Vaccine Utilization and Timing of Administration in Pregnant Women

A South African Perspective

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Background: Maternal immunization is a valuable public health measure protecting the mother, fetus and newborn infant against targeted infectious diseases, playing an integral role in pregnancy outcomes. Limited literature exists from the African continent pertaining to the timing and utilization of maternal influenza and tetanus toxoid immunization. Maintaining high vaccine coverage is imperative for successful disease control, highlighting the importance of continued maternal immunization. We aimed to describe the utilization and timing of influenza and tetanus vaccinations during pregnancy, within South African publicly financed antenatal care facilities.

Methods: A secondary analysis was conducted of clinical antenatal, vaccination and delivery data collected during a retrospective review of randomly selected maternity charts of women who delivered between July 2018 and June 2019 in Johannesburg and Cape Town, South Africa.

Results: Influenza vaccination uptake within the sampled population was 16.6% (806/4851), with significantly higher odds of influenza vaccination in women 21-30 years of age and women with ≥6 antenatal care visits. Of 7031 (99.0% of the population) women who received at least 1 dose of tetanus toxoid–containing vaccine (TTCV), 39.2% (2759) received 1 dose; 51.0% (3590) received 2 and 9.7% (682) received 3 doses in their index pregnancy.

Conculsions: Antenatal facilities are ideally suited to administer vaccines to pregnant women; however, targeted educational campaigns and immunization promotion by antenatal staff will improve maternal influenza immunization coverage. There is high utilization of TTCV in South Africa, with over 99% of women receiving at least 1 dose of TTCV, which is encouraging, especially considering that South Africa is implementing a single dose of a combination tetanus-diphtheria-acellular pertussis vaccine to replace tetanus toxoid (TT) in pregnancy.

Key Words: tetanus toxoid–containing vaccine, influenza vaccine, pregnant women, South Africa, vaccine utilization

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BACKGROUND

Maternal immunization is a valuable public health measure protecting the mother, fetus and newborn infant against targeted infectious diseases, playing an integral role in pregnancy outcomes.[1,2] During pregnancy, maternal immune system changes are believed responsible for the heightened vulnerability of pregnant women to certain diseases such as influenza, which has been shown to disproportionally burden pregnant women and adversely affect pregnancy outcomes.[3] Tetanus has a high (80%–100%) mortality rate in infected neonates in the absence of medical intervention. The environmental origin of tetanus makes eradication impossible, highlighting the importance of maternal vaccination to maintain elimination.[4–6]

Maternal vaccination against tetanus and influenza[7] is recommended by the World Health Organization (WHO), and South African schedules align with WHO recommendations.[6] Over 80% coverage with 6 doses of tetanus toxoid–containing vaccine (TTCV) is recommended during childhood and adolescence to provide full protection against tetanus; however, as 80% coverage is not achieved in some regions, at least 1 dose of TTCV is recommended in pregnancy.[6] TTCV schedule for previously unvaccinated pregnant women includes 3 doses, with the first 2 doses administered a month apart and the third dose administered 6 months after the second dose.[6] Compliance with a 7-month-long vaccination schedule during a 9-month-long pregnancy is challenging and impractical, especially when women present late for antenatal care (ANC). Influenza vaccines are usually available annually in South Africa between March and September and are available at ANC clinics.[8] The vaccination of pregnant women against influenza and tetanus has been utilized successfully as a public health strategy globally to improve maternal and neonatal health.[2] Other vaccines, including pertussis[9,10] and SARS-CoV-2[11,12] vaccines, are recommended for use in pregnant women and have been implemented in most high-income countries and some low- and middle-income countries (LMICs). Immunization against pertussis has been introduced into South African publicly financed ANC in 2024.

Maternal immunization uptake is affected by social factors such as lower education status, ethnicity and vaccine safety concerns, as well as positive HIV status.[13–15] Initiation of ANC late in pregnancy and limited ANC clinic visit attendance reduces adequate TTCV coverage in LMICs.[16] In addition, there are numerous barriers within health systems in LMICs, which reduce vaccine delivery and uptake, including a lack of coordination of immunization services for pregnant women, cold-chain management issues and limited health workforce capacity.[17] Though globally well-described, there is limited literature from Africa on the utilization and timing of these vaccines. Conferring high-income country statistics to LMIC populations is inappropriate due to differences in health-seeking behaviors and care practices.[16]

This study aimed to describe the timing and utilization of recommended and available maternal immunizations (tetanus toxoid and influenza) and describe demographic and clinical factors

affecting the utilization of vaccines in South African pregnant women accessing ANC at public healthcare facilities.

