734 364.00	
Difference			-71	R 60 877 000.00	-R 854 053.42	R 58 737 800.00	-R 824 042.23	R 67 297 400.00	-R 944 126.26

ICER (Vaccinate vs No Vaccine)

[is equal to ((Avg cost V+)-(Avg cost V-)) / ((Avg Effect V+)-(Avg Effect V-))]:

8.6 ANNEXURE F: a) Sensitivity analysis - Laboratory confirmed influenza amongst HIV-infected, vaccinated pregnant women

A: BASE MODEL

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 50 650.26	2	R 5 065 025 571.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 547 893 000.00	-R 69 118 114.05

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 33 775.91	1	R 3 377 590 898.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 962 061 680.00	-R 159 134 365.50

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000802655	R 4 460.41	80	R 446 041 136.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			102	-R 121 754 000.00	-R 1 197 779.79

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000498959	R 2 206.11	50	R 220 611 364.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			71	-R 60 877 000.00	-R 854 053.42

B: LOW INCIDENCE

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.14262E-05	R 50 650.26	2	R 5 065 025 571.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 547 893 000.00	-R 70 849 497.32

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	4.69425E-06	R 33 775.91	0	R 3 377 590 898.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-7	R 962 061 680.00	-R 143 393 045.22

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000510407	R 4 460.41	51	R 446 041 136.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			-131	R 121 754 000.00	-R 930 311.19

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000206712	R 2 206.11	21	R 220 611 364.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			-101	R 60 877 000.00	-R 605 712.15

C: HIGH INCIDENCE

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	2.92319E-05	R 50 650.26	3	R 5 065 025 571.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-7	R 547 893 000.00	-R 80 454 168.39

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	2.25E-05	R 33 775.91	2	R 3 377 590 898.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-5	R 962 061 680.00	-R 195 196 387.84

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.001294486	R 4 460.41	129	R 446 041 136.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			-52	R 121 754 000.00	-R 2 320 599.27

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.00099079	R 2 206.11	99	R 220 611 364.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			-22	R 60 877 000.00	-R 2 754 993.30

ICER (Vaccinate vs No Vaccine)

[is equal to ((Avg cost V-)-(Avg cost V+)) / ((Avg Effect V-)-(Avg Effect V+))]:

8.6 ANNEXURE F: b) Sensitivity analysis - Influenza-associated hospitalisation HIV-infected, vaccinated pregnant women

A: BASE MODEL

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 50 650.26	2	R 5 065 025 571.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 547 893 000.00	-R 69 118 114.05

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 33 775.91	1	R 3 377 590 898.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 962 061 680.00	-R 159 134 365.50

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000802655	R 4 460.41	80	R 446 041 136.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			102	-R 121 754 000.00	-R 1 197 779.79

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000498959	R 2 206.11	50	R 220 611 364.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			71	-R 60 877 000.00	-R 854 053.42

B: LOW INCIDENCE OF MATERNAL HOSP (HIV+, VAC+)

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 47 578.13	2	R 4 757 813 420.60	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 240 680 849.60	-R 30 362 509.49

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 30 703.79	1.1	R 3 070 378 747.60	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 654 849 529.60	-R 108 318 485.76

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000312011	R 2 924.35	31	R 292 435 060.80	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			-151	-R 31 852 075.20	R 211 341.11

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	8.31599E-06	R 670.05	1	R 67 005 288.80	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			-120	-R 92 729 075.20	R 770 530.86

C: HIGH INCIDENCE OF MATERNAL HOSP (HIV+, VAC+)

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 52 212.35	2	R 5 221 235 139.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 704 102 568.00	-R 88 824 353.66

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 35 338.00	1	R 3 533 800 466.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 1 118 271 248.00	-R 184 972 948.41

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.001052134	R 5 241.46	105	R 524 145 920.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			-77	R 199 858 784.00	-R 2 605 660.35

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000748439	R 2 987.16	75	R 298 716 148.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			-46	R 138 981 784.00	-R 2 999 684.93

ICER (Vaccinate vs No Vaccine)

[is equal to ((Avg cost V-)-(Avg cost V+)) / ((Avg Effect V-)-(Avg Effect V+))]:

8.6 ANNEXURE F: c) Sensitivity analysis -HIV prevalence amongst vaccinated pregnant women

A: BASE MODEL

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 50 650.26	2	R 5 065 025 571.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 547 893 000.00	-R 69 118 114.05

