Syphilis in Pregnancy: Exploring the prevalence and vertical transmission prevention cascade of syphilis using routinely collected electronic health data, Cape Town Metropolitan District, 2017–2022

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Student: Dr Jessica Gammon

Supervisors: Dr Alex de Voux / Dr Dave Le Roux

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Abstract

Introduction

Congenital Syphilis (CS), an important cause of perinatal morbidity and mortality, is notifiable in South Africa. CS results from vertical transmission of inadequately treated syphilis in pregnancy, a treatable sexually transmitted infection caused by *Treponema pallidum*. Gaps in our understanding of syphilis epidemiology exist amidst concerns of penicillin stockouts increasing CS cases. We evaluated current management and outcomes of syphilis in pregnancy in Cape Town.

Methods

We retrospectively reviewed routinely collected electronic health data on a pregnant cohort and their infants from the Western Cape Provincial Health Data Centre. Clinical administration data, pharmacy and laboratory data were collated for patients identified as pregnant between January 2017 and December 2022. Pregnant women's laboratory TPAb (Treponema pallidum antibody) and RPR (rapid plasma reagin) results were reviewed.

Results

419 376 pregnancies were identified, resulting in 425 128 outcomes. 47% of pregnancies had a documented laboratory syphilis test, with 6812 (1.6%) of total pregnancies testing RPR positive. A total of 996 infants had a positive RPR, with a RPR seropositivity in infants of 267 per 100 000 live births. 636 (64%) of these infants were born to mothers who had tested positive for syphilis in pregnancy, and the remainder were either born to mothers who did not have a lab test for syphilis in pregnancy, or who had screened negative for syphilis in pregnancy. The proportion of seropositive pregnancies increased over time from 764 (1.2%) in 2017 to 1324 (1.9%) in 2022. Testing practices differed between geographic service areas with some doing laboratory tests for syphilis for all pregnancies and others doing confirmatory laboratory tests only after positive point-of-care treponemal tests.

Of the syphilis seropositive pregnancies, 69% had no electronic evidence of appropriate treatment. 28% had recorded benzathine benzylpenicillin; 3% received amoxicillin with enzyme inhibitor; <1% received ceftriaxone. Only 23% of syphilis-positive women had a follow-up RPR titre. The risk of adverse pregnancy outcomes was higher among syphilis seropositive compared to seronegative women; neonatal deaths RR 1.91 (95% CI 1.53-2.38) and RR of stillbirths 2.52 (95% CI 2.25, 2.82). The risk of adverse perinatal outcomes was higher in those with high-titre active syphilis than low-titre syphilis.

Conclusion

Routine electronic health data can provide oversight of CS prevention. Electronic capturing of pharmacy data is suspected to be incomplete and requires independent verification. There is an increasing prevalence trend of syphilis in pregnancy, resulting in preventable stillbirths and neonatal deaths. Increasing syphilis prevalence requires a public health response to ensure adequate treatment and repeat RPR titres to monitor response. Cases treated with an alternative regimen should be audited to assess outcomes. RPR seropositivity in infants is higher than national estimates, and is likely an underestimate.

Purpose

Syphilis, caused by *Treponema pallidum,* is a treatable sexually transmitted infection that continues to result in perinatal morbidity and mortality. Syphilis in pregnancy can result in adverse pregnancy outcomes (1) and therefore, screening for and treating syphilis forms part of routine antenatal care in many countries, including South Africa (SA).

Congenital syphilis is a notifiable condition in SA and is tracked by the National Institute of Communicable Diseases (NICD), although reporting has been described as inconsistent and under-reporting is suspected (2). In addition to this, national antenatal seroprevalence surveys estimate the prevalence of syphilis in the country and for each province, however there is a gap in our understanding of the epidemiology of syphilis in pregnancy and congenital syphilis at a District level. At a local level in the Cape Town Metro District in the Western Cape there have been anecdotal reports from paediatricians of an increase in congenital syphilis cases.

The first-line treatment for syphilis is benzathine penicillin, given intramuscularly. This is the only treatment that is effective in treating both mother and fetus in pregnancy – as alternative therapies are either not safe in pregnancy or do not cross the placenta to treat the unborn fetus (1). *Treponema pallidum* remains sensitive to benzathine penicillin and benzathine penicillin is inexpensive, however global stock-outs of benzathine penicillin have been described since 2013 resulting in sub-optimal treatment of syphilis (3). SA and the Western Cape have experienced benzathine penicillin stock-outs and shortages (2), and health care providers have been required to use alternative therapies. In the SA Standard Treatment Guidelines for STIs (2018), the suggested alternative therapy for pregnant women with syphilis if penicillin is unavailable, is amoxicillin with probenecid (4). These guidelines fail to state that this treatment does not sufficiently treat the fetus. In the maternal STI treatment guidelines, no alternative option is suggested in treating syphilis in pregnancy (5).

The COVID-19 pandemic and mitigation measures have negatively impacted routine health services including reproductive services and may have also contributed to variations in routine testing and treatment of syphilis in pregnant women(6).

Given the gaps in our understanding of the syphilis epidemic at a local level, which limit our ability to inform the syphilis prevention cascade, there is a need to describe the epidemiology of syphilis in pregnancy and understand the management and outcomes of women who test positive for syphilis in pregnancy in Cape Town including whether this has changed over time. If there has been an increase in syphilis in pregnancy, and an increase in cases of congenital syphilis over time - reasons for this should be understood to avert transmission of this preventable condition.

Literature Review

A literature search was done on PubMed and conducted on 4 July 2022, and repeated periodically to ensure that recent publications were considered. Keywords included (("Congenital Syphilis" OR "Maternal Syphilis" OR "Neonatal Syphilis" OR "Syphilis in Pregnancy") AND ("Diagnosis" OR "Detection" OR "Treatment")) AND ("Outcomes"). . An additional search was done for “Epidemiology” AND “South Africa” AND “Syphilis” OR “Syphilis in Pregnancy” OR “Congenital Syphilis”. Results were filtered for the English Language and any articles published prior to 2000 were excluded given the poor yield of citations in preceding decades. Abstracts reviewed, and full texts reviewed where the abstracts were specific to syphilis in pregnancy, were relevant to the research question and the full text was accessible. Additional relevant references were obtained through citations within literature reviewed, as well as reviews of gray literature, local protocols / policies and guidelines and references from experts in the field.

Background

Syphilis is first widely described in the 15th century at a time where rapid spread was seen across Europe, however the theories regarding the origins of the condition remain debated and theoretical (7). It was only later in the early 1900s that the spirochaete causing syphilis was discovered and named *Treponema pallidum*, and in 1906 and 1910 detection of syphilis through dark-field microscopy and serological tests were first described (7). Despite various treatments described for syphilis including mercury and Bismuth salts, it was only in the 20th Century that penicillin was discovered. In 1943 penicillin became the treatment modality of choice for syphilis, which it remains today (7). Globally, there was an initial decline in clinical cases of syphilis in the 1940s and 1950s following the introduction of penicillin, however syphilis remains a public health concern and continues to result in morbidity and mortality worldwide (8).

Globally there has been an estimated reduction in syphilis cases in pregnant women and cases of congenital syphilis between 2012 and 2016 (9), however, this has varied between regions. The United States of America (USA) is one of the countries in which an increase in the rates of congenital syphilis was seen (10) and it is thought that multiple factors could contribute to the variation in the reduction of antenatal syphilis between regions, including health care accessibility, acceptability and use of barrier contraception and socioeconomic factors including social disruption and inequity (11). Findings from Brazil suggest that reasons for ongoing congenital syphilis cases despite health system efforts to reduce congenital syphilis include inadequate prenatal care (associated with ineffective treatment) and untreated sexual partners. (12)

In women with untreated syphilis in pregnancy, a greater proportion of adverse birth outcomes (specified as stillbirth and fetal loss, neonatal death, prematurity and clinical evidence of syphilis) is seen as compared to women without syphilis in pregnancy (13). The World Health Organization (WHO) goal, set in 2007, was to eliminate congenital syphilis by 2015 through increased testing and treating, however this goal is not yet achieved (8,9). The WHO target agreed upon in 2012 is to have a congenital syphilis case rate of less than 50 cases per 100 000 live births (14).

WHO process targets for congenital syphilis elimination include(14):

i) At least 95% coverage of antenatal care (ANC) with at least one visit attained
ii) At least 95% of pregnant women in ANC tested for syphilis
iii) At least 95% of women tested positive for syphilis received adequate treatment

The clinical presentation of syphilis in pregnancy, similar to the presentation in a non-pregnant population, consists of a range of symptoms and can also be asymptomatic – thus screening is required. Screening for and treating syphilis in pregnancy remains essential in detecting syphilis in pregnancy and preventing congenital syphilis. Screening and treating for syphilis, however, is not without challenges. In addition to patient and health provider factors, the global shortage of penicillin is one of these challenges (3).

Pathophysiology / Biology of Syphilis

Syphilis is acquired from person-to-person through direct spread, either from an open syphilitic sore or through sexual transmission. It can also be vertically transmitted from a pregnant mother to her unborn baby trans placentally, at any stage of the pregnancy (1,15).

In adults, early syphilis will usually occur within 1 year following exposure – and can be further categorized into primary syphilis, secondary syphilis, and latent syphilis. Primary syphilis is characterized by a painless genital ulcer (known as a chancre, usually present on the vagina or cervix in females) and painless lymphadenopathy which may go unnoticed in women (8). Secondary syphilis presents with a wide range of symptoms including rashes and systemic symptoms that if left untreated will resolve within 1 to 6 months, after which a patient will enter the latent phase of disease.

As per the CDC definition, late syphilis occurs more than 1 year after initial exposure and can present >10 years after exposure(16). It can further be described as latent or tertiary syphilis. Latent late syphilis refers to a patient with positive syphilis serology, however the patient is asymptomatic and possible exposure is >1 year old or unknown. Tertiary syphilis includes symptoms that manifest more than 1 year after exposure and can affect the cardiovascular system and central nervous system (16). Syphilis affecting the central nervous system is referred to as neurosyphilis and can occur in both early and late disease(16).

Vertical transmission of syphilis occurs in two-thirds of cases of untreated primary or secondary syphilis in pregnant women (17). Adverse pregnancy outcomes associated with syphilis in pregnancy include congenital syphilis, premature birth, low birth weight, fetal death, still-birth and neonatal death; and these adverse outcomes are 12 times as likely to occur among untreated syphilitic-infected pregnant women as compared to uninfected pregnant women (8,9).

Diagnosis of Syphilis

Diagnosis of Syphilis in Adults

The diagnosis of syphilis is based on the combination of clinical history, examination, and investigations (laboratory tests and other); however, laboratory testing is essential in detecting latent infections without

clinical manifestations. Investigations include direct tests such as microscopy (presence of spirochetes under Dark field microscopy) or polymerase chain reaction (PCR), or indirect tests which test for antibodies (8). Direct tests are not widely available, and therefore the commonly used tests are serology.

The serological tests that are used are either Treponemal or Non-Treponemal. The United States Centers for Disease Control and Prevention (CDC) specifies that the diagnosis of syphilis requires both test types, and it is not sufficient to only use one test type as those tested during primary syphilis may have false-negative results, and those with previous syphilis (or no syphilis) may have false-positive results (otherwise known as a sero-fast state) (18).

Treponemal tests detect IgG and IgM antibodies to *Treponema pallidum* and include *Treponema pallidum*-particle agglutination assays (TP-PA), Fluorescent Treponemal Antibody-Absorption assay (FTA-ABS) and can remain positive for life, however 15%–25% of patients who are treated when in the primary stage of syphilis may have a negative treponemal test after 2–3 years (18,19).

Non-treponemal tests detect non-specific IgG and IgM antibodies that are released subsequent to infection with *Treponema pallidum* as a result of cell wall damage (8). Non-Treponemal tests commonly used include the Venereal disease research laboratory (VDRL) and Rapid Plasma Reagin (RPR) test. The RPR is widely used in South Africa and can be reported on qualitatively (reactive or non-reactive) as well as quantitatively (as a titre). RPR titres fluctuate according to disease stage, respond to treatment and thus can be used to monitor a patient's response to treatment (8), however false-positive RPR results can be seen in a number of medical conditions including infections (like HIV), pregnancy and autoimmune conditions (18).

Given the potential for asymptomatic disease and high rates of adverse pregnancy outcomes in untreated cases of maternal syphilis, ensuring that syphilis is diagnosed and treated early in pregnancy is essential to preventing adverse outcomes. The WHO recommends that all pregnant women be screened for syphilis during their antenatal care (10,15). Laboratory screening employs a combination of both treponemal and non-treponemal antibody tests in an algorithm and two common algorithms are described, the traditional syphilis algorithm and the "reverse" algorithm (19).

Importantly, point-of-care tests are being increasingly used in antenatal care settings to diagnose syphilis in pregnancy and enable same-day treatment(20).

Testing Algorithms

In the traditional testing algorithm, a non-treponemal antibody test is done first (both qualitatively and quantitatively). If reactive, a treponemal antibody test is done to confirm that the non-treponemal antibody detected is due to syphilis. The traditional algorithm may miss early active infections.

In the reverse testing algorithm, the testing begins with a treponemal antibody test. If positive, a non-treponemal antibody test is then done and quantified if reactive. The reverse algorithm will detect past infections that may have been treated (by doing the treponemal test in the first step of the algorithm) and has been described as preferable in laboratories with high testing volumes as the initial treponemal assays are less resource intensive from a laboratory perspective (19).

Table 1: Possible Syphilis diagnoses by Test Type and Result

		Treponemal Test	
		Reactive	Non-Reactive
Non-treponemal Test	Reactive	Syphilis Likely	Biological false positive
	Non-reactive	Possible past infection	Syphilis unlikely

Diagnosis of Congenital Syphilis

The diagnosis of congenital syphilis follows the same principles as that used in adults, however clinical features are different and specific to neonates and include an enlarged placenta that is typically pale and "hydropic"(8). Signs of congenital syphilis in neonates and young infants include a rash, rhinitis, hepatosplenomegaly and growth faltering (21). Clinical signs in untreated older infants and young children can include developmental delay, impaired hearing or sight, frontal bossing, "Hutchinson teeth", joint swelling and "sabre shins" (21).

In order to assist with global surveillance of congenital syphilis, and to assess the progress towards the WHO targets, a surveillance definition of congenital syphilis was agreed upon by experts in the field in 2012 (14). It is acknowledged that this definition is intended to standardize reporting, and account for different levels of the health care provision with different resource constraints – however not intended for clinical management(14).

The WHO defines a surveillance case of congenital syphilis as(14):

> *A stillbirth, live birth or fetal loss at >20 weeks gestation or >500g birthweight born to a syphilis seropositive mother without adequate syphilis treatment*
>
> *OR*
>
> *A stillbirth, live birth or child age <2 years born to a woman with positive syphilis serology or unknown sero-status, and with laboratory and/or radiologic and/or clinical evidence of syphilis infection (regardless of the timing and adequacy of maternal treatment* (9)

In South Africa, the National Institute of Communicable Diseases (NICD) has defined the congenital syphilis surveillance case definition in line with the WHO definition above. The NICD does however specify the phrase "syphilis seropositive" to be "a woman with positive non-treponemal syphilis serology (RPR/VDRL)" (21) and specifies the laboratory, radiological and/or clinical evidence of syphilis as discussed above and shown in Appendix A.

If the surveillance definition is considered, it is evident that an asymptomatic neonate may well meet the NICD case criteria for congenital syphilis based on maternal syphilis status alone. This emphasizes the importance of testing pregnant women for syphilis and treating where appropriate. Screening pregnant women for syphilis (usually at the first antenatal visit) is recommended by the WHO as part of the basic antenatal care package (22), however, guidelines regarding rescreening for syphilis in the third trimester differs between different countries and the cost-effectiveness of rescreening in the third trimester is dependent on the local context. The CDC recommends retesting for pregnant women who live in areas where there is a high prevalence of syphilis, have had no prior testing in pregnancy, are uninsured or low income, are diagnosed with an STI during pregnancy or exchange sex for money and or drugs (8,18).

Treatment of Syphilis in Pregnancy

Intramuscular benzathine penicillin is the only treatment for syphilis in pregnancy that has been shown to adequately treat both mother and fetus (1). When given prior to 28 weeks, benzathine penicillin will prevent almost all cases of congenital syphilis, and completion of treatment with benzathine penicillin at any stage of pregnancy is associated with a reduction in the risk of congenital syphilis when compared to those who did not complete treatment(10). Benzathine Penicillin treatment has also been shown to reduce the risk of syphilis-associated adverse birth outcomes which includes outcomes that are not included in the definition of congenital syphilis (10).

The WHO recommends one dose of 2.4 million units (2.4 MU) intramuscular (IM) benzathine penicillin for primary or secondary syphilis, or three doses of 2.4 MU IM benzathine penicillin for latent syphilis (or late syphilis) to treat maternal syphilis (including preventing transmission to the unborn fetus). A 2014 systematic review of treatment of syphilis reported that the WHO standard of care for syphilis based on disease stage was sufficient for pregnant women (16). The UK guidelines suggest a different treatment approach; early syphilis detected after 27 weeks should be managed with 2 doses of Benzathine Penicillin (2.4 MU, 1 week apart) and 3 doses if the stage of disease is unknown (1).

Serial non-treponemal test titre measurements are suggested to monitor for treatment failure especially in contexts where the prevalence of syphilis is high, or the woman is at a high risk for reinfection (10). A fourfold reduction in titres is regarded as an adequate response to therapy, and a suggested measurement interval is to measure titres at treatment, again between 28–32 weeks and finally at delivery (8,10). It could be argued that serial non-treponemal test titre measurement in pregnancy may not be meaningful given that the gestational period is insufficient time to assess for serological response, as it may take up to 12 months to appreciate a fourfold reduction in the RPR titre(23). A study in Poland evaluated pregnant women with syphilis' serological response after treatment with Benzathine penicillin, and compared outcomes between the group with and without a 4-fold decline in RPR titre(23). Although limited by a small sample size, the lack of serological response was not found to be associated with adverse outcomes(23).

