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Maternal vaccination in South Africa: timing and completeness

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Research Report

MSc(Med)-Vaccinology

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Declaration

I, Julia Bourne, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Science (Medicine) in the field of Vaccinology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

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Dedication

In loving memory of my mum, Sheila. You inspire me daily.

Abstract

Maternal immunisation is an invaluable public health measure that protects not only the mother, but also the foetus and new-born infant against a host of diseases; and is recommended by both the World Health Organisation (WHO) and South African national health authorities. Pregnancy induces a heightened state of immune system vulnerability, leaving women more susceptible to severe influenza outcomes, whilst neonatal tetanus has a fatality rate of between 80-100% in the absence of medical intervention. Maternal immunisation against influenza and tetanus has been successfully utilised as a public health strategy across the globe to uphold maternal and neonatal health. Maintaining coverage is imperative for both diseases as influenza strains change seasonally and tetanus cannot be eliminated, highlighting the importance of continued maternal immunisation. This study aimed to describe the uptake of both influenza and tetanus vaccinations during pregnancy, the completion of the tetanus vaccination schedule and the timing of both influenza and tetanus immunisation within South African antenatal care facilities. In addition, this study described clinical and demographic factors affecting maternal immunisation uptake. Clinical and demographic data were collected in a parent study and were retrospectively analysed in this study using the statistical software Stata. Influenza vaccination uptake within the sampled population was found to be 16.62% (806/4851). The odds of influenza vaccination were significantly higher in women aged 21-30 years, and women with six or more ANC visits. Metro East Cape Town site in the Western Cape outperformed Gauteng sites, with significantly increased odds of influenza vaccination amongst women frequenting that site. Appropriate influenza immunisation: defined as immunisation occurring during the period of either 01/04/2017-31/07/2017 or 01/04/2018-30/06/2018, occurred in 74.86% (530/708) of the cohort. Women who were alcohol users were significantly more likely to receive an influenza vaccine – yet this may be explained by the Metro East site which had the higher influenza coverage having the highest prevalence of alcohol use during pregnancy. Of 7105 women, 7031 (98.96%) received at least one dose of tetanus toxoid vaccine (TTV). Of these women, 39.24% (2759) received one dose; 51.06% (3590) received two doses and 9.70% (682) received the recommended three doses of TTV in their index pregnancy. Tetanus schedule completion was significantly more likely in women $\leq$20 years, and those who presented for their booking antenatal care (ANC) visit in the first trimester. In addition, women with more than three visits had an increased likelihood of TTV schedule completion. The odds of TTV schedule completion were decreased by negatively parity and gravidity, values over one and less than six, and greater than one respectively. Women with hypertension were significantly less likely to receive three TTV doses compared to women without hypertension.

Tetanus immunisation schedule adherence prevalence was 0.60% (4/670) in women with three doses and 90.34% (3209/3552) in women with two. Improvements may be made in South African maternal immunisation coverage, with this study supporting the idea of targeted educational campaigns and a revision of the maternal immunisation schedule to include the tetanus, diphtheria & acellular pertussis vaccine instead of the tetanus toxoid vaccine.

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Table of Contents

List of Abbreviations

ANC	Antenatal Care
aOR	Adjusted Odds Ratio
CDC	Centres for Disease Control and Prevention
CI	Confidence Interval
ELISA	Enzyme Linked Immunosorbent Assay
FAMCRU	Family Centre for Research with Ubuntu
FcRn	Neonatal Fc Receptor
HAI	Haemagglutination Assay
HIV	Human Immunodeficiency Virus
HREC	Human Research Ethics Committee
IgG	Immunoglobulin G
IQR	Interquartile Range
NICD	The National Institute for Communicable Diseases
OR	Odds Ratio
REDCap	Research Electronic Data Capture
Tdap	Tetanus, diphtheria acellular pertussis
Th	T helper
TT	Tetanus Toxoid
TTV	Tetanus Toxoid Vaccination
WHO	World Health Organisation
Wits-VIDA	Wits Vaccines and Infectious Diseases Analytics Unit (formerly known as: RMPRU)
RMPRU	Respiratory and Meningeal Pathogens Research Unit
WRHI	Wits Reproductive Health and HIV Institute

List of Figures

Chapter Three

List of Tables

Chapter One

Chapter Three

Chapter One: Literature Review

1.1. Introduction

Pregnant women and their infants are disproportionately burdened by vaccine-preventable diseases, due to immunomodulation that occurs during pregnancy and the immaturity of the infant's immune system before the age of six months (1,2). Maternal vaccination is an invaluable public health measure that protects not only the mother, but also the foetus and new-born infant against a host of diseases; subsequently playing an integral role in neonatal outcomes (3,4). Maternal immunisation strategies targeting influenza and neonatal tetanus have shown great success in reducing disease, not only amongst pregnant women but also their infants through the transplacental transfer of antibodies (5,6). The optimal timing of maternal vaccination is a contested topic, with first trimester vaccination protecting the mother primarily, whilst vaccination in the second and third trimester allows for maximal transplacental antibody transfer to the foetus (7). Limited literature exists from the African continent pertaining to the timing of maternal immunisation and factors affecting the uptake and completion of the recommended schedules, highlighting the need for further research.

This literature review summarises the importance and significance of maternal immunization, examines existing public health policies in South Africa related to maternal vaccinations and the observable successes thereof, optimal timing of vaccine dosages, as well as known factors affecting vaccine uptake amongst pregnant women. To achieve this, a literature search on the Google Scholar database was performed using the following keywords: maternal immunisation, tetanus, influenza, optimal timing, vaccine uptake, coverage, recommendations, and pregnancy. Over 503 000 hits were presented, from which relevant material was extracted between February 2022 and November of 2022.

1.2. Importance of Maternal Vaccination

1.2.1. *Immunomodulation in Pregnancy*

During pregnancy, the maternal immune system undergoes a series of changes in order to protect the semi-allogeneic foetus from the maternal immune response, as the embryo and placenta both express foreign antigens due to paternal genetic contribution (1). Fuhler's 2020 review concludes that successful pregnancies involve differing immunological profiles, with the first trimester of pregnancy characterised by the immune system exhibiting a pro-inflammatory Th1 cell profile, whilst the second and third trimesters are characterized by an anti-inflammatory tolerance-associated Th2 cell profile (1). These changes appear to be the

result of elevated progesterone levels seen in pregnancy and are evident at the foeto-maternal interface, however, the degree to which these translate to the peripheral immune system remains contested in the literature (1,8). Lissauer *et al's* 2015 study on the effects of progesterone on maternal T cells revealed a skewing of cytokine profiles amidst the CD8+ and CD4+ T cell populations, a reduction in the polyfunctionality of the T cells and decreased T cell proliferation (8). These effects were noted to occur in a dose-dependent manner, evidencing that whilst an anti-inflammatory, dampened immune profile may be present at the foeto-maternal interface, peripheral effects are less pronounced due to lower levels of progesterone in the maternal sera (8). Therefore whilst evidence suggests pregnancy is accompanied by a degree of immune-suppression, Lissauer *et al* propose that the periphery is less affected by pregnancy's immunomodulation – in order to maintain the integrity of the maternal immune system (1,8). Kourtis *et al's* 2014 review however argues that the Th2 immunological profile which favours the innate immune response and decreases the strength of cell-mediated immunity by suppressing cytotoxic T cell action may be responsible for the increased burden of certain diseases in pregnancy, calling into question Lissauer's theory (9). Regardless of the physiological mechanisms behind immunomodulation and the degree to which this occurs in pregnancy, the literature firmly supports that pregnant women are at a heightened vulnerability regarding certain infections such as Hepatitis E, Herpes Simplex, Malaria and several vaccine-preventable diseases including measles, varicella and influenza (9).

1.2.2. *Heightened Severity of Influenza Infection During Pregnancy*

Pregnant women are disproportionately affected by severe influenza complications, which is believed to be the result of cardiopulmonary adaptations and reduced adaptive immune response, leading to reduced viral clearance and delayed recovery (5). Evidence for a heightened burden of influenza complications amongst pregnant women was formally documented during the Spanish influenza pandemic in 1918 (10), and is supported by more recent data (9). The 2009 influenza A H1N1 pandemic was no exception to this, with pregnant women, who made up 1% of the population, contributing 5% of all influenza deaths in the United States (11). The report which examined all cases of symptomatic H1N1 infection amongst pregnant women reported to the Centres for Disease Control and Prevention (CDC) between April 2009 and August 2009 ascertained that pregnant women were more susceptible to severe illness and even death as a result of infection than non-pregnant adults (11). In addition to these findings, pregnancy complication rate and illness severity was higher in later stages of pregnancy, including an elevated rate of pre-term births within the sample compared to the national rate (30.2% vs. 13%) (11). However, Siston *et al* acknowledge the limitations of their

report in that it likely under-represents the pregnant American population who contracted the H1N1 strain as it considered only cases reported to the CDC (11). Additionally, the data likely overestimates the severity of disease complications – particularly as the sample had an elevated rate of underlying medical conditions which may have been risk factors in themselves for hospitalisation, pre-term delivery and death (11). Despite these limitations, Vousden *et al's* 2021 observational study supported the conclusions of Siston *et al*, finding elevated severity of influenza infection amongst pregnant women infected with seasonal influenza (12). The United Kingdom based study found that pregnant women with influenza had an adjusted odds ratio (aOR) of 21.3 (2.78–163.1) of being admitted into an intensive care unit, 3.86 (0.39-37.9) of pregnancy loss, 1.60 (0.94-2.73) for pre-term delivery, and 3.89 (0.64-23.4) for stillbirth/perinatal death compared to pregnant women without influenza infection (12). Exact statistics quantifying these risk estimates vary between studies, possibly due to virulence variation between seasons, health system dynamics and health-seeking behaviours; however, it is evident that overall pregnancy appears to heighten the risk of severe illness and complications during influenza infection (13).

1.2.3. *Influenza in Pregnancy: South Africa*

Limited literature is available detailing the implications of influenza infection during pregnancy within sub-Saharan Africa (14). However, high risk groups for influenza-associated hospitalisation in South Africa have been identified and include pregnant women, and infants younger than six months of age (15). Pregnant women in South Africa have been found to be disproportionately affected by influenza compared to non-pregnant individuals, with a heightened influenza-associated mortality rate of 12.6 compared to 7.3 (crude death rate per 100 000 person-years) (14). Between the years 1999 to 2009, pregnant women in South Africa were found to have three times the risk of death compared to non-pregnant women as a result of seasonal and H1N1 influenza infection (14). An analysis of the burden of the 2009 H1N1 influenza pandemic in the country found pregnant women constituted 56% of influenza case fatalities amongst women of reproductive age – supporting that pregnancy is a possible risk factor for death as a result of H1N1 infection (16). In addition to the above, pregnancy has been associated with an increased risk of hospitalisation as a result of severe acute respiratory illness associated to influenza infection in South Africa (15). Overall, maternal influenza-related complications in unvaccinated individuals include increased risk of hospitalization, morbidity, and mortality; and though evidence for such is limited in sub-Saharan Africa – that which is available is in line with other global findings. Influenza infection is not only a threat to maternal

health, but additionally compromises foetal and neonatal health, increasing the risk of stillbirth, preterm delivery, low birth weight and foetal distress (5).

1.2.4. *Influenza Infection in Neonates and Infants*

Influenza complications have been documented in infants younger than six months of age, who have been identified to be at a heightened susceptibility for severe influenza-associated disease and hospitalization (5). Amongst the high risk groups for hospitalisation as a result of severe acute respiratory illness associated with influenza infection in South Africa are infants below the age of six months, with an aOR of 37.6 compared to individuals between the ages of five to twenty four years of age (15). Furthermore, infants below the age of one year display a significantly elevated influenza and respiratory syncytial virus (RSV) associated mortality rate compared to those between the ages of one and four years (15). In line with these observations, an estimated 44% of hospitalisations and 59% of deaths associated with influenza occur during infancy according to Wang *et al's* global model, with 23% of these hospitalisations and 36% of the in-hospital deaths occurring in infants younger than six months of age (17). These figures are likely an underestimate of the burden of influenza infection during infancy, as the model did not account for primary infections or secondary bacterial infection exposure that may be caused by influenza, without the detectable presence thereof in pathological samples (17). These vulnerabilities to respiratory viruses are a result of the neonatal immune system which favours an anti-inflammatory profile in order to permit the establishment of the microbiome (2). In addition to vulnerabilities to viral infections, neonates are also vulnerable to a host of bacterial infections, including vaccine-preventable tetanus infection as a result of environmental exposure (18).

1.2.5. *Neonatal Tetanus*

Tetanus is a vaccine-preventable disease that adversely affects foetal and neonatal outcomes – therefore maternal tetanus vaccination is imperative in maintaining tetanus elimination (19). Tetanus is caused by *Clostridium tetani,* a bacteria that produces an exotoxin which affects the central nervous system; causing muscle rigidity and spasms (19,20). The risk of neonatal tetanus exposure in Africa is increased by poor sanitation and traditional birth practices pertaining to the umbilical cord, such as use of unsterile cutting equipment and the application of herbs, cow or rat faeces to the umbilical stump (18). The disease is fatal in 80-100% of neonates in the absence of medical intervention, and due to its environmental origin eradication is impossible; highlighting the importance of maternal vaccination to achieve elimination (20,21). South Africa reports less than one case of neonatal tetanus per 1000 live births per

district – therefore achieving elimination goals (22), however, vaccination remains essential in maintaining cases below this threshold, due to the impossibility of eradication.

The neonatal immune system exhibits alterations in not only the innate system which reduces capacity for viral clearance, but also in the adaptive immune system – compromising antigen-specific immunological action and immunological memory (2). Therefore, neonates are at heightened vulnerability to disease that cannot be prevented by currently available vaccines dependent on evoking an immunological memory response – thus extending the importance of maternal vaccination beyond the mother's health to that of the neonate through the transplacental antibody transfer pathway (2,5).

1.3. Maternal Antibody Transfer

The vertical transmission of maternal antibodies provides a mechanism of protecting neonates from potentially fatal diseases in the first few months of life (5). This movement of antibodies which involves only the IgG class is facilitated via the neonatal Fc receptor (FcRn) (4,23). FcRn abundance has been accredited as a limiting factor in transplacental transfer, however a recent study by Clements *et al* disputes this, finding no correlation between placental FcRn levels and IgG titres in neonates (4,24). IgG transfer has consistently been documented to be dependent on maternal IgG levels, with maternal sera antibody levels correlating to those of the neonatal cord (4). Interestingly, Palmeira *et al's* review notes that an inverse relationship has been observed in the literature between maternal IgG levels and antibody transfer ratios – whereby elevated maternal levels result in reduced transfer efficacy, commonly reported in African studies. These observations, though dated, are supported by Clements *et al's* 2020 findings, whereby a negative correlation was observed between total maternal IgG levels and transfer ratios, specifically those of IgG1, IgG2 and IgG3; whilst IgG4 was the least affected by maternal IgG levels (24). The significance thereof lies in the potential to investigate optimal levels of maternal IgG classes for antibody transfer to the neonate to maximise conferred immunity, and the effects of this inverse relationship on pathogen-specific antibody transfer (24). Though the exact relationship between maternal IgG levels and transplacental transfer ratios is yet to be fully elucidated, a clear relationship exists between gestational age and the degree of antibody transfer to the foetus (4).

The transplacental transfer is initiated early in the second trimester at around 13 weeks, steadily increasing throughout the pregnancy with the maximal rate of transfer occurring in the third trimester – particularly in the final month of pregnancy wherein foetal antibody levels usually surpass those of the mother (4). Consequentially, infants born prematurely do not get exposed

to the full transfer window, therefore have lower antibody titres, and thus weaker immune systems compared to infants carried to term (4). Overall, due to this natural maternal ability to confer protection against diseases to the foetus, maternal immunisation has been adopted as a strategy to capitalise on this natural immunity and tailors this antibody transfer to be pathogen-specific through vaccination – successfully protecting not only mothers but also the vulnerable neonates until such a time that they are eligible for vaccination themselves (3,4).

1.4. Vaccination During Pregnancy

1.4.1. *Vaccine Recommendations*

Maternal vaccination protecting against tetanus and influenza is recommended by both the World Health Organisation (WHO) and South African national health authorities, with South African maternal immunisation schedules aligning with WHO recommendations (25,26). Due to the disproportionate adverse outcomes associated with influenza infection during pregnancy, the WHO has recommended that pregnant women are vaccinated with inactivated influenza vaccines (25), a decision supported by the South African National Institute for Communicable Diseases (26,27). Influenza vaccines are generally available annually from March in South Africa, with seasonal influenza circulation occurring any time between April to September (27,28). Vaccination of pregnant women against influenza may safely occur at any stage of pregnancy, even two weeks following birth (27,28). Tetanus vaccination is also recommended in pregnancy, with up to three doses recommended during pregnancy, and an additional two post-delivery, as described below (29).

Tetanus vaccination in pregnancy follows a less straight-forward set of guidelines than influenza immunisation, complicating completion of the suggested schedule of doses. In previously unvaccinated pregnant women, a first dose is recommended upon first antenatal clinic attendance, a second at least four weeks following the first yet at least two weeks prior to birth, and then a third dose six months after the second dose, and during the pregnancy. These doses should be followed by an additional fourth and fifth, either a year later or in later pregnancies (29). A minimum of two doses should be administered in women with previously unknown immunisation status (29). As more than half of pregnant women in South Africa only present for antenatal care during their second trimester of pregnancy (30), the likelihood of a woman receiving three tetanus toxoid vaccines during her pregnancy, and therefore completing the schedule, is small.

An additional disease immunised against in pregnancy is pertussis, administered in the form of the tetanus, diphtheria and acellular pertussis (Tdap) vaccine (31). Tdap vaccination is recommended to pregnant women by national health authorities across the globe, however it is not routinely administered in South Africa (7). The risk of pertussis in South Africans is highest amongst infants under the age of one year, with the majority of in-hospital pertussis deaths occurring in infants under the age of six months (32). With an overall case-fatality rate of 4.2%, pertussis poses a significant threat to health in South Africa, disproportionately affecting HIV-positive individuals as well as infants under the age of one year (32). These findings advocate for the addition of Tdap vaccination to the South African maternal immunisation schedule, which is further backed by the success of maternal Tdap vaccination in reducing the burden of pertussis amongst infants in other countries (32). Continued surveillance is necessary in South Africa as it is unclear whether the current burden of disease is in line with pertussis's natural cycle or the result of compromised immunity within the population due to the switch from the whole cell vaccine to the acellular pertussis vaccine (32). Overall, the success of global and local immunisation campaigns reinforce the continued importance of this public health strategy (6).

1.4.2. *Success of Maternal Immunisation: Influenza, Tetanus and Pertussis*

Maternal immunization's success in reducing maternal and neonatal disease burden has garnered the public health strategy widespread advocation (6). McMorrow *et al* found that amongst high risk South African groups, influenza vaccination campaigns averted the most hospitalisations amongst pregnant women relative to other groups, as well as proving cost effective, which in conjunction with the adverse outcomes associated with maternal influenza infection supports the targeting of pregnant women for influenza immunisation (33). In addition, maternal immunisation successfully reduces the risk of influenza infection in neonates for up to six months, estimated to avert 45-63% of neonatal and infant laboratory-confirmed influenza cases (34). This is supported by South African findings, whereby maternal immunisation with the trivalent inactivated influenza vaccine was found to successfully protect neonates for six months following birth, reducing the attack rate of confirmed influenza illness amongst HIV-uninfected mothers from 3.6% to 1.8%, whilst reducing that of HIV-infected mothers from 17.0% to 7.0% (35).