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 33 775.91	1	R 3 377 590 898.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 962 061 680.00	-R 159 134 365.50

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000802655	R 4 460.41	80	R 446 041 136.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			102	-R 121 754 000.00	-R 1 197 779.79

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000498959	R 2 206.11	50	R 220 611 364.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			71	-R 60 877 000.00	-R 854 053.42

B: LOW PREVALENCE OF MATERNAL HIV (HIV+, VAC+)

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.24335E-05	R 50 580.12	2	R 5 058 011 583.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 540 879 012.00	-R 69 942 499.92

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	3.81513E-06	R 33 635.63	1.0	R 3 363 562 922.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 948 033 704.00	-R 153 436 083.17

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000556799	R 4 460.41	56	R 446 041 136.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			-126	R 121 754 000.00	-R 964 500.46

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000168	R 2 182.73	17	R 218 273 368.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			-104	R 58 539 004.00	-R 560 847.21

C: HIGH PREVALENCE OF MATERNAL HIV (HIV+, VAC+)

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	2.10061E-05	R 50 686.93	2	R 5 068 692 783.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 551 560 212.00	-R 71 323 714.23

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.52605E-05	R 33 849.25	2	R 3 384 925 322.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 969 396 104.00	-R 171 494 560.20

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000931198	R 4 460.41	93	R 446 041 136.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			-89	R 121 754 000.00	-R 1 371 175.28

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000671999	R 2 218.34	67	R 221 833 768.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			-54	R 62 099 404.00	-R 1 150 497.86

ICER (Vaccinate vs No Vaccine)

[is equal to ((Avg cost V-)-(Avg cost V+)) / ((Avg Effect V-)-(Avg Effect V+))]:

8.6 ANNEXURE F: d) Sensitivity analysis -Influenza-associated hospitalisation HIV-uninfected, vaccinated pregnant women

A: BASE MODEL

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 50 650.26	2	R 5 065 025 571.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 547 893 000.00	-R 69 118 114.05

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 33 775.91	1	R 3 377 590 898.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 962 061 680.00	-R 159 134 365.50

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000802655	R 4 460.41	80	R 446 041 136.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			102	-R 121 754 000.00	-R 1 197 779.79

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000498959	R 2 206.11	50	R 220 611 364.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			71	-R 60 877 000.00	-R 854 053.42

B: LOW INCIDENCE OF MATERNAL HOSP (HIV-, VAC+)

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 49 114.19	2	R 4 911 419 495.80	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 394 286 924.80	-R 49 740 311.77

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 33 775.91	1.1	R 3 377 590 898.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 962 061 680.00	-R 159 134 365.50

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000504021	R 2 924.35	50	R 292 435 060.80	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			-132	-R 31 852 075.20	R 242 196.93

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000498959	R 2 206.11	50	R 220 611 364.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			-71	R 60 877 000.00	-R 854 053.42

C: HIGH INCIDENCE OF MATERNAL HOSP (HIV-, VAC+)

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 51 431.30	2	R 5 143 130 355.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 625 997 784.00	-R 78 971 233.85

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 33 775.91	1	R 3 377 590 898.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 962 061 680.00	-R 159 134 365.50

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000954502	R 5 241.46	95	R 524 145 920.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			-86	R 199 858 784.00	-R 2 311 442.45

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000498959	R 2 206.11	50	R 220 611 364.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			-71	R 60 877 000.00	-R 854 053.42

ICER (Vaccinate vs No Vaccine)
[is equal to ((Avg cost V-)-(Avg cost V+)) / ((Avg Effect V-)-(Avg Effect V+))]:

8.6 ANNEXURE F: e) Sensitivity analysis -Cost of maternal diagnostic HIV test

A: BASE MODEL

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 50 650.26	2	R 5 065 025 571.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 547 893 000.00	-R 69 118 114.05

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 33 775.91	1	R 3 377 590 898.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 962 061 680.00	-R 159 134 365.50

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000802655	R 4 460.41	80	R 446 041 136.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			102	-R 121 754 000.00	-R 1 197 779.79

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000498959	R 2 206.11	50	R 220 611 364.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			71	-R 60 877 000.00	-R 854 053.42

B: LOW COST OF MATERNAL HIV-DIAGNOSTIC TEST

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 50 604.07	2	R 5 060 406 954.00	
VACC-	9.7332E-05	R 45 125.14	10	R 4 512 513 954.00	
Difference			-8	R 547 893 000.00	-R 69 118 114.05