There is minimal evidence to support alternative treatment for syphilis in pregnancy, and therefore in the context of penicillin allergy or stock-outs of penicillin, therapies are limited. For pregnant patients allergic to penicillin, penicillin desensitization is recommended (1,16). A Cochrane review in 2010 set out to determine what antibiotic treatment regimen was most effective in treating pregnant women infected with syphilis, however *no* articles were found that met the criteria for comparison groups between two treatment methods and no groups were randomly allocated (17). The review goes on to discuss how penicillin was established as effective at treating syphilis (including syphilis in pregnant women) based on early studies (in the 1940s and 1950s) that would not be considered acceptable for drug trials today – as participants were not randomized and comparisons between different treatment regimens was not done. (10,17). Current treatment guidelines for pregnant women are based on these early studies, specialists in the field, case series' and clinical trial – although clinical trial data is insufficient to inform the optimum dose and duration of penicillin or provide alternative evidence based therapies to treat syphilis in pregnancy(17).

The authors recommend that trials be considered to assess the effectiveness of oral antibiotics as an alternative to the intramuscular benzathine penicillin.

A case-study from Japan in 2017 reported successful treatment of syphilis in pregnancy and prevention of congenital syphilis for two patients who received alternative treatment to penicillin. The first case was a patient in which amoxicillin and probenecid was given; and in the second case amoxicillin, probenecid and ceftriaxone were given (24). In a 2018 review of strategies to prevent congenital syphilis (10), only 2 reports of alternative therapies were described where azithromycin and ceftriaxone were used for pregnant patients allergic to penicillin. In the first report, a series of 11 pregnant women in China were treated with ceftriaxone in pregnancy and ceftriaxone was shown to cure 10 of the 11 patients and prevented congenital syphilis in all 11 cases (25). The second report described the use of azithromycin and demonstrated that it was not successful at preventing congenital syphilis (10). Therefore, although Intravenous (IVI) ceftriaxone or a combination of amoxicillin and probenecid can be used to treat the mother and has been shown to successfully treat the fetus in a handful of cases described above, there is not enough robust evidence to suggest that it reliably treats the fetus.

Management of patients with syphilis includes considering the syphilis status of sexual partners, and therefore partner notification and treatment should be initiated. Partner notification has been suggested to improve the treatment of partners; however, no studies have shown a reduction in the incidence of congenital syphilis as a result of partner notification (10). Notably, implementation of partner treatment is poorly facilitated through partner notification. A 2019 systemic review of partner notification and treatment of sexually transmitted infections in Sub-Saharan Africa showed that 53% of partners were successfully notified (this is likely a subset), but only ¼ of partners who were notified responded by accessing healthcare and evaluation (26).

Epidemiology of Syphilis in Pregnancy & Congenital Syphilis

Syphilis Globally

It is estimated that in 2016 the global burden of syphilis in pregnant women was 0.99 million women (95% CI 0.81–1.41 million) with an estimated prevalence of 0.69%, stable from estimates from 2012 of 0.70% (9). Between 2012 and 2016 there has been a global improvement in antenatal attendance, syphilis screening and syphilis treatment coverage, however these rates are all below the WHO targets of 95%, 95%, 95% (9). It is estimated that in 2016, 661 000 babies were born with congenital syphilis worldwide, translating to an estimated 473 congenital syphilis cases per 100,000 live births, nearly 10 times the WHO target of 50 cases per 100,000 live births (9). Although the incidence estimates for 2016 reflect a reduction from 2012 estimates – we are far from eliminating congenital syphilis, a preventable fatal condition. Notably, over half of the congenital syphilis cases are estimated to occur in Africa (9).

A systematic review and meta-analysis of observational studies published in 2013 (13) looked at adverse birth outcomes in pregnant women with syphilis compared to women without syphilis. The adverse outcomes that were included were stillbirth and fetal loss, neonatal deaths, clinical evidence of syphilis and prematurity or low birth weight. When these adverse outcomes were pooled, 66.5% of women with untreated syphilis experienced an adverse outcome compared to 14.3% of pregnant women without

syphilis in pregnancy (13). The authors of this review do note limitations of these observational studies in their analysis, however given these limitations and potential biases the analysis demonstrates the sizable difference in adverse outcomes between these two groups of women and highlight the importance of screening for and treating syphilis in pregnancy.

In addition to this it should be noted that many adverse pregnancy outcomes described in women with untreated syphilis (e.g., intra-uterine growth restriction, low birth weight, preterm labour) are not specific to congenital syphilis. These adverse outcomes could also be prevented by accessing timeous quality antenatal care, which women who are screened and treated for syphilis in pregnancy are more likely to have received as compared to women with untreated syphilis in pregnancy (10). There is therefore a potential for confounding factors like access to antenatal care that could bias the associations seen between untreated syphilis in pregnancy and adverse pregnancy outcomes.

Syphilis in South Africa

In South Africa, the prevalence of syphilis in adults (ages 15–49 years) was estimated in 2017 to be 0.5% for women (95% CI: 0.32–0.80%), and 0.97% (95% CI 0.19–2.28%) for men. This is a reduction from 11.3% in 1990 for women and 8.2% in 1995 for men (27) and is thought to be due to multiple factors, including STI management protocols and behaviour change as a response to HIV prevention messages (27).

The prevalence of syphilis in pregnant women is higher when compared to the general population, and is monitored regularly in national antenatal surveys. In the 2022 National Antenatal HIV and Syphilis Prevalence survey[1], the seroprevalence of syphilis in pregnant women nationally was estimated to be 3.1%, an increase from the 2.6% prevalence in 2019 and 2% prevalence found in 2017(29,30). In 2019, the antenatal seroprevalence of syphilis in the Cape Town Metropolitan District was below the national average, at 1.8%(29). Limitations of the antenatal survey include excluding the population of women who have not been booked for antenatal care (unbooked women), who may be at an increased risk of having syphilis when compared to the cohort of booked patients. In a cohort of neonates with congenital syphilis treated at a tertiary hospital in Cape Town, over half of the cases had mothers whose pregnancies were not booked (31).

Another limitation of the antenatal survey is that it does not specify the testing algorithms and diagnostic criteria used to determine the syphilis status. As discussed by Ham et al, if a single test type is used to test for syphilis, a correction factor should be applied when extrapolating the prevalence of syphilis to account for false positive and false negative results(32). This is because persons who have had syphilis will continue to test positive on a treponemal test even after successful treatment. As such, two test types (a treponemal and non-treponemal test) are needed to distinguish an active syphilitic infection from a past one.

A review of all laboratory data for children <2 years who had an RPR result was done over a 10-year period in South Africa using the National Health Laboratory Service (NHLS) data to better understand RPR seropositivity in this population (2). Based on these data, the prevalence of congenital syphilis in South

[1] The 2022 National Antenatal HIV and Syphilis Prevalence survey enrolled sample of pregnant women that was nationally representative from 1 589 public health facilities across all districts in the country using multistage stratified cluster sampling. 35 900 pregnant women (age range 15-49 years) were included in the analysis of syphilis screening coverage. There was inter-provincial variation in the proportion of women who had syphilis screening done, with an overall weighted proportion of 96.3% of pregnant women being screened for syphilis. (28)

Africa was estimated to be 174 per 100 000 live births in 2019 (2). This rate varied between provinces and is an increase from the 2010 RPR seropositivity of 111 per 100 000 live births. While some provinces have seen a significant increase in seropositivity rates (like KwaZulu-Natal and Free State), the Western Cape saw a reduction in RPR seropositivity in infants in this time-period from ~300 per 100 000 live births in 2010 to 174 per 100 000 live births in 2019. These rates are well above the WHO target of <50 per 100 000 live births. (2)

In South Africa, Congenital Syphilis (CS) is a notifiable medical condition and has been included on the Notifiable Medical Conditions (NMC) surveillance since 2017 (33). Healthcare providers are required to notify the NICD through electronic and paper-based forms, and in addition to this the NICD receives information on the number of positive RPR results in children < 2 years of age from the NHLS. In an NICD report of congenital syphilis cases from 2017–2020, a number of gaps in reporting as well as congenital syphilis prevention and management were identified (33). Of note, during this time-period, 794 congenital syphilis cases were notified however during the same period a total of 11 170 laboratory RPR positive results were detected through the NHLS which suggests under-reporting of congenital syphilis through NMC surveillance (33).

Despite suspected under-reporting of congenital syphilis, the NMC surveillance does illustrate important potential vulnerabilities in the vertical transmission prevention (VTP) of syphilis in the local context. Of the mothers of notified CS cases, 66% were treated with at least one dose of Benzathine penicillin – which is considered adequate in some international guidelines(33). The analysis does not describe the group of infants who were notified who had received at least 1 dose of penicillin sufficiently enough to understand the group. The authors suggest that infants could have been incorrectly notified, or the mother may have received treatment too late to prevent Vertical Transmission (VT) of syphilis (33), although as described in the treatment section above, a single dose of penicillin *can* prevent congenital syphilis - and this group of notified infants could include "surveillance cases" (the definition is purposefully sensitive) and may not all represent clinical cases of congenital syphilis. A minority of the mothers of infants who were notified with CS (3.1%) were treated with ceftriaxone or amoxicillin with probenecid, which confirms that this regimen is being used to treat pregnant women with syphilis in South Africa as per protocol if there are stockouts – noting that these regimens are not considered adequate to treat the fetus.

There was a predominance of neonates in the cases notified, and only 38% of the notified CS cases had clinical signs present or reported (33). Most notified cases of CS were RPR positive (86.6% of cases). There is insufficient detail in the report regarding the age distribution of all CS cases with RPR results, as well as the distribution of the RPR titres, which could assist in understanding how notified CS cases differ from all infants with positive RPR results. Recent improvements in the CS notification forms have begun to address previous deficiencies in the data on notified cases of congenital syphilis.

South African Guidelines on the management of syphilis

In the South African Public Health Sector, healthcare is delivered in different provinces by Provincial Health Departments. In addition to this, certain metropolitan municipalities also provide health care – and primary health care is provided by City of Cape Town clinics as well as the Provincial Department of Health clinics. National programmes and guidelines exist for some conditions, however provincial-,

district-, and facility-level guidelines are also in place – at times for the same condition. This can create some confusion regarding the guideline that should be followed.

Guidelines on syphilis are present in various national guidelines, including the STI Guidelines, Maternity Care Guidelines and Elimination of Mother to Child Transmission Guidelines (now Vertical Transmission Prevention Guidelines, as of 2023)(5,18,34,35). In Cape Town, clinical practice is also guided by local guidelines, and these include the Basic Antenatal Care (BANC) Guidelines of 2017, the Metro West Maternity and Obstetrics Unit (MOU) Guidelines of 2020 and a provincial circular from 2019(36–38). It is noted that there are some discrepancies between these guidelines, particularly around testing.

Testing and treating the mother

In all the guidelines (except the Western Cape BANC guidelines (36)), which are summarized in Appendix B, there is agreement that testing for syphilis should happen at the first antenatal visit, and again in the 3rd trimester if the first test is negative. The more recent national guidelines (STI guidelines of 2018 (4) and the VTP guidelines of 2023(35)) specify that both treponemal and non-treponemal tests should be done and describe the testing algorithms and how results should be interpreted.

The testing flow charts set out in the national guidelines prior to 2023 do not specify what test should be used by the health care provider. This highlights the lack of a "nationally validated testing algorithm for syphilis and absence of quality assurance programme for rapid syphilis tests" in South Africa, as described by the NICD in a 2020 Congenital Syphilis Surveillance Report (33). The 2023 Guidelines for Vertical Transmission Prevention (VTP) have begun to address this, and comprehensive algorithms have been introduced (See Appendix F).

In the Western Cape Guidelines, the testing is specified, however testing differs between guidelines. The BANC guideline suggests that a point-of-care RPR test should be done, whereas the Level 1 guidelines in Metro West suggest a treponemal point-of-care test (TPHA), as well as a laboratory TPHA and reflex RPR if the TPHA is positive (37). Interestingly, the tests that are being used in the laboratory are the Treponemal Antibody Tests (TPAb), and not the TPHA. In the Western Cape, any syphilis tests that are sent to the National Health Laboratory Service (NHLS), the primary laboratory servicing public health sector, undergo the reverse algorithm (since 2017). A treponemal test is first done (TPAb, on a commercial chemiluminescent platform) and then a reflex manual RPR agglutination with titres is done for all TPAb-positive or low positive samples(39). The lack of agreement on nomenclature between what is in protocols and what is done adds to clinician confusion.

As per South African National guidelines, all syphilis-positive pregnant women are treated with three doses of 2.4 MU IM Benzathine Penicillin, regardless of the stage of infection. This could mean that some patients are "overtreated", and some would be regarded as "incompletely treated", even if staged as having primary or secondary syphilis where one dose of Benzathine Penicillin would be clinically effective, according to these guidelines (and could result in a "surveillance case" of congenital syphilis) but be adequately treated according to WHO and other international guidelines should they have early syphilis.

In these maternity guidelines, no alternative treatment options are suggested in the context of a pregnant patient with a penicillin allergy or in the context of penicillin shortages. In the National STI guidelines produced in 2018, it specifies that if Benzathine Penicillin is unavailable, pregnant women testing positive for syphilis should receive amoxicillin 1g 8-hourly for 14 days and probenecid 250mg 8-hourly for 14 days

(4). The guideline, however, does not describe that this therapy does not adequately treat the unborn fetus. For pregnant patients with penicillin allergy, penicillin desensitization is suggested (4).

Following penicillin stock-outs in the country, a national circular was sent out in 2019 detailing alternative treatment recommended instead of benzathine penicillin which stated that benzathine penicillin could be procured for pregnant women or cases of congenital syphilis through a Section 21 application (40). In the Western Cape an additional circular (H119/2019(38)) was then sent out in response to a lag period in sourcing benzathine penicillin through Section 21, and specified that if benzathine penicillin was unavailable, amoxicillin and probenecid could be used to treat pregnant women with syphilis. The circular emphasized that this treatment was not sufficient for the fetus, and therefore the newborn would also need to be managed as per a newborn exposed to syphilis (with incomplete maternal treatment).

Testing and treating the baby

CS should be suspected in a child under 2 years of age with known syphilis exposure or if the child has clinical signs of CS (as described above). Laboratory diagnostic criteria include a positive non-treponemal syphilis test on the baby with a titre that is at least 4-fold higher than the titre of the mother. Additional clinical and radiological features will support the diagnosis. (41)

The South African treatment guidelines (Essential Drug List) for Paediatrics (2017) (41) specify treatment required for a neonate with suspected CS based on the presence of symptoms. If the mother is seropositive and untreated (or inadequately treated) and the baby is asymptomatic and well, then the baby can be treated with a single intramuscular dose of benzathine penicillin 50 000 units / kg. In a symptomatic baby, the treatment recommended is either intravenous benzylpenicillin G 50 000 units/kg 12 hourly for 10 days, or intramuscular procaine penicillin 50 000 units / kg daily for 10 days. (41)

It is recommended that all children treated for CS as above should have follow-up non-treponemal tests until the test becomes non-reactive. It is suggested that the child be retreated if the drop in titre is less than four-fold. (41)

Penicillin Stock-outs

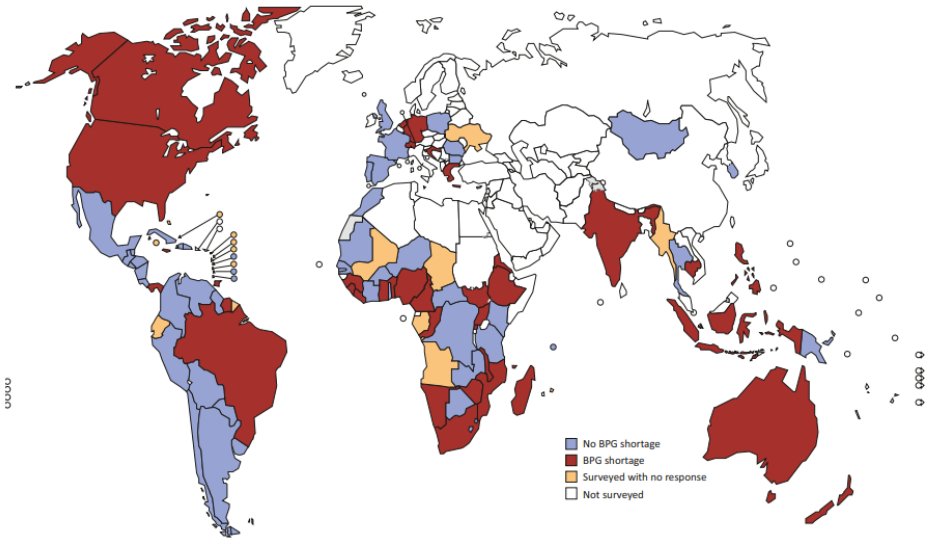
Benzathine penicillin has been used as the antibiotic of choice for several medical conditions since the 1950s; however, the demand for benzathine penicillin has fallen as newer antibiotics have been developed, and as the prevalence of conditions that require benzathine penicillin (e.g., Yaws, Lyme disease, syphilis and prophylaxis to prevent recurrences of rheumatic fever) has decreased in high income countries (42). Partly due to its importance in the prevention and treatment of CS, benzathine penicillin is considered an essential medicine by the WHO (3), and it is with concern that in the last decade, shortages of penicillin stock-outs have been described both in South Africa as well as in literature from other parts of the world (3,24,40,43).

Benzathine penicillin is off-patent and is available as either a suspension or as powder for reconstitution. It has been described as inexpensive to procure, estimated in a South African economic evaluation in 2010 to be $1 per 1.2MU vial (3,44), however, because it is a sterile injectable medication it is relatively

expensive to manufacture, and the combination of the production costs and the market price therefore make it undesirable for pharmaceutical companies to produce from an economic perspective (3).

The WHO recognized Benzathine Penicillin to be "an essential medicine at high risk for stock-out" in 2016 and partnered with other stakeholders to evaluate the shortages of benzathine penicillin for prevention of vertical transmission of syphilis in multiple countries (3). Due to recent reports of country-level shortages of BPG, an evaluation was undertaken to quantify countries that have experienced shortages in the past 2 years and to describe factors contributing to these shortages (3). Of the 95 countries evaluated by the WHO and partners, 41% had experienced shortages of Benzathine Penicillin between 2014 and 2016 (see figure 3). Twelve percent (12%) of the countries (both with and without reported shortages) indicated that antibiotics other than benzathine penicillin were being used for the treatment of syphilis in pregnancy (3). Shortages were described to be either due to supply-side or demand-side factors.