Maternal immunisation programs implemented in the 1980s demonstrated a 96% global reduction of neonatal tetanus-related mortality in 2015, and 79% of the African WHO member countries achieved elimination by 2016 – including South Africa (18,22). In 2018 it was

estimated that 90% of neonates in South Africa were protected at birth through maternal vaccination, and no cases of neonatal tetanus were reported during that year, however these data may exclude rural cases of tetanus that went unreported (21). From the start of January 2020 to the end of April 2020, two cases of neonatal tetanus were recorded in South Africa, with one resulting in death (22). In addition to the above, though not currently practised in South Africa, maternal immunisation against pertussis has proven successful in reducing the burden of disease in infants not yet eligible for immunisation themselves (36).

The implementation of maternal immunisation against pertussis in the United Kingdom following the 2012 pertussis outbreak has demonstrated notable success in targeted groups (37). A notable drop in infant laboratory-confirmed pertussis infections and pertussis-related hospitalizations were observed specifically in the age group targeted by maternal immunisation campaigns, relative to other population groups (37). Vaccine efficacy was observed to be 91% in infants younger than three months whose mothers were vaccinated between 7-28 days before birth, with this level falling when vaccination occurred between six days before to up to two weeks following birth (37). Following the implementation of the maternal pertussis program, a 79% reduction in infant deaths was observed, which was supported by later reviews on the program's efficacy whereby the vaccine was estimated to be 95% effective against infant deaths (36,37). Maternal immunisation against pertussis is further supported in Sandmann *et al*'s mathematical model study, wherein halting the program in the UK would result in an estimated mean hospitalisation of 972 infants annually as opposed to 308 that are currently estimated with the intervention in practice (38). The success of the program has been attributed to two factors: reduction of disease in mothers which reduces exposure of neonates, and transplacental antibody transfer (37).

Evidently, maternal immunisation plays an integral role in improving both maternal and neonatal health, highlighting the importance of establishing what factors influence immunisation in pregnancy. Physiologically maternal immunisation has been determined to be affected by the immunogenicity of the vaccines in pregnancy, transplacental antibody transfer and the timing of vaccination during pregnancy (7).

1.5. Optimal Timing of Maternal Vaccination

1.5.1. *Maternal Tetanus Immunisation*

The optimal window for maternal immunisation to maximise antibody titres in the foetus extends from the second half of pregnancy, peaking in the final month, and is influenced by not

only the afore-mentioned gestational age at birth and maternal IgG titres but also the timing of maternal vaccination during pregnancy (4). The timing of maternal immunisation is a complex matter requiring consideration of who the protection is primarily aimed at (7). As seen in Table 1, the majority of the literature shows that maternal immunisation against tetanus and pertussis is optimal when performed in the late second to early third trimester. Eberhardt *et al's* findings suggest however that earlier second trimester immunisation is superior to that in the third trimester, evidenced by elevated anti-pertussis and anti-filamentous haemagglutinin geometric mean antibody concentrations and seropositivity rates in the earlier immunised infants (39). The importance of these findings lies in allowing for a greater window period for immunisation, potentially minimising the chance of vaccinations being missed or occurring too close to delivery to allow for sufficient transplacental transfer (39). In addition to this, Eberhardt *et al* speculated on the potential benefit this early immunisation would have in the context of preterm infants, which was confirmed in later research (39,40). The Tdap window in the United Kingdom was changed from 28-32 weeks to 20-32 weeks in 2016, and following this policy change a significant reduction whereby premature neonate pertussis hospitalisations were halved was observed (40). There is a lack of literature surrounding not only the timing but also the completion of maternal tetanus immunisation in South Africa, highlighting a gap in the knowledge around maternal tetanus vaccination within the country and factors that may affect it.

1.5.2. *Maternal Influenza Immunisation*

Similarly, limited literature exists around the optimal timing for maternal influenza immunisation, which is thought to be the result of varied recommendations from governing health bodies (41). Overly-complicated and cautious language used in package inserts has the potential to cause reluctance of healthcare professionals to administer influenza vaccines to pregnant women (42). Prior to 2018, influenza vaccine package inserts included statements indicating that lack of foetal harm and adverse impact on reproductive capacity caused by the product had not been excluded, and that immunisation must only take place when absolutely necessary following a risk-benefit assessment, leading to hesitancy to utilise the product during pregnancy despite immunisation committee recommendations (42,43). This is further complicated by the seasonal availability of the vaccine as opposed to continuous access, like in the case of Tdap vaccines. Influenza therefore represents a complex problem in pregnancy, requiring the consideration of how much of the pregnancy will occur during the influenza season in order to ascertain who best to aim the protection at (34). Maternal influenza complication severity is the worst in the third trimester – calling for early gestational

vaccination to maximise protection in the mother, whilst foetal targeting should focus on optimal transplacental antibody transfer windows – which is later in pregnancy (7). First trimester immunisation primarily protects the mother, with neonatal antibody titres comparable to those in infants of unvaccinated mothers. Based on when influenza vaccinations become available, immunisation conferred by the vaccination will protect mothers from adverse events during their pregnancy, who will likely give birth as the influenza season is ending or has elapsed; therefore prioritizing optimal transplacental antibody transfer is unlikely to be a priority given that the infant will be at minimal risk for influenza infection (34).

Later immunisation prioritises the protection of neonates who will likely be born in the influenza season – eliciting high anti-influenza antibodies. Optimal timing for antibody transfer to the foetus is contested, however in terms of eliciting anti-influenza antibodies, second and third trimester immunisation has been established as superior to that in the first trimester (34,44). Interestingly, as seen in Table 1.1, though Zhong *et al* determined a specific timeframe for optimal antibody transfer, Katz *et al* found no significant difference between second and third trimester antibody levels (34,44). This may be explained by the different methods between the studies, whereby Zhong *et al* recruited from all trimesters, whilst Katz *et al's* sample had a minimum gestational age of 17 weeks – not fully encompassing the second trimester. Overall, influenza immunisation during any trimester has been shown to reduce influenza symptoms in both neonates and mothers (45), which supports the continued policy of immunising upon vaccine availability (34). This will allow for the optimal protection of the most vulnerable target, be that the neonate with later immunisation, or the mother with earlier trimester immunisation (34).

Overall, further research is required in the field of optimal maternal immunisation timing, in order to fully assess the benefits associated with vaccination in different trimesters with consideration of who the immunisation will be targeting (46). In addition to this, the comparability of available studies is limited due to differing methods, including measures of assessment and gestational age inclusions within the samples, as seen in Table 1. Despite this, the purpose of the following study is to investigate the timing of maternal immunisation for the purpose of assessing whether pregnant women are presenting early enough to complete the tetanus dose recommendations. Research in resource-limited developing countries such as South Africa should be prioritised in the future, as it is impossible to generalise data from developed countries to these populations due to differences in infrastructure, health care availability and a host of other factors that may be influencing maternal vaccine uptake.

1.6. Factors affecting vaccine uptake in pregnancy in South Africa

1.6.1. *Maternal Vaccine Coverage*

Despite numerous health policies promoting maternal immunisation, and a high acceptability thereof, influenza vaccine uptake remains suboptimal in South Africa, with the estimated coverage in 2015 standing at 14% (26,33,47). Routine antenatal influenza vaccination coverage in South Africa was found to be less than 16% (48,49), with no available data for maternal tetanus vaccination uptake. Despite these levels, Bishop *et al* demonstrated the capacity for maternal immunisation successes through enhanced targeting measures, increasing maternal influenza vaccination coverage to 78.7% at targeted clinic sites between 2015-2018 (49). There is therefore a need for further studies in South Africa to determine actual uptake levels in the absence of targeted immunisation measures.

1.6.2. *Factors Affecting Maternal Immunisation Uptake*

Suboptimal uptake has been linked to fear of adverse outcomes, lower education status and ethnicity in the United Kingdom, whilst the prime cause behind suboptimal vaccine coverage in the United States is believed to be vaccine safety concerns amongst mothers (50,51). The link to ethnicity has also been observed in the United States, with black pregnant women being less likely to be administered an influenza vaccine than white pregnant women (52), however these results cannot be generalised to the South African population – requiring a study into whether ethnicity influences maternal vaccine uptake within the nation. In addition to several of the above-mentioned factors, misinformation also plays a role in maternal vaccine uptake in South Africa; affecting not only the mother's but also their support system's opinion on the safety of vaccination during pregnancy (47).

In rural Kwa-Zulu Natal, care-givers' and partners' perceived acceptability of maternal immunisation plays a major role in pregnant women's vaccine uptake, particularly when the women are financially dependent on these individuals (53). Vaccine uptake is additionally influenced by traditional beliefs which may supersede the perceived value of immunisation schedules (53). Chimukuche *et al* further identified poor service delivery as a modifiable factor hindering maternal immunisation efforts, with study participants complaining of long queues at antenatal clinics, unfriendly attitudes of health care workers and a lack of education around the importance of maternal immunisation (53). In Gauteng vaccine acceptability was found to be high amongst South African women, antenatal health care workers and community leaders, with men being the most wary of vaccines (47).

Table 1.1: Studies Assessing the Optimal Timing of Maternal Immunisation for Influenza and tetanus, diphtheria and acellular pertussis vaccinations

Study period	Country	Vaccine	Study Design	Sample	Neonatal measures	Optimal timing (weeks)	Compares all 3 trimesters	Reference
2013-2016	United Kingdom	Influenza	Prospective cohort	96	HAI	24-36	Yes	(34)
2011-2013	Rural Nepal	Influenza	Randomised control	3693	HAI	N/A	No	(44)
2016-2018	India	Influenza	Retrospective cohort	346	Influenza symptoms	N/A	Yes	(45)
2014	Switzerland	Tdap	Prospective observational non-inferiority	335	ELISA	13-25	No	(39)
2013-2014	Israel	Tdap	Prospective observational	61	ELISA	27-30	No	(54)
2013-2014	North America	Tdap	Prospective observational cohort	626	ELISA	27-30	No	(55)
2014-2018	United Kingdom	Tdap	Retrospective cohort	346	Hospitalisations	20-32	No	(40)
2013-2014	United States of America	Tdap	Retrospective cohort	74504	Pertussis infections	27-36	Yes	(56)
2014	Australia	Tdap	Randomised control	116	ELISA	28-32	No	(57)

HAI: Haemagglutination Assay, ELISA: Enzyme-linked Immunosorbent Assay, Tdap: Tetanus diphtheria acellular pertussis

Age was also found to be influential in vaccine uptake, with younger pregnant women less likely to get vaccinated due to visiting antenatal facilities too far into their pregnancies (47).

In addition to personal factors, timing complications relating to the tetanus vaccination strategy may impair adequate uptake levels, as completion may be challenging in patients presenting for antenatal care for the first time at later stages of pregnancy. Poor attendance of antenatal care visits has been identified as a barrier to maternal immunisation in developing countries (58). In Malawi, low coverage of antenatal visits amongst other factors such as socioeconomic status and parity were found to influence maternal immunisation uptake, however no comparable literature is available for South Africa (58). Similar findings were observed in the Ivory Coast, with higher parity found to be negatively associated with tetanus vaccine uptake, whilst increasing age was positively associated with maternal tetanus immunisation (59). The 2019 Ivory Coast study further identified a positive association between increased antenatal care visits and the uptake of the tetanus toxoid vaccine, with women attending at least four antenatal visits having an OR of 2.347 compared to women with less visits (59). A similar association was identified whereby having at least four antenatal visits significantly increased the odds of sufficient tetanus toxoid dose uptake, with an OR of 2.347 (95% CI: 1.384–3.981) relative to women with less than four antenatal visits (59). These observations were only true of rural-residing women and not of urban-residing women (59), and cannot be extrapolated to South Africa due to cultural and infrastructure differences.

In terms of antenatal care coverage, a 2015 study from Eswatini found a high usage rate of 97.3%; however this study utilised data from 2006 to 2007, therefore is out of date (60). South African antenatal care guidelines are in line with those suggested by the WHO, as described in Table 1.2, recommending a total of eight visits. Recent data available within South Africa regarding antenatal care coverage shows that of the recommended 8 antenatal contact visits, pregnant women attended an average of 5.9 in the public sector (61). This study did not however examine maternal immunisation uptake and whether or not this correlated to the number of antenatal care visits, suggesting the need for further research in the country, and whether this high antenatal visit coverage observed in 2016 remains accurate is yet to be determined. Another variable of consideration possibly affecting maternal vaccination uptake is human immunodeficiency virus (HIV) status (62).

Table 1.2 : Antenatal Visit Recommendations According to the World Health Organisation (63)

	Timing							
Trimester	**1**	**2**		**3**				
Visit number	1	2	3	4	5	6	7	8
Schedule (weeks)	≤12	20	26	30	34	36	38	40

Maternal HIV status may affect vaccine uptake, however data investigating such are limited. Positive HIV status was found to be negatively associated with influenza and tetanus vaccination uptake amongst pregnant women in the United States of America (62), however the HIV group made up a small proportion of the sample, limiting the statistical power of the finding. In addition, the study cannot be generalised to a South African population with different health-seeking behaviours and health care practices. Only one South African study has examined the effect of HIV status on maternal vaccination uptake, and though it found HIV status to have no relation to vaccine uptake, it was conducted in an environment wherein uptake was purposefully promoted, therefore it may not reflect standard conditions and may have masked any association between the variables (49). The HIV burden in South Africa is high and these individuals are at an increased risk of adverse influenza outcomes, with an increased risk of influenza-associated mortality (64), however little literature exists examining the effect of HIV status on maternal vaccination uptake in South Africa, highlighting a key gap in the knowledge.

1.7. Conclusion

Current literature on the timing of maternal immunisation is limited and contested, with poor comparability levels between studies. The literature is even more limited regarding factors that may be influencing maternal vaccine uptake in developing countries, particularly on the African continent. There is therefore a need for African research into the optimal timing of maternal immunisation, uptake coverage, and factors that may be influencing these variables such as antenatal care visit attendance and HIV status. This highlights the importance of the study: Maternal vaccination in South Africa: timing and completeness, as this will give updated information on maternal vaccine coverage and the completion of the recommended schedule, as well as the timing of immunisation from 3 urban sites in Gauteng and the Western Cape. Outputs from this study, which utilised data collected in a retrospective record review, describe the uptake of influenza and tetanus vaccines in antenatal attendees at public healthcare facilities. Study results will be useful for identifying limitations and challenges associated with maternal

immunisation and enable scientifically supported communication strategies and training to encourage uptake and improve acceptance of maternal immunisation in South Africa.

1.8. Study Aims & Objectives

1.8.1. *Aims:*

1. Assess the uptake and adherence to the maternal immunisation government schedule in South Africa.
2. Determine factors affecting maternal immunisation within the South African population.

1.8.2. *Objectives:*

- Describe the uptake and timing (gestational age) of influenza vaccines amongst pregnant women in 3 regions of South Africa: Soweto, Inner city Johannesburg and Metro East Cape Town.
- Describe the uptake, timing (gestational age) and completeness of tetanus vaccines amongst pregnant women in 3 regions of South Africa: Soweto, Inner city Johannesburg and Metro East Cape Town.
- Estimate the effect of demographic and clinical factors on the uptake of influenza and tetanus vaccines amongst pregnant women in 3 regions of South Africa: Soweto, Inner city Johannesburg and Metro East Cape Town.

Chapter Two: Methods

2.1. Ethics Approval

Permission to conduct the study was obtained from the University of the Witwatersrand's Human Research Ethics Committee, independently of the parent project, reference number: M211181 MED21-11-044. Ethics for the parent project was obtained from both the University of the Witwatersrand and Stellenbosch University Human Research Ethics Committees, with the following respective reference numbers: 180707 and N18/10/122.

2.2. Study Design

The study design was a retrospective review of medical maternity charts. This was a secondary analysis of a dataset that was established by the parent project: Epidemiology of obstetric and neonatal outcomes in South Africa.

2.3. Sample

The study participants comprised of 9371 pregnant women who gave birth at any of the following sites between the period of 1st July 2017 and 30th June 2018:

In the Gauteng province:

- in Soweto: Chris Hani Baragwanath Academic Hospital, Bheki Mhlangeni Hospital, 5 Midwife Obstetric Units (Lillian Ngoyi, Chiawelo, Zola, Michael Maponya, Mofolo)
- in Inner City Johannesburg: Charlotte Maxeke Johannesburg Academic hospital and Shandukani Midwife Obstetric Unit

In the Western Cape province:

- in Metro East Cape Town: Tygerberg, Khayelitsha, Helderberg, and Karl Bremer hospitals and the Midwife Obstetric Unit: Michael Mapongwana Community Health Centre.

The principal investigators for the above sites were Dr Clare Cutland (Soweto), Professor Lee Fairlie (Inner City Johannesburg) and Dr Shaun Barnabas (Metro East Cape Town). There were no exclusion criteria for the parent project sample; provided the women gave birth within the established time frame their records were used in the study.

2.4. Procedure

For this study, previously collected data from the parent project, 'Epidemiology of obstetric and neonatal outcomes in South Africa', Wits HREC 180707, U.Stellenbosch HREC

N18/10/122, were utilised. The parent study collected maternity chart data for randomly selected deliveries at study sites, during the period of 1st July 2017 and 30th June 2018. Data pertaining to maternal, foetal and neonatal health and antenatal care visits were abstracted from the maternity charts and captured on the Research Electronic Data Capture (Redcap) database (65).

This project consisted of a secondary analysis of pre-existing data from the parent database. Pertinent variables from the parent project database were selected for this study. These included data variables necessary for assessing the timing and uptake of both influenza and tetanus vaccination amongst pregnant women, and possible demographic and clinical factors affecting maternal immunisation uptake.

2.4.1. *Variable Definitions*

Outcome Variables

The dependent variables of the study included:

- the uptake of the influenza vaccine in pregnancy, a binary variable;
- the completion of the tetanus immunisation schedule in the index pregnancy, a binary variable split into either complete (three doses) or incomplete (one to two doses);
- the timing/gestational age of tetanus vaccination (first, second or third trimester) and influenza vaccination (trimesters and in season versus out of season), categorical variables;
- the number of tetanus doses received (one, two or three doses), a categorical variable.

Explanatory Variables

- Maternal age variable was established by taking the maximum age value recorded for each participant in their maternity record (latest recorded age at any visit) which was then categorised into five groups: ≤20 years, 21-30 years, 31-40 years, women aged ≥ 41 years, and women of unknown age.
- The region variable was split according to study site, with the Soweto (Wits-VIDA) and Inner-City Johannesburg (WRHI) representing Gauteng, and the Metro East Cape Town (FAMCRU) site representing the Western Cape.
- Tobacco smoking, drug usage and alcohol usage during pregnancy were described categorically by defining status according to user, non-user, quitter or unknown.
- The history of other vaccine uptake was defined as either yes, no or unknown.

- Race was categorised into six groups encompassing the four commonly reported groups within the country: Black African, Coloured, Indian/Asian and White, as well as other and unknown (66).
- Birth history was described using parity and gravidity which were categorised numerically, and included an unknown category. Women with a recorded gravidity of zero were recategorized as unknown due to the impossibility of such pertaining to this study.
- Gestational age at the booking visit was categorised according to trimester, first (<12 weeks); second (13-26 weeks) or third (27-48 weeks). Any value below zero or above 48 weeks were categorised as unknown due to the improbability/impossibility of such.
- Gestational age at delivery was categorised according to pre-term and not viable (<28 weeks), preterm but viable (29-36 weeks), term (37-42 weeks) and post-term (43-48 weeks) (67). Women with a gestational age above 48 weeks or below zero were categorised as unknown due to these ages being highly improbable or impossible.
- The season of delivery used in the influenza uptake analysis was divided into two groups: in season, from when the vaccine is typically available in South Africa to the later end of flu season (from April to September) and out of season (October to March) (27,28).
- In addition, the overall cohort was analysed by the variable 'visits in influenza vaccine season', which was binary and categorised as yes or no. The 'visits in influenza vaccine season' variable defined mothers who attended at least one antenatal visit during the period of national influenza vaccine availability. The vaccine availability period was established as having commenced in April for both 2017 and 2018 (W. Ramkrishna, personal communication, July 29th 2022). In 2017 the end of the period was designated to be the 31st of July, given that the influenza peak is typically seen at the commencement of July (28), therefore vaccine administration beyond this point is improbable. The end of the vaccine period in 2018 was the end date for the study, June 30th.