METHODS

Study Participants and Oversights

We conducted a secondary analysis of maternal, fetal and neonatal health and ANC visit data abstracted from the maternity charts of women enrolled in the parent project, "Epidemiology of obstetric and neonatal outcomes in South Africa."[18] The parent project was a retrospective record review of maternity charts across 3 regions in South Africa: (1) Soweto; (2) Inner City Johannesburg, both in Gauteng; and (3) Metro East Cape Town in Western Cape, with each site comprised of a tertiary hospital and referring primary health centers. Permission to conduct the parent project was obtained from the Human Research Ethics Committees of the University of the Witwatersrand and Stellenbosch University (reference numbers: 180707 and N18/10/122), and approval was obtained from Wits Human Research Ethics Committees for this project (reference number: M211181 MED21-11-044).

Study Procedures

Participant Selection and Oversight

In the parent study, which has been described elsewhere,[18] data from maternity records of 9371 pregnant women who gave birth at a participating site between July 1, 2017, and June 30, 2018, were abstracted retrospectively and captured on a study-specific Research Electronic Data Capture database.[19]

Data Abstraction

Pertinent variables from the parent project database were selected for this study, including those necessary for assessing the timing and utilization of influenza and tetanus vaccines, and demographic and clinical factors potentially affecting maternal immunization utilization.

Statistical Analysis

The data were analyzed using STATA version 16.1 (StataCorp, Texas). The distribution of nonnormally distributed continuous variables was expressed using the median and interquartile ranges (IQRs), which were compared between vaccine groups (influenza and tetanus) using the Wilcoxon rank-sum test. Univariate logistic regression was used to assess variable relationships. The data are described using odds ratios with a 95% confidence interval and percentages. A P value of <0.05 was considered significant for all statistical tests.

RESULTS

Participants

Of 9371 women, 375 (4.0%) had no antenatal visits (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/G20). Of the remaining 8996 participants, 85.9% lived in Gauteng, and 54.2% were between 21 and 30 years of age (see Tables, Supplemental Digital Content 2, http://links.lww.com/INF/G21, and Supplemental Digital Content 3, http://links.lww.com/INF/G22). Most women (96.9%) were Black African and reported no pre-existing noninfectious medical conditions (89.6%; see Table, Supplemental Digital Content 3, http://links.lww.com/INF/G22). The HIV prevalence was 28.0% overall, and 4.0%, 0.5% and 7.2% of women reported smoking, use of recreational drugs or alcohol use, respectively. Most (79.7%) women attended at least 4 ANC visits, with 61.6% having their first ANC visit during their second trimester (13–27 weeks). Most women (71.8%) were multiparous and delivered live infants (98.1%), most commonly via vaginal delivery (63.2%; see Tables, Supplemental Digital Content 2, http://links.lww.com/INF/G21, and Supplemental Digital Content 3, http://links.lww.com/INF/G22).

Factors Affecting Influenza Immunization During Pregnancy (See Table, Supplemental Digital Content 4, http://links.lww.com/INF/G23, and Figures, Supplemental Digital Content 1, http://links.lww.com/INF/G20, 5, http://links.lww.com/INF/G24, and 6, http://links.lww.com/INF/G25)

Influenza vaccine records were available for 4851/8996 (53.9%) of women who had at least 1 antenatal visit during the vaccine availability period (April 1, 2017, to July 31, 2017, or April 01, 2018, to June 30, 2018). Women who did not attend ANC visits in these periods were excluded. There was no difference in median gestational age at the first ANC visit (booking visit) of the immunized [18.0 (IQR, 13.0–23.0) weeks; see Table, Supplemental Digital Content 4, http://links.lww.com/INF/G23] and nonimmunized women [18.1 (IQR, 12.9–23.0) weeks]. Women who booked at ANC in their third trimester (≥28 weeks) were significantly less likely to be vaccinated than those who presented in their first trimester [≤12 weeks; odds ratio (OR), 0.7 (95% confidence interval [CI], 0.6–1.0)]. Women 21-30 years old were more likely to have received an influenza vaccination compared with women of ≤20 years of age [OR, 1.44 (95% CI, 1.1–1.9)].