Figure 1: Countries with reported shortages of benzathine penicillin during 2014-2016 (3)



On the supply-side it was noted that the production of benzathine penicillin is commercially unattractive, and the infrastructure requirements for producing the sterile injection is off-putting for new manufacturers entering the industry as well as contributing to manufacturers exiting the market (3). It was noted that since the early 2000s, more than 40 pharmaceutical manufacturers who had previously produced the active ingredients or packaged the final product had stopped producing benzathine penicillin (3). Despite these market exits, there are sufficient manufacturers of benzathine penicillin to meet the global demand, however the supply chain is complicated by minimum purchase order quantities, manufacturer quality concerns and differences in technical specifications which can all result in delays or difficulties with the supply of the final product to countries(3).

Stock-outs were also influenced by demand-side factors, essentially resulting in countries under-procuring benzathine penicillin. These factors included countries inaccurately estimating how much benzathine penicillin they required, having purchasing cycles that were fixed and potentially unresponsive to mid-cycle shortages, funding shortages and single tender suppliers (making the country vulnerable to stock-outs should the single supplier not be able to meet the demand within certain time periods) (3) .

This multi-country evaluation highlighted the vulnerability of both high-income and low to middle income countries to the stockout of an essential medicine required for the treatment of syphilis, particularly syphilis in pregnancy. It emphasized the need to address both supply and demand factors that result in country-level benzathine penicillin stock-outs to ensure that supply chains can support the appropriate treatment of syphilis, and importantly syphilis in pregnancy to prevent adverse birth outcomes as a result of inappropriately treated syphilis in pregnancy.

Conclusion and Rationale for Study

It is therefore evident that syphilis in pregnancy and congenital syphilis remains a problem globally and locally, and although preventing congenital syphilis has been identified as a health priority - we are still far from eliminating congenital syphilis. Challenges in screening and treatment are worsened by the lack of evidence-based alternative treatment regimens for syphilis in pregnancy, and benzathine penicillin stock-outs which are multi-factorial.

Despite congenital syphilis being a notifiable medical condition in South Africa, significant reporting gaps exist. In addition to this, there are discrepancies in the national guidelines both in terms of testing algorithms and treatment options in the absence of benzathine penicillin availability. In the Western Cape, gaps in care pathways are suspected. There is a need to describe the treatment of pregnant women who have tested positive for syphilis, and what the outcomes of those pregnancies are over time and whether the outcomes differ by treatment status.

If deficiencies in the testing and treatment pathways are described, and opportunities are identified for improvement, steps can then be taken in the Western Cape province to improve the detection and treatment of syphilis in pregnancy to prevent unnecessary adverse pregnancy outcomes.

Definitions

<table>
<tr><td>Congenital Syphilis</td><td colspan="2">As per the NICD surveillance case definition(21):
1) Live birth or fetal death at >20 weeks gestation or >500g (including stillbirth) born to a woman with positive non-treponemal syphilis serology (RPR / VDRL) and without adequate syphilis treatment

OR

2) Stillbirth, live birth or child <2 years born to a woman with positive non-treponemal syphilis serology (RPR / VDRL) or unknown serostatus, and with laboratory and/or radiographic and /or clinical evidence of syphilis infection, regardless of the timing or adequacy of maternal treatment.</td></tr>
<tr><td>Positive Syphilis Serology
(45)</td><td colspan="2">In the Western Cape, the reverse testing algorithm is used by the NHLS. For this study a woman is regarded as having active syphilis if she has a NHLS (laboratory-confirmed) positive treponemal antibody test and a follow-up positive non-treponemal antibody test (RPR) recorded. For this study, “Screened syphilis positive” is regarded as every pregnant woman with a positive RPR test.

• High-titre active syphilis: Positive Treponemal test, RPR ≥1:8
• Low-titre active syphilis: Positive Treponemal test, RPR <1:8</td></tr>
<tr><td rowspan="5">Syphilis Status in Pregnancy Category</td><td>No test</td><td>No NHLS laboratory test done for TPAb or RPR during pregnancy</td></tr>
<tr><td>Negative (Syphilis Screen Negative)</td><td>TPAb negative, RPR negative OR TPAb negative, no RPR done OR RPR negative no TPAb done during pregnancy</td></tr>
<tr><td>Previous Syphilis</td><td>TPAb Positive, RPR negative during pregnancy</td></tr>
<tr><td>Syphilis Positive (Syphilis Screen Positive)</td><td>RPR positive during pregnancy</td></tr>
<tr><td>Test Error</td><td>Evidence of test done, but no valid / interpretable result</td></tr>
<tr><td>Adverse Birth Outcomes</td><td colspan="2">Stillbirth, Neonatal death</td></tr>
<tr><td>Inadequate Treatment for Mother
(34)</td><td colspan="2">• Mother not treated
• Mother received less than three doses of benzathine penicillin
• Mother delivered within four weeks of commencing treatment</td></tr>
<tr><td>Booking Category</td><td colspan="2">Booked Early: First electronic evidence of accessing health services before 20 weeks gestation

Booked Late/Unbooked: Electronic evidence of accessing health services after 20 weeks. Includes those who booked between 20 weeks and delivery and those who did not receive antenatal care “unbooked”.</td></tr>
</table>

Research Question

What is the seroprevalence, management and outcomes of laboratory-confirmed syphilis during pregnancy in the Cape Town Metropolitan District between 2017 to 2022 and is there a difference in the response to treatment and the pregnancy outcome for those treated per Maternity Guidelines (Benzathine Penicillin 3X 2.4 MU 1 week apart for 3 weeks) as compared to those inadequately treated.

Aims and Objectives

Aim

Describe the distribution, management and outcomes of pregnant women diagnosed with syphilis during pregnancy in the Cape Town Metro District from 2017–2022 in the public sector and determine whether there is a difference in response to treatment or pregnancy outcome between those who were appropriately fully treated with Benzathine Penicillin compared to those inadequately treated or treated with alternative treatment regimens.

Objectives

- Determine the proportion of pregnant women who have a laboratory result for syphilis during their pregnancy
- Describe the population of pregnant women who have positive syphilis serology in pregnancy in terms of their baseline characteristics and pregnancy outcomes over time.
- Describe pregnancy outcomes by syphilis status
- Identify treatment regimens dispensed for pregnant women with positive syphilis serology
- Describe the proportion of participants (i)adequately and (ii)partially treated with Penicillin, and (iii) those treated with alternative treatment regimens
- Describe the pregnancy outcomes by treatment status

Methodology

Study Design

This is a retrospective cohort study of pregnant women identified by the Western Cape Provincial Health Data Centre (PHDC) with laboratory (NHLS) positive syphilis serology.

The PHDC is a Western Cape Government: Health & Wellness hosted digital platform that, using a unique patient identifying number, consolidates data from routinely used electronic clinical information systems which includes pharmacy, laboratory, and administrative data (46).

Population

The population of interest is all pregnant women in the Cape Town Metropolitan Municipality (CPT), an Urban District in the Western Cape Province of South Africa. CPT has a population estimate in 2022 of 4.78 million, with just over 1/3rd of the city (35.7%) living below the poverty line(47). The majority of the population utilize the public health sector and 72% of the population of Cape Town do not have medical aid (48). In 2022, 74.5% of pregnancies in Cape Town have at least one antenatal care visit as measured by the national indicator "Antenatal 1st visit coverage by district", which is below the national average of 76.4% (49). The antenatal seroprevalence for HIV in Cape Town is 20.3%, above the provincial average of 16.3% but below the national average of 27.5% (30).

All women treated in the public sector who have a pregnancy outcome recorded between January 2017 and December 2022, who have been identified as "pregnant" with a high level of confidence by the Provincial Health Data Centre (see Appendix E) using a combination of electronic evidences specific to pregnancy (e.g. ICD-10 diagnosis codes, procedure codes, registration in labour delivery ward and other)(50). The outcomes of these pregnancies are of interest, and therefore the infants that are linked to each pregnancy also form part of the population of interest. To fulfill the analytic objectives, a sub-population within this cohort was identified, which included pregnant women with laboratory-confirmed syphilis (detected using the reverse testing algorithm used routinely by the NHLS in the Western Cape) between January 2017 and December 2022.

The full population was included in the analysis and therefore a sample size calculation was not done. Women who had more than one pregnancy during the study period were counted twice if they tested positive for syphilis twice and were considered as two separate cases as they should be treated for syphilis on both occasions.

Inclusion Criteria	Women identified as pregnant by the PHDC accessing care in the public health sector for their pregnancy. Have a pregnancy outcome recorded on the PHDC
Exclusion Criteria[2]	Women aged <10 or >45 years Pregnancies where the recorded birth weight <500g or >5499g Parity > 10

Research Procedures and Data Collection Methods

Secondary data from the PHDC was analysed. These data are collected from routine data collection systems used in the province, and each individual who accesses the public health system receives a unique patient identifier that is linked to care / investigations and treatment received. This includes Patient administration systems (Clinicom / PHCIS/ Premis), the National Health Laboratory System (NHLS), The

[2] Exclusion criteria were determined by considering plausible values and the proportion of participants expected to be above that value. Implausible values affecting small numbers were excluded for data quality purposes, as assumed to be less reliable than plausible values.

electronic pharmacy system and the electronic discharge tool – Electronic Continuation of Care Record (ECCR) and the Electronic Pharmacy Management System, known as JAC.

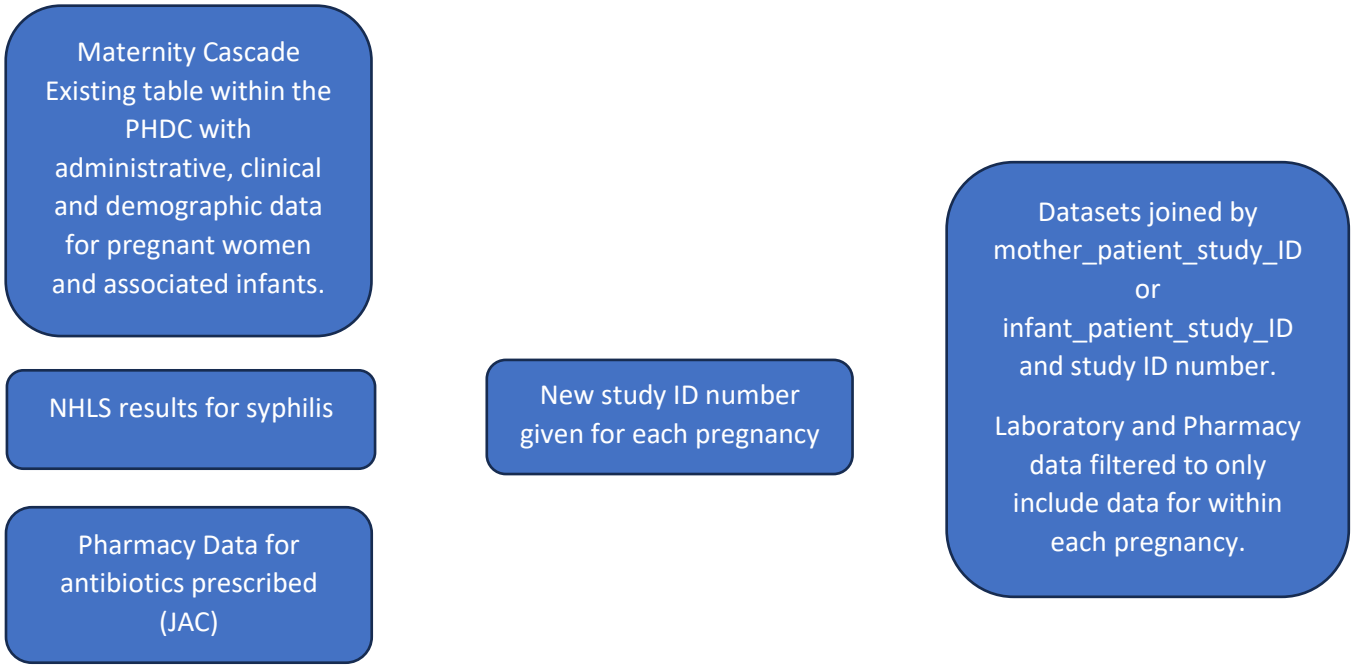
Pregnant women are identified on the PHDC using a combination of the above data sources, but generally rely on data at delivery and so pregnancies may also be identified "retrospectively". NHLS data links to the Patient Master Identifier (PMI), the unique individual patient number that is given to each client who uses the public health system in the Western Cape, and so pregnant women can be filtered for all pregnant women with a positive syphilis test. Pregnancy outcomes are routinely recorded, and the neonate is linked to the mothers' PMI which enables further information to be gathered about the pregnancy outcome and neonate.

Three different datasets were collated by the PHDC for analysis. The first (the maternity cascade) was an existing dataset including all pregnancy details and linked the mother and infant PMIs. The second dataset included all laboratory results for syphilis for mothers or their infants. The third dataset included pharmacy records for mothers from the Electronic Pharmacy Management System (JAC).

The pharmacy dataset included any antibiotic prescription prescribed to a pregnant woman in this cohort. We filtered this dataset to only include relevant antibiotics for our study: "Benzathine benzyl penicillin", "Benzathine penicillin", "Ceftriaxone" and "Amoxicillin and enzyme inhibitor". Probenecid was not a category on JAC, and the enzyme inhibitor used with amoxicillin in this category was not specified. For purposes of analysis, the two penicillin categories were considered together, and "Amoxicillin and enzyme inhibitor" was included.

The three datasets were joined using the mother and infant PMI and separated into individual pregnancies based on the start and end of different pregnancy episodes for those mothers for which there was more than one pregnancy. Multiple pregnancies were included, and although the maternal information was deduplicated for the description of the maternal cohort, each pregnancy outcome was considered separately in the description of the outcomes to ensure that each infant in multiple pregnancies was considered separately. The pharmacy dataset was joined to a dataset limited to women who were both TPAb and RPR positive.

Data cleaning and joining



Validity and Reliability of Data

The data used is secondary data that is routinely collected, and therefore it is recognized that there are limitations with regards to the data quality. Facilities may differ with regards to their electronic data capturing, both in terms of administrative data (including ICD 10 codes / admissions) as well as pharmacy data and recording the treatment given to a specific patient. If the incorrect PMI is used on an NHLS form, there is a chance that the result will not be linked to the patient of interest, and this could result in missing data.

Limitations of these data include that point-of-care (POC) syphilis tests are not captured electronically and do not capture antibiotics administered outside of the public sector. Although clinical data such as infant outcomes are captured for patients accessing care within the system, there may be gaps in data capture at primary care level and infants accessing care outside of the public health sector would not be represented in these data. Treponemal POC tests are currently used in the Cape Town Metro, and as guided by clinical guidelines, all positive POC tests should be followed by laboratory testing for confirmation. Given that the POC tests are not captured electronically, we do not have a full understanding of syphilis testing practices in the Cape Town Metro by looking at these laboratory data alone. While we can measure the prevalence of the laboratory seroprevalence, there is a chance that this may exclude patients with a positive POC test who may have been appropriately treated with penicillin but did not get formal laboratory tests. It could also exclude those with a false negative POC test.

Data Safety and Monitoring

The secondary data were received in a password-protected Microsoft Excel file and available to only the primary researcher and research supervisor. Data were de-identified to maintain confidentiality.

Data Analysis

The data were analyzed in R (Version 4.3).

Following data cleaning, categories were created as per definitions for analysis to meet the study objectives. Descriptive statistics were reported, numeric data were reported as means with standard deviations and medians with inter-quartile range. Categorical data were reported as absolute numbers and percentages. Differences between groups were tested using the t-test or Wilcoxon sum rank test or Kruskal Wallace for numerical variables and the Chi Squared test for categorical variables. Statistical tests were reported on with p values and a p value of <0.05 was considered statistically significant.

Ethics

The study was approved by the Human Research Ethics Committee of the University of Cape Town for ethics approval (398/2023) and to the Western Cape Province Department of Health to obtain permission to use these data. All data were stored in password protected documents and accessed only by the main investigator and supervisors.

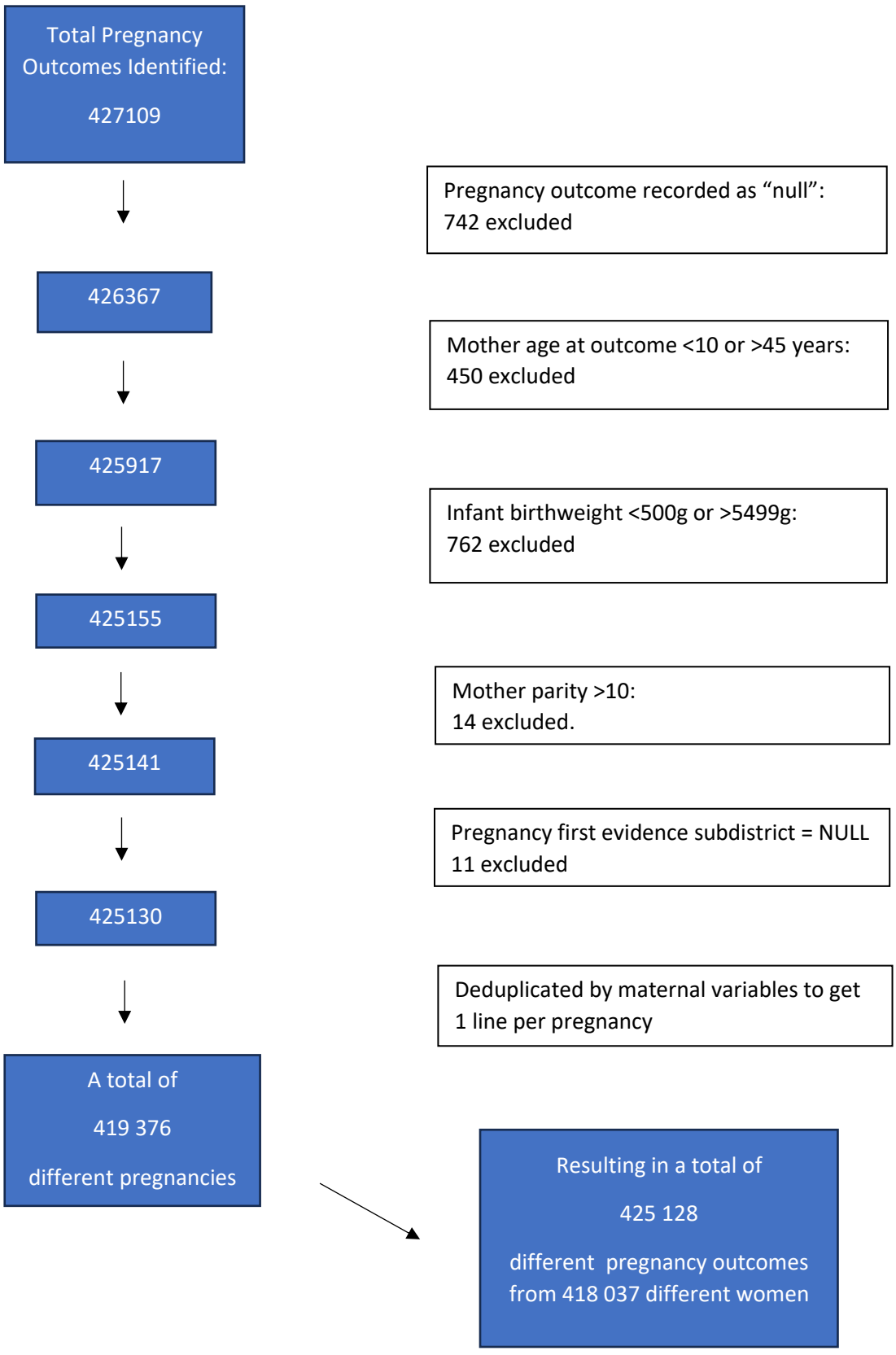
Data was de-identified data to maintain patient confidentiality. Individual addresses were not used, and facilities were categorized by facility type and sub-district to avoid the possibility of identification. Because routine data is being used, and de-identified, non-maleficence will be upheld and there is minimal risk to the individual study participant.