Further categorical variables included: pre-existing medical conditions, HIV status and number of antenatal care visits.

2.4.2. *Calculated Variables*

The gestational age at immunisation was established for both influenza and tetanus doses. This was calculated by determining the difference in weeks between the recorded gestational age at

booking to the date of the respective vaccine doses. This difference was then added to the gestational age in weeks at booking and categorised according to trimester. Following the establishment of the gestational age at each tetanus dose, the intervals between dose administrations were assessed to determine whether immunisation guidelines were adhered to. This analysis was performed on individuals with two and three tetanus doses. Correct adherence was defined as individuals having at least four weeks between their first and second dose, and at least 24 weeks between doses two and three (29). Individuals with correct intervals were distinguished from those with incorrect intervals between all doses, between doses one and two, or doses two and three.

2.5. Exclusions

Women were excluded from the sample if they lacked an antenatal booking visit, as these women presented at a clinic for the first time when they were delivering, therefore lacked data pertaining to antenatal care visits that was relevant to the study.

2.6. Data Analysis

The data were analysed using version 16.1 of the statistical software STATA (StataCorp, Texas, United States). The distribution of the following continuous variables was established by assessing skewness and kurtosis: maternal age, the number of ANC visits, and gestational age at both the booking and delivery visits. These variables were not normally distributed, (maternal age, number of ANC visits, gestational age at delivery – right skewed; gestational age at booking – left skewed) and the data were subsequently expressed using the median and interquartile ranges (IQRs). The variables were compared between the respective groups (influenza and tetanus samples) using the Wilcoxon rank-sum test. The effect of the explanatory variables (including the categorised continuous variables) on the binary outcome variables were analysed using univariate logistic regression. The data are described using odds ratios with a 95% confidence interval. A p-value of less than 0.05 was considered to be significant for all statistical tests.

Percentages were used to describe the following:

- Proportion of women immunised against influenza: number of women who presented per month who were immunised against influenza across the three study sites as a percentage of all women who presented for antenatal care in that month and had not yet received an influenza vaccine for that season.

- Proportion of women who were immunised in their first, second or third trimester: number of women immunised within defined trimesters in the vaccine availability periods over the number of women immunised within the respective vaccine availability period.
- Proportion of women who were immunised in their first, second or third trimester with their first tetanus dose according to their dose completion and gravidity: number of women immunised in their first tetanus dose in defined trimesters over the number of number of women who received only one dose, two doses or three.
- Proportion of women with correct adherence to the timing guidelines between tetanus doses in women who received two doses: the number of women vaccinated within correct or incorrect time frames over the number of women who received two doses in their pregnancy.
- Proportion of women with correct adherence to the timing guidelines between tetanus doses in women with the complete schedule administered during their pregnancy: the number of women vaccinated within correct or incorrect time frames over the number of women who received three doses in their pregnancy.

Chapter Three: Results

3.1. Sample Characteristics

A total of 9371 mothers were recorded on the study database, of which 375 (4.0%) were excluded; all had no antenatal booking visits. The demographic, followed by the clinical characteristics of the remaining 8996 participants are presented in Table 3.1, ordered according to the format of an antenatal card from which the data were extracted. Most of the sample originated from Gauteng study sites (85.88%), and most of the participants had a maximum recorded age of between 21-30 years old. The sample consisted primarily of African women (96.87%), with minor representation of other races within the group. Most of the women reported no pre-existing medical conditions (89.62%), with an HIV prevalence of 28.01% and reported use of teratogenic substances (smoking, recreational drugs or alcohol) of 3.96%, 0.45% and 7.17% respectively. The majority (79.74%) of the women attended at least four antenatal care visits, with 61.63% of women presenting in their second trimester for their booking visit. Of the population, 71.81% of the women had been pregnant at least once before participation in the study, with only 32.36% of the participants being nulliparous. Most of the women delivered live neonates (98.09%) with birthweights within a normal range (84.72%), more commonly via vaginal than caesarean delivery (63.31% as opposed to 36.69%) (Table 3.1).

3.2. Influenza Analysis

3.2.1. *Factors Affecting Influenza Immunisation During Pregnancy*

Of the 8996 participants, data on influenza uptake were available for 6941 (77.16%), with the remaining 2055 having no influenza immunisation recorded in their maternity chart. Of these 6941 women, 4851 (69.89%) had at least one antenatal visit during the vaccine availability period (01/04/2017-31/07/2017 or 01/04/2018-30/06/2018), whilst 2090 (30.11%) did not. These 2090 women were excluded from the subsequent influenza analysis to reduce bias. The median gestational age at booking of the influenza immunised group was 18.00 (13.00-23.00), similar to that of the non-immunised group: 18.14 (12.85-23.00) weeks, ($P>0.05$) (Table 3.2). Women who presented in their third trimester were significantly less likely to receive the influenza vaccine than women who presented in their first trimester (OR: 0.73, CI: 0.55-0.98), with no significant differences in the second trimester relative to the first ($P>0.05$). The median age of women who received the influenza vaccine was 27.30 (23.36-31.73) years, whilst that of women who did not receive the influenza vaccine was 27.53 (23.30-32.56) years, ($P=0.38$).

Table 3.1: Maternal characteristics of the population.

Variable	**Total**	**Percentage**
Total	**8996**	**100%**
Region		
Soweto	5189	57.68
Inner City Johannesburg	2505	27.96
Metro East Cape Town	1265	14.12
Maternal age (years)		
Median (IQR)	27.67 (23.42-32.70)	
≤20	819	10.09
21-30	4400	54.23
31-40	2543	31.34
≥41	351	4.33
Race		
Black African	7405	96.87
Coloured	144	1.88
Asian/Indian	51	0.67
White	12	0.16
Other	32	0.42
Pre-existing medical conditions		
None reported	7526	89.62
Hypertension	206	2.45
Asthma	88	1.05
Tuberculosis	49	0.58
Known allergy	39	0.46
Diabetes	35	0.42
Epilepsy	28	0.33
Cardiac condition	25	0.30
*Other**	113	1.35
HIV status		
Negative	6063	71.99
Positive	2359	28.01
Smoking		
Non-user	6840	94.15
User	288	3.96
Quitter	137	1.89
Recreational drug use		

Non-user	6107	98.61
Quitter	58	0.94
User	28	0.45
Alcohol consumption		
Non-user	6321	86.93
User	521	7.17
Quitter	429	5.90
Number of ANC visits		
(Median [IQR])	6 (4-7)	
1	525	5.91
2-3	1275	14.35
4-5	2582	29.05
5-7	2745	30.88
≥8	1761	19.81
Gestational age at 1st ANC visit		
Median (IQR)	19.85 (14.00-25.00)	
1st trimester	1640	18.96
2nd trimester	5330	61.63
3rd trimester	1679	19.41
Parity		
0	2887	32.36
1	3063	34.33
2-3	2684	30.09
4-5	270	3.03
≥6	17	0.19
Gravidity		
1	2514	28.19
2-3	4927	55.25
4-5	1313	14.72
≥6	164	1.84
Gestational age at delivery		
Median (IQR)	38.57 (36.57-40.00)	
≤28 weeks	205	2.56
29-36 weeks	1592	19.90
37-42 weeks	6038	75.47
43-48 weeks	166	2.07
Neonate status at delivery		
Liveborn	8607	98.09

Stillborn	168	1.91
Mode of delivery		
Vaginal	5769	63.31
Caesarean	3344	36.69
Birth weight (grams)		
Median (IQR)	3085 (2750-3400)	
Underweight (150-2500)	1379	15.28
Normal weight (2503-5400)	7645	84.72
Visits in influenza vaccine season		
Yes	4851	69.89
No	2090	30.11

*Other - medical condition not specified on the antenatal card.

Visits in influenza vaccine season: Yes: between 01/04/2017-31/07/2017 or 01/04/2018-30/06/2018, No: outside of these dates.

Totals may not match overall total due to missing data.

Women aged 21-30 years were more likely to have received an influenza vaccination compared to women of ≤20 years of age (P<0.05). Women between the ages of 31-40 years had a 14.46% influenza vaccine uptake with the difference relative to those aged ≤20 years not found to be significant (13.54%) (P>0.05). No significant difference was observed between women older than 41 years and the comparison age group, with women older than 41 years having an influenza uptake prevalence of 10.19%. No significant associations were found between influenza uptake and race, pre-existing medical conditions, HIV status, smoking or recreational drug use (P>0.05). In addition, no significant associations were found between influenza immunisation and categories for parity or gravidity (P>0.05) (Table 3.2).

Between mothers who consumed alcohol and non-users and quitters, non-users and quitters were significantly less likely to receive an influenza vaccine during their pregnancy compared to women who used alcohol during their pregnancy (OR: 0.64, CI: 0.48-0.87; OR: 0.63, CI: 0.40-0.9 respectively) (Table 3.2). Alcohol use by site amongst mothers with confirmed influenza uptake was 17.95% (7/39) at Metro East Cape Town, 4.96% (6/121) at Inner-City Johannesburg and 7.45% (48/644) at Soweto. There were significant differences between regions for influenza vaccine uptake; mothers from the Gauteng sites (Soweto and Inner-City Johannesburg) were less likely to receive influenza immunisation during pregnancy compared to women at the Western Cape site (Metro East Cape Town) (OR: 0.28, CI: 0.18-0.44 0.23; OR: 0.11, CI: 0.07-0.18 respectively) (Table 3.2). A large amount of data were missing for the

Metro East Cape Town site, with only 95 out of 1265 (7.51%) women having recorded influenza uptake data.

Women with reported influenza immunisation data who had six or more antenatal care visits had significantly greater odds of receiving the influenza vaccine compared to women with only one antenatal visit (OR: 1.79, CI: 1.05-3.06 for 6-7 visits; OR: 2.01, CI: 1.17-3.46 for ≥8 visits). There was no significant difference in the likelihood of receiving the influenza vaccine between mothers who had one antenatal visit and mothers who had between two to five visits, despite these women exhibiting slightly higher vaccine uptake relative to women with only one visit. Women who received a dose of the tetanus vaccine during pregnancy were less likely to receive the influenza vaccine during pregnancy when compared to women who did not receive the tetanus vaccine at all (OR: 0.04, CI: 0.02-0.07) (Table 3.2).

Table 3.2: Comparison of demographic and clinical characteristics between mothers who attended at least one ANC visit during the influenza vaccine availability period (01/04/2017-31/07/2017 or 01/04/2018-30/06/2018) stratified according to influenza vaccine uptake.

		Influenza Vaccine Uptake				
	Total	**Yes**		**No**		
Variable		**N**	**Row %**	**N**	**Row %**	**OR (95% CI)**
Total	**4851**	**806**	**16.62**	**4045**	**83.38**	
Maternal age (years)						
Median (IQR)		27.30 (23.36-31.73)		27.53 (23.30-32.56)		
≤20	485	62	13.54	396	86.46	Reference
21-30	2428	447	18.41	1981	81.59	1.44 (1.08-1.92)*
31-40	1342	194	14.46	1148	85.54	1.08 (0.79-1.47)
≥41	108	11	10.19	97	89.81	0.72 (0.37-1.43)
Race						
Black African	4006	664	11.72	3342	83.42	1.72 (0.52-5.71)
Coloured	86	9	7.56	77	89.53	1.01 (0.25-4.03)
Asian/Indian	29	3	10.34	26	89.66	Reference
White	5	0	0.00	5	100.00	1
Other	21	5	23.81	16	76.19	2.71 (0.57-12.90)
Region						
Soweto	3333	644	19.32	2689	80.68	0.28 (0.18-0.44)*
Inner City Johannesburg	2121	121	8.55	1295	91.45	0.11 (0.07-0.18)*

Metro East Cape Town	95	39	45.88	46	54.12	Reference
Pre-existing medical conditions						
None reported	4263	721	16.91	3542	83.09	1.20 (0.94-1.54)
Hypertension	100	10	10.00	90	90.00	0.55 (0.29-1.07)
Asthma	47	4	8.51	43	91.49	0.46 (0.17-1.30)
Known allergy	27	7	25.93	20	74.07	1.76 (0.74-4.18)
Tuberculosis	16	5	31.25	11	68.75	2.29 (0.79-6.61)
Diabetes	12	0	0.00	12	100.00	1
Epilepsy	14	3	21.43	11	78.57	1.37 (0.38-4.92)
Cardiac condition	7	1	14.29	6	85.71	0.84 (0.10-6.96)
*Other**	42	8	19.05	34	80.95	1.18 (0.55-2.56)
Unknown	277	35	12.64	242	87.36	0.71 (0.50-1.03)
HIV status						
Negative	3383	561	16.58	2822	83.42	0.95 (0.79-1.13)
Positive	1215	211	17.37	1004	82.63	Reference
Smoking						
Non-user	3674	601	16.36	3073	83.64	1.07 (0.70-1.64)
User	168	26	15.48	142	84.52	Reference
Quitter	81	17	20.99	64	79.01	1.45 (0.74-2.86)
Recreational drug use						
Non-user	3205	494	15.41	2711	84.59	0.59 (0.27-1.32)
Quitter	34	8	23.53	26	76.47	Reference
User	16	4	25.00	12	75.00	1.08 (0.27-4.31)

Alcohol consumption						
Non-user	3410	544	15.95	2866	84.05	0.64 (0.48-0.87)*
Quitter	250	39	15.60	211	84.40	0.63 (0.40-0.98)*
User	268	61	22.76	207	77.24	Reference
Parity						
0	1639	291	17.75	1348	82.25	Reference
1	1634	281	17.20	1353	82.80	0.96 (0.80-1.15)
2-3	1392	208	14.94	1184	85.06	0.81 (0.67-0.99)
4-5	138	19	13.77	119	86.23	0.74 (0.45-1.22)
≥6	10	2	20.00	8	80.00	1.16 (0.24-5.48)
Gravidity						
1	1430	261	18.25	1169	81.75	Reference
2-3	2636	443	16.81	2193	83.19	0.90 (0.76-1.07)
4-5	664	88	13.25	576	86.75	0.68 (0.53-0.89)*
≥6	84	8	9.52	76	90.48	0.47 (0.22-0.99)
Vaccination uptake history						
Yes	28	1	3.57	27	96.43	Reference
No	4778	781	16.35	3997	83.65	5.28 (0.72-38.87)
Tetanus vaccine uptake						
Yes	4781	747	15.62	4034	84.38	0.04 (0.02-0.07)*
No	68	57	83.82	11	16.18	Reference
Number of ANC visits						
1	144	16	11.11	128	88.89	Reference

2-3	529	62	11.72	467	88.28	1.06 (0.59-1.90)
4-5	1424	205	14.40	1219	85.60	1.35 (0.78-2.31)
6-7	1688	309	18.31	1379	81.69	1.79 (1.05-3.06)*
≥8	1065	214	20.09	851	79.91	2.01 (1.17-3.46)*
Gestational Age at 1st ANC visit						
Median (IQR)		18.00 (13.00-23.00)		18.14 (12.85-23.00)		
1st trimester	1068	173	16.20	895	83.80	Reference
2nd trimester	3006	532	17.70	2474	82.30	1.11 (0.92-1.34)
3rd trimester	598	74	12.37	524	87.63	0.73 (0.55-0.98)*
Season of delivery						
Influenza season (Mar-Sep)	3421	660	19.29	2761	80.71	2.10 (1.74-2.54)*
Out of season (Oct-Feb)	1430	146	10.21	1284	89.79	Reference
Estimated delivery season						
Influenza season (Mar-Sep)	2825	558	19.75	2267	80.25	1.94 (1.61-2.33)*
Out of season (Oct-Feb)	1510	170	11.26	1340	88.74	Reference

The reference group for pre-existing medical conditions is women who did not have the condition.

*Other - medical condition not specified on the antenatal card.

Statistical significance $p<0.05$ indicated by '*'. IQR: interquartile range; N: population; ANC: antenatal care.

Wilcoxon rank-sum test and logistic regression were used to assess intervariable relationships and statistical significance thereof.

N varies in the population due to some participants lacking data on the variable in question.

Totals may not match overall total due to missing data.

Fifty seven women of 806 (7.07%) immunised against influenza had no reported TTV uptake. Of these 57 women, 51 (89.47%) had less than three prior pregnancies, and six (10.53%) had a parity of three or more. Women without influenza immunisation during their index pregnancy were significantly more likely to have a completed TTV schedule compared to women who received the influenza vaccine (OR: 1.43, CI: 1.07-1.90) (Table 3.4). Of 806 women with influenza vaccine uptake and ANC visits within the influenza season, 747 (92.78%) received both the tetanus and flu vaccines (Table 3.2), whilst of 7031 women with TTV uptake only 760 (10.81%) received both vaccines during their pregnancy (Table 3.4). Co-administration of the influenza and tetanus vaccines occurred within the sample, with 279 women of 760 (36.71%) receiving a flu vaccine and their first TTV dose at the same time, 106 (13.95%) receiving the flu vaccine at the same visit as their second tetanus dose, and 64 (8.42%) receiving it concurrently with their reported third TTV dose.

More vaccinations were done at Soweto compared to Inner City Johannesburg and Metro East Cape Town (Figure 3.1). A greater number of vaccines were administered before the spike in influenza cases across all sites, with the greatest number of vaccines administered in April of both 2017 and 2018 compared to other months of the year. The percentage of women who were immunised out of those eligible who presented for an antenatal visit at the sites by month is described in Figure 3.2, demonstrating the efficiency of each site at immunising eligible mothers presenting for antenatal care before, during, and after the influenza season. Eligibility of women was determined by whether they had yet received a vaccine in either the 2017 vaccine season or the 2018 season, respectively, commencing in April when the vaccines were rolled out. Metro East Cape Town vaccinated the greatest proportion of women, peaking at 50%, compared to Soweto and Inner-City Johannesburg with respective maximum coverage of 14.89% and 6.51%. As expected, all sites demonstrated an increase in the proportion of women immunised around the time of the respective 2017 and 2018 influenza seasons (Figure 3.2). Soweto and Inner-City Johannesburg coverage ranged from 1.33%-14.89% and 0.45%-6.51% in the 2017 vaccine period from 01/04/2017-31/07/2017. During the 2018 period (01/04/2018-30/06/2018) coverage did not exceed 5% at either site (Figure 3.2). Coverage at Metro East Cape Town ranged between 0%-31.25% and 5.77%-50% in the 2017 and 2018 periods respectively (Figure 3.2).