Most women receiving the influenza vaccine also received the tetanus vaccine (92.7%; 747/806; see Table, Supplemental Digital Content 4, http://links.lww.com/INF/G23). No significant associations were found between influenza uptake and other observed variables.

Factors Affecting Tetanus Immunization During Pregnancy (See Tables, Supplemental Digital Content 7, http://links.lww.com/INF/G26, and Supplemental Digital Content, http://links.lww.com/INF/G27)

Of 7105 women with TTCV recorded, 74 (1.0%) were excluded because of incomplete data. Of women with recorded TTCV status, 39.2% (2759/7031) had 1 dose, 51.1% (3590/7031) had 2 doses and 9.7% (682/7031) had 3 doses (see Figure, Supplemental Digital Content 1, http://links.lww.com/INF/G20). Women with 1 or 2 TTCV doses were significantly older [median age, 27.7 (IQR, 23.5–32.7) years] than those with 3 doses of TTCV [26.7 (IQR, 22.2–31.6) years; $P < 0.01$). Compared with younger women (≤20 years), women 31-40 years of age were significantly less likely to receive 3 doses of TTCV [OR, 0.64 (95% CI, 0.48–0.84)]. Multiparous women had decreased odds of receiving 3 doses of TTCV than primigravid women (see Table, Supplemental Digital Content 4, http://links.lww.com/INF/G23).

Women who had 3 doses of TTCV presented significantly earlier for their booking visit [16.4 (95% CI, 11.1–21.3) weeks] than those with <3 doses of TTCV [20 (95% CI, 14.7–25) weeks; $P < 0.01$; see Table, Supplemental Digital Content 8, http://links.lww.com/INF/G27].

Timing of Tetanus Immunization (See Table, Supplemental Digital Content 7, http://links.lww.com/INF/G26, and Figures, Supplemental Digital Content 9, http://links.lww.com/INF/G28, Supplemental Digital Content 10, http://links.lww.com/INF/G29, Supplemental Digital Content 11, http://links.lww.com/INF/G30, and Supplemental Digital Content 12 http://links.lww.com/INF/G31)

Of the 7031 participants with confirmed TTCV receipt, data on the timing of their first dose were available for 6669 (94.9%) individuals (see Table, Supplemental Digital Content 7, http://links.lww.com/INF/G26). Of these women, 2615 (39.2%)

received only 1 dose and 3412 (51.2%) received 2 doses, while 642 (9.6%) received 3 doses of TTCV. Women were most likely to receive their first dose of TTCV in their second trimester (63.0% overall). Almost 30% of women who received 3 TTCV doses received their first dose in their first trimester compared with 12.9% and 17.2% of women who received 1 or 2 doses of TTCV (see Table, Supplemental Digital Content 7, http://links.lww.com/INF/G26). Only 12.4% (235/1894) of primigravida women, 8.8% (325/3681) of women with 2-3 pregnancies and 7.5% (82/1094) of women with >3 pregnancies received 3 TTCV doses.

Of the 3412 women who received 2 doses of TTCV, the majority (90.3%) received the doses a month apart. Of the 642 women who received 3 doses of TTCV, most (87.9%) had the first 2 doses administered a month apart. The interval between the second and third doses was correct (6 months apart) in just 2.6% of women (see Figure, Supplemental Digital Content 13, http://links.lww.com/INF/G32).

DISCUSSION

TTCVs and influenza vaccines are recommended for pregnant women and are available in public ANC facilities in South Africa; however, data have been limited on vaccine utilization and the timing of administration of these vaccines in pregnancy. We conducted a secondary analysis of data abstracted retrospectively from maternity (ANC and delivery) records of women who delivered in 3 urban areas in South Africa from July 2017 to June 2018 to ascertain vaccine utilization and timing.

Influenza vaccines are available seasonally (April to July annually), and vaccine administration peaks in April and May, preceding the influenza season. Women who presented for antenatal visits during the period when vaccines were available (beginning of April to the end of July) or delivered within the influenza season (April to September) had significantly increased odds of influenza vaccine utilization.

Despite high ANC attendance (69.9% of women had at least 1 ANC visit during the influenza vaccine availability window), influenza vaccine utilization was low (16.6%). Many influenza vaccines were administered during the second (45.5%, 322/708) or third (47.2%, 334/708) trimesters of pregnancy, which aligns with low ANC utilization during the first trimester (only 18.2% of women had a first trimester ANC visit).