There is, however, potential for benefit for participants planning future pregnancies and benefit for the population of Cape Town should gaps in the treatment of syphilis in pregnancy be identified and mitigated. To uphold the principle of justice, the findings will be shared with relevant stakeholders in the Department of Health including those involved with laboratory services, antenatal care, and pharmacy services. The findings will also be published in a relevant academic journal to enable dissemination of new knowledge.

Results

A total of 419 376 pregnancies in the Cape Town Metropolitan District were identified from 2017–2022, resulting in 425 128 pregnancy outcomes. For the entire pregnant cohort, the median age was 27 (IQR 23–32) years and median parity was 0 (nulliparous). The pregnancies were distributed between the two geographic service areas (GSA) within the Metro (see Appendix D), with 47% (n = 198 578) of pregnancy outcomes occurring at Metro East facilities, and 49% (n=204 600) occurring in Metro West. Among pregnancies with evidence of antenatal care in the Metro, 5409 (1.3%) of had a pregnancy outcome in a rural district in the Western Cape, while the district of outcome was not recorded in 2.6% (n=10 789) of pregnancies. Forty-one percent (n= 171 220) of pregnancies initiated antenatal care (booked) before 20 weeks gestation. Overall, 21% (n=87 535) of pregnancies were among mothers who were HIV positive. (Table 1)

Flowchart to show data cleaning and demonstrate numbers of pregnancies that met exclusion criteria.



Testing Practices and Results

Women in the study population (women who had ever been pregnant during the time-period from 2017 – 2022) had up to 20 tests for syphilis during this period. These tests were categorized as either within or outside the pregnancy window based on the estimated dates of the pregnancy. Of the women tested during pregnancy, 78% were tested once, 20.1% had two laboratory syphilis tests during their pregnancy and a minority (1.9% of those with a laboratory test) had three or more laboratory tests for syphilis within the pregnancy window. WHO and South African guidelines recommend all pregnant women be screened for syphilis during pregnancy; in 6812 / 419 376 pregnancies there was a documented positive RPR, giving an overall seroprevalence of 1.6% (table 2).

Less than half (47%, n = 197 732) of pregnancies had a laboratory test for syphilis (either TPAb and/or RPR). Of the pregnancies with a syphilis laboratory test, 6 812 pregnancies (3.4%) ever had a positive RPR, while 8 974 (4.5%) of tested pregnancies had a positive treponemal test but negative RPR (which suggests previously treated syphilis) and 180 648 (91%) screened negative (see figure 1, table 2). The majority of negative screens followed the reverse testing algorithm, and therefore had a TPAb negative with no RPR, although a pregnancy was also classified as "screened negative" if there was no TPAb done and the RPR was negative (following a traditional testing algorithm). Ninety-three percent (n=6 359) of RPR-positive women were both TPAb and RPR positive, however any RPR positive result was considered as "Syphilis Screen Positive" given that only an RPR test was done on some pregnancies, and it is assumed that these cases had a POC test done first and only a follow up RPR was requested – as per the national guidelines.

Repeat laboratory tests were done for 22% of pregnancies with a laboratory test, which represents both retesting (as per the guidelines) as well as the serological monitoring done for those with syphilis through repeat RPR titres. The benefit of retesting was seen in these data, as 424 (6.3%) of women who screened positive did not screen positive on their first test in pregnancy, and these cases would have been missed had they not been retested in pregnancy

On average, those with a laboratory test for syphilis were older than those without a laboratory test for syphilis (median age 28 compared to median age of 27 years, table 1). A greater proportion of those who had a syphilis laboratory test booked before 20 weeks gestation (58% of those with a test booked before 20 weeks compared to 26% of those without a test, table 1), and over half (54%) of those who did not have a laboratory test for syphilis booked within a month of delivery (data not shown). We saw differences in laboratory testing patterns by GSA of outcome—considered a proxy for where antenatal care is received. 75% of pregnancies who had a laboratory result for syphilis were from Metro West, 72% (n= 147 741) of pregnancies in Metro West had a lab test done, compared to 20% (n= 56 859) of pregnancies in Metro East (table 1).

Trends over time and per Geographic Service Area.

There has been an overall increase in the proportion of pregnancies with formal laboratory testing for syphilis between 2017 (40%) and 2022 (53%), except for 2020 when laboratory testing dropped to 41% from 47% in 2019 (table 3)[3]. Trends from 2021–2022 show improved early booking compared to pre-

[3] This excludes point of care tests

pandemic years (41% booked before 20 weeks in 2017 vs. 44% in 2022, table 3). There has been an absolute year on year increase in the number of women who have syphilis in pregnancy (figure 2), and this number has increased across the Metro, in both GSAs.

In 2017, 1.2% (764) of all pregnancies screened syphilis positive (positive RPR within the pregnancy window). In 2022, 1324 women (1.9%) screened positive for syphilis which represents a 73% increase in the number of cases over 5 years. Cases of previous syphilis (positive TPAb, negative RPR) also increased from 1 352 (2.1%) in 2017 to 1739 (2.5%) in 2022. (table 3)

The prevalence of syphilis in pregnancy was higher in Metro West compared to Metro East, with 2% (4094) of all pregnancies in Metro West screening positive for syphilis compared to 1.2% (2460) in Metro East (table 5). Similarly, there was a greater proportion of pregnancies in Metro West with previous syphilis, 5841 (2.9%) in Metro West were TPAb positive and RPR negative compared to 2690 (1.4%) in Metro East. Only 18% of pregnancies in Metro East had a formal lab screen that was negative, compared to 67% in Metro West. The cohort of patients (n = 5409) whose pregnancy outcomes were in rural districts had the highest prevalence of syphilis (126, 2.3%), with 4.2% having had previous syphilis.

Pregnancy Outcomes

There were a total of 425 128 outcomes for 419 376 pregnancies over the 5 years, multiple pregnancies accounted for the additional outcomes (8 289 outcomes, 1.9%, were from multiple pregnancies). Outcomes in this cohort included both early pregnancy outcomes such as ectopic pregnancies (1.1%, n=4 819), miscarriages (2.3%, n=9 772) and termination of pregnancy (TOP) (4.9%, n=21 041) as well as perinatal outcomes categorized as either neonatal survivors (86%, n=367 360), stillbirth (1.5%, n=6 520), early neonatal death (0.6%, n=2 541) or late neonatal death (0.1%, n=630) (table 7). The total live births for this cohort, therefore, would be the sum of neonatal survivors, early neonatal deaths, and late neonatal deaths – so this should be considered when interpreting these results. The median birth weight for this cohort was 3110 grams (IQR 2730–3460), with the proportion of low-birth-weight deliveries at 16%. The average gestational age (GA) was 38 weeks (IQR 36–40) for those with a recorded estimated GA at outcome.

Among 35 632 early pregnancy outcomes (table 9), TOP[4] was the most common outcome (21 041, 59%) followed by miscarriages (9 772, 27%) and ectopic pregnancies (4 819, %). Most early pregnancy outcomes did not have laboratory testing performed (25 359, 71%). Prevalence of active syphilis (positive RPR) was similar among miscarriages and ectopic pregnancies (1.4%) but rare among TOPs (only 0.4%). Previous syphilis (TPAb positive, RPR negative) was more common among ectopic pregnancies (3.0%) than among miscarriages (2.1%) or TOPs (0.6%).

Positive syphilis screen (RPR positive) was associated with adverse perinatal outcomes (still birth, early or late neonatal death), table 10. Women with an RPR positive result in pregnancy had 2.5 times the risk of having a stillbirth compared to their counterparts who screened syphilis negative in pregnancy [5] (RR 2.52, 95% CI 2.25, 2.82) and 1.91 times as likely to have an early neonatal death than those who were negative

[4] Termination of Pregnancy episode defined by the PHDC using administrative data as outlined in Appendix E.
[5] Screened negative for syphilis in pregnancy includes: TPAb negative, no RPR done **OR** TPAb negative, RPR negative **OR** RPR negative

(RR 1.91, 95% CI 1.53, 2.38). When stratified by RPR titre, outcomes were worse in the group with high-titre syphilis (RPR titre ≥ 8) compared to the low-titre group (table 11a).

Pregnancies with high-titre active syphilis were at a significantly greater risk of having an adverse perinatal outcome compared to syphilis negative pregnancies (RR 3.72, 95% CI 3.34, 4.15), whereas the risk of an adverse perinatal outcome in the low-titre group was similar to the syphilis negative cohort (RR 1.08, 95% CI 0.88, 1.33), table 11b.

In the cohort of pregnancies with a perinatal outcome recorded (neonate survived, stillbirth, early and late neonatal death), 65% (95% CI 60.4-68.3%) of stillbirths born to syphilis positive women are attributed to syphilis, while 3% (95% CI 2.47% – 3.46%) of stillbirths in the total population are attributed to syphilis. 49% (95% CI 36.1% - 58.6%) of neonatal deaths born to syphilis positive women were attributed to syphilis and 1.6% (95% CI 0.88% - 2.28%) of neonatal deaths in the total population were attributed to syphilis (Appendix G).

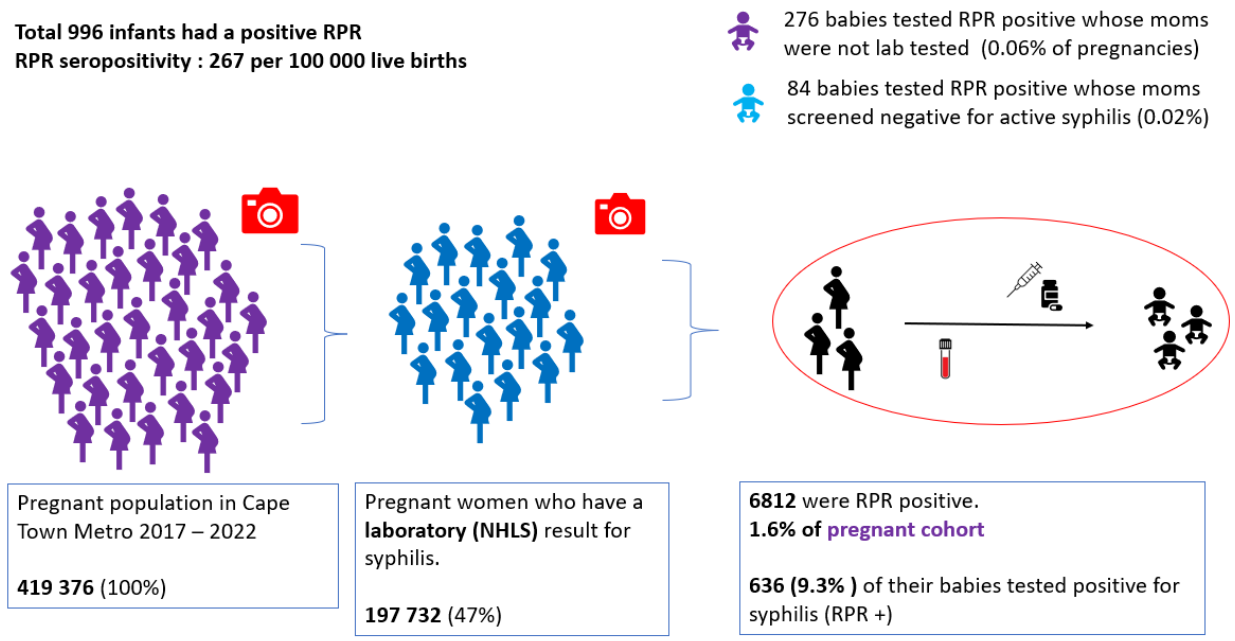
Testing of infants

When reviewing the full cohort of infants for this pregnant population, a total of 996 infants[6] had a positive RPR – which translates to a RPR seropositivity of 267 per 100 000 live births. Of the RPR-positive infants, 64% (n=636) were born to women known to have syphilis in pregnancy, while 28% (n= 276) were born to mothers without a formal laboratory test for syphilis. The infant outcome was unknown for 5 of the RPR positive infants (0.5% of the infants who tested RPR positive).

Most of the infants born to mothers without a laboratory test for syphilis were born in Metro East (76%, n=209); and the majority (255/276, 92%) had booked late (after 20 weeks) or were unbooked (table 14). Of the 996 RPR-positive infants, 84(8%) were born to mothers who screened negative for active syphilis in pregnancy (women either TPAb positive and RPR negative, TPAb negative with no RPR test, RPR negative with no TPAb test or both TPAb and RPR negative). Of 6812 mothers with syphilis in pregnancy, only 636 (9.3%) of infants had a positive RPR (See figure A below for graphic representation of VTP cascade).

[6] RPR results for infants linked to pregnancies between 2017 and 2022 were obtained. Of the 996 RPR positive results, 9 positive results (0.9%) were for children who tested RPR positive for the first time over the age of 2 years. These results were included in this analysis.

Figure A: Graphic Representation of Pregnancy Cascade showing Total pregnant population (purple), pregnant women tested for syphilis (blue) and women with syphilis in pregnancy (black). Numbers and percentages shown below icons.



There was an absolute increase in the number of infants who tested RPR positive, from 142 in 2017 to 180 in 2022, figure 4. This was driven by increasing numbers of RPR-positive infants in Metro East (from 62 to 139) despite decreasing numbers of RPR-positive infants in Metro West (from 77 to 39), figure 5/6. While there has been an increase of RPR positive pregnancies, with syphilis diagnosed more frequently in Metro West compared to Metro East, the proportion of infants who test RPR positive is higher in Metro East (649, 0.4%) compared to Metro West (320, 0.2%) (table 16). Testing criteria and characteristics of infants who received a test was not explored in this project.

Pregnancy outcomes over time and per geographic service area

Between 2017 and 2020 there was an increase in pregnancies in the Metro, however, with year-on-year reductions in 2021 and 2022 (table 15). The number of live births has followed a similar pattern; however, it is noted that the proportion of pregnancies with an outcome of a survived infant decreased in 2021 and 2022. Notably, there has been an increase in the number and proportions of both miscarriages and terminations over these five years. There were 934 miscarriages (1.5% of outcomes) in 2017, and this increased to 2 670 (3.9%) in 2022. Terminations increased from 2 995 (5%) in 2017 to 4 155 (6.1%) in 2022.

The absolute number of still births has reduced slightly from 1054 in 2017 to 1006 in 2022, but both early and late neonatal deaths have increased: ENND's increased from 344 in 2017 to 472 in 2022, and LNND increased from 84 to 111, table 15. When early pregnancy outcomes are excluded, the still birth rate has decreased from 19.4 to 17.1 per 1000 births, and the early neonatal death rate has increased from 6.3 to 8.0 per 1000 live births, figure 3. The low-birth-weight rate has not changed between 2017 and 2022 at

16%, although reduced to 15% in 2019 and 2020, table 15. Perinatal outcomes are very similar in both Metro East and Metro West (table 16).Evidence of Treatment of Syphilis in Pregnancy

Of the pregnancies that were both TPAb and RPR positive (n= 6 444), 4 462, (69%) had no appropriate treatment for syphilis in pregnancies captured electronically, while 1 775 (28%) had a record of receiving at least one dose of IMI benzathine penicillin. Penicillin alternative treatment was documented in 207 pregnancies not documented to have received penicillin; 183 (2.8% of those with treatment captured) had received amoxicillin with an enzyme inhibitor, and 24 (0.4%) received ceftriaxone (table 17). The dosages and specific duration were not included.

Perinatal outcomes for those with evidence of penicillin treatment were similar to those who had no treatment for syphilis electronically captured (table 19). No stillbirths were noted in the group who had received ceftriaxone, although these numbers were very small (n=24).

Given the incompleteness of the pharmacy data, no meaningful analysis of treatment received and comparison of outcomes between treatment groups could be done, as there was a very high risk of misclassification of exposure status if we consider the treatment received as an exposure.

Discussion

In this retrospective analysis of syphilis in pregnancy we report increasing seroprevalence of syphilis in pregnancy over the study period from 1.2% in 2017 to 1.9% in 2022. Additionally, we show an increase in the RPR positivity in infants over the same time-period:142 in 2017 (260 per 100 000 live births) to 180 in 2022 (303 per 100 000 live births in 2022). The impact of syphilis in pregnancy on adverse pregnancy outcomes is undeniable in our population: 65% of stillbirths born to syphilis positive women are attributed to syphilis and 49% of neonatal deaths born to syphilis positive women were attributed to syphilis. Out of the total population, 3% of stillbirths and 1.6% of early neonatal deaths are attributed to syphilis.

As a country, the stillbirth rate (>1000g) has gradually improved from 20.9 per 1000 live births in 2014 to 19.9 per 1000 live births in 2019 (51). While the Western Cape is below the national target at 16.6 per 1000 live births, this remains above the WHO endorsed Every Newborn Action Plan of reducing the stillbirth rate to less than 12 stillbirths per 1000 live births by 2030 (51,52).