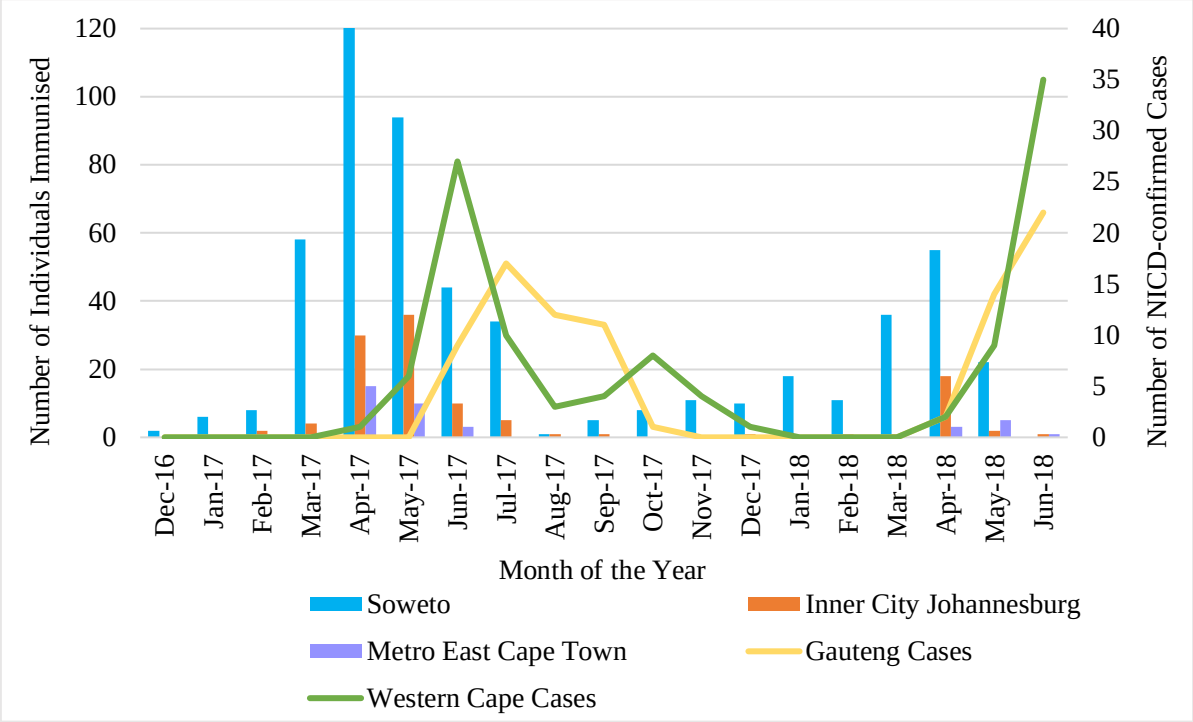

Figure 3.1: Influenza immunisation during pregnancy across study sites relative to monthly NICD-confirmed provincial influenza cases, among those with at least one reported visit during the vaccine availability period (01/04/2017-31/07/2017 or 01/04/2018-30/06/2018) between December 2016 - June 2018 (C. Cohen, personal communication, June 15th 2022).

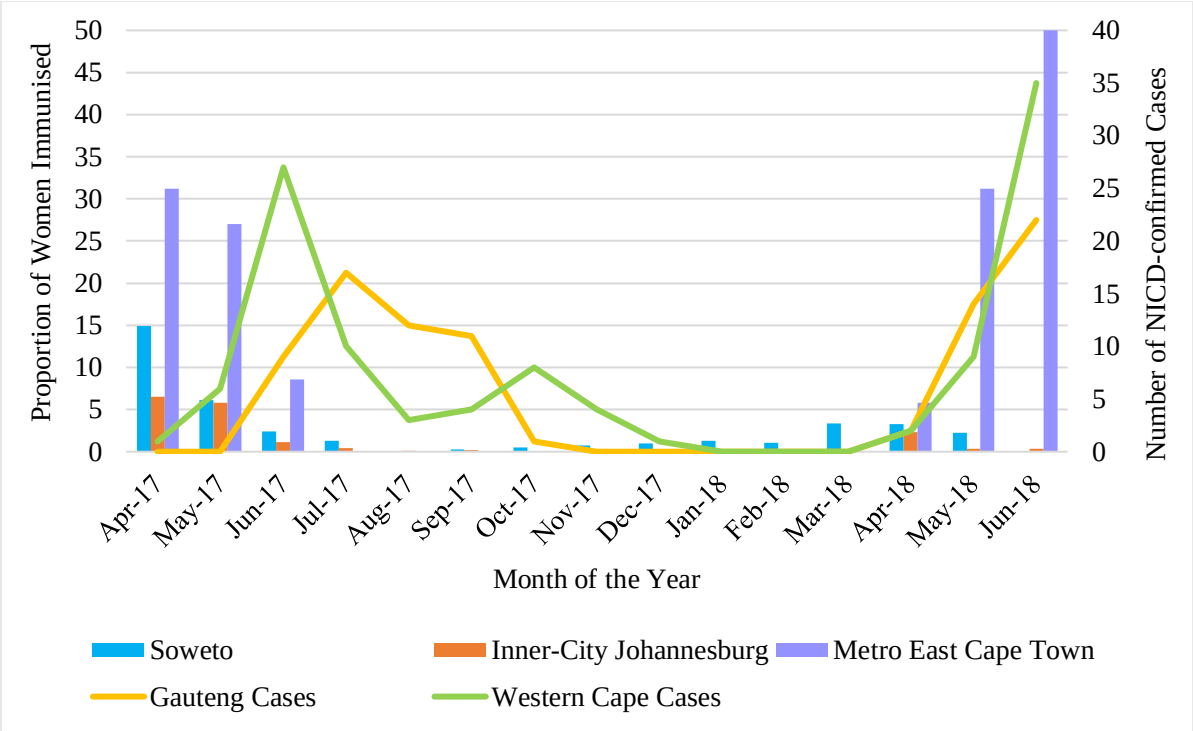

Figure 3.2: Proportion of women in each month immunised against influenza among those eligible* with at least one reported visit during the vaccine availability period (01/04/2017-31/07/2017 or 01/04/2018-30/06/2018), between April 2017-June 2018 across study sites relative to monthly NICD-confirmed influenza cases (C. Cohen, personal communication, June 15th 2022). (**eligible: women who had not yet received an influenza vaccine for that season from the vaccine rollouts in April 2017 & 2018.)*

3.2.2. *Timing of Influenza Immunisation*

Of the 806 women immunised against influenza, 414 (51.36%) were immunised at their antenatal booking visit, with 390 (48.38%) immunised at a follow-up visit and only two women (0.25%) received the influenza vaccine upon admission for delivery. Women whose estimated delivery date fell within the influenza season (between April and September) had a significantly increased odds of receiving an influenza vaccine during their pregnancy compared to women with estimated due dates between October and March (OR: 1.94, CI: 1.61-2.33). (Table 3.2). In line with this observation, women with actual delivery dates for within the influenza season had significantly increased odds of influenza immunisation compared to women who delivered outside of the season (OR: 2.10, CI: 1.74-2.54). Of 806 participants with influenza uptake in their pregnancy, data on the gestational age at influenza immunisation and season of immunisation were available for 708 (87.87%) (Figure 3.3). Most women with visits during the vaccine availability period were vaccinated within the period (530/708, 74.86%), however 25.14% (178/708) were vaccinated outside of the period. Most immunisations occurred during the second and third trimesters of pregnancy both 'in season' (93.2%) and 'out of season' (91.0%), with less than ten percent of immunisations occurring in the first trimester, both within and outside of the vaccine availability period (Figure 3.3).

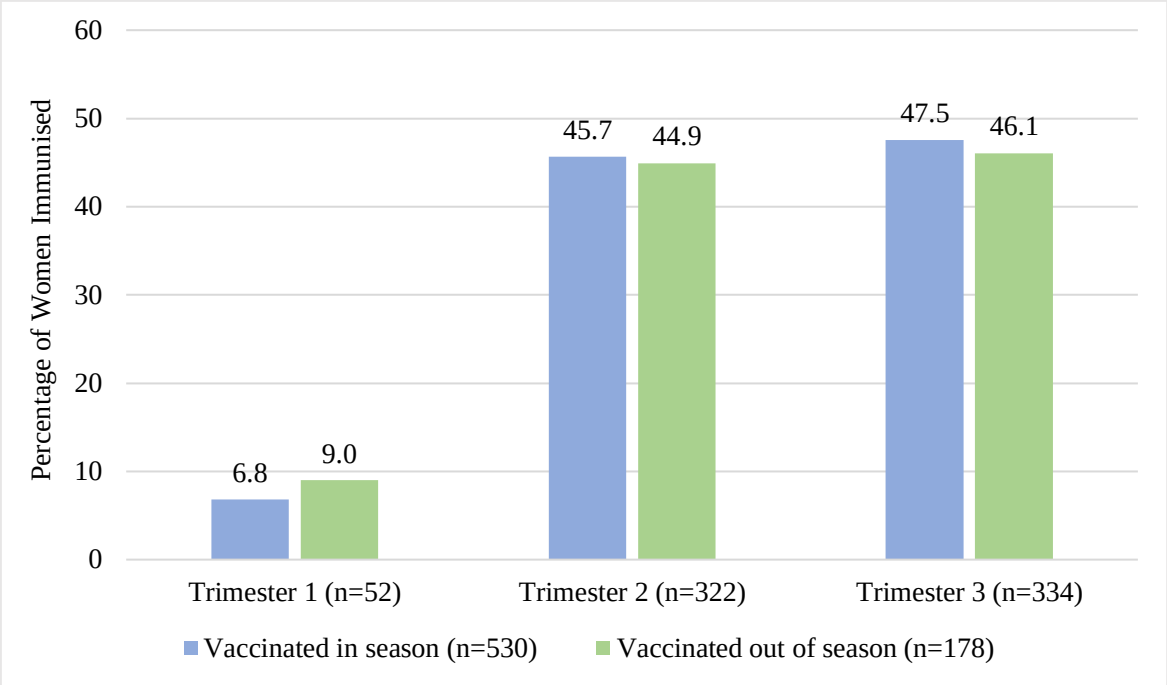

Figure 3.3: Proportion of 708 participants vaccinated against influenza according to trimester among those with at least one ANC visit during the influenza vaccine availability period (01/04/2017-31/07/2017 or 01/04/2018-30/06/2018). (**in season vaccination was during the vaccine availability period, out of season was outside of these dates*).

3.3. Tetanus Immunisation Analysis

3.3.1. *Factors Affecting Tetanus Immunisation During Pregnancy*

Of the 8996 participants, tetanus immunisation data were available for 7105 (78.98%) participants. Of these participants, medical records of 74 (1.04%) recorded no receipt of tetanus immunisation at all during the pregnancy and were subsequently excluded from the comparison analysis. The majority of women with no tetanus toxoid vaccination (TTV) uptake were African (55/57, 96.49%) and from the Metro East Cape Town (44/74, 59.49%) or the Soweto (27/74, 36.49%) sites (Table 3.3). The median age of TTV unvaccinated women was 27.31 (IQR: 23.62-28.87), with the majority of women aged between 21-30 years (56/70, 80.00%). Most women reported no pre-existing medical conditions (57/74, 77.03%), and a 43.28% (29/67) prevalence of HIV was observed amongst these participants. The use of teratogenic substances was low, however not absent, with 5.08 (3/59) being smokers, 1.92% (1/52) using recreational drugs and 16.95% (10/59) consuming alcohol during their pregnancy. The 74 unvaccinated women had a median of 7 (IQR: 5-8) antenatal visits during their pregnancy, with the majority having five or more visits (55/74, 74.32%). The median gestational age at the booking visit was 16.14 (IQR: 11.00-23.29) weeks, with most women presenting for booking in the second trimester (39/71, 54.93%). Most of the participants with no TTV uptake had a parity of less than four (73/74, 98.65%) and 86.48% (64/74) had a gravidity of less than four.

Of the 7031/8996 (78.16%) women who had TTV uptake recorded in their maternity charts, 90.30% (6349/7031) had an incomplete TTV status and 9.70% (682/7031) had a complete schedule of doses in their pregnancies at the time of the study (Table 3.4). Of those with incomplete TTV status, 2759/7031 (39.24%) had one dose only and 3590/7031 (51.06%) had two doses. Women with incomplete TTV status were significantly older (median age 27.72 years (IQR: 23.45-32.71)) than those with complete TTV status (26.68 years (IQR: 22.24-31.58)) ($P<0.01$). Compared to younger women ($\leq$20 years), women aged 31-40 years at their booking visit, were significantly less likely to achieve a complete TTV status during their index pregnancy (OR: 0.64, CI: 0.48-0.84). Aside from low TTV completion amongst women with hypertension (5/132, 3.79%) compared to those without hypertension (OR: 0.36, CI: 0.15-0.89), no other medical conditions were found to be significantly associated with tetanus uptake in pregnancy. Having a parity of greater than zero demonstrated significantly decreased odds of TTV completion, among women with a parity of one (198/2401, 8.25%), between two to three (187/2088, 8.96%); and between four and five (11/215, 5.12%) compared to women with a parity of zero (OR: 0.63, CI: 0.52-0.76; OR: 0.69, CI: 0.57-0.84; OR: 0.38, CI: 0.20-0.70 respectively).

Table 3.3: Clinical and demographic characteristics of mothers with no TTV uptake

Variable	**Total**	**Percentage**
Total	**74**	**100%**
Region		
Soweto	27	36.49
Metro East Cape Town	44	59.49
Inner City Johannesburg	3	4.05
Maternal age (years)		
Median (IQR)	27.31 (23.62-28.87)	
≤20	4	5.71
21-30	56	80.00
31-40	7	10.00
≥41	3	4.29
Race		
Black African	55	96.49
Coloured	1	1.75
Asian/Indian	1	1.75
White	0	0
Other	0	0
Pre-existing medical conditions		
None reported	57	77.03
Hypertension	2	2.70
Tuberculosis	2	2.70
Epilepsy	1	1.35
Diabetes	0	0
Cardiac condition	0	0
Asthma	0	0
Known allergy	0	0
*Other**	5	6.76
Unknown	2	2.70
HIV status		
Negative	38	56.72
Positive	29	43.28
Smoking		
Non-user	56	94.92
User	3	5.08
Quitter	0	0

Recreational drug use		
Non-user	51	98.08
User	1	1.92
Quitter	0	0
Alcohol consumption		
Non-user	47	79.66
User	10	16.95
Quitter	2	3.39
Number of ANC visits		
Median (IQR)	7 (5-8)	
1	2	2.70
2-3	4	5.41
4-5	13	17.57
6-7	31	41.89
≥8	24	32.43
Gestational Age at 1st ANC visit		
Median (IQR)	16.14 (11.00-23.29)	
1st trimester	22	30.99
2nd trimester	39	54.93
3rd trimester	10	14.08
Parity		
0	26	35.14
1	23	31.08
2-3	24	32.43
4-5	1	1.35
≥6	0	0
Gravidity		
1	24	32.43
2-3	40	54.05
4-5	9	12.16
≥6	1	1.35

*Other - medical condition not specified on the antenatal card.

Totals may not match overall total due to missing data.

Additionally, women with gravidity values greater than one had significantly decreased odds of complete TTV scheduling, with completion of 6.86% (338/3850) of women with a gravidity of two to three, 5.86% (77/1005) of those with four to five and 4.27% (7/132) of women with

six or more (OR: 0.65, CI: 0.55-0.77; OR: 0.56, CI: 0.43-0.73; OR: 0.38, CI: 0.18-0.82 respectively) (Table 3.4).

Women with complete TTV status had significantly more ANC visits than women with incomplete TTV, with medians of 6 (IQR: 5-8) and 5 (IQR: 4-7) visits, respectively ($P<0.01$). Compared to women with only one ANC visit, women with four or more visits displayed significantly increased TTV schedule completion, with 8.84% (191/2160) of participants having between four and five visits, 12.58% (283/2249) with six to seven and 13.09% (172/1314) participants with eight or more visits having a complete TTV schedule (OR: 7.11, CI: 2.62-19.27; OR: 10.54, CI: 3.90-28.50; OR: 11.03, CI: 4.06-29.98, respectively). Participants with completed TTV status presented significantly earlier in their pregnancy for their booking visit (16.43 (11.14-21.29) weeks) compared to women in the incomplete TTV status group (20 (14.71-25) weeks), ($P<0.01$). Furthermore, women who presented for their first antenatal visit in their second or third trimester had significantly decreased odds of TTV schedule completion relative to women who presented in their first trimester (OR: 0.55, CI: 0.46-0.66; OR: 0.20, CI: 0.14-0.28, respectively). No significant associations were found between race, region, HIV status, the use of teratogenic substances (smoking, alcohol, recreational drugs), vaccination uptake history (other than influenza immunisation) and participants having a complete tetanus immunisation schedule during their pregnancy ($P>0.05$) (Table 3.4).

Table 3.4: Demographic and clinical factors affecting TTV uptake during pregnancy in women presenting for antenatal care between July 2017-June 2018.

	TTV Uptake in Index Pregnancy					
	Total	**Complete TTV status (3 doses)**		**Incomplete TTV status (1 - 2 doses)**		
Variable		**N**	**Row %**	**N**	**Row %**	**OR (95% CI)**
Total	**7031**	**682**	**9.70**	**6349**	**90.30**	
Maternal age (years)						
Median (IQR)		26.68 (22.24-31.58)		27.72 (23.45-32.71)		
≤20	670	82	12.24	588	87.76	Reference
21-30	3451	351	10.17	3100	89.83	0.81 (0.63-1.05)
31-40	2008	164	8.17	1844	91.83	0.64 (0.48-0.84)*
≥41	252	19	7.54	233	92.46	0.68 (0.38-1.21)
Race						
Black African	5835	576	9.87	5259	90.13	0.86 (0.49-1.51)
Coloured	124	14	11.29	110	88.71	Reference
Asian/Indian	40	0	0.00	40	100.00	1
White	10	0	0.00	10	100.00	1
Other	27	1	3.70	26	96.30	0.30 (0.04-2.40)
Region						
Soweto	4798	495	10.32	4303	89.68	1.96 (0.61-6.29)
Inner City Johannesburg	2155	182	8.45	1973	91.55	1.57 (0.48-5.07)
Metro East Cape Town	54	3	5.56	51	94.44	Reference

Pre-existing medical conditions						
None reported	6238	609	9.76	5629	90.24	1.07 (0.83-1.38)
Hypertension	132	5	3.79	127	96.21	0.36 (0.15-0.89)*
Asthma	66	3	4.55	63	95.45	0.44 (0.14-1.41)
Known allergy	33	2	6.06	31	93.94	0.60 (0.14-2.51)
Tuberculosis	26	4	15.38	22	84.62	1.70 (0.58-4.94)
Diabetes	23	3	13.04	20	86.96	1.40 (0.41-4.72)
Epilepsy	17	3	17.65	14	82.35	2.00 (0.57-6.97)
Cardiac condition	15	0	0.00	15	100.00	1
*Other**	53	3	5.66	50	94.34	0.56 (0.17-1.79)
Unknown	378	40	10.58	338	89.42	1.11 (0.79-1.55)
HIV status						
Negative	4920	484	9.84	4436	90.16	1.07 (0.89-1.29)
Positive	1750	162	9.26	1588	90.74	Reference
Smoking						
Non-user	5402	539	9.98	4863	90.02	1.74 (1.01-3.01)
User	234	14	5.98	220	94.02	Reference
Quitter	124	7	5.65	117	94.35	0.94 (0.37-2.39)
Recreational drug use						
Non-user	4711	457	9.70	4254	90.30	0.75 (0.32-1.78)
Quitter	48	6	12.50	42	87.50	Reference
User	22	0	0.00	22	100.00	1
Alcohol consumption						

Non-user	5025	496	9.87	4529	90.13	0.96 (0.67-1.36)
Quitter	375	30	8.00	345	92.00	0.76 (0.46-1.26)
User	361	37	10.25	324	89.75	Reference
Parity						
0	2260	282	12.48	1978	87.52	Reference
1	2401	198	8.25	2203	91.75	0.63 (0.52-0.76)*
2-3	2088	187	8.96	1901	91.04	0.69 (0.57-0.84)*
4-5	215	11	5.12	204	94.88	0.38 (0.20-0.70)*
≥6	14	1	7.14	13	92.86	0.54 (0.07-4.14)
Gravidity						
1	1989	256	10.18	1733	87.13	Reference
2-3	3850	338	6.86	3512	91.22	0.65 (0.55-0.77)*
4-5	1005	77	5.86	928	92.34	0.56 (0.43-0.73)*
≥6	132	7	4.27	125	94.70	0.38 (0.18-0.82)*
Vaccination uptake history						
Yes	27	1	3.70	26	96.30	Reference
No	6905	676	9.79	6229	90.21	2.82 (0.38-20.83)
Influenza immunisation						
Yes	760	55	7.24	705	92.76	Reference
No	6107	612	10.02	5495	89.98	1.43 (1.07-1.90)*
Number of ANC visits						
Median (IQR)		6 (5-8)		5 (4-7)		
1	297	4	1.35	293	98.65	Reference

2-3	1009	32	3.17	977	96.83	2.40 (0.84-6.84)
4-5	2160	191	8.84	1969	91.16	7.11 (2.62-19.27)*
6-7	2249	283	12.58	1966	87.42	10.54 (3.90-28.50)*
≥8	1314	172	13.09	1142	86.91	11.03 (4.06-29.98)*
Gestational Age at 1st ANC visit						
Median (IQR)		16.43 (11.14-21.29)		20 (14.71-25)		
1st trimester	1232	197	15.99	1035	84.01	Reference
2nd trimester	4362	412	9.45	3950	90.55	0.55 (0.46-0.66)*
3rd trimester	1182	44	3.72	1138	96.28	0.20 (0.14-0.28)*

2759 individuals obtained 1 dose only, 3590 individuals obtained two.