Tetanus toxoid vaccine utilization was high, with 99% (7031/7105) of women receiving at least 1 TTCV dose in the index pregnancy. Women who were younger, had fewer previous pregnancies and/or had more ANC visits had an increased likelihood of receiving >1 dose of TTCV than older, multiparous women, as multiparous women would have received TTCV in previous pregnancies. Most women who received 3 doses of TTCV were primigravida; however, despite primigravida participants accounting for 28.9% of the cohort, only 9.1% of all participants received 3 doses of TTCV. In countries with good childhood TTCV coverage, such as South Africa,[20] 3 doses of TTCV in pregnancy are not required to provide adequate protection against maternal and neonatal tetanus.[6] Unfortunately, the lack of electronic- and life-course vaccination records and the retrospective design of this study limited ascertainment of how many women required >1 dose of TTCV.

Differences in uptake of TTCV and influenza vaccines differ significantly in this population. TTCVs are routinely administered throughout the year at booking ANC visits, whereas influenza vaccines are administered seasonally and at any ANC visit. Health systems barriers including lack of coordinated communication between healthcare providers in immunization services and ANC and vaccine seasonal availability or stockouts[17] could have contributed to the lower uptake of influenza vaccine compared with TTCV. In addition, the paper-based maternity record has a dedicated section to record TTCV but not influenza vaccines. This may have impacted the completeness of the recording of influenza vaccines by healthcare provider and data extraction by study staff.

Timing of TTCV Doses

Most women received their first TTCV in their second trimester of pregnancy, aligning with the median gestational age at ANC booking; therefore, the likelihood of women receiving 3 TTCV doses, which accurately aligned with the WHO-recommended dosing schedule (1 month between doses 1 and 2, and 6 months between doses 2 and 3), was small. Adherence to the recommended time window between the first 2 TTCV doses (1 month) was good (90.3% in time window); however, most third doses of TTCV (56.5%) were administered between 4 and 12 weeks (1–3 months) apart.

The influenza vaccine utilization in South Africa between 2011 and 2018 was consistently low (<16%)[21] and similar to our findings. Bishop et al[21] demonstrated significant success with targeted influenza campaigns, achieving a coverage rate of 78.7% from 2015 to 2018 at selected sites in South Africa. Their findings highlight that a major barrier to vaccination was stockouts, accounting for more than half of the instances where individuals were not vaccinated.[21] This underscores the potential for enhancing resource allocation and improving vaccine campaigns to increase maternal influenza vaccine utilization. The finding from this study, which was similarly observed by Bishop et al,[21] that increasing age negatively affects influenza vaccine uptake contrasts with French research, which found that younger women had lower uptake compared with those over 35 years of age.[22] In South Africa, no effect of HIV status on influenza vaccine utilization was found,[21] which contrasts with American findings that Women living with HIV had lower maternal vaccination uptake.[15] These differences cannot be generalized to South Africa due to varying disease burdens, with South Africa having a high HIV burden and limited representation of HIV-positive individuals in the American study.[15] Coadministration of influenza vaccine and TTCV was common, with over 60% of women who received both vaccines having received them concurrently. Consistent with findings from other LMICs, greater attendance at ANC visits increases the likelihood of immunization.[23,24] This is supported by findings from Malawi where poor ANC attendance reduced maternal immunization coverage.[16] These results underscore the importance of increasing maternal immunization through recommendations for improving ANC visit attendance.

Timing of Influenza Immunization

Similar to findings from France,[22] most women in our study were immunized in their second trimester. The later gestational age at ANC booking in our population aligns with a Nigerian population mean of 19.1 ± 7.8 weeks.[25] The observed low utilization may be explained by LMIC findings that earlier ANC presentation is associated with higher vaccine utilization due to increased opportunity for immunization advocacy, supporting that targeted vaccine campaigns increase utilization.[23] Immunization in the second or third trimester primarily protects the neonate, and no difference in vaccine efficacy has been reported when vaccines are administered in the second or third trimester.[26] This reinforces the recommendation that influenza immunization occur as soon as vaccines become available.[26] Therefore, in our study, influenza immunization occurred at the optimal gestational age for neonatal antibody transfer.