As described by a 2022 report on stillbirths done by United Nations Inter-agency Group for Child Mortality Estimation (UN IGME) (a collaboration between UNICEF, WHO, The World Bank and the UN Department of Economic and Social Affairs) counting stillbirths remains a challenge in many parts of the world and the problem of stillbirths are often left off the health agenda with regards to mortality reduction (52). Global estimates are often a challenge due to differences in definitions used in collecting stillbirth data. In the UN IGME report, the late gestation stillbirth definition (stillbirth at more than 28 weeks gestation, or >1000g) is used to count stillbirths. In South Africa, both early gestation and late gestation stillbirths are counted in the Perinatal Problem Identification Programme (PPIP), although the latest Saving Mothers and Babies report only provides a target for late gestation stillbirths (>1000g) of < 15/1000 live births by 2030(51). Our data provides an opportunity to include all stillbirths above 500g .

We show a stillbirth rate of 17.7 per 1000 live births for the entire cohort across the 5 years, with a gradual decrease in the stillbirth rate over time, from 19.4 per 1000 live births in 2017 to 17.1 per 1000 live births in 2022. The transient in increases in 2020 and 2021, possibly due to Covid-19 service disruption(6), were reversed in 2022. There is, however, progress to be made for us to reach the WHO target of 12 per 1000 live births by 2030 (53). Syphilis is a preventable cause of stillbirths, and preventing gestational syphilis (and ensuring that it is treated timeously and appropriately) is low hanging fruit to prevent stillbirths both in our district and our country.

Our data show an increase in the neonatal mortality rate. The neonatal mortality rate (number of deaths during the first 28 completed days of life per 1000 live births) and the under 5 mortality rate are key indicators used to monitor our progress as per the Sustainable Development Goal (SDG) 3.2 to end preventable deaths of newborns and children (54,55). South Africa has appreciated a decrease in the infant and under-5 (U5) mortality rates between 2006 and 2022 from 93 per 1000 live births in 1990 to 34.5 per 1000 live births in 2022 (49,56). This decline in the U5 mortality rate has slowed since 2015. In 2022, neonatal deaths made up 31% of the U5 deaths(56). The neonatal mortality rate in South Africa is 12 per 1000 live births according to our District Health Information System (DHIS) – South Africa reached this rate in 2012, which was a welcome improvement from the estimated neonatal mortality rate of 21 in 1990, however as a country the rate has been stagnant since 2012 and in 2022 the DHIS neonatal mortality rate remains at 12 (56).

Although the neonatal mortality rate in the Western Cape and in our population is below the national average, we see an increase in both the Early and Late Neonatal deaths during this time-period. We demonstrate that 1.6% of early neonatal deaths in our population can be attributed to syphilis. If reducing child mortality and neonatal deaths is a priority, then we cannot accept these 41 neonatal deaths in the population that are attributed to syphilis, a preventable condition.

We demonstrate the power of routinely collected electronic medical record data and the ability to link maternal and infant administrative and laboratory data The ability to link a mother and infant dyad provides an opportunity to review the VTP cascade. 6812 of the pregnancies in our cohort were RPR positive, and 9.3% of their infants were RPR positive. We were able to identify that of the 991 infants with a positive RPR test, 28% (274) were born to mothers with no formal laboratory test. The majority (55%) of mothers of RPR-positive infants (i.e., RPR-positive infants born to mothers without a formal laboratory test) had booked between 20 and 37 weeks, and over a third had their first encounter with the health system in their pregnancy after 37 weeks.

This analysis shows that earlier antenatal care attendance is associated with having a laboratory test for syphilis. The reduction in the proportion of pregnancies booking before 20 weeks receiving a formal lab test for syphilis in 2020 is noted – this year was impacted by service disruptions and lockdowns due to the COVID-19 pandemic (6). There is evidence in the literature that early antenatal care is associated with decreased adverse outcomes due to syphilis(57).

A higher seroprevalence in pregnancies who had outcomes in rural districts could demonstrate that women accessing antenatal care providers across different districts in the province (women who migrate during their pregnancies) may be at a higher risk of adverse pregnancy outcomes associated with risks such as infections during pregnancy.

This cohort includes early pregnancy complications (such as ectopic pregnancies and miscarriages) that may not be represented in other surveys such as the antenatal survey. We show an increase in terminations: Reasons for this are unknown, and there is a possibility that implementation of electronic data capture / ICD-10 coding of early pregnancy outcomes may have improved within these time windows and the increase in numbers may have resulted from improved data capture. There may be better access to termination of pregnancy services for vulnerable populations, which could also contribute to this.

According to the latest antenatal survey, the coverage of syphilis screening nationally in 2022 was 97.5%, 1.1% higher than the coverage in 2019 (coverage is defined as the number of women with a record of a syphilis screening test / number of women who completed the antenatal survey questionnaire) (30). The coverage in the Western Cape had increased across the 2017, 2019 and 2022 antenatal survey and was similar to the national average(30). All provinces had a coverage of over 90%, and the Western Cape was the province with the lowest proportion of syphilis screen results missing (2.6% of results missing from the notes)(30). Given the antenatal survey results and trends, and the guidelines being followed, we are assuming that the majority those without a laboratory test screened negative on a treponemal point-of-care (POC) test. A limitation of this study is that we do not have the results of POC tests, as these are not routinely captured electronically.

In the Cape Town Metro, POC treponemal tests are distributed by the Central Medicines Depot (CMD) to facilities. The currently distributed POC test[7] has a reported sensitivity of 100% and specificity of 99.6% using "ACON device" as the gold standard according to the package insert, but there is no indication of whether this performance is tested on whole blood or serum(58). There is no evidence of what the performance of this test is in our context, and no current standardized quality control process in place (59). This is an important gap and opportunity for improvement. Twenty-eight percent of infants with a positive RPR (n=274) were born to mothers without a formal laboratory test for syphilis in their pregnancy. While it is possible that these women had a positive POC test for syphilis, and were initiated on treatment, it is also possible that the mothers could have either had a false negative POC test, or tested negative and later seroconverted in pregnancy. Benefits of POC tests are widely acknowledged and allow for same day treatment(20), however for this to prevent cases of congenital syphilis by detecting and treating positive syphilis cases in mothers, acceptable sensitivity and specificity of the POC test needs to be ensured.

While our findings are specific to our context, it is possible that other provinces have similar gaps in their vertical transmission prevention cascade of syphilis.

Testing practices

These data demonstrate discrepancies in testing practices between Metro West and Metro East . While this was suspected given the different protocols followed – this had not been previously been appreciated at a district or provincial level. Given the recent dissemination of the 2023 Vertical Transmission Prevention (VTP) guidelines (35) and Adult Primary Care (PACK) Guidelines(60), there is an opportunity to clarify testing practices in the Metro and ensure alignment of district testing algorithms. 2023 guidelines (shown in Appendix F) suggest an increase in frequency of testing (1st booking visit and at every scheduled antenatal care visit at approximately 4 weekly intervals and during labour), and the use of the dual

[7] Avacare™ One Step Rapid Test, by Nantong Egens Biotech.

HIV/syphilis point of care test (35), and therefore it is important to understand the potential financial implications of different testing practices should the increased frequency of testing be implemented.

It is noted that in the geographic service area where a lower proportion of pregnancies have formal laboratory tests for syphilis (Metro East), the prevalence of gestational syphilis (ever RPR positive in pregnancy) is lower than Metro West (1.3% vs. 2.1% of pregnancies in Metro West). The infant RPR seropositivity, however, in Metro East is higher than in Metro West, with 649 (0.4%) infants in Metro East having a positive RPR vs. 320 (0.2%) infants in Metro West. Testing practices in infants needs to be further explored to understand reasons for this, and other data sources such as ICD-10 codes for congenital syphilis and using the NICD Notifiable Conditions data should be analysed to determine whether this finding truly represents the pattern of congenital syphilis prevalence in the Metro. While the finding may represent different RPR testing practices for infants, this could also represent true cases of symptomatic congenital syphilis and indicate that a higher number of pregnant women in Metro East are "falling through the cracks" of the congenital syphilis prevention cascade.

Prevalence of gestational syphilis in the Metro

There is an increasing prevalence trend of syphilis in pregnancy in the Cape Town Metro over time. Most women with a positive RPR in pregnancy (94%) had an RPR titre done (therefore 6% of women with a positive RPR did not have a titre as per the guidelines). Of the 6413 women with an RPR titre, over half (51%) had an RPR titre more than 8, indicating high titre active syphilis during their pregnancy. There was a year-on-year reduction in the proportion of women with a first RPR titre in pregnancy greater than or equal to 8 between 2017 to 2020 (61% to 45%) however this progress then reversed in 2021 with 51% of titres being >=8 in 2021, and 54% in 2022 which further suggests that there is an uptick of incident / active syphilis amongst pregnant women.

Our results of a RPR seroprevalence in pregnancies of 1.6% during 2017 to 2022 differ to the results from the most recent antenatal survey in 2022, which indicated that the antenatal seroprevalence of syphilis in the Western Cape was 3.7% (30). There are a few potential reasons for this difference. The antenatal survey estimates for syphilis in pregnancy are for the entire province – and are not available at a district level. The 2019 antenatal survey estimate for Cape Town was 1.9%, which was below the provincial average of 2.2% - and it may be that the prevalence of syphilis in pregnancy is lower in the metro than in rural subdistricts.

Other possible reasons for the difference relates to the definitions used for "syphilis in pregnancy". For the antenatal survey, a woman is considered to have syphilis if they have a positive RPR or VDRL, regardless of the titre – or if they were treated for syphilis according to their medical record (61). Given that the point of care test done is a treponemal test, it may be that some pregnant women who have a positive point of care test are recorded as positive in their medical record and treated as such, regardless of their formal laboratory test result. Including women who test positive on a treponemal point of care test without reviewing their RPR status would result in the antenatal survey overestimating the true number of active syphilis cases. As shown in these data, 8974 (2.1%) of pregnancies had a positive TPAb and a negative RPR – and if any of these cases were counted as positive for syphilis in the antenatal survey – it would inflate the true prevalence of active syphilis. Interestingly, in our cohort, the sum of previous syphilis and current RPR positive is 3.7% - which is the 2022 antenatal survey seroprevalence.

The prevalence of syphilis that we describe in this cohort of pregnancies (1.6% of the total pregnancies between 2017 and 2022) is above the estimates from 2016 where the estimated global prevalence of syphilis in pregnancy was 0.69%, the African Region, and the sub-Saharan estimate 1.52% (9).

High RPR titre pregnancies had worse outcomes, with the risk of an adverse outcome in syphilis positive pregnancies with an RPR titre <8 was comparable to syphilis negative pregnancies (RR1.08, 95% CI 0.88 - 1.33) whereas the risk of an adverse outcome for high-titre active syphilis was 3.7 times the risk of their syphilis counterparts (RR 3.72, 95% CI 3.34-4.15). This is not surprising, and it is possible that some of the cohort classified as syphilis positive with low titre active syphilis may represent women who have been previously treated for syphilis and did not have a new active infection.

Despite the prevalence of syphilis being below the antenatal survey estimates, the year-on-year increase in the prevalence of gestational syphilis in the Metro is concerning. This is resulting in preventable stillbirths and neonatal deaths. Opportunities to improve the cascade include retesting in pregnancy, which has been re-emphasized in the 2023 National Vertical Transmission Guidelines(35).

Electronic evidence of pharmacological management of syphilis in pregnancy

Benzathine penicillin is ward stock item used in antenatal clinics, Maternity Obstetric Units (MOUs) and emergency centres and at a central level Benzathine penicillin stock outs were noted during the study period, although the stock-outs were not explored in detail in this research. It does not need to be issued by a pharmacist and is administered as a single STAT dose, therefore, incomplete electronic capturing was anticipated. In our cohort, we observed similar and relatively low adverse perinatal outcomes were between women with gestational syphilis who had no record of appropriate treatment and those who had evidence of receiving penicillin. Of those who had no treatment recorded, 4.8% (n=200) had a stillbirth and 1.4% (n=57) had an early neonatal death vs. 4.3% (n=73) in those who received penicillin had a stillbirth and 1.4% (n=23) had an early neonatal death.

A 2013 systematic review showed that in pregnant women with untreated syphilis, 25.6% (95% CI 18.5-34.2) experienced stillbirths and 12.3% (95% CI 9.3 – 16.2) experienced neonatal deaths (9,13). WHO estimates assume that when syphilis in pregnancy is adequately treated, stillbirths can be reduced by 82% and neonatal deaths by 80%. In our cohort, Given the low coverage of evidence of treatment and similar perinatal outcomes between those with and without evidence of treatment, we suspect that more women were treated with Benzathine penicillin not captured as receiving it.

Less than 1/3rd of women testing positive for syphilis in pregnancy in our cohort were recorded to have received at least one dose of benzathine penicillin or benzylpenicillin. Incomplete electronic capture of antibiotics in pregnant women in this setting has previously been described Mehta et al in 2018 (50), where only half of the antibiotics dispensed and recorded in the maternity case record were also recorded electronically. Incomplete electronic record of antibiotics was seen for antibiotics used to treat sexually transmitted infections and urinary tract infections, for which ward stock was used. Mehta et al do however describe that for chronic medication, electronic records provided more information than maternal case records and highlight the utility of electronic capture of pharmacy data for understanding drug exposures and therapy in pregnancy (50).

Linking pharmacy data from JAC to laboratory and administrative data using the PMI for other conditions (such as HIV, TB and Diabetes) has proven to be valuable and has resulted in opportunities for epidemiological analysis and clinical tools to understand treatment history and adherence patterns(62,63). For the treatment of syphilis, however, the use of JAC data is limited.

Further audits would need to be conducted to understand whether patients given alternative treatment regimens (Amoxicillin and Probenecid or Ceftriaxone) had not also received STAT doses of penicillin, as the current data is not reliable due to the high risk of misclassification bias. In addition to incomplete capturing of pharmacy data limiting the research, there are other limitations of incomplete capturing of pharmacy data.

Opportunities also exist should capturing of pharmacy data improve. Firstly, from a health system perspective, in the context of penicillin stock outs resulting from multiple factors including inaccurate quantities ordered and procured from relevant countries, having an accurate oversight of how much penicillin is being used – and for what conditions – would be a crucial step to planning penicillin orders. The current system has the potential to do this, and it may be an important consideration to optimize accurate capturing of penicillin administration to ensure that sufficient stock is ordered and procured for the district. This may be a key strategy to addressing gaps in care in the vertical prevention of syphilis strategy, as at a national level it is suspected that we severely underestimate the doses of benzathine penicillin that are being used and insufficient doses are ordered from our single local supplier, resulting in stock outs and clinicians needing to obtain stock through Section 21 processes which add an administrative barrier and burden to the treatment of syphilis in this vulnerable population(64).

Secondly, this research has shown the potential for current routine data collected within the health system to provide oversight of the syphilis treatment cascade, and strengthening the quality and completeness of the data could assist policy makers and those implementing policies to identify gaps and opportunities in the management of syphilis in pregnancy. Should the coverage of pharmacy data capture improve significantly, electronic alerts could be developed for pregnant women (and their health care providers) with high-titre active syphilis who have not received appropriate treatment, or for women with latent syphilis who have not returned for 2^{nd} / 3^{rd} doses.

Thirdly, complete, and accurate capturing of pharmacy data could provide opportunity for further interrogation of alternative treatment regimens. This could be a way to meaningfully explore the efficacy of ceftriaxone and amoxicillin and probenecid, as this is a cohort of pregnant women who have received different treatment regimens. These alternative therapies are being used with insufficient data on their efficacy in treating both mother and baby, and randomised control trials are not feasible given the ethical considerations of an intervention trial for this condition.

Congenital Syphilis

Estimations of congenital syphilis using these data are a challenge as a case of congenital syphilis is inferred based on clinical and laboratory data available. There is also a discrepancy between the definition of a "surveillance case" of congenital syphilis (which would include an asymptomatic infant born to a mother with incompletely treated congenital syphilis) compared to a clinical definition of congenital syphilis – an infant with signs, symptoms, and investigations compatible with congenital syphilis.

For this analysis, a positive RPR in the infant is used to infer a case of congenital syphilis. The use of a single positive RPR result in an infant to infer a case of syphilis, however, does not consider the nuance of syphilis testing and considerations for diagnosing congenital syphilis. While laboratory testing is likely to pick up all symptomatic cases of congenital syphilis, as it will form part of the work up, it may miss asymptomatic cases whose mothers were incompletely treated – as these infants will be treated with a STAT dose of penicillin without being tested. A single RPR positive result also does not take into consideration the mothers' RPR titre, a low RPR titre in an asymptomatic infant whose mother was completely treated may represent treated infection in the mother and not active infection in the infant (as per the diagnostic criteria, syphilis would be suspected if the baby has a positive non-treponemal test at birth where the titre is 4-fold higher than that of the mothers,(41)).

However, all limitations and challenges considered, when using a crude measure of congenital syphilis in this population (of any RPR positive), our estimated RPR seropositivity of 267 per 100 000 live births over the five years is **higher** than national estimate of 174 per 100 000 live births in 2019, and the Western Cape Estimate of 174 per 100 000 live births (2). Given that asymptomatic infants whose mothers were incompletely treated will be notified as congenital syphilis and treated for congenital syphilis without needing any laboratory testing (as discussed above), this RPR seroprevalence in infants is likely an underestimate.

It is notable that one third of infants with a positive RPR (n= 360) were born to a mother who either did not have a formal laboratory test (n=276, 76%) or had tested negative (n=84, 23%), and therefore we are not identifying all pregnant women with gestational syphilis. Either these women are testing negative on a point of care test and therefore not having further testing (either false negative, or these cases represent incident cases of syphilis in pregnancy), or the minimum guidelines for laboratory testing of doing follow up laboratory tests for a positive point of care test are not being followed and these women with incident syphilis are not being tested. The cohort of infants who test positive should be further described to understand their risk factors and the antenatal care that their mothers received. Efforts should be made to link the congenital syphilis cases detected in our dataset to the cases reported to the Notifiable Medical Conditions surveillance system – as is done in other settings such as Brazil (65)– to further explore formally notified cases and identify whether their mothers had been identified as having syphilis. It should be ensured that tests with appropriate sensitivity and specificity are being utilized to ensure that they are fit for purpose as a screening test. Health care workers conducting point of care tests also need to be trained to perform and read the test results for point of care tests for optimum screening.