The reference group for pre-existing medical conditions is women who did not have the condition.

*Other - medical condition not specified on the antenatal card.

Statistical significance p<0.05 indicated by '*'. IQR: interquartile range; N: population, ANC: antenatal care.

Wilcoxon rank-sum test and logistic regression were used to assess intervariable relationships and statistical significance thereof.

N varies in the population due to some participants lacking data on the variable in question.

Totals may not match overall total due to missing data.

3.3.2. Timing of Tetanus Immunisation

Of the 7031 participants with confirmed TTV uptake, data on the timing of their first dose were available for 6723 (95.62%) individuals (Figure 3.4). Of these 6723 mothers, 2632 (39.15%) received only one dose, 3445 (51.24%) received two doses, whilst 646 (9.61%) received all three doses. Women who received three doses were more likely to receive their first dose in the first or second trimester compared to women with only one dose who were more likely to receive their first dose after the first trimester (Figures 3.4). Most women who received two doses were immunised with their first tetanus dose in the second trimester, with less than 15% of first dose immunisations happening after the second trimester (Figure 3.4).

Of the 6723 participants with available data on gestational age at first tetanus dose administration, 1894 (28.17%) were pregnant for the first time (Figure 3.5). Of these women, 27.82% (527/1894) received one dose, 59.77% (1132/1894) received two doses, whilst 12.41% (235/1894) received the complete three doses (Figure 3.5). Primigravid women were most likely to receive their first TTV dose in their second trimester regardless of how many doses they received. Women who only received one TTV dose were however more likely than women with two or three TTV doses to be immunised in their third trimester. Over half (54.75%) of the 6723 mothers had between two to three prior pregnancies, with 41.16% (1515/3681) having received only one TTV dose, 50.01% (1841/3681) having received two and 8.83% (325/3681) having received three TTV doses (Figure 3.6). Across all doses, women were most likely to be immunised in their second trimester. Women with three TTV doses were the most likely to receive their first dose in their first trimester and least likely to receive the first dose in their third trimester, whilst women with one dose were most likely to receive their first dose in their third trimester and least likely to receive it in their first trimester (Figure 3.6). Women with two doses were more likely to receive their first dose in the first trimester as opposed to the third, however predominantly immunisation occurred in the second trimester (Figure 3.6).

Women who had been pregnant more than three times made up 16.27% (1094/6723) of the cohort. Of these women, 52.38% (573/1094) received one TTV dose, 40.13% (439/1094) received two TTV doses and 7.50% (82/1094) received three TTV doses (Figure 3.7). The distribution of the trimester of the first dose followed the trends of the abovementioned primigravid and multigravida women, with all women regardless of the number of doses received being most likely to receive their first tetanus vaccination in their second trimester (Figure 3.7). Of the primigravida women, only 12.87% (256/1989) received the complete TTV schedule (Figure 3.8). This figure was lower in multigravida women with between two and

three pregnancies, or more than three pregnancies: with respective proportions of 8.78% (338/3850) and 7.39% (84/1137). Most women with more than three pregnancies only received one TTV dose (593/1137, 52.15%) whilst most women with between two to three pregnancies received two TTV doses (1916/3850, 49.77%). The same was true of the primigravida participants, with 59.38% (1181/1989) of first-time pregnancy participants receiving two TTV doses (Figure 3.8).

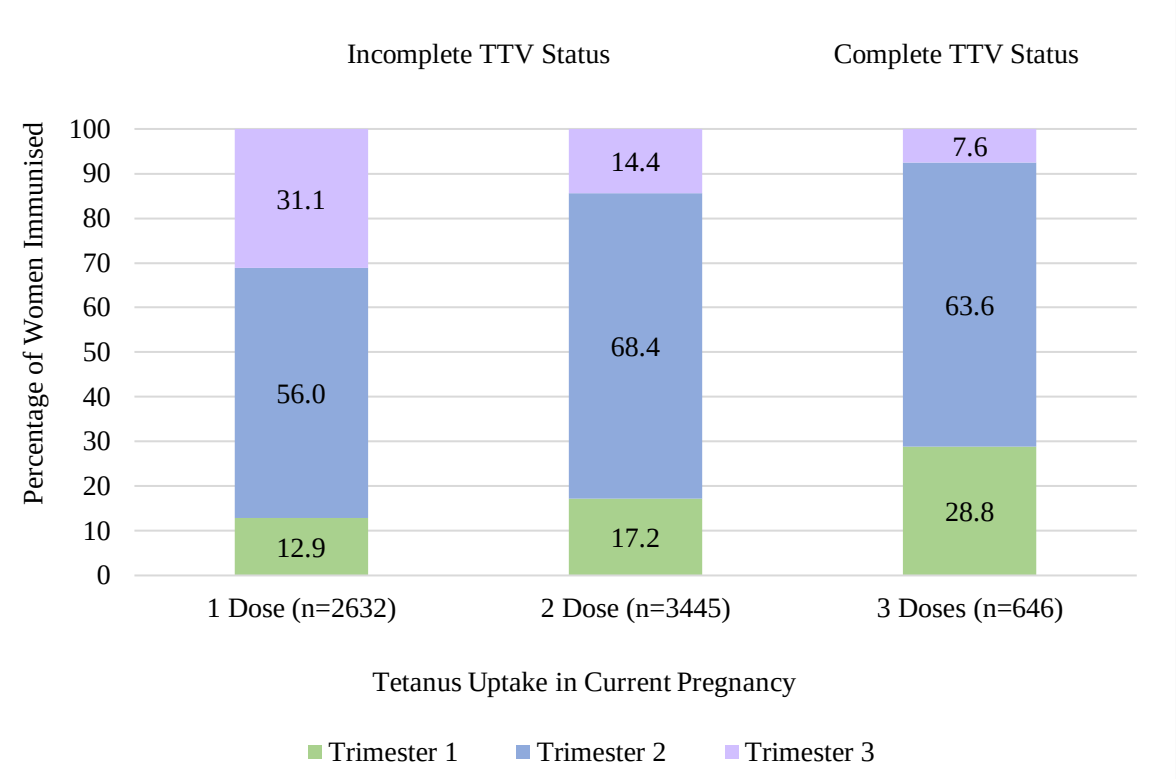

Figure 3.4: Timing (trimester) of receipt of **1st tetanus toxoid vaccine dose** in 6723 pregnant women with complete (3 doses) or incomplete (1 or 2 doses) TTV uptake in their index pregnancy.

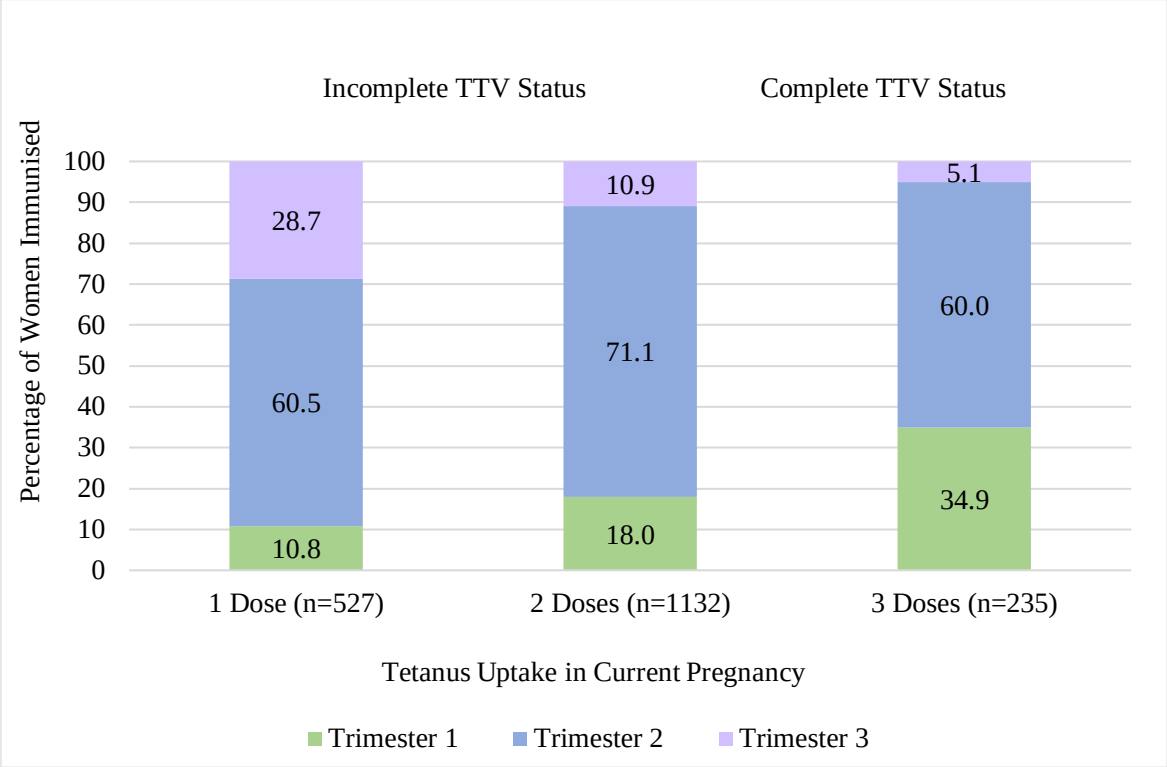

Figure 3.5: Timing (trimester) of receipt of **1st tetanus toxoid vaccine dose** in **1894 primigravida** women with complete (3 doses) or incomplete (1 or 2 doses) TTV uptake in their index pregnancy.

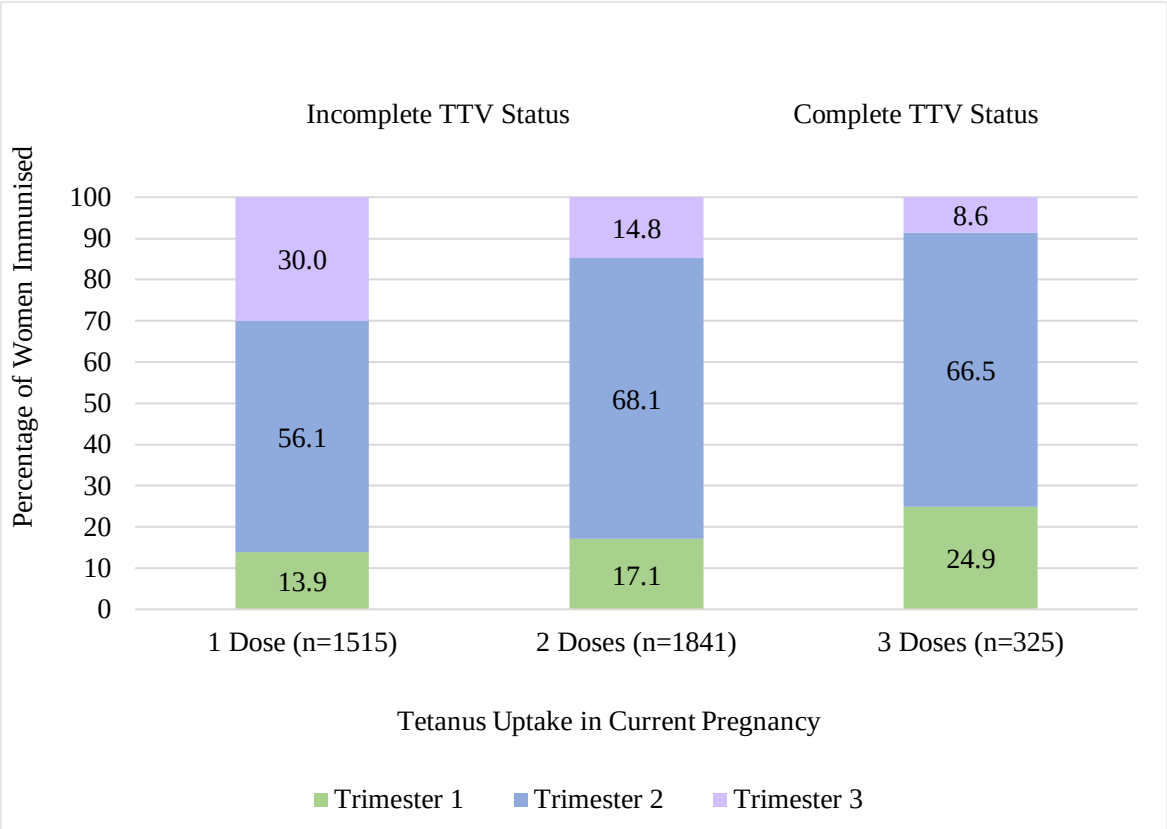

Figure 3.6: Timing (trimester) of receipt of **1st tetanus toxoid vaccine dose** in **3681 multigravida (2-3)** women with complete (3 doses) or incomplete (1 or 2 doses) TTV uptake in their index pregnancy.

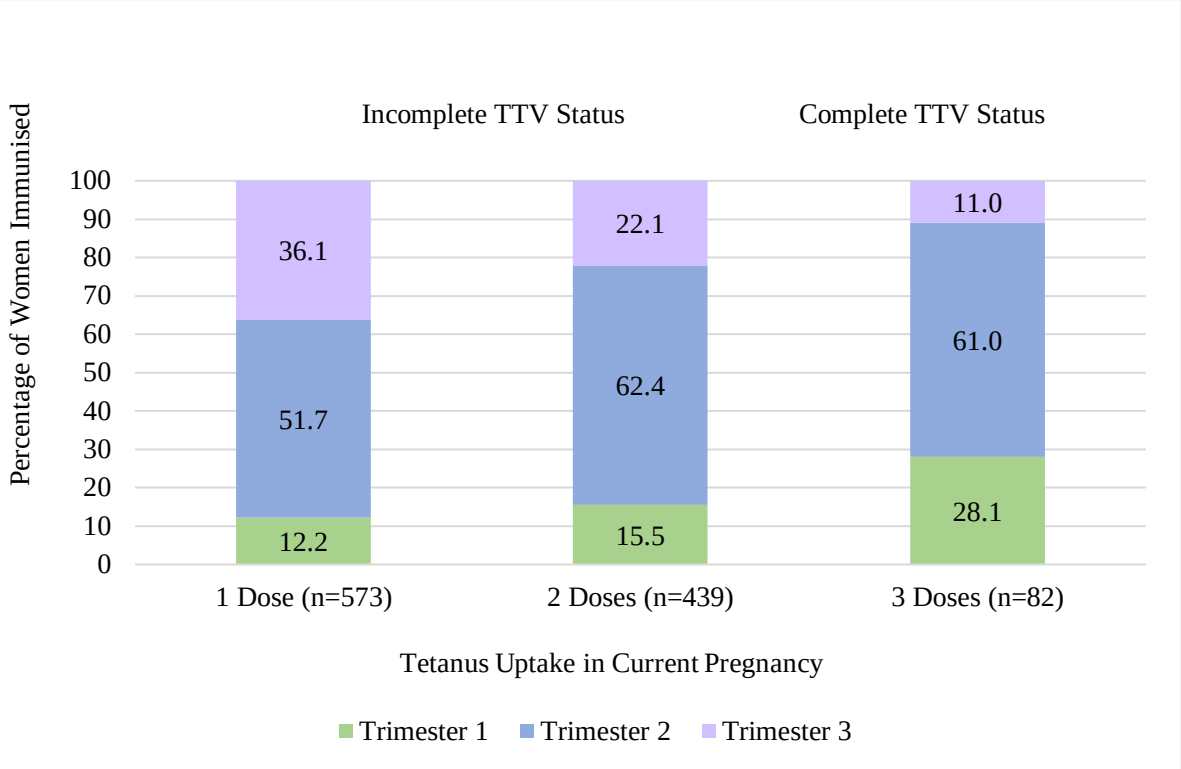

Figure 3.7: Timing (trimester) of receipt of **1st tetanus toxoid vaccine dose** in **1094 multigravida (>3)** women with complete (3 doses) or incomplete (1 or 2 doses) TTV uptake in their index pregnancy.

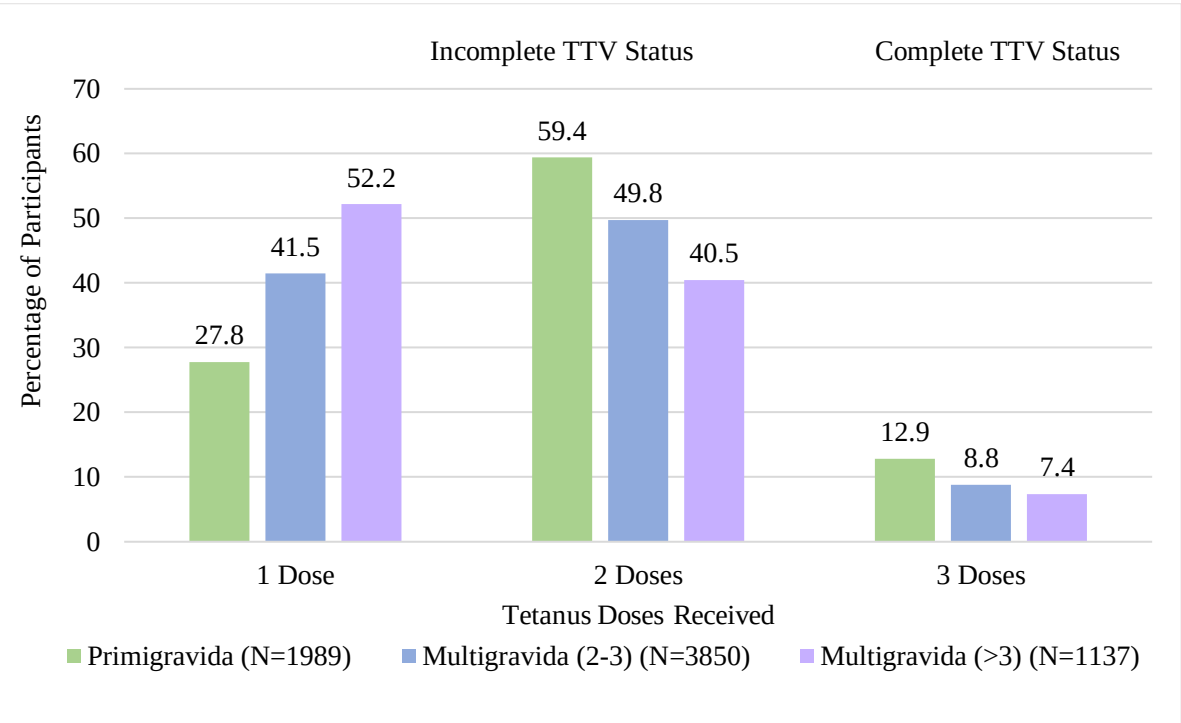

Figure 3.8: Proportion of primigravida, multigravida (2-3) and multigravida (>3) participants who received TTV doses in their index pregnancy.