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 33 754.76	1.1	R 3 375 475 664.00	
VACC-	7.17869E-05	R 24 137.67	7	R 2 413 766 523.00	
Difference			-6	R 961 709 141.00	-R 159 076 052.11

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000802655	R 4 448.54	80	R 444 854 136.00	
VACC-	0.001819152	R 3 231.00	182	R 323 100 136.00	
Difference			-102	R 121 754 000.00	-R 1 197 779.79

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000498959	R 2 202.59	50	R 220 258 825.00	
VACC-	0.00121176	R 1 593.82	121	R 159 381 825.00	
Difference			-71	R 60 877 000.00	-R 854 053.42

C: HIGH COST OF MATERNAL HIV-DIAGNOSTIC TEST

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 50 696.44	2	R 5 069 644 188.00	
VACC-	9.7332E-05	R 45 217.51	10	R 4 521 751 188.00	
Difference			-8	R 547 893 000.00	-R 69 118 114.05

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 33 797.06	1	R 3 379 706 132.00	
VACC-	7.17869E-05	R 24 172.92	7	R 2 417 291 913.00	
Difference			-6	R 962 414 219.00	-R 159 192 678.88

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000802655	R 4 472.28	80	R 447 228 136.00	
VACC-	0.001819152	R 3 254.74	182	R 325 474 136.00	
Difference			-102	R 121 754 000.00	-R 1 197 779.79

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000498959	R 2 209.64	50	R 220 963 903.00	
VACC-	0.00121176	R 1 600.87	121	R 160 086 903.00	
Difference			-71	R 60 877 000.00	-R 854 053.42

ICER (Vaccinate vs No Vaccine)
[is equal to ((Avg cost V-)-(Avg cost V+)) / ((Avg Effect V-)-(Avg Effect V+))]:

8.6 ANNEXURE F: f) Sensitivity analysis -Laboratory confirmed influenza amongst HIV-uninfected, vaccinated pregnant women

A: BASE MODEL

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 50 650.26	2	R 5 065 025 571.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 547 893 000.00	-R 69 118 114.05

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 33 775.91	1	R 3 377 590 898.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 962 061 680.00	-R 159 134 365.50

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000802655	R 4 460.41	80	R 446 041 136.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			-102	R 121 754 000.00	-R 1 197 779.79

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000498959	R 2 206.11	50	R 220 611 364.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			-71	R 60 877 000.00	-R 854 053.42

B: LOW INCIDENCE OF LAB-CONFIRMED MATERNAL INFLUENZA (HIV-,VAC+)

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 50 650.26	2	R 5 065 025 571.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 547 893 000.00	-R 69 118 114.05

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 33 775.91	1.1	R 3 377 590 898.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 962 061 680.00	-R 159 134 365.50

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000684551	R 4 460.41	68	R 446 041 136.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			-113	R 121 754 000.00	-R 1 073 099.55

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000498959	R 2 206.11	50	R 220 611 364.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			-71	R 60 877 000.00	-R 854 053.42

C: HIGH INCIDENCE OF LAB-CONFIRMED MATERNAL INFLUENZA (HIV-,VAC+)

NEONATAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.80629E-05	R 50 650.26	2	R 5 065 025 571.00	
VACC-	9.7332E-05	R 45 171.33	10	R 4 517 132 571.00	
Difference			-8	R 547 893 000.00	-R 69 118 114.05

NEONATAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	1.13309E-05	R 33 775.91	1	R 3 377 590 898.00	
VACC-	7.17869E-05	R 24 155.29	7	R 2 415 529 218.00	
Difference			-6	R 962 061 680.00	-R 159 134 365.50

MATERNAL HOSPITALISATION: ALL WOMEN

ALL	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000971374	R 4 460.41	97	R 446 041 136.00	
VACC-	0.001819152	R 3 242.87	182	R 324 287 136.00	
Difference			-85	R 121 754 000.00	-R 1 436 154.87

MATERNAL HOSPITALISATION: HIV WOMEN

HIV	Probability	ZAR	100000 women vaccinated		ICER (100000)
VACC+	0.000498959	R 2 206.11	50	R 220 611 364.00	
VACC-	0.00121176	R 1 597.34	121	R 159 734 364.00	
Difference			-71	R 60 877 000.00	-R 854 053.42

ICER (Vaccinate vs No Vaccine)
[is equal to ((Avg cost V-)-(Avg cost V+)) / ((Avg Effect V-)-(Avg Effect V+))]:

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