Our findings of an increase in cases of congenital syphilis (defined by RPR seropositivity as a proxy, given that we did not include clinical data for infants or link to the notified conditions) is concerning and on a global setting highlight the challenge of regional variability with regards to the WHO goal of congenital syphilis elimination. Mathebula et al showed a reduction in the number of RPR positive children <2 between 2010-2011 (n=639) and 2018-2019 (n = 392) in the Western Cape (2), yet we have seen increases in RPR positive infants since 2020. A global review of congenital syphilis epidemiology published in 2023 describes maternal syphilis prevalence and congenital syphilis per region – and describe a wide variation between different countries with regards to elimination of congenital syphilis (66). Some regions, such as South East Asia and Western Pacific, have had stability or reductions in cases of maternal syphilis and congenital syphilis. Countries like Thailand (in 2016), the Maldives and Sri Lanka (in 2019) achieved the WHO target of <50 per 1000 live births(66). Other regions, however, like the Americas have seen increases in cases of congenital syphilis resulting from increases in gestational syphilis and the incidence of syphilis

in the adult population; in the United States a 147% increase in cases of syphilis were seen in women between 2016 and 2020.

Limitations

This research was reliant on routinely collected health data, which is complete and accurate to different extents and varies between health facility and data source. The pregnancy data relies on inferring episodes of pregnancy – which will never be as reliable as a physical folder review or prospective study in our context where data capture is at times inconsistent. Our data were limited in terms of understanding the quality of antenatal care received,and did not include point of care test results or any clinical assessments. We had a limited understanding of pharmacologic treatment, including that Probenecid was not a category on the electronic pharmacy management system and the enzyme that was included with amoxicillin was not specified and may have been clavulanic acid and not probenecid. It is appreciated that adverse infant outcomes are multifactorial, and adjusting for potential confounding factors was not done as part of this analysis.

Using these data, however, allows us to obtain a snapshot of the entire metro – which would otherwise not be possible. It also allows us to have oversight of linked maternal and infant data.

Conclusion

There is an increasing prevalence of syphilis in pregnancy, resulting in preventable stillbirths and neonatal deaths. Within the metro there are discrepant testing strategies, and more research needs to be done to understand whether there is an association between testing strategies and adverse pregnancy outcomes. While electronic pharmacy data does provide the opportunity for interrogation of alternative treatment regimens used for syphilis in pregnancy, the electronic capturing of pharmacy data for benzathine penicillin is incomplete and so no meaningful analysis of these data is possible. Improvements in the reliability of electronic pharmacy data has the potential for other improvements in vertical transmission prevention of syphilis. Congenital syphilis, as measured by infant RPR positivity, is higher than the national estimate and is likely an underestimate. Gaps in the prevention of congenital syphilis cascade is suspected, as one third of infants with a positive RPR were born to mothers who did not have a formal laboratory test for syphilis, or who had tested negative for syphilis in pregnancy.

Recommendations

Attention should be given to syphilis in pregnancy in the Cape Town Metro as it is a preventable infection that results in adverse perinatal outcomes and contributes to stillbirths and neonatal deaths in the district. There is an opportunity to clarify the testing protocol for syphilis in pregnancy for the district, to standardize the tests and testing algorithms used and ensure that the relevant health care workers are trained appropriately. Point of care tests used should be validated and have acceptable sensitivity and specificity, with ongoing quality control monitoring in place.

Further research is recommended to explore the follow up RPR titres that are currently being done, including the timing of titre tests and their trends, and to further examine the congenital syphilis prevention cascade outcomes by reviewing infants with an ICD-10 code for congenital syphilis and include those who have been notified to the NICD as congenital syphilis. There is also a potential opportunity for cost-saving, as some follow-up titres may be done too soon after treatment is initiated and a reduction in RPR titre frequency could be more efficient and economical without compromising patient care.

Finally, electronic capture of pharmacy data was not complete enough to meaningfully compare outcomes between treatment groups. Further audits should be done on maternal cases who have been treated with alternative treatment regimens to both describe the population who is being treated with these regimens, why they are being used, and their associated pregnancy outcomes. Access to penicillin for treatment of syphilis in pregnancy needs to be ensured, and barriers to adequate supply including the need for S21 application should be addressed to enable easy access to benzathine penicillin. Improved capture of pharmacy data could have the added benefit of improving supply chain management processes for penicillin stock.

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Appendices

Appendix A: NICD Congenital Syphilis Surveillance Case Definition

[3]

Congenital syphilis surveillance case definition

The surveillance definition considers the following as cases of congenital syphilis:

1. Live birth or foetal death at >20 weeks of gestation or >500 g (including stillbirth) born to a woman with positive non-treponemal syphilis serology (RPR/ VDRL) and without adequate syphilis treatment

OR

2. Stillbirth, live birth or child age <2 years born to a woman with positive non-treponemal syphilis serology (RPR/ VDRL) or unknown serostatus, and with laboratory and/or radiographic and/or clinical evidence of syphilis infection (regardless of the timing or adequacy of maternal treatment).

Laboratory, radiographic or clinical evidence consistent with a diagnosis of congenital syphilis includes any of the following:

Laboratory

a) Demonstration by dark-field microscopy or detection by fluorescent antibody testing of Treponema pallidum in the umbilical cord, placenta, nasal discharge or skin lesion material or autopsy material of a neonate or stillborn infant;
b) Analysis of cerebrospinal fluid (CSF) is reactive for Venereal Disease Research Laboratory (VDRL) test or elevated CSF cell count or protein without other cause;
c) Infant with a reactive non-treponemal serology test with titre fourfold or more than that of the mother;
d) Infant with a reactive non-treponemal serology test with titre less than fourfold more than that of the mother but that remains reactive >=6 months after delivery;
e) Infant with a reactive non-treponemal serology test of any titre AND any of the clinical signs born to a mother with positive or unknown serology, independent of treatment;

Radiological features

f) Long bone radiographs suggestive of congenital syphilis (e.g. osteochondritis, diaphyseal osteomyelitis, periostitis;

Clinical signs and symptoms

g) In settings where a non-treponemal titre is not available, an infant born to a mother with positive or unknown serology, independent of treatment, and whose 6-month examination demonstrates any of the clinical signs of early congenital symptoms. These include non-immune hydrops, hepatosplenomegaly, rhinitis (snuffles), and skin rash, pseudoparalysis of an extremity or failure to thrive or achieve developmental milestones. An older infant or child may develop additional signs or symptoms such as frontal bossing, notched and pegged teeth (Hutchinson teeth), clouding of the cornea, blindness, bone pain, decreased hearing or deafness, joint swelling, sabre shins, and scarring of the skin around the mouth, genitals and anus.
h) For stillborn infants, maternal syphilis serostatus should be determined. Any stillbirth case from a woman with a reactive maternal syphilis antibody test should be considered a congenital syphilis case.

Appendix B: Comparison of Testing and Treatment of Syphilis guidelines in different protocols

Summary of Guidelines on Treatment of Syphilis in Pregnancy

	Testing the mother	Treating the mother	Penicillin Alternatives
National Guidelines			
Guidelines for Maternity Care in South Africa (2016) (5)	*"Syphilis serology. Rapid tests are preferable, as results are immediately available. Take care to follow the instructions from the manufacturer carefully to avoid false negative results"* (5, p.31) "Syphilis and Positive RPR Tests" (5, p. 104) *Syphilis Screening in Pregnancy* • *Rapid syphilis screening must be done at the first antenatal visit* • *If the first test is performed before 20 weeks and is negative, a second test should be done at 32-34 weeks* • *A rapid card test, done in the antenatal clinic, gives a result before the woman goes home. This allows immediate treatment.*	• *Treat all women with a positive screening test, irrespective of titre* • *Give benzathine penicillin, 2.4 million units IM once weekly, for three doses*	Penicillin Allergy: • Admit to hospital for penicillin desensitization. Only penicillin will adequately prevent transmission to the fetus and prevent congenital syphilis. There are no proven alternatives.
STI Guidelines (2018) (4)	Describes syphilis serology and recommends using both RPR and	• Benzathine penicillin 2.4 MU IMI once weekly for 3 weeks.	• In case of penicillin allergy: Refer for penicillin desensitization

	treponemal test (either TPHA, TPPA, FTA, Treponema pallidum ELISA or TPAb). Suggests traditional algorithm but describes reverse algorithm too. "[Test] all pregnant women at first antenatal visit and repeat testing at 32 weeks for women testing negative in the first trimester". "Take blood for RPR test (always)		• The guideline specifies that if Benzathine Penicillin is unavailable, pregnant women testing positive for syphilis should receive Amoxicillin 1g 8 hourly for 14 days and Probenecid 250mg 8 hourly for 14 days [1].
PMTCT Guidelines (2019) (34)	Describes the need for both treponemal and non-treponemal tests, and describes using both the traditional or the reverse testing algorithm. Test all pregnant women at first visit, and repeat testing at 32-34 weeks for women testing negative in the first trimester.	Benzathine penicillin 2.4MU IMI once weekly for 3 weeks.	Penicillin Allergy: Refer for penicillin desensitization.
Provincial and District Guidelines			
BANC Handbook Feb 2017(36)	Screen for syphilis at the first visit. "Syphilis Screening: This is best done on-site at the clinic using the RPR test. The results are available immediately and treatment can be started the same day"	"If the RPR is positive and there is no previous test result, irrespective of the RPR titre (level), treat for late syphilis: Benzathine benzylpenicillin, IM, 2.4MU once weekly for 3 weeks."	Penicillin Allergy: Refer for consideration of penicillin desensitization. Erythromycin or azithromycin may not be sufficient to cure syphilis in the fetus.

Protocols for Clinical Practice at Level 1 Maternity Care Facilities in the Metro West. (37) (pg. 34)	"All pregnant women undergo a rapid syphilis test (Treponema Pallidum Hemagglutination Test), and bloods are sent to the laboratory for formal testing (TPHA) at the first antenatal clinic visit. If the first test is performed before 20 weeks gestation and is negative, a second test should be done at 36 weeks."	"If the rapid test (TPHA) is positive, give first dose of Benzathine penicillin. Subsequent treatment is given according to the serology result (available in one week). A positive TPHA indicates current or previous infection. The laboratory will then automatically do an RPR titre which donates current infection. If RPR negative, no further treatment is needed. If both TPHA and RPR positive: Benzathine Penicillin 2.4MU IMI once weekly for 3 doses. Repeat RPR after 3 months to confirm a four-fold reduction in RPR titres.	Penicillin Allergy: Admit to level 2 hospital for confirmation and desensitization.
Western Cape Government: Circular No H119/2019 (38) "Stock-out of Benzathine Penicillin Intramuscular Injection: Long Acting (LA) Circular was in response to stock-outs of Penicillin and a lag period in sourcing Benzathine Penicillin through section 21.			If no Benzathine Penicillin can be sourced: (for pregnant women) Early Syphilis Amoxicillin oral 1g 8hrly for 14 days with probenecid 250mg 8 hrly for 14 days Late Syphilis Amoxicillin oral 1g 8 hrly for 28 days with

			probenecid 250mg 8 hrly for 28 days It is noted that this regimen will not prevent congenital syphilis and that the neonates will require Benzathine penicillin as they are partially treated. "It is imperative that facilities reserve supplies of benzathine penicillin for these neonates. All syphilis exposed newborns should be followed up for examination and repeat RPR after 3 months".

Appendix C: Tables & Figures

Table 1: Demographics of the Study Population: Total and per laboratory test for syphilis status

	Total Study Population N= 419376[1]		No Laboratory Test done for syphilis during pregnancy N= 221 644[1]		Laboratory Test done for Syphilis during pregnancy N = 197 732[1]		P-Value[2]
Mother age at pregnancy outcome	27	(23-32)	27	(23-32)	28	(23-32)	<0.001
Parity	0	(0-1)	0	(0,1)	0	(0,1)	
Geographic Service Area of Outcome							<0.001
Metro East	198 578	(47%)	158 194	(71%)	40 384	(20%)	
Metro West	204 600	(49%)	56 859	(26%)	147 741	(75%)	
Other	16 198	(3.9%)	6 591	(3%)	9 607	(4.9%)	
Evidence of Maternal HIV during pregnancy							
HIV Positive Pregnancy (ante or perinatal)	87 535	(21%)	41 993	(19%)	45 542	(23%)	
No Evidence of HIV in pregnancy	331 841	(79%)	179 651	(81%)	152 190	(77%)	
Antenatal Booking Status[3]							
Booked Early	171 220	(41%)	57 190	(26%)	114 030	(58%)	
Booked Late	248 156	(59%)	164 454	(74%)	83 702	(42%)	
Laboratory Test for Syphilis Done During Pregnancy			221 644	(53%)	197 721	(47%)	

[1] Median (IQR), n(%)
[2] Wilcoxon Mann-Whitney Test
[3] Booked Early = Booked before 20 weeks, Booked Late = booked after 20 weeks or unbooked

Table 2: Table to show laboratory results for syphilis

	Syphilis Status in Pregnancy According to Laboratory (NHLS) Results N= 419 376[1]	
No test	221 644	(53%)
Negative	180 648	(43%)
Previous Syphilis	8 974	(2.1%)
Positive	6 812	(1.6%)
Test Error	1 298	(0.3%)
[1] n (%)		

Table 3: Demographic, Booking Status and Maternal Syphilis Category of pregnancies over time

	2017 N= 64 553[1]		2018 N= 68 904[1]		2019 N= 72 798[1]		2020 N = 73 249[1]		2021 N = 71 333[1]		2022 N = 68 539[1]	
Mother age at pregnancy outcome	27	(23,32)	27	(23,32)	27	(23,32)	27	(23,32)	28	(23,32)	28	(23,32)
Parity	0	(0,1)	0	(0,1)	0	(0,1)	0	(0,1)	0	(0,1)	0	(0,1)
Booking Status[2]												
Booked Early	26 550	(41%)	27 435	(40%)	28 985	(40%)	27 209	(37%)	30 722	(43%)	30 319	(44%)
Booked Late	38 003	(59%)	41 469	(60%)	43 813	(60%)	46 040	(63%)	40 611	(57%)	38 220	(56%)
Maternal Syphilis Category[3]												
No test	38 819	(60%)	34 369	(50%)	38 851	(53%)	43 354	(59%)	33 795	(47%)	32 456	(47%)
Negative	23 609	(37%)	31 872	(46%)	31 106	(43%)	26 551	(36%)	34 534	(48%)	32 976	(48%)
Previous Syphilis	1 352	(2.1%)	1 523	(2.2%)	1 342	(1.8%)	1 289	(1.8%)	1 729	(2.4%)	1 739	(2.5%)
Positive	764	(1.2%)	1 128	(1.6%)	1 225	(1.7%)	1 151	(1.6%)	1 220	(1.7%)	1 324	(1.9%)
Test Error	9	(<0.1%)	12	(<0.1%)	274	(0.4%)	904	(1.2%)	55	(0.1%)	44	(<0.1%)

[1] n (%)

[2] Booked Early = Booked before 20 weeks, Booked Late = booked after 20 weeks or unbooked

[3]According to Laboratory (NHLS) Result.

Table 4: Table to describe baseline characteristics by maternal syphilis status in pregnancy

	Syphilis Screen Negative N= 180 648[2]		Syphilis Screen Positive N = 6 812[2]		Previous Syphilis[1] N= 8 974[2]		Test Error N= 1 298[2]		p-value[3]
Mother age at pregnancy outcome	27	(23,32)	28	(24, 32)	32	(27,36)	27	(22,32)	<0.001
Parity	0	(0,1)	1	(0,2)	1	(0,2)	1	(0,1)	<0.001
Booking Status[4]									<0.001
Booked Early	105 411	(58%)	3 280	(48%)	4 597	(51%)	742	(57%)	
Booked Late	75 237	(42%)	3 532	(52%)	4 377	(49%)	556	(43%)	

[1]TPAb positive, RPR negative

[2]Median (IQR), n(%)

[3]Kruskal-Wallis rank sum test; Pearson's Chi Squared test

[4] Booked Early = Booked before 20 weeks, Booked Late = booked after 20 weeks or unbooked

Table 5: Maternal Syphilis in Pregnancy per GSA of Outcome

	Metro East N= 198 578[1]		Metro West N= 204 600[1]		Rural N= 5 409[1]		Null N= 10 789[1]		p-value[2]
Maternal Syphilis Category[3]									<0.001
No test	158 194	(80%)	56 859	(28%)	2 255	(42%)	4336	(40%)	
Negative	35 069	(18%)	136 734	(67%)	2 788	(52%)	6057	(56%)	
Previous Syphilis	2 690	(1.4%)	5 841	(2.9%)	225	(4.2%)	218	(2%)	
Positive	2 460	(1.2%)	4 094	(2.0%)	126	(2.3%)	132	(1.2%)	
Test Error	165	(<0.1%)	1072	(0.5%)	15	(0.3%)	46	(0.4%)	

[1] n (%)
[2] Pearson's Chi-squared test
[3] According to Laboratory (NHLS) Result.