Of the women who received at least one TTV dose, 50.52% (3552/7031) received two doses and had data available on the timing between their doses (Figure 3.9). The majority, 90.34% (3209/3552) had an appropriate time interval between the doses, with less than ten percent having an incorrect interval between the first and second dose (Figure 3.9). Out of the 682 women who received the complete TTV schedule of three doses in their pregnancy, data on the spacing between all three tetanus doses were available for 670 (98.24%) (Figure 3.10). Most women were incorrectly immunised (666/670, 99.40%), with a small proportion (4/670, 0.60%) receiving all three of their tetanus doses in line with established timing guidelines (Figure 3.10). Of those with incorrectly timed schedules, 11.79% (79/670) received all doses incorrectly. Only a small proportion of women had an incorrect time space between their first two doses (2/670, 0.30%), with the majority of incorrectly immunised women having too short a time period between doses two and three (585/670, 87.31%).

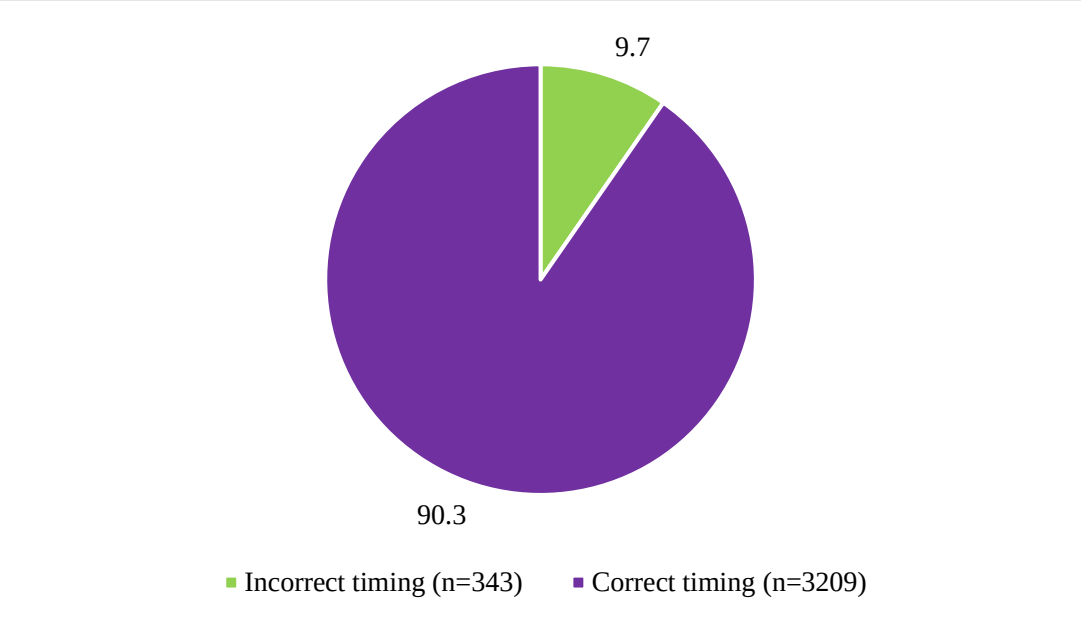

Figure 3.9: Proportion of 3552 pregnant women with two TTV doses schedule in their index pregnancy by the adherence to tetanus timing guidelines.

Of 682 women who received three TTV doses, 671 (98.39%) had recorded time intervals between their second and third doses. Only 2.68% (18/671) women who achieved complete TTV status had a time interval of 24 weeks between their second and third tetanus dose, with the majority (230/671, 34.28%) receiving their third dose between eight and 12 weeks after the second (Figure 3.11). A small number of individuals received their third dose less than a month after the second (6/671, 0.89%), with 76.75% of women (515/671) receiving their third dose between one to four months after the second.

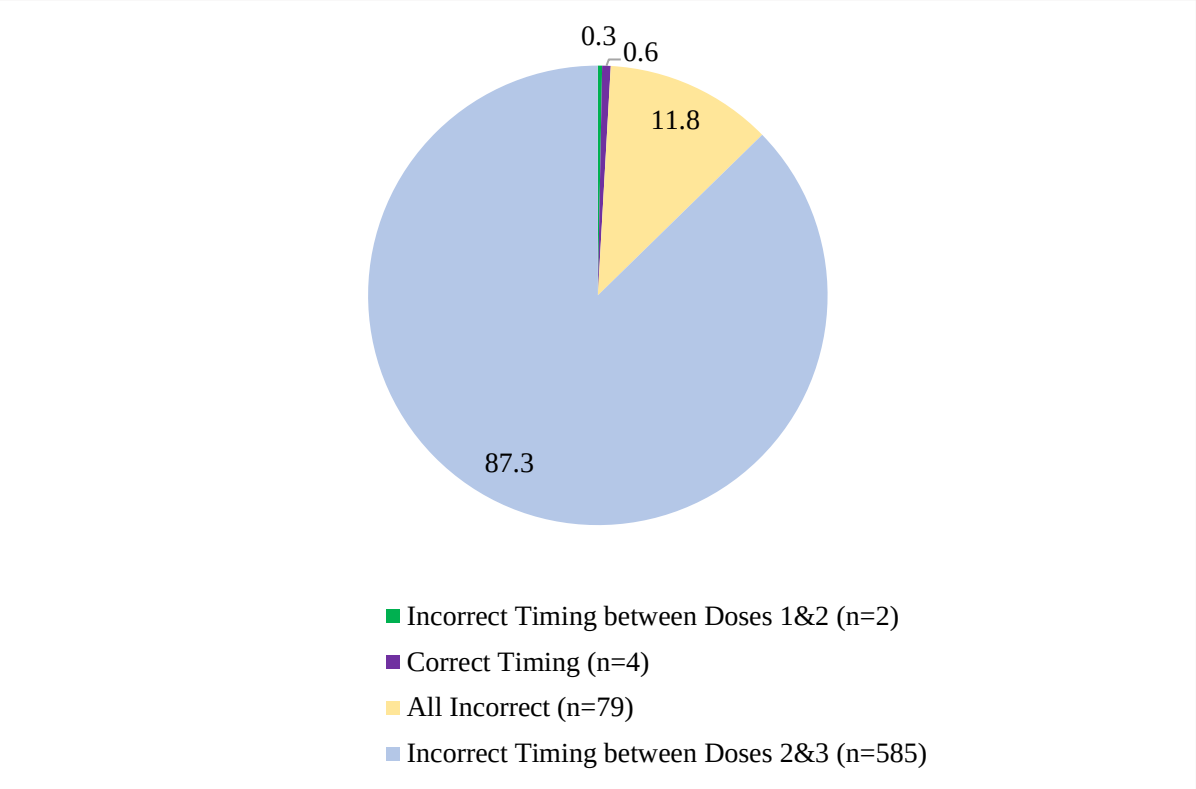

Figure 3.10: Proportion of 670 pregnant women with complete TTV status (3 doses) in their index pregnancy by the adherence to tetanus timing guidelines.

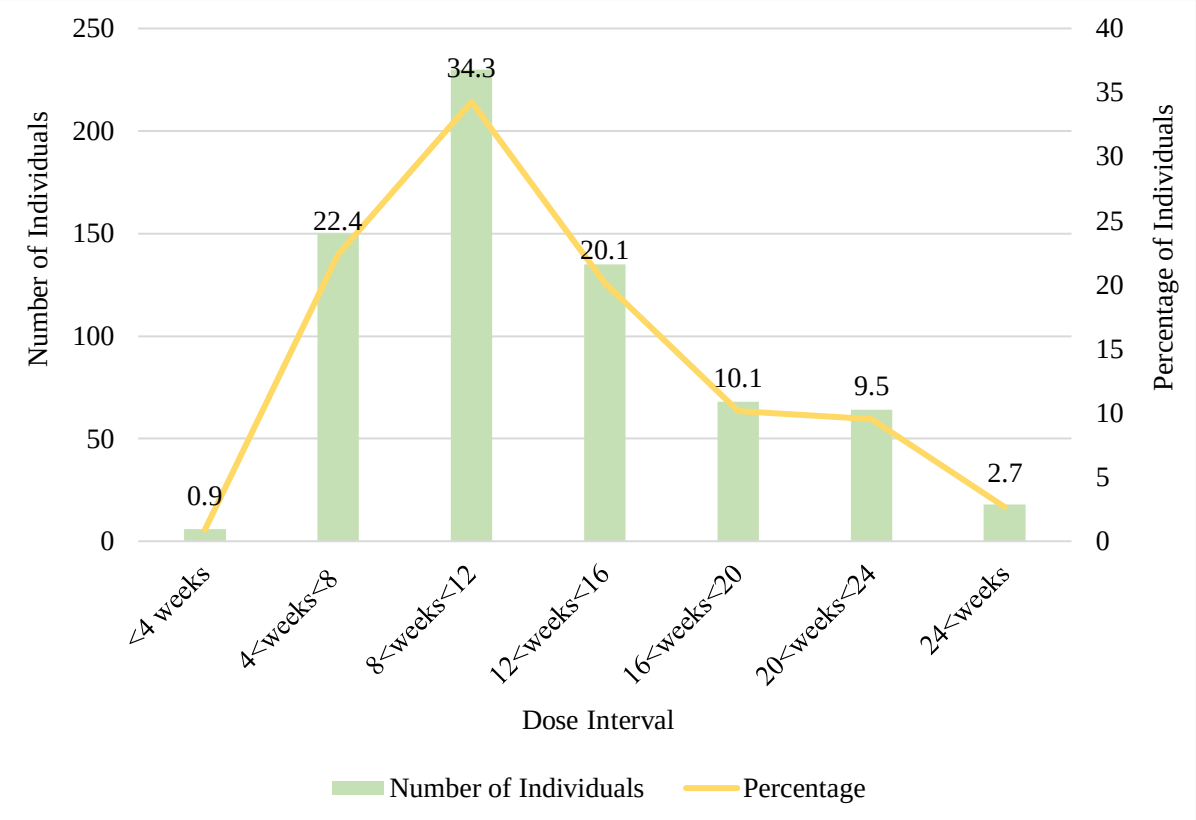

Figure 3.11: Graph showing the time difference between the second and third dose of 671 pregnant women with three TTV doses in their index pregnancy.

Chapter Four: Discussion

4.1. Maternal Influenza Immunisation Uptake in South Africa

This is the first South African study assessing the uptake and the timing of routinely administered influenza and TT vaccines during pregnancy, within the government healthcare sector in the absence of a targeted intervention. Most women had no reported pre-existing medical conditions, were HIV uninfected and few reported the use of potentially teratogenic substances during their pregnancy (smoking, alcohol, or recreational drugs). Overall, influenza vaccine uptake was low (16.62%) among women who attended ANC visits during the influenza vaccination season (806/4851), while TTV uptake was high in the cohort (7031/7105, 98.96%). Pregnant women aged 21-30 years were significantly more likely to have an influenza vaccine, compared to mothers younger than 20 years. Increased exposure to the healthcare system increased the likelihood of influenza vaccine uptake among women of the cohort. Alcohol use increased the odds of maternal influenza vaccine uptake, whilst the uptake of tetanus vaccines during pregnancy decreased the odds of influenza immunisation.

Maternal influenza vaccine uptake was significantly higher in the Western Cape region of the study compared to both Gauteng regions; however, all regions show an increase in maternal immunisation numbers that precedes the provincial influenza waves, demonstrating that the respective sites were immunising women ahead of the influenza season in line with guidelines. The Metro East Cape Town site had a large amount of missing data regarding influenza immunisation uptake, indicating the need for further investigation as to why these records were incomplete.

4.2. Timing of Influenza Immunisation

Influenza vaccine coverage ranged between 6.51%-31.25% across study regions in April 2017 when the vaccine became available and dropped thereafter. A spike observed in April of 2018 where coverage ranged between 2.31%-5.77% is lower than that observed in 2017, however coverage in May 2018 ranged from 0.38%-31.25%. This suggests vaccine administration may have been delayed in 2018 compared to 2017. The peaks in the months of April and May demonstrates a pattern where influenza immunisation coverage is typically highest just before the commencement of the flu season and falls as the flu season commences and progresses. In line with this finding, women who presented for any antenatal visits during the vaccine availability period (beginning of April to the end of July), or had an estimated delivery date or delivered within the flu season (April-September) had a significantly increased odds of receiving the influenza vaccine. This reflects the seasonality component of influenza

immunisation which is expected given the seasonality of influenza and the subsequent seasonal vaccine availability.

Most of the influenza immunisations occurred within the appropriate period to confer immunity for the flu season, however 25.14% (178/708) of immunisations were reported outside of the appropriate months. Vaccine administration was uncommon, though not absent, in the months following the end of the influenza season. This is irregular and suggests the need for an audit investigating why women are receiving vaccines beyond the relevant season, as these vaccines will be incapable of conferring protection and are likely to be expired, thus posing a potential threat to health. Considering that 4851 of 6941 participants (69.89%) had at least one ANC visit during the influenza season, the reported coverage for women with visits in season of 16.62% is of concern. Women were typically immunised in their second or third trimester, with only a small proportion of women receiving their influenza immunisation during the first trimester. This may be explained by the median gestational age of presentation for the booking visit of the overall population being 19.85 (IQR: 14.00-25.00) weeks, with only 18.23% (1640/8996) women having at least one ANC visit during the first trimester, thus it would be unlikely for the participants to present early enough for first trimester immunisation.

4.3. Maternal Tetanus Immunisation Uptake in South Africa

Tetanus toxoid vaccine uptake was well recorded, with available data for 7105 participants (78.98%). A total of 7031 women (98.96%) received at least one tetanus vaccine during their pregnancy, with only 74 (1.04%) having received no tetanus vaccinations, or no vaccination having been recorded in their medical notes, during their pregnancy. No obvious differences exist between the 74 participants with no tetanus uptake compared to the 7031 with at least one dose administered during pregnancy, with most participants being African, between the ages of 20 and 40 years and few reporting pre-existing medical conditions. Of the 74 participants with no TTV uptake, 98.65% had a parity of less than four, thus would have not had the opportunity to receive the recommended five doses and should have at least received one dose, in line with antenatal immunisation guidelines (29).

In participants with at least one TTV dose, women with hypertension had a decreased odds of having completed TTV status, which may be a result of these women being less vigilant with their antenatal care visits relative to healthy women. This is supported by the observed increased likelihood of TTV schedule completion in women with an increased number of antenatal care visits, indicative of increased exposure to the healthcare system being positively associated with

maternal vaccine uptake. Increasing age decreased the likelihood of participants achieving complete TTV status (3 doses), significantly so in the 31-40 year age group relative to mothers less than 20 years of age. In addition to this, increased parity and gravidity decreased the odds of completion of the TTV schedule in the index pregnancy. These results may be explained by these women having received three doses in their previous pregnancies, thus not necessitating a complete schedule in their index pregnancy. The largest proportion of women who received three tetanus doses were primigravid participants, followed by women with a gravidity of between two and three, and finally those with a gravidity higher than three. Only 9.7% of the participants with reported TTV received a complete schedule of three doses despite primigravida participants accounting for 28.29% of the sample. It is unclear why women with more than three prior pregnancies have been receiving a full TTV schedule and indicates that either they were not immunised in their previous pregnancy, or that they received additional unnecessary doses.

Most primigravid mothers and mothers with a gravidity between two and three received two TTV doses. The lack of third dose in primigravid mothers may be a result of a later presentation for booking the visit, which corresponds to the observed increased odds of TTV schedule completion in women presenting in the first trimester compared to women presenting in their second or third trimester: in line with the recommended guidelines on tetanus dose intervals. The additional dose in multigravida mothers, who, if previously immunised according to guidelines should only receive one booster dose, may be a result of a missed dose or be explained as an unnecessary dose, depending on their vaccine history in the previous pregnancy.

4.4. Timing of TTV Doses

Most women, regardless of gravidity or how many doses they received, were immunised with their first TT dose in their second trimester. This timing is undesirable given the guidelines on spacing between tetanus doses, thus prohibiting women from receiving the complete schedule of doses. Considering that the median age of presentation for booking was in the second trimester for both women with complete, incomplete or absent schedules, and that the overall population median was at 19.85 (IQR: 14.00-25.00) weeks, the likelihood of women in our population receiving three TTV doses in accordance to guidelines is small. However, the data show that adherence to the TTV interval guidelines was poor within the population. This adherence was better amongst people with only two tetanus doses (90.34%) than it was amongst those with three doses (0.60%), which may be a result of the recommended timing interval between the first two doses being at least a month.

Amongst participants with three doses, the most common point of incorrect schedule adherence was between doses two and three (87.31%), which require a six-month interval. This was followed by incorrect timing between all three doses (11.79%) and lastly, incorrect timing between the first and second dose (0.30%). The most common interval between doses two and three was found to be between eight to twelve weeks (34.28%) followed by an interval of four to eight weeks (22.35%). This indicates that the majority of women have too short an interval between their last two doses, and the data reflect that health care practitioners are not managing to correctly immunise mothers with three TTV doses. The timing anomalies may be explained by the lengthy six-month interval between doses two and three, as fitting a seven-month schedule into a nine-month pregnancy may be difficult if not impossible given that the majority of women present for their first visit beyond the second month of pregnancy. However, this does not explain or justify practitioners failing to follow the recommended schedule intervals. Considering these data, the maternal tetanus immunisation schedule is perhaps in need of revision, given that so few women have been fully immunised in accordance with recommended guidelines.

4.5. Limitations

The retrospective nature of this study did not allow us to consider or investigate additional social factors such as religion, personal beliefs or beliefs of friends, family, and the community, that may influence vaccine uptake decision-making. These factors have been shown to influence women's decisions regarding maternal immunisation uptake (53). A prospective study with an embedded qualitative research component would be better suited to identifying reasons for non-vaccination amongst women as it could accommodate for factors beyond the scope of the maternal health card. We were also unable to account for a woman's prior history of vaccine uptake in previous pregnancies as this retrospective medical chart review was limited to the information detailed in the current maternity case record. This is particularly relevant for TTV as guidelines for doses vary according to whether or not a woman's TT immunisation history is known (29). Additional external and health system related factors were not available to provide further insight into why vaccines were not administered, preventing determination of whether this be health-personnel dependent, patient-dependent or system dependent (e.g. stockouts, waiting periods, resource expiration). Nonetheless, this study appropriately addresses vaccine coverage and baseline clinical and demographic variables that may affect uptake, laying the foundation for future research into the detailed determinants of vaccine uptake amongst pregnant women within the government healthcare system in South Africa. In

addition to this, our findings may be supplemented by recently published South African research covering personal factors influencing immunisation uptake during pregnancy (47). An unavoidable caveat of the study is the inability to account for the effect of the 2020 SARS-CoV-2 pandemic on maternal immunisation uptake, however the study provides insight into pre-pandemic uptake: offering a comparison point for future South African studies. This will be imperative in assessing the effect of the pandemic on South African antenatal visit attendance, with available literature demonstrating a decline in visits due to fear of illness in several countries (including three African sites) (68). In addition, although there was minor race representation other than African in the population, the proportion of Africans in this study closely reflects the South African 2021 mid-year population estimates (66). In conjunction, the government health sector serves 71.5% of the population, the majority of whom are non-white individuals with only 9.9% of African individuals, 17.1% of Coloured individuals and 52.0% of Indian/Asian individuals being members of private medical aid schemes in 2018, as opposed to 72.9% of White individuals (69). Furthermore, the data quality is negatively affected by the missing variables amongst participants. However, care was taken to exclude these missing variables from the denominators where applicable, reducing the impact thereof. These missing data give insights into the room for improvement that exists within record-keeping in the government health sector.