TTCV Coverage and Adherence

The observed coverage of at least 1 TTCV dose among our population was high (99.0%). This aligns closely with rates observed in other African countries: 83.9% in Nigeria,[27] 99.6% in Sierra Leone[28] and 88.2% in The Gambia.[29] However, coverage with at least 2 doses was lower in our population (60.8%) compared with Nigeria (84.9%)[27] but higher than in The Gambia (34.8%) and similar to Ethiopia (51.8%).[30] According to WHO guidelines, individuals should ideally receive 6 tetanus doses in their lifetime, but, for pregnant women with an unknown tetanus immunization history, WHO recommends at least 2 doses, followed by a third at least 6 months later.[6] Only 51.1% of our population received at least 2 doses of TTCV; however, this is not concerning due to the high utilization of TTCV in childhood[20] and in each pregnancy in South Africa.

Our finding that increased ANC visits correlate with higher odds of utilization of multiple doses of TTCV is supported by global literature,[4,16] highlighting the positive impact of increased health system exposure on maternal immunization coverage. In addition, these studies have found that higher parity is negatively associated with TTCV multiple dose utilization, likely due to prior TTCV doses. However, caution is needed in interpreting the low odds of receiving 3 doses of TTCV in older women in our cohort, as older women are less likely to require 3 TTCV doses due to vaccine utilization in prior pregnancies.

Timing of Maternal TTCV Immunization

Women presenting in the first trimester were more likely to receive 3 doses of TTCV than women presenting later in gestation, which is expected given the 7-month TTCV immunization schedule.[6] This finding aligns with previous studies showing that increased health system exposure is positively associated with maternal immunization utilization.[4,16,28] This study contributes to the body of evidence on the utilization of TTCV in South Africa and alignment with the WHO-recommended schedule. The challenge of schedule completion has been acknowledged by the WHO, largely attributed to late presentation for booking visits. In regions with suboptimal childhood and adolescent TTCV coverage, failure to appropriately implement TTCV in pregnancy can lead to insufficient antibody titers, impacting immunogenicity and duration of protection.[6]

LIMITATIONS AND FUTURE DIRECTIONS

This retrospective design of this study limited consideration and investigation of additional social factors influencing vaccine uptake decision-making.[31,32] We were unable to account for a woman's vaccine history in childhood or previous pregnancies, as the availability of documentation of life-course vaccinations is limited, and the study abstracted data retrospectively from paper-based maternity case records. In addition, the study did not address challenges related to missing records in paper-based systems or underreporting due to time-constrained ANC personnel. Moreover, external and health system–related information was not available to determine reasons for missed vaccinations, such as health personnel issues or system constraints such as stockouts, waiting periods or resource expiration. Nevertheless, the study effectively addresses vaccine utilization and baseline clinical and demographic variables influencing uptake.

Future Directions

Given the low influenza vaccine utilization identified in this and other[21] South African studies, implementing influenza health campaigns could enhance coverage among South African pregnant women.

An increase in pertussis cases identified in South Africa, particularly in young infants, prompted the South African Department of Health to introduce pertussis-containing vaccination into ANC in 2024 as a single dose of a combination tetanus-diphtheria-acellular pertussis (Tdap) vaccine administered in every pregnancy.[33] This change could better accommodate ANC initiation in later pregnancy, with optimal administration of Tdap vaccines in the second and third trimesters.

Given limited context-specific vaccine acceptability information in South Africa,[31,32] future research should include qualitative studies involving pregnant women, healthcare workers and community leaders to identify context-specific barriers to maternal vaccine uptake and utilization.

CONCLUSIONS

In conclusion, influenza vaccine utilization among the sampled pregnant population was low (16.6%), even during peak immunization periods. Despite spikes in immunization before the influenza season, utilization reached only 50% of eligible women at most. No associations were observed between influenza uptake and pre-existing medical conditions, race, HIV status, parity, gravidity, smoking or recreational drug use.

Antenatal population coverage with at least 1 TTCV dose during pregnancy was high (99.0%), and if there are no logistic issues with vaccine supply, we anticipate good utilization of a single dose of Tdap during pregnancy after its inclusion into South African ANC in 2024. Overall, maternal immunization utilization improvement strategies through educational campaigns within the health system are warranted. Nonadherence to immunization guidelines suggests the need for interventions, and high TTCV coverage in childhood in South Africa supports revising the maternal schedule to replace TTCV with a single dose of Tdap. This study provides insights into the clinical and demographic factors influencing maternal vaccine utilization and could serve as a benchmark for future studies assessing maternal immunization uptake.

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