Table 6: Pregnancy characteristics of pregnancies screening positive for syphilis per year

	2017 N= 764 [1]		2018 N= 1 128 [1]		2019 N= 1 225 [1]		2020 N= 1 151 [1]		2021 N= 1 220 [1]		2022 N= 1 324 [1]	
Mother Age (years)	28	(24,32)	28	(24,32)	28	(24,33)	28	(24,33)	28	(24,32)	28	(23,33)
Booking Status [2]												
Booked Early	316	(41%)	514	(46%)	579	(47%)	578	(50%)	590	(48%)	703	(53%)
Booked Late	184	(24%)	225	(20%)	204	(17%)	185	(16%)	260	(21%)	228	(17%)
RPR Titre Category on first lab test												
< 8	248	(32%)	462	(45%)	643	(52%)	600	(52%)	548	(45%)	566	(43%)
Greater than or equal to 8	347	(45%)	585	(52%)	539	(44%)	497	(43%)	583	(48%)	657	(50%)
No RPR titre on first laboratory test for syphilis in pregnancy	169	(22%)	81	(7%)	43	(4%)	54	(5%)	89	(7%)	87	(7%)

[1] n (%), Median (IQR)
[2] Booked Early = Booked before 20 weeks, Booked Late = booked after 20 weeks or unbooked

Table 7: Pregnancy Outcomes (Full Cohort)

	N = 425 128[1]	
Pregnancy Outcome		
Neonate Survived	367 360	(86%)
Still Birth	6 520	(1.5%)
Early Neonatal Death	2 541	(0.6%)
Late Neonatal Death	630	(0.1%)
Ectopic Pregnancy	4 819	(1.1%)
Miscarriage	9 772	(2.3%)
Termination	21 041	(4.9%)
Infant Outcome Unknown	12 445	(2.9%)
[1]n, %		

Table 8: Pregnancy Outcomes by Maternal Syphilis Status

	No laboratory test done for syphilis N= 224 101 [1]		**Previous Syphilis** N = 9 111[1]		**Syphilis Screen Negative** N= 183 687[1]		**Syphilis Screen Positive** N = 6 909[1]		**Test Error** N = 1 320[1]	
Pregnancy Outcome										
Neonate Survived	187 758	(84%)	8 065	(89%)	164 313	(89%)	6021	(87%)	1203	(91%)
Still Birth	2 705	(1.2%)	199	(2.2%)	3 280	(1.8%)	314	(4.5%)	22	(1.7%)
Early Neonatal Death	1 234	(0.6%)	72	(0.8%)	1 142	(0.6%)	83	(1.2%)	10	(0.8%)
Late Neonatal Death	306	(0.1%)	25	(0.3%)	279	(0.2%)	16	(0.2%)	4	(0.3%)
Ectopic Pregnancy	2 480	(1.1%)	143	(1.6%)	2 121	(1.2%)	68	(1%)	7	(0.5%)
Miscarriage	5 046	(2.3%)	208	(2.3%)	4 350	(2.4%)	139	(2%)	29	(2.2%)
Termination	17 833	(8%)	145	(1.5%)	2 965	(1.6%)	80	(1.2%)	29	(2.2%)
Unknown	6 739	(3%)	265	(2.9%)	5 237	(2.9%)	188	(2.7%)	16	(1.2%)
[1] n (%)										

Table 9: Early Pregnancy Outcomes and Syphilis Status in pregnancy

		Ectopic Pregnancy n = 4819[1]		Miscarriage n = 9772[1]		Termination of pregnancy n = 21 041[1]	
No lab test	n= 25359	2480	(51%)	5046	(52%)	17833	(85%)
Previous Syphilis	n= 485	143	(3.0%)	208	(2.1%)	134	(0.6%)
Syphilis Screen Negative	n= 9436	2121	(44%)	4350	(45%)	2965	(14%)
Syphilis Screen Positive	n= 287	68	(1.4%)	139	(1.4%)	80	(0.4%)
Test Error	N=65	7	(0.1%)	29	(0.3%)	29	(0.1%)
	Total 35632		(100%)		(100%)		(100%)

[1] n (%)

Table 10: Perinatal outcomes by maternal syphilis status in pregnancy

	Neonate Survived N= 367360[1]		Still Birth N=6520[1]		Early Neonatal Death N = 2541[1]		Late Neonatal Death N= 630[1]	
No lab test done	187758	(51%)	2705	(41%)	1234	(49%)	306	(49%)
Previous Syphilis	8065	(2.2%)	199	(3.1%)	72	(2.8%)	25	(4.0%)
Syphilis Screen Negative	164313	(45%)	3280	(50%	1142	(45%)	279	(44%)
Syphilis Screen Positive	6021	(1.6%)	314	(4.8%)	83	(3.3%)	16	(2.5%)
Test Error	1203	(0.3%)	22	(0.3%)	10	(0.4%)	4	(0.6%)

[1] n, %

Table 11a: Outcome of pregnancy in syphilis positive (RPR positive) cohort who have an RPR titre, by RPR titre category of the first laboratory test for syphilis done in pregnancy

	RPR titre <8 N= 3 117[1]		**RPR titre greater than or equal to 8** N= 3 265[1]		**No RPR titre on first syphilis test in pregnancy** N= 527[1]	
Pregnancy Outcome						
Neonate Survived	2826	(91%)	2 711	(83%)	484	(92%)
Still Birth	61	(2%)	244	(7.5%)	9	(1.7%)
Early Neonatal Death	22	(0.7%)	58	(1.8%)	3	(0.6%)
Late Neonatal Death	4	(0.1%)	12	(0.4%)	0	(0%)
Ectopic Pregnancy	40	(1.3%)	26	(0.8%)	2	(0.4%)
Miscarriage	64	(2.1%)	65	(2%)	10	(1.9%)
Termination of Pregnancy	35	(1.1%)	42	(1.3%)	3	(0.6%)
Unknown Infant Outcome	65	(2.1)	107	(3.3%)	16	(3%)

[1] n (%)

Table 11b : Risk of Adverse Perinatal Outcomes in Syphilis Positive Group compared to syphilis negative group

Exposure Status	Adverse Outcome[1]	No Adverse Outcome	Risk Ratio	95% CI	
All RPR positive pregnancies	413	6021	2.31	(2.09, 2.54)	
RPR titre < 8	88	2844	1.08	(0.88, 1.33)	
RPR titre ≥ 8	314	2720	3.72	(3.72, 4.13)	
Syphilis Negative	4 701	164 313	1.00		----

[1] Adverse Outcome**:** Stillbirth, early neonatal death or late neonatal death

Table 12: Pregnancy Characteristics and Perinatal Outcomes by Infant Syphilis Status

	No syphilis positive test in infant N=375 042[1]		Infant RPR Positive N= 991[1]		Infant TPAb Positive, RPR Negative N = 833[1]		Infant TPAb positive, No RPR result N= 185[1]	
Pregnancy Outcome [2]								
Neonate Survived	365 426	(97%)	943	(95%)	811	(97%)	180	(97%)
Still Birth	6 517	(1.7%)	2	(0.2%)	1	(0.1%)	0	(0%)
Early Neonatal Death	2 490	(0.7%)	35	(3.5%)	13	(1.6%)	3	(1.6%)
Late Neonatal Death	609	(0.2%)	11	(1.1%)	8	(1%)	2	(1.1%)
Booking Category[3]								
Booked Early	154 084	(41%)	226	(23%)	253	(30%)	43	(23%)
Booked Late	220 958	(59%)	765	(77%)	580	(70%)	142	(77%)
Birth Weight								
<2500 g	55 833	(16%)	431	(46%)	335	(42%)	57	(33%)
>= 2500g	304 085	(84%)	507	(54%)	460	(58%)	116	(67%)
Unknown	15 124		53		38		12	
Reported Gestational Age								
Median (IQR)	38	(36, 40)	37	(34, 39)	37	(34, 39)	38	(36, 39)
Unknown	295 550	(79%)	802	(81%)	657	(79%)	152	(82%)

[1] n (%)

[2] Infants for which pregnancy outcome was unknown were excluded from this table (n=5)

[3]Booked Early = Booked before 20 weeks, Booked Late = booked after 20 weeks or unbooked

Table 13: Maternal syphilis status, booking category and GSA of outcome of RPR Positive Infants born to mothers who had not Screened to have active syphilis in pregnancy.

	RPR Positive Infants born to mothers who were not screened as syphilis positive in pregnancy N = 360[1]	
Maternal Syphilis Category		
No lab test done for syphilis	276	(77%)
Previous Syphilis	46	(13%)
Syphilis Screen Negative	35	(9.7)
Test Error	3	(0.8%)
Booking Category [2]		
Booked Early	44	(12%)
Booked Late	316	(88%)
Geographic Service Area of Outcome		
Metro East	248	(69%)
Metro West	108	(30%)
Other	4	(1.1%)

[1]n, (%)
[2] Booked Early = Booked before 20 weeks, Booked Late = booked after 20 weeks or unbooked

Table 14: RPR Positive RPR Positive Infants born to mothers who had not Screened to have active syphilis: Booking category and GSA outcome by Maternal Syphilis Status

	No laboratory test done for syphilis in mother in pregnancy N = 276[1]		Mother screened to have Previous Syphilis N= 46[1]		Syphilis Screen Negative N = 35[1]		Test error N = 3[1]	
Booking Category [3]								
Booked Early	21	(8%)	4	(9%)	19	(54%)	0	(0%)
Booked Late	255	(92%)	42	(91%)	16	(46%)	3	(100%)
Geographic Service Area of Outcome								
Metro East	209	(76%)	24	(52%)	14	(40%)	1	(33%)
Metro West	64	(23%)	22	(48%)	20	(57%)	2	(67%)
Other	3	(1.1%)	0	(0%)	1	(2.9%)	0	(0%)

[1] n, (%)
[2] Mother tested TPAb Positive, RPR Negative in pregnancy
[3] Booked Early = Booked before 20 weeks, Booked Late = booked after 20 weeks or unbooked

Table 15: Pregnancy outcomes over time

	2017 N= 65 381[1]		2018 N= 69 812		2019 N= 73 903		2020 N= 74 284		2021 N= 72 301		2022 N= 69 447	
Pregnancy Outcome												
Neonate Survived	54 316	(90%)	60 360	(90%)	65 038	(90%)	66 190	(90%)	62 568	(88%)	58 888	(86%)
Still Birth	1 054	(1.7%)	1 116	(1.7%)	1 089	(1.5%)	1 139	(1.6%)	1 116	(1.6%)	1 006	(1.5%)
Early Neonatal Death	344	(0.6%)	438	(0.7%)	451	(0.6%)	447	(0.6%)	389	(0.5%)	472	(0.7%)
Late Neonatal Death	84	(0.1%)	103	(0.2%)	122	(0.2%)	108	(0.1%)	102	(0.1%)	111	(0.2%)
Ectopic Pregnancy	660	(1.1%)	722	(1.1%)	791	(1.1%)	699	(1%)	854	(1.2%)	1 093	(1.6%)
Miscarriage	934	(1.5%)	1 243	(1.9%)	1 420	(2%)	1 372	(1.9%)	2 133	(3%)	2 670	(3.9%)
Termination	2 995	(5%)	3 205	(4.8%)	3 666	(5.1%)	3 235	(4.4%)	3 785	(5.3%)	4 155	(6.1%)
Unknown	4 994		2 625		1 326		1 094		1 354		1 052	
Birth Weight [2]												
<2500g	8 861	(16%)	9 366	(16%)	9 524	(15%)	9 645	(15%)	9 892	(16%)	9 459	(16%)
>= 2500g	46 822	(84%)	50 939	(84%)	52 093	(85%)	55 065	(85%)	51 492	(84%)	49 121	(84%)
Unknown	9 698		9 507		12 286		9 574		10 917		10 867	

[1] n, (%)

[2] Note that the % is the proportion / percentage of all those with a birth weight recorded

Table 16: Perinatal outcome, lab test, prevalence of gestational syphilis and infant RPR positivity per Geographic Service Area of Outcome

	Metro East N= 182 593[1]		Metro West N = 181 232[1]		Other N= 13 226[1]		P-value
Perinatal Outcome[2]							<0.001
Neonate Survived	177 847	(97%)	176 515	(97%)	12 998	(98%)	
Still Birth	3 216	(1.8%)	3 156	(1.7%)	148	(1.1%)	
Early Neonatal Death	1 217	(0.7%)	1 255	(0.7%)	69	(0.5%)	
Late Neonatal death	313	(0.2%)	306	(0.2%)	11	(<0.1%)	
Lab Test Done for Syphilis In Pregnancy (For mother)	37 133	(20%)	139 849	(77%)	8 066	(61%)	<0.001
Mother RPR Positive in Pregnancy	2 341	(1.3%)	3 869	(2.1%)	224	(1.7%)	<0.001
Infant tested RPR Positive	649	(0.4%)	320	(0.2%)	22	(0.2%)	<0.001

[1] n, (%)

[2] Perinatal Outcome only includes pregnancies with late pregnancy outcomes: Ectopics, Terminations, Miscarriages and Unknown outcomes excluded.

Table 17: Evidence of appropriate treatment to treat syphilis in pregnancy for those testing TPAb and RPR positive on first laboratory test in pregnancy

	Women who tested TPAb and RPR positive on first laboratory syphilis test in pregnancy N= 6 444[1]	
Treatment Status		
No treatment for syphilis captured electronically	4 462	(69%)
Received Amoxicillin and Enzyme Inhibitor	183	(2.8%)
Received Benzylpenicillin	1 775	(28%)
Received Ceftriaxone	24	(0.4%)

[1] n, (%)

Table 18: Outcome of pregnancy by treatment category for pregnancies testing TPAb and RPR positive on first laboratory test in pregnancy

	No treatment for syphilis captured electronically N = 4 462[1]		**Received Amoxicillin and Enzyme Inhibitor N = 183[1]**		**Received Benzylpenicillin N = 1 775[1]**		**Received Ceftriaxone N = 24[1]**	
Pregnancy Outcome								
Neonate Survived	3 884	(89%)	162	(91%)	1 603	(93%)	21	(91%)
Still Birth	200	(4.6%)	8	(4.5%)	73	(4.2%)	0	(0%)
Early Neonatal Death	57	(1.3%)	1	(0.6%)	23	(1.3%)	0	(0%)
Late Neonatal Death	11	(0.3%)	1	(0.6%)	3	(0.2%)	0	(0%)
Ectopic Pregnancy	59	(1.4%)	1	(0.6%)	3	(0.2%)	1	(4.3%)
Miscarriage	106	(2.4%)	4	(2.2%)	16	(0.9%)	0	(0%)
Termination	63	(1.5%)	2	(1.1%)	10	(0.6%)	1	(4.3%)
Unknown	112		4		44		1	

[1] n, (%)

Table 19: Perinatal Outcome by Treatment Category

	No treatment N=4152		**Penicillin N=1603**		**Alternative Regimens N=193**	
Neonate Survived	3884.00	93.55%	1603	94.18%	183	94.82%
Still Birth	200.00	4.82%	73	4.29%	8	4.15%
Early Neonatal Death	57.00	1.37%	23	1.35%	1	0.52%
Late Neonatal Death	11.00	0.26%	3	0.18%	1	0.52%

Figure 1: Syphilis Status in Pregnancy

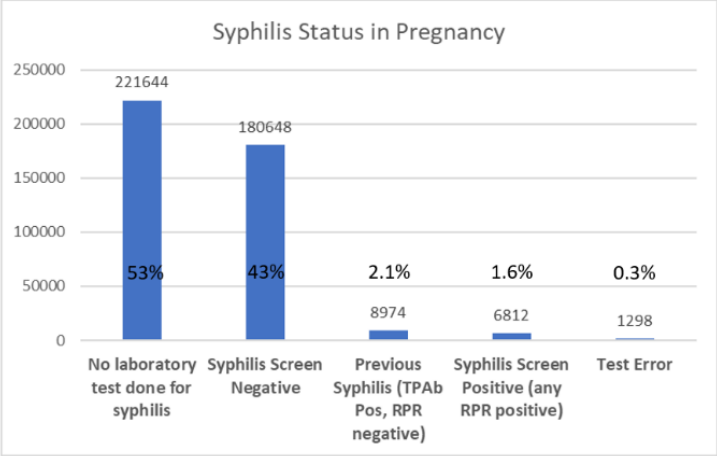


Figure 2: Total number of pregnancies and pregnancies with gestational syphilis over time

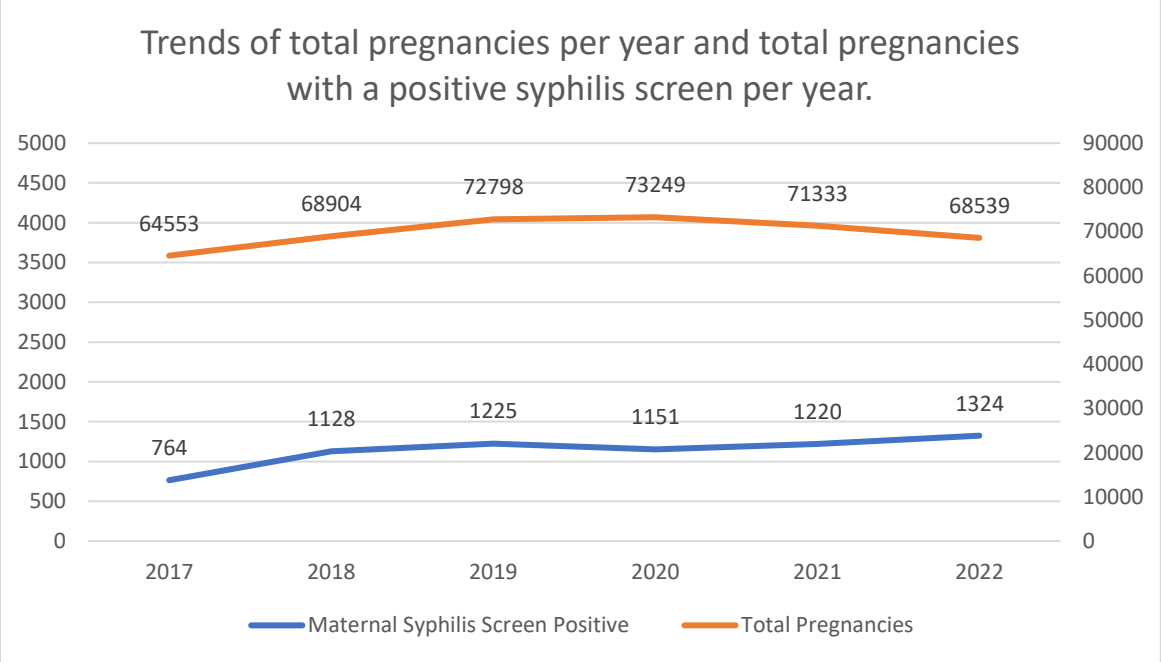
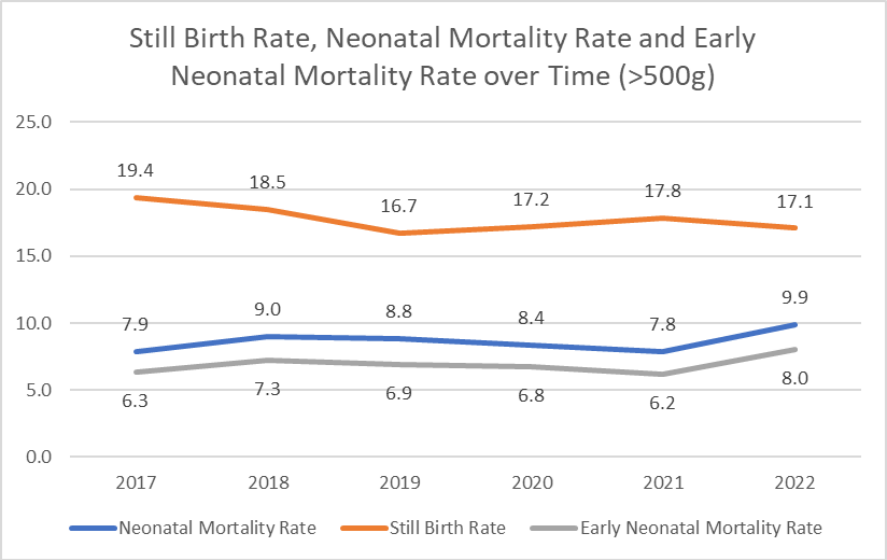