4.6. The Research in Context

4.6.1. Influenza Coverage

Between 2011 and 2018, national maternal influenza coverage was found to be similar to that observed in the above findings, being less than 16% (48,49). Bishop *et al* however demonstrated the power of targeted influenza campaigns, achieving a coverage of 78.7% from 2015 to 2018 at designated sites within South Africa (49). Insight into non-vaccination within our study may be derived from this literature, as more than half of Bishop *et al's* sample that were unvaccinated reported stockouts as the reason for not receiving the vaccine (49). This suggests that with improved resource allocation, as well as implementation of educational campaigns on vaccine advocacy targeted at both mothers and health care workers – maternal influenza vaccine uptake may be improved (49). Lengana *et al's* 2015 collaboration with the department of health to increase vaccine availability in the public sector reinforces this notion, showing maternal uptake of 67.6% (70). Similarly, in those unvaccinated, the primary reason for such was vaccine unavailability due to either late facility arrival or stockouts (61.1%) (70).

A similar observation of increasing age being negatively associated with influenza vaccine uptake was noted by Bishop *et al,* with women older than 35 years being less likely to be vaccinated; as was the case with women over the age of 41 years in our study, relative to younger women. This is the converse of French research, wherein younger age groups demonstrated lower uptake compared to women over the age of 35 years (71). Bishop *et* al observed that women from the Western Cape region were more likely to receive the influenza vaccine during pregnancy compared to those from Gauteng (49), as was observed in our findings. This suggests that despite the large amount of missing data for the Metro East Cape Town site, the observation that vaccine uptake was superior in the Western Cape relative to Gauteng may be regarded as accurate, based off of previous literature (49). No effect on HIV status on influenza vaccine uptake was observed in either sample (49), which contradicts American findings that positive HIV status is negatively associated with maternal immunisation against both tetanus and influenza (62). This may be explained in that the American literature cannot be generalised to a South African context due to differences: specifically, those in disease burden. South Africa is heavily burdened by HIV (64), whilst the American study had little representation of HIV positive participants – reducing comparability between populations (62).

The increased likelihood of maternal influenza immunisation amongst alcohol users may be explained as coincidental, with an estimated South African prevalence of alcohol consumption during pregnancy of 13.2% (72). Given than 5.79% of the population reported alcohol consumption during pregnancy, this result is likely due to the high prevalence of maternal alcohol use in South Africa (73), with no other literary corroborations on such a relationship. This result may also be explained by both alcohol use and influenza vaccine uptake being higher in the Western Cape region compared to Gauteng sites. The decreased likelihood of influenza immunisation uptake in women with recorded TTV uptake is unprecedented, though may have been affected by the seasonal, and limited availability of influenza vaccines compared to the constant availability of tetanus toxoid vaccines – with only one million influenza vaccine doses distributed annually for all identified high-risk groups utilising the government health sector (48,49). It is unlikely either of the vaccines decreasing the odds of obtaining the other is associated with healthcare worker reluctance to co-administer the vaccines, as 60.12% (449/747) of women who received both an influenza and TT vaccine in their index pregnancy (who attended visits during the influenza season) received them concurrently. Few of the 57 women who received an influenza vaccine, but no TTV doses had a parity of greater than three (10.53%, 6/57), therefore their lack of TTV administration cannot be attributed to the schedule

being completed in a prior pregnancy. In line with findings from other low and middle income countries, the more antenatal care visits a women attended, the greater the likelihood of immunisation (74,75). This is additionally supported by Malawian findings of poor antenatal clinic attendance being identified as a barrier to appropriate maternal immunisation coverage (58). These results reflect the success of increasing antenatal care visit recommendations, positively increasing maternal immunisation (61).

4.6.2. Timing of Influenza Immunisation

Similarly to French findings, most women were immunised in their second trimester (71). The gestational age at immunisation may be explained by the later gestational age at participant booking visit. The later gestational age of presentation of our population mimics that observed of a Nigerian population which had a mean gestational age of ANC booking of 19.1 ± 7.8 weeks (76). This contrasts Raut *et al's* review of factors affecting influenza uptake in low and middle income countries, wherein earlier antenatal care presentation and offering of the vaccine was associated with higher maternal influenza immunisation uptake (74). Raut *et al* justified this in that earlier engagement allowed for improved advocating of health practitioners on maternal immunisation – which corroborates with Bishop *et al's* demonstration that with targeted vaccine campaigns – uptake can be improved (49,74). Based off of previous literature, the observed majority second or third trimester immunisation would primarily protect the neonate (34), yet Katz *et al* reported no change in vaccine efficacy between second or third trimester immunisation (44). This, in combination with findings that optimal neonatal protection was attained when immunisation occurred at least four weeks before delivery – reinforces Zhong *et al's* recommendation that influenza immunisation occurs as soon as vaccines become available (34). Therefore, within South Africa, the gestational age of influenza immunisation is most commonly at a point whereby optimal antibody transfer to the neonate is achieved. The influenza vaccine is recommended to pregnant women regardless of foetal gestational age, yet requires around two weeks to develop a protective antibody response and should ideally occur prior to circulation as a result (26). Subsequently, the irregular timing of roughly one quarter (25.14%) of the maternal vaccinations against influenza suggests the need for an audit. The remaining 74.86% of participants were appropriately immunised, with peak immunisation occurring predominantly ahead of the influenza season onset – which is in line with recommendations (26).

4.6.3. Maternal Tetanus Toxoid Uptake

Tetanus toxoid vaccine coverage within our population was high, with at least one dose administered in 98.96% of participants. This is similar to that observed in other African countries, including 83.9% in Nigeria, 99.6% in Sierra Leone and 88.2% in the Gambia (77–79), yet is considerably higher than that observed in Ethiopia (63.2%) (80). Coverage with at least two doses was lower in our population than coverage seen in Nigeria (60.76% versus 84.95%), however our coverage of at least two doses was higher than that seen in the Gambia (34.80%) and similar to that observed in Ethiopia (51.80%) (77,78,80). Optimally, individuals should receive six tetanus doses over their lifetime to attain lifelong immunity, however in pregnant women with an unknown tetanus immunisation history – the WHO recommends at least two doses, followed by a third at least six months later to attain lasting protection (29,81). Based on WHO recommendations, 51.06% of our population had adequate (two doses) tetanus immunisation during their pregnancy – however given the lack of data on participant's prior TTV schedule completion it is impossible to determine whether this was sufficient.

Our findings that increased antenatal care visits increased the odds of TTV completion is supported by other African studies as well as global literature (20,47,58,59), emphasizing that increased health system exposure positively increases maternal immunisation coverage. Additionally, these studies found higher parity to be negatively associated with tetanus uptake – similar to our observation of higher parity and gravidity being decreasing the odds of tetanus schedule completion (20,58,59). These observations are likely the result of these women having completed the schedule in prior pregnancies, therefore rendering three doses in their index pregnancy unnecessary (29). Godongwana *et al* discovered older women to be more accepting of maternal immunisations than younger women who infrequently attended antenatal visits (47), which stands in contrast to our finding that increasing age reduced the odds of tetanus completion. Global literature supports the association between increasing age and tetanus vaccine uptake, however does not examine the association between age and schedule completion (20). Care must be taken in interpreting this as older women in our population being less accepting than younger women of maternal immunisation, as older women are more likely to not need complete TTV status due to TTV in previous pregnancies. We found an unexpected negative effect of pre-existing hypertension on TTV schedule completion which is to our knowledge a novel observation. This may be explained by the high burden of hypertension (30.80%) in South Africans utilising government health care, with this burden being higher in females than in males (82).

4.6.4. Timing of Maternal TTV Immunisation

Generally, women presented in the second trimester for their first antenatal booking visit, though those who had their booking visit in the first trimester were more likely to have a completed schedule – which is expected as it facilitates adherence to the seven-month three-dose immunisation schedule (29). This is additionally in line with previous findings of increased health care system exposure being positively associated with maternal immunisation uptake (20,47,58,59). To our knowledge, this is the first study examining antenatal TTV schedule adherence – which was determined to be poor within the South African population. Difficulty of schedule completion has been acknowledged by the WHO and has been attributed largely to late presentation for booking visits (29). Adherence to the schedule is important, as failure to appropriately space the doses leads to antibody titres below the protective threshold, with these intervals determining the magnitude of immunogenicity and duration of protection (29,81). Poor adherence within the South African population is likely to compromise vaccine efficacy and therefore highlights the need for improved practices around maternal tetanus immunisation administration or perhaps the revision of the maternal immunisation schedule entirely.

4.7. Future Directions

Bishop *et al's* findings in conjunction with the observed low influenza immunisation uptake support the annual implementation of influenza health campaigns to improve coverage within maternity patients in South Africa. Budgetary revisions should be made and increased allocation of the budget towards purchasing influenza vaccines should be considered, since low uptake has been predominantly attributed to vaccine stockouts (49). An audit into the incorrect administration of influenza vaccines to pregnant women is necessary to determine the reasons for such – which will enable countermeasures to be implemented to protect against this threat to health.

In addition to influenza interventions, considering the poor adherence to the timing of the TTV schedule, South Africa stands to benefit perhaps from changing the maternal immunisation schedule, exchanging the tetanus toxoid vaccine instead for the Tdap vaccine. Motivation for this includes not only that this vaccine has been successfully implemented overseas (37), but also as pertussis is a threat to health in South Africa and this vaccine swap may reduce disease burden in neonates (32). Additionally, only one dose of Tdap is required in each pregnancy (83), which would eliminate the complexity of the current tetanus toxoid schedule. Replacement of the tetanus toxoid vaccine with Tdap in pregnancy would suit the South African

context, with optimal Tdap administration time occurring in the second and third trimester – accommodating for the late initial presentation observed within our population. To recommend this switch with confidence, we propose an immunogenicity trial to see if Tdap elicits equivalent tetanus protection in neonates born to women previously unvaccinated with TT in adulthood. Additionally, a feasibility study would be advised to assess the cost of replacing the TTV schedule with the Tdap vaccine. Should the Tdap swap not be feasible or prove inferior to the efficacy of the tetanus toxoid schedule, similar campaigns to those recommended for influenza need to be implemented, ensuring that health care practitioners are advocating for maternal immunisation and that the government is appropriately stocking health facilities. This would need to occur on a continuous basis, given that TTV lacks the influence of seasonality.

Context-specific vaccine acceptability information is lacking in South Africa. Barriers to vaccine uptake may differ between provinces and between urban and rural areas. Future research should include qualitative studies that engage pregnant women, health care workers and community leaders which may be invaluable in determining context-specific barriers to vaccine uptake during pregnancy. In addition, the above study could be revised in the post-pandemic context within the country to see if similar decreases in coverage as a result of decreased antenatal visits have occurred, as have been seen elsewhere (68).

Chapter Five: Conclusions

In conclusion, influenza coverage within the population sampled was low (16.62%) – even in the peak immunisation periods ahead of the influenza season. The data indicates that influenza campaigns should focus on women above the ages of 21-30 years and those with fewer ANC visits. In addition, the Gauteng region appears to require further influenza vaccine campaigning, due to its underperformance regarding coverage relative to the Metro East Cape Town study site. The odds of influenza immunisation uptake were decreased in women with TTV uptake during the index pregnancy, whilst the odds of receiving three TTV doses were decreased in women who received the influenza vaccine. Despite appropriate spikes in coverage preceding the commencement of the influenza season, uptake only ever reached a maximum of 50% of women who attended an ANC visit during the vaccination season. Furthermore, despite most vaccinations occurring within the appropriate period – the occurrence of 25.14% of immunisations outside of this period requires further investigation due to the potential health risks of expired vaccinations. No associations were observed between influenza uptake and pre-existing medical conditions, race, HIV status, parity, gravidity, smoking or recreational drug use.

Though coverage with at least one TTV dose in pregnancy was high within the population (98.96%), coverage with two doses and the complete three dose schedule was lower, respectively 51.06% and 9.70%. TTV schedule completion was more likely in women with younger age, earlier presentation for antenatal care and a greater numbers of antenatal care visits. Schedule completion was less likely in women with increased parity and gravidity, and with hypertension. No other medical conditions were implicated in completion of the schedule. Our findings are in line with expectations that older women and those with previous pregnancies will be less likely to need the full schedule of doses due to previous exposure in the health care system. TTV interval schedule adherence was low amongst women with three doses (0.60%) yet was high in those with only two doses (90.34%). Schedule adherence shortcomings may be explained by late presentation for ANC booking visits, as has been recognised by the WHO as a barrier to maternal immunisation.

Overall, maternal coverage for both influenza and TTV immunisations requires improvement which may be achieved by implementing educational campaigns within the health care setting, targeted at both practitioners and patients. Irregular adherence to immunisation guidelines suggests the need for investigations into the determinants thereof, whilst the low completion of

the tetanus schedule in conjunction with observed international success of the Tdap vaccine implementation, supports a revision of the maternal schedule to replace the tetanus toxoid vaccine with the tdap vaccine. This study has provided insight into clinical and demographic factors affecting the uptake of maternal vaccines in a pre-pandemic context, setting a comparison point for future studies assessing the impact of the pandemic on maternal health care.

Reference list:

1. Fuhler GM. The immune system and microbiome in pregnancy. Best Pract Res Clin Gastroenterol. 2020 Feb 1;44–45:101671.

2. Crofts KF, Alexander-Miller MA. Challenges for the Newborn Immune Response to Respiratory Virus Infection and Vaccination. Vaccines [Internet]. 2020;8(4):558. Available from: www.mdpi.com/journal/vaccines

3. Nunes MC, Madhi SA. Prevention of influenza-related illness in young infants by maternal vaccination during pregnancy. F1000Research [Internet]. 2018 [cited 2022 Mar 2];7. Available from: /pmc/articles/PMC5791002/

4. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol. 2012;2012.

5. Buchy P, Badur S, Kassianos G, Preiss S, Tam JS. Vaccinating pregnant women against influenza needs to be a priority for all countries: An expert commentary. Int J Infect Dis. 2020 Mar 1;92:1–12.

6. Beigi RH, Fortner KB, Munoz FM, Roberts J, Gordon JL, Han HH, et al. Maternal immunization: Opportunities for scientific advancement. Clin Infect Dis. 2014;59:S404–14.

7. Abu-Raya B, Maertens K, Edwards KM, Omer SB, Englund JA, Flanagan KL, et al. Global Perspectives on Immunization During Pregnancy and Priorities for Future Research and Development: An International Consensus Statement. Front Immunol. 2020 Jun 24;11:1282.

8. Lissauer D, Eldershaw SA, Inman CF, Coomarasamy A, Moss PAH, Kilby MD. Progesterone promotes maternal-fetal tolerance by reducing human maternal T-cell polyfunctionality and inducing a specific cytokine profile. Eur J Immunol. 2015 Oct 1;45(10):2858–72.

9. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and Infection. http://dx.doi.org/101056/NEJMra1213566 [Internet]. 2014 Jun 4 [cited 2021 Sep 16];370(23):2211–8. Available from: https://www.nejm.org/doi/full/10.1056/NEJMra1213566

10. Harris JW. Influenza Occurring in Pregnant Women: A Statistical Study of Thirteen Hundred and Fifty Cases. J Am Med Assoc [Internet]. 1919 Apr 5 [cited 2022 Feb 22];72(14):978–80. Available from: https://jamanetwork.com/journals/jama/fullarticle/220686

11. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, William Callaghan BM, et al. Pandemic 2009 Influenza A(H1N1) Virus Illness Among Pregnant Women in the United States [Internet]. 2010. Available from: https://jamanetwork.com/

12. Vousden Id N, Bunch K, Knight M. Incidence, risk factors and impact of seasonal influenza in pregnancy: A national cohort study. 2021; Available from: https://doi.org/10.1371/journal.pone.0244986

13. Meijer WJ, Noortwijk AGA van, Bruinse HW, Wensing AMJ. Influenza virus infection in pregnancy: a review. Acta Obstet Gynecol Scand [Internet]. 2015 Aug 1 [cited 2021 Oct 3];94(8):797–819. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/aogs.12680

14. Tempia S, Walaza S, Cohen AL, von Mollendorf C, Moyes J, McAnerney JM, et al. Mortality Associated With Seasonal and Pandemic Influenza Among Pregnant and Nonpregnant Women of Childbearing Age in a High-HIV-Prevalence Setting—South Africa, 1999–2009. Clin Infect Dis [Internet]. 2015 Oct 1 [cited 2021 Sep 17];61(7):1063–70. Available from: https://academic.oup.com/cid/article/61/7/1063/289192

15. Tempia S, Walaza S, Moyes J, Cohen AL, Von Mollendorf C, Treurnicht FK, et al. Risk Factors for Influenza-Associated Severe Acute Respiratory Illness Hospitalization in South Africa, 2012–2015. Open Forum Infect Dis [Internet]. 2017 [cited 2021 Nov 26];15. Available from: https://academic.oup.com/ofid/article/4/1/ofw262/2900559

16. Archer BN, Cohen C, Naidoo D, Thomas J, Makunga C, Blumberg L, et al. Interim report on pandemic H1N1 influenza virus infections in South Africa. Eurosurveillance. 2009;14(42):19369.

17. Wang X, Li Y, O'Brien KL, Madhi SA, Widdowson MA, Byass P, et al. Global burden of respiratory infections associated with seasonal influenza in children under 5 years in 2018: a systematic review and modelling study. Lancet Glob Heal. 2020 Apr 1;8(4):e497–510.

18. Shibeshi Messeret E, Masresha B, Yakubu A, Daniel F, Nshimirimana D, Okeibunor J, et al. Maternal and Neonatal Tetanus Elimination (MNTE) in The WHO African Region. Journal of Immunological Sciences Research Article. 2018.

19. Maertens K, Orije MRP, Van Damme P, Leuridan E. Vaccination during pregnancy: current and possible future recommendations. Eur J Pediatr 2020 1792 [Internet]. 2020 Jan 7 [cited 2021 Sep 18];179(2):235–42. Available from: https://link.springer.com/article/10.1007/s00431-019-03563-w

20. Faria APV, da Silva TPR, Duarte CK, Mendes LL, Santos FBO, Matozinhos FP. Tetanus vaccination in pregnant women: a systematic review and meta-analysis of the global literature. Public Health. 2021 Jul 1;196:43–51.