Figure 3: Still Birth Rate, NNMR and ENMR over time (>500g)



To note, for the graphs showing pregnancies that are RPR positive over time and infant RPR positivity, the pregnancies are not deduplicated and therefore the mother of a multiple pregnancy will be counted twice. (figures 4 – 6)

Figure 4:

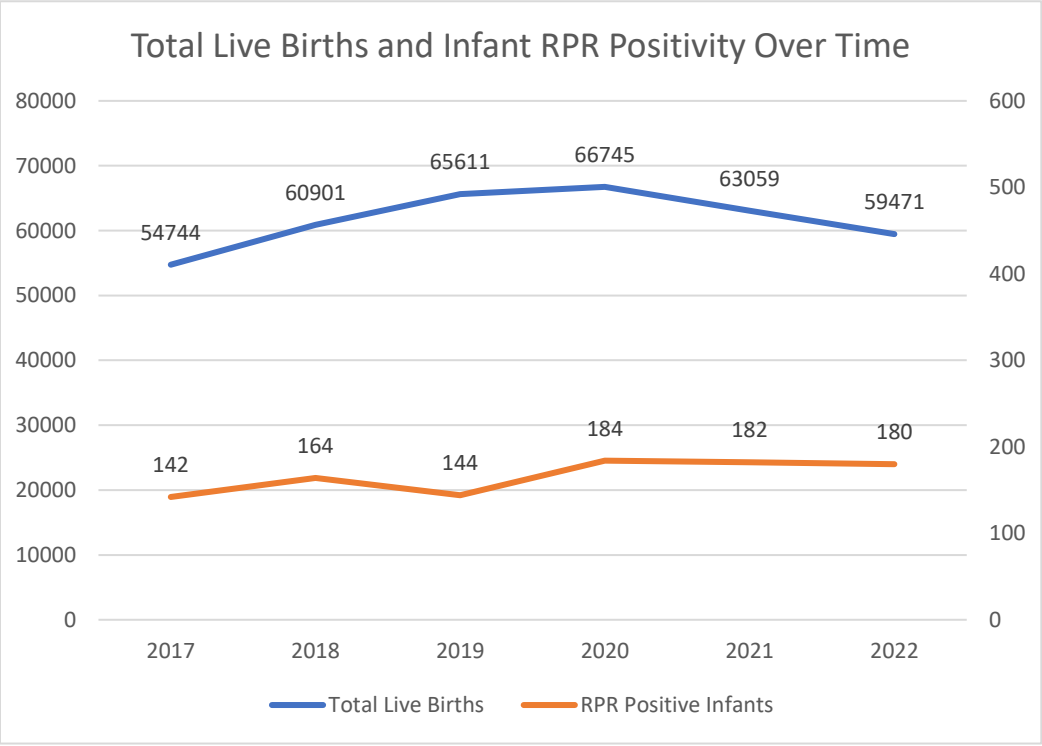


Figure 5:

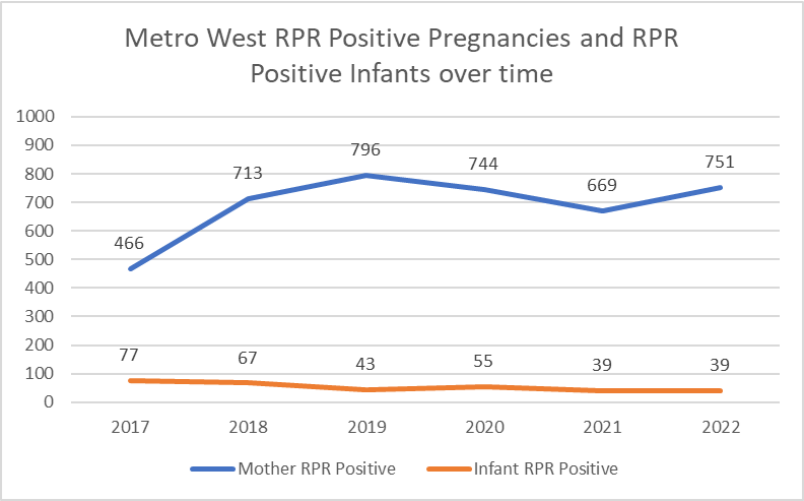
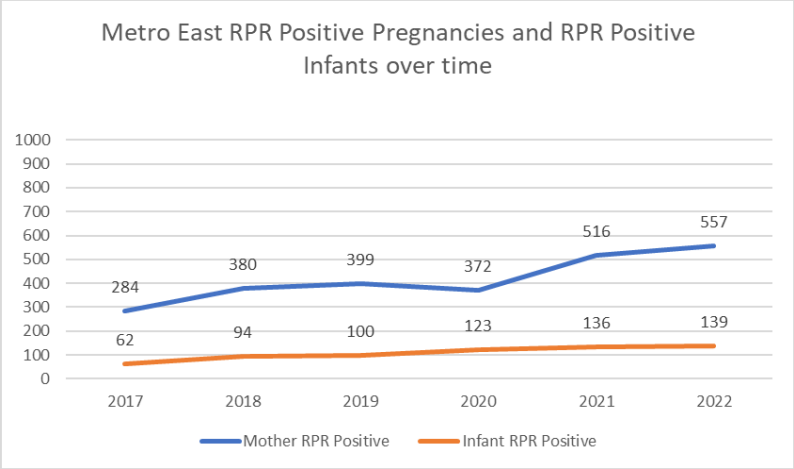
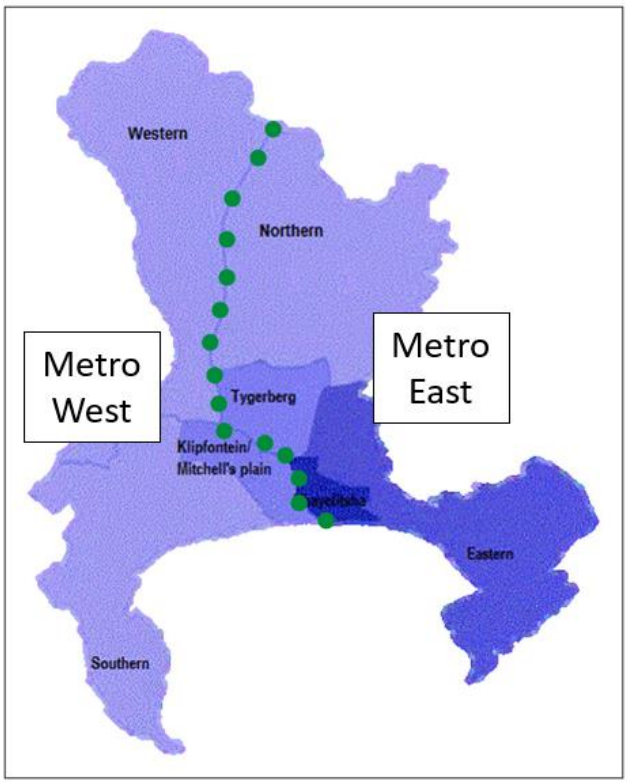


Figure 6:



Appendix D: Geographic Service Areas

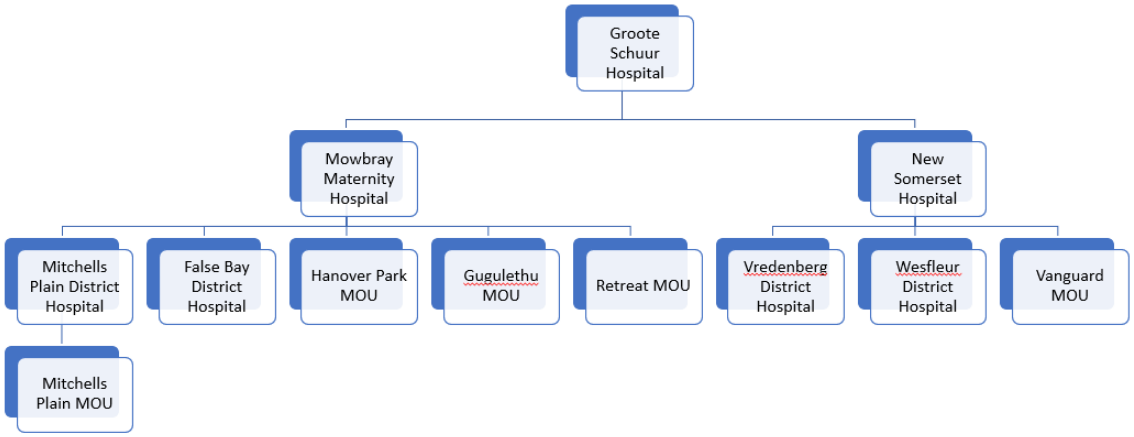


The Cape Town Metropolitan District comprises of 8 subdistricts : Western, Southern, Klipfontein, Mitchells Plain, Northern, Tygerberg, Khayelitsha and Eastern.

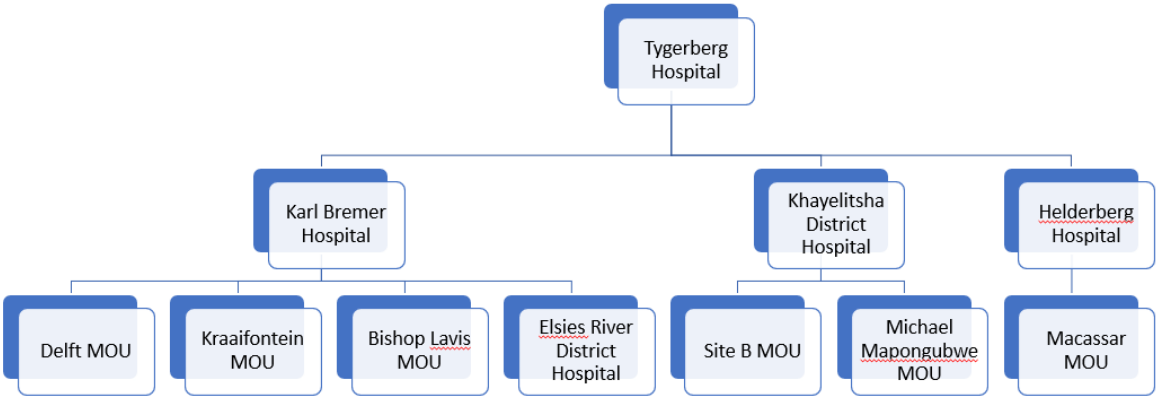
Metro Health Services District Office oversees all 8 subdistricts, and the governance of these subdistricts is arranged into substructures known as Southern & Western, Klipfontein & Mitchells Plain, Khayelitsha & Eastern and Northern & Tygerberg. There is a substructure manager at each of these substructures.

There are two tertiary hospitals which drain the Metro: Groote Schuur Hospital and Tygerberg Hospital. The referral pathways / pyramids are divided into Metro East (drains to Tygerberg) and Metro West (drains to Groote Schuur). These, in general, follow the accompanying map and referral patterns below.

Metro West Referral Pyramid



Metro East Referral Pyramid



Appendix E: PHDC Episode of Pregnancy

Category	Event type	Evidence Name	Evidence Description
High confidence defining	Admission	Delivery in summary	This evidence identifies patients with a maternal discharge summary captured in ECCR, with a date of delivery recorded. Only discharge summaries with a delivery date or a delivery type recorded in their discharge summary are included.
	Birth record	Birth Register	Any deliveries that were recorded in the PHCIS, PPIP or Clinicom birth registers without an outcome are included in this evidence.
		Live Birth	We maintain a register of births compiled from registers in the hospital system (Clinicom), provincial primary care system (PHCIS), and the Perinatal Problem Identification Programme (PPIP), and we infer additional births based on folder registrations of newborns. Any live births recorded in the registers are included in this evidence.
		Miscarriage	Any miscarriages recorded in the PHCIS, PPIP or Clinicom birth registers are included in this evidence.
		Neonatal death	Any neonatal deaths recorded in the PHCIS, PPIP or Clinicom birth registers are included in this evidence.
		Still birth	Any still births recorded in the PHCIS, PPIP or Clinicom birth registers are included in this evidence.
	Death record	Sinjani maternal	Any person recorded in the maternal death register in Sinjani
	Drug dispensed	Drug TOP	Dispensing of mifepristone is primarily used for termination of pregnancy.
	Lab test	Other Lab evidence	Any lab tests that are only done on pregnant women, such as foetal lung maturity, tests on amniotic fluid, chronic villus analysis, kleihauer test,down-syndrome screen, APT tests on foetal haemoglobin
		Pregnancy test	Any positive pregnancy test recorded in NHLS.
		Rhesus test	Rhesus tests are done almost exclusively on pregnant women in the public sector. The Rh factor is a protein that is found on blood cells. People without this protein are Rh-negative. During pregnancy, the mother and infant's blood can mix. If the mother is Rh-negative and the infant is Rh-positive the mother's body will produce antibodies that can damage the infant's red blood cells, leading to potential health complications for the newborn.
	Observations	Booking visit	This evidence identifies patients captured in the maternity module in PHCIS, which captures details regarding the pregnancy booking visit.
		PHC Outcome	Any outcome recorded in the PHCIS pregnancy register
		Valid Pregnancy Outcome PHC	Valid pregnancy outcomes recorded in the PHCIS pregnancy register that can be used to corroborate the outcome date evidence. It is not set to an outcome evidence as the observation is stored against the treatment start date.

Appendix F: 2023 VTP Guidelines

(35)

Frequency of syphilis testing

A pregnant woman should be screened and tested for syphilis

- at her 1st/booking visit in antenatal care.
- If she tests negative, syphilis testing should be repeated:
  - Scheduled antenatal visits, at approximately 4-weekly intervals, e.g., for BANC+ clients, this could be at 20, 26, 30, 34, and 38 weeks gestation
  - During her labour/delivery admission
  - At the time of diagnosis of an intrauterine death or miscarriage
  - At any time, if the mother has clinical symptoms or signs suggestive of syphilis

Syphilis testing should be aligned with the HIV testing schedule:

- If a woman tests positive for HIV, but tests negative for syphilis, repeat syphilis testing should continue at the intervals described above.
- If a woman tests positive for syphilis but tests negative for HIV, repeat HIV testing should continue at recommended intervals

NOTE: If a client is CURRENTLY being treated for syphilis during their current pregnancy, they should NOT be re-tested for syphilis apart from the recommended RPR titre test which is performed a minimum of 3 months after concluding syphilis treatment.

TYPES OF SYPHILIS TESTS AND THEIR USES

- **Rapid syphilis tests** use a type of test known as a specific (or treponemal) test for syphilis. Rapid syphilis tests remain positive for life, even if the infection has been treated.
- **RPR type syphilis tests** are known as non-specific (or non-treponemal) tests and are usually done in a laboratory. RPR titres change in response to treatment or disease progression.
- If a rapid test is used as the screening test (preferred), a positive result should be confirmed using an RPR test. The RPR will determine if the positive rapid result indicates a current active infection or an earlier infection, and the baseline titre allows the response to treatment to be monitored
- Once a woman has tested positive using a rapid test, a rapid test should no longer be used for routine screening to identify new infections at subsequent visits. A rapid test cannot differentiate between a new and a previous infection. A RPR should then be used as the screening test to identify new infections

When available and appropriate, **rapid testing is the preferred first-line test in pregnancy**, as it allows for immediate treatment.

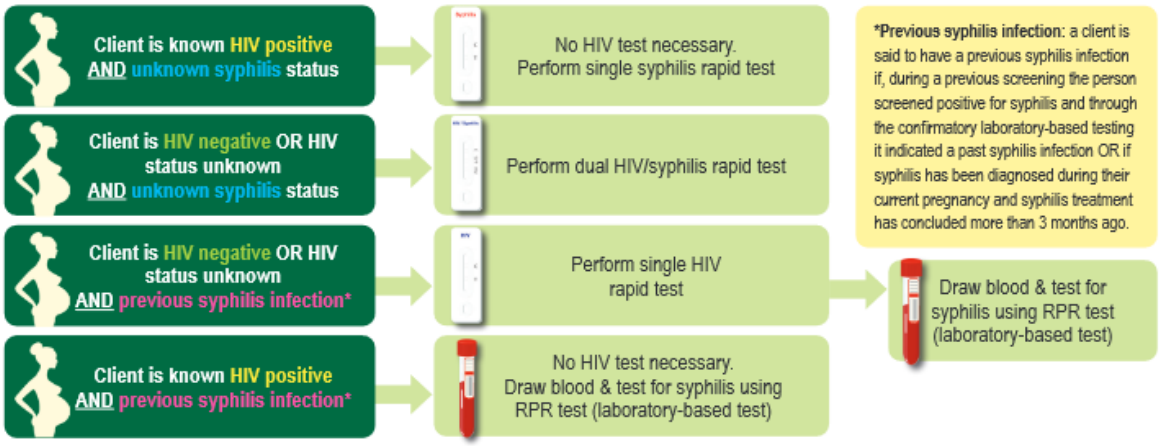
Rapid syphilis tests are available as a **single** rapid diagnostic test (RDT) that tests only for syphilis, and a **dual** RDT which tests for both syphilis and HIV using the same drop of blood.

Dual syphilis and HIV rapid tests should only be used in clients

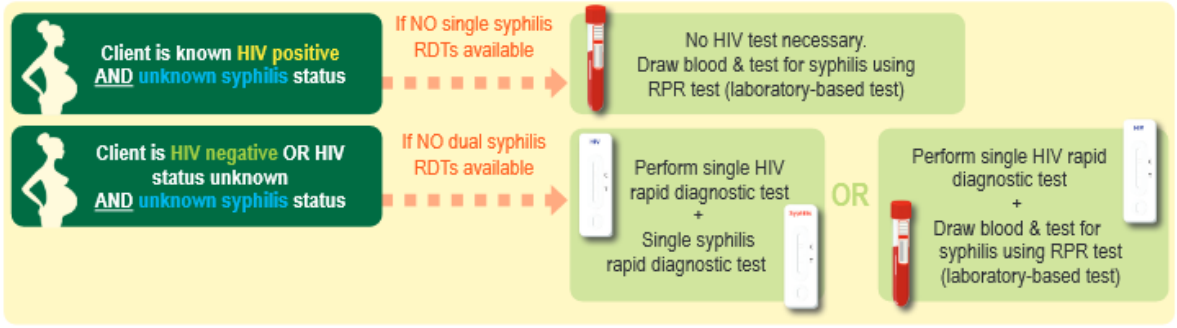
- **Whose HIV status is negative or unknown AND**
- **Who have not had a previous syphilis infection**