21. Njuguna HN, Yusuf N, Raza AA, Ahmed B, Tohme RA. Progress Toward Maternal and Neonatal Tetanus Elimination — Worldwide, 2000–2018. Morb Mortal Wkly Rep [Internet]. 2020 May 1 [cited 2021 Oct 2];69(17):515. Available from: /pmc/articles/PMC7206986/

22. Suchard M. Neonatal tetanus [Internet]. Vol. 19, Communicable Diseases Communiqué. 2020 [cited 2021 Sep 19]. Available from: https://www.nicd.ac.za/wp-content/uploads/2020/04/NICD-Communicable-Disease-Communique-April-2020-Neonatal-

tetanus.pdf

23. Simister NE, Mostov KE. An Fc receptor structurally related to MHC class I antigens. Nat 1989 3376203 [Internet]. 1989 [cited 2022 Mar 1];337(6203):184–7. Available from: https://www.nature.com/articles/337184a0

24. Clements T, Rice TF, Vamvakas G, Barnett S, Barnes M, Donaldson B, et al. Update on Transplacental Transfer of IgG Subclasses: Impact of Maternal and Fetal Factors. Front Immunol. 2020 Sep 11;11:1920.

25. World Health Organization. Safety of Immunization during Pregnancy Safety of Immunization during Pregnancy A review of the evidence Global Advisory Committee on Vaccine Safety. 2014 [cited 2021 Sep 19]; Available from: www.who.int

26. Walaza S, Cohen C. Recommendations pertaining to the use of influenza vaccines and influenza antiviral drugs, 2016. South African Med J. 2016 Mar 1;106(3):251–3.

27. Blumberg L, Cohen C, Dawood H, Hellferscee O, Karstaedt A, Mccarthy K, et al. Influenza NICD recommendations for the diagnosis, prevention, management and public health response [Internet]. 2020 [cited 2021 Sep 20]. Available from: https://www.nicd.ac.za/wp-content/uploads/2020/04/INFLUENZA-GUIDELINES-2020.pdf

28. McAnerney JM, Cohen C, Moyes J, Besselaar TG, Buys A, Schoub BD, et al. Twenty-five Years of Outpatient Influenza Surveillance in South Africa, 1984–2008. J Infect Dis [Internet]. 2012 Dec 15 [cited 2021 Nov 23];206(suppl_1):S153–8. Available from: https://academic.oup.com/jid/article/206/suppl_1/S153/984432

29. World Health Organization. Tetanus vaccines: WHO position paper – February 2017. 2017 [cited 2021 Sep 20]; Available from: https://www.who.int/publications/i/item/tetanus-vaccines-who-position-paper-february-2017

30. Stats SA. Maternal Health Indicators | Statistics South Africa [Internet]. 2020 [cited 2022 May 3]. Available from: https://www.statssa.gov.za/?p=13100

31. Jones CE, Calvert A, Le Doare K. Vaccination in pregnancy - Recent developments. Pediatr Infect Dis J [Internet]. 2018 Feb 1 [cited 2022 Mar 3];37(2):191–3. Available from: https://journals.lww.com/pidj/Fulltext/2018/02000/Vaccination_in_Pregnancy_Recent_Developments.19.aspx

32. Wolter N, Cohen C, Tempia S, Walaza S, Moosa F, du Plessis M, et al. Epidemiology of Pertussis in Individuals of All Ages Hospitalized With Respiratory Illness in South Africa, January 2013—December 2018. Clin Infect Dis [Internet]. 2021 Aug 2 [cited 2022 Mar 3];73(3):e745–53. Available from: https://academic.oup.com/cid/article/73/3/e745/6126768

33. McMorrow ML, Tempia S, Walaza S, Treurnicht FK, Ramkrishna W, Azziz-Baumgartner E, et

al. Prioritization of risk groups for influenza vaccination in resource limited settings – A case study from South Africa. Vaccine. 2019 Jan 3;37(1):25–33.

34. Zhong Z, Haltalli M, Holder B, Rice T, Donaldson B, O'Driscoll M, et al. The impact of timing of maternal influenza immunization on infant antibody levels at birth. Clin Exp Immunol [Internet]. 2019 Jan 13 [cited 2022 Mar 7];195(2):139–52. Available from: https://academic.oup.com/cei/article/195/2/139/6403715

35. Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, et al. Influenza Vaccination of Pregnant Women and Protection of Their Infants. N Engl J Med [Internet]. 2014 Sep 4 [cited 2022 Mar 10];371(10):918–31. Available from: https://www.nejm.org/doi/10.1056/NEJMoa1401480

36. Amirthalingam G, Campbell H, Ribeiro S, Fry NK, Ramsay M, Miller E, et al. Sustained Effectiveness of the Maternal Pertussis Immunization Program in England 3 Years Following Introduction. Clin Infect Dis [Internet]. 2016 Dec 1 [cited 2022 Mar 3];63(suppl_4):S236–43. Available from: https://academic.oup.com/cid/article/63/suppl_4/S236/2526423

37. Amirthalingam G, Andrews N, Campbell H, Ribeiro S, Kara E, Donegan K, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet. 2014 Oct 25;384(9953):1521–8.

38. Sandmann F, Jit M, Andrews N, Buckley HL, Campbell H, Ribeiro S, et al. Evaluating the impact of a continued maternal pertussis immunisation programme in England: A modelling study and cost-effectiveness analysis. Vaccine [Internet]. 2021 Jul 22 [cited 2022 May 8];39(32):4500–9. Available from: https://doi.org/10.1016/j.vaccine.2021.06.042

39. Eberhardt CS, Blanchard-Rohner G, Lemaître B, Boukrid M, Combescure C, Othenin-Girard V, et al. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis. Clin Infect Dis An Off Publ Infect Dis Soc Am [Internet]. 2016 Apr 1 [cited 2022 Mar 9];62(7):829. Available from: /pmc/articles/PMC4787611/

40. Tessier E, Campbell H, Ribeiro S, Fry NK, Brown C, Stowe J, et al. Impact of Extending the Timing of Maternal Pertussis Vaccination on Hospitalized Infant Pertussis in England, 2014–2018. Clin Infect Dis [Internet]. 2021 Nov 2 [cited 2022 Mar 9];73(9):e2502–8. Available from: https://academic.oup.com/cid/article/73/9/e2502/5860914

41. Purandare CN, Preiss S, Kolhapure S, Sathyanarayanan S. Expert opinion on the way forward for improving maternal influenza vaccination in India. https://doi.org/101080/1476058420211932474 [Internet]. 2021 [cited 2022 Mar 16];20(7):773–8. Available from: https://www.tandfonline.com/doi/abs/10.1080/14760584.2021.1932474

42. Top KA, Arkell C, Scott H, McNeil SA, Mannerfeldt J, Ortiz JR, et al. Effect of package insert language on health-care providers' perceptions of influenza vaccination safety during pregnancy. Lancet Glob Heal [Internet]. 2016 Oct 1 [cited 2022 May 10];4(10):e690–1. Available from: http://www.thelancet.com/article/S2214109X16301826/fulltext

43. Sanofi Pasteur Ltd. Summary of Product Characteristics: Vaxigrip Tetra [Internet]. 2020 [cited 2022 May 10]. Available from: https://www.fda.moph.go.th/sites/drug/Shared Documents/Vaccine/U1DR2C1072611500311C-SPC.pdf

44. Katz J, Englund JA, Steinhoff MC, Khatry SK, Shrestha L, Kuypers J, et al. Impact of Timing of Influenza Vaccination in Pregnancy on Transplacental Antibody Transfer, Influenza Incidence, and Birth Outcomes: A Randomized Trial in Rural Nepal. Clin Infect Dis [Internet]. 2018 Jul 18 [cited 2022 Mar 7];67(3):334–40. Available from: https://academic.oup.com/cid/article/67/3/334/4857181

45. Singh M, Tanvir T, Nagoji D, Madan A, Gattem S, Singh H. Influenza vaccine: A viable option to protect pregnant women and infants from seasonal flu: A retrospective hospital-based study in India. Int J Clin Pract [Internet]. 2019 Jul 1 [cited 2022 Mar 16];73(7):e13361. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/ijcp.13361

46. Abu-Raya B, Edwards KM. Optimizing the Timing of Vaccine Administration during Pregnancy. JAMA - J Am Med Assoc. 2019 Mar 12;321(10):935–6.

47. Godongwana M, Myburgh N, Adedini SA, Cutland C, Radebe N. Knowledge and attitudes towards maternal immunization: perspectives from pregnant and non-pregnant mothers, their partners, mothers, healthcare providers, community and leaders in a selected urban setting in South Africa. Heliyon. 2021 Jan 1;7(1):e05926.

48. Ramkrishna W, Moonasar D, Tempia S, McMorrow M, Walaza S, Cohen C. Policy implementation to improve seasonal influenza vaccination of targetgroups in South Africa, 2011-2018. [Unpublished]. 2019;

49. Bishop K, McMorrow M, Meiring S, Walaza S, Rossi L, Mhlanga S, et al. An evaluation of an influenza vaccination campaign targeting pregnant women in 27 clinics in two provinces of South Africa, 2015 – 2018. BMC Heal Serv Res 2021 211 [Internet]. 2021 Sep 9 [cited 2021 Oct 3];21(1):1–8. Available from: https://link.springer.com/articles/10.1186/s12913-021-06962-8

50. Lutz CS, Carr W, Cohn A, Rodriguez L. Understanding barriers and predictors of maternal immunization: Identifying gaps through an exploratory literature review. Vaccine [Internet]. 2018 Nov 26 [cited 2021 Nov 26];36(49):7445–55. Available from: https://pubmed.ncbi.nlm.nih.gov/30377064/

51. Sebghati M, Khalil A. Uptake of vaccination in pregnancy. Best Pract Res Clin Obstet Gynaecol. 2021 Apr 6;

52. Arnold LD, Luong L, Rebmann T, Chang JJ. Racial disparities in U.S. maternal influenza vaccine uptake: Results from analysis of Pregnancy Risk Assessment Monitoring System (PRAMS) data, 2012–2015. Vaccine. 2019 Apr 24;37(18):2520–6.

53. Chimukuche RS, Ngwenya N, Seeley J, Nxumalo PS, Nxumalo ZP, Godongwana M, et al. Assessing Community Acceptance of Maternal Immunisation in Rural KwaZulu-Natal, South Africa: A Qualitative Investigation. Vaccines [Internet]. 2022;10(415). Available from: https://doi.org/10.3390/vaccines10030415

54. Abu Raya B, Srugo I, Kessel A, Peterman M, Bader D, Gonen R, et al. The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels – A prospective study. Vaccine. 2014 Oct 7;32(44):5787–93.

55. Healy CM, Rench MA, Swaim LS, Smith EOB, Sangi-Haghpeykar H, Mathis MH, et al. Association Between Third-Trimester Tdap Immunization and Neonatal Pertussis Antibody Concentration. JAMA [Internet]. 2018 Oct 9 [cited 2022 Mar 9];320(14):1464–70. Available from: https://jamanetwork.com/journals/jama/fullarticle/2706137

56. Winter K, Nickell S, Powell M, Harriman K. Effectiveness of Prenatal Versus Postpartum Tetanus, Diphtheria, and Acellular Pertussis Vaccination in Preventing Infant Pertussis. Clin Infect Dis [Internet]. 2017 Jan 1 [cited 2022 Mar 14];64(1):3–8. Available from: https://pubmed.ncbi.nlm.nih.gov/27624955/

57. Naidu MA, Muljadi R, Davies-Tuck ML, Wallace EM, Giles ML. The optimal gestation for pertussis vaccination during pregnancy: a prospective cohort study. Am J Obstet Gynecol. 2016 Aug 1;215(2):237.e1-237.e6.

58. Pathirana J, Nkambule J, Black S. Determinants of maternal immunization in developing countries. Vaccine. 2015 Jun 12;33(26):2971–7.

59. Yaya S, Kota K, Buh A, Bishwajit G. Antenatal visits are positively associated with uptake of tetanus toxoid and intermittent preventive treatment in pregnancy in Ivory Coast. BMC Public Health [Internet]. 2019 Nov 6 [cited 2022 May 8];19(1):1–12. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-019-7847-1

60. Tsawe M, Moto A, Netshivhera T, Ralesego L, Nyathi C, Susuman AS. Factors influencing the use of maternal healthcare services and childhood immunization in Swaziland. Int J Equity Health [Internet]. 2015 Mar 27 [cited 2022 Mar 16];14(1):1–11. Available from: https://equityhealthj.biomedcentral.com/articles/10.1186/s12939-015-0162-2

61. Hlongwane TMAG, Bozkurt B, Barreix MC, Pattinson R, Gülmezoglu M, Vannevel V, et al.

Implementing antenatal care recommendations, South Africa. Bull World Health Organ [Internet]. 2021 Mar 1 [cited 2022 Mar 16];99(3):220. Available from: /pmc/articles/PMC7941100/

62. Doraivelu K, Boulet SL, Biswas HH, Adams JC, Haddad LB, Jamieson DJ. Predictors of tetanus, diphtheria, acellular pertussis and influenza vaccination during pregnancy among full-term deliveries in a medically underserved population. Vaccine. 2019 Sep 24;37(41):6054–9.

63. WHO. WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience 1 WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience: Summary [Internet]. 2018 [cited 2022 May 10]. Available from: www.mcsprogram.org

64. Tempia S, Walaza S, Moyes J, Cohen AL, Von Mollendorf C, Treurnicht FK, et al. Risk Factors for Influenza-Associated Severe Acute Respiratory Illness Hospitalization in South Africa, 2012–2015. Open Forum Infect Dis [Internet]. 2017 Jan 1 [cited 2022 Feb 24];4(1). Available from: https://academic.oup.com/ofid/article/4/1/ofw262/2900559

65. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009 Apr 1;42(2):377–81.

66. Stats SA. Mid-year population estimates [Internet]. 2021 [cited 2022 Jul 16]. Available from: https://www.statssa.gov.za/publications/P0302/P03022021.pdf

67. Quinn J-A, Munoz FM, Gonik B, Frau L, Cutland C, Mallett-Moore T, et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data q. Vaccine [Internet]. 2016;34:6047–56. Available from: http://dx.doi.org/10.1016/j.vaccine.2016.03.045

68. Naqvi F, Naqvi S, Billah SM, Saleem S, Fogleman E, Peres-da-Silva N, et al. Knowledge, attitude and practices of pregnant women related to COVID-19 infection: A cross-sectional survey in seven countries from the Global Network for Women's and Children's Health. BJOG An Int J Obstet Gynaecol [Internet]. 2022 Jul 1 [cited 2022 Sep 13];129(8):1289–97. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/1471-0528.17122

69. Stats SA. General Household Survey [Internet]. 2018 [cited 2022 Sep 9]. Available from: http://www.statssa.gov.za/publications/P0318/P03182018.pdf#page=37

70. Lengana SGP, McMorrow M, Tshangela A, Meiring S, Nunes M, Cutland C, et al. Evaluation of an influenza vaccination campaign among pregnant women in two provinces in South Africa, 2015. Int J Infect Dis [Internet]. 2016 Dec 1 [cited 2022 Sep 9];53:146–7. Available from: http://www.ijidonline.com/article/S1201971216315776/fulltext

71. Corbeau M, Mulliez A, Chenaf C, Eschalier B, Lesens O, Vorilhon P. Trends of influenza

vaccination coverage in pregnant women: a ten-year analysis from a French healthcare database. Sci Reports 2022 121 [Internet]. 2022 May 3 [cited 2022 Sep 12];12(1):1–9. Available from: https://www.nature.com/articles/s41598-022-11308-3

72. Popova S, Lange S, Probst C, Shield K, Kraicer-Melamed H, Ferreira-Borges C, et al. Actual and predicted prevalence of alcohol consumption during pregnancy in the WHO African Region. Trop Med Int Health [Internet]. 2016 Oct 1 [cited 2022 Sep 12];21(10):1209–39. Available from: https://pubmed.ncbi.nlm.nih.gov/27429168/

73. May PA, Marais A-S, De Vries MM, Buckley D, Kalberg WO, Hasken JM, et al. The prevalence, child characteristics, and maternal risk factors for the continuum of fetal alcohol spectrum disorders: A sixth population-based study in the same South African community. Drug Alcohol Depend. 2021 Jan 1;218(108408).

74. Raut S, Apte AI, Srinivasan M, Dudeja N, Dayma G, Sinha B, et al. Determinants of maternal influenza vaccination in the context of low- and middle-income countries: A systematic review. 2022; Available from: https://doi.org/10.1371/journal.pone.0262871

75. Arriola CS, Vasconez N, Thompson M, Mirza S, Moen AC, Bresee J, et al. Factors associated with a successful expansion of influenza vaccination among pregnant women in Nicaragua. Vaccine. 2016 Feb 17;34(8):1086–90.

76. Ifenne DI, Utoo BT. Gestational age at booking for antenatal care in a tertiary health facility in north-central, Nigeria. Niger Med J [Internet]. 2012 [cited 2022 Sep 12];53(4):236. Available from: /pmc/articles/PMC3640246/

77. Imaralu J, Adekoya A, Akadri A, Bamidele F, Nwankpa C, Sotunsa J. A facility-based survey of maternal anti-tetanus vaccination schedule completion in a Nigerian university community. Ann Heal Res [Internet]. 2022 Jun 1 [cited 2022 Sep 13];8(2):141–53. Available from: https://www.ajol.info/index.php/ahr/article/view/226374

78. Barrow A, Barrow S, Jobe A. Differentials in prevalence and correlates on uptake of tetanus toxoid and intermittent preventive treatment with sulfadoxine-pyrimethamine during pregnancy: A community-based cross-sectional study in The Gambia. https://doi.org/101177/20503121211065908 [Internet]. 2022 Jan 5 [cited 2022 Sep 13];10:205031212110659. Available from: https://journals.sagepub.com/doi/full/10.1177/20503121211065908

79. Yaya S, Kota K, Buh A, Bishwajit G. Prevalence and predictors of taking tetanus toxoid vaccine in pregnancy: a cross-sectional study of 8,722 women in Sierra Leone. BMC Public Health [Internet]. 2020 Jun 5 [cited 2022 Sep 13];20(1). Available from: /pmc/articles/PMC7273659/

80. Gebremedhin TS, Welay FT, Mengesha MB, Assefa NE, Werid WM. Tetanus Toxoid Vaccination Uptake and Associated Factors among Mothers Who Gave Birth in the Last 12 Months in Errer District, Somali Regional State, Eastern Ethiopia. Biomed Res Int. 2020;2020.

81. Borrow R, Balmer P, Roper MH. Immunological basis for immunization : Molule 3 : Tetanus (update 2006). World Health Organization. Department of Immunization, Vaccines and Biologicals.; 2018.

82. Kohli-Lynch CN, Erzse A, Rayner B, Hofman KJ. Hypertension in the South African public healthcare system: a cost-of-illness and burden of disease study. BMJ Open [Internet]. 2022 Feb 1 [cited 2022 Sep 13];12(2):e055621. Available from: https://bmjopen.bmj.com/content/12/2/e055621

83. Centers for Disease Control and Prevention. Tdap (Pertussis) Vaccine and Pregnancy | CDC [Internet]. 2017 [cited 2022 Sep 13]. Available from: https://www.cdc.gov/vaccines/pregnancy/hcp-toolkit/tdap-vaccine-pregnancy.html

Appendix A: Plagiarism Declaration

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PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I Julia Bourne (Student number: 1634880) am a student registered for the degree of MSc(Med) Vaccinology in the academic year 2.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
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R14/49 Miss Julia Bourne

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M211181

NAME: (Principal Investigator)	Miss Julia Bourne
DEPARTMENT:	School of Pathology
PROJECT TITLE:	Maternal vaccination in South Africa: timing and completeness
DATE CONSIDERED:	26/11/2021
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr C. Cutland
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	20/01/2022

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I **agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore be due in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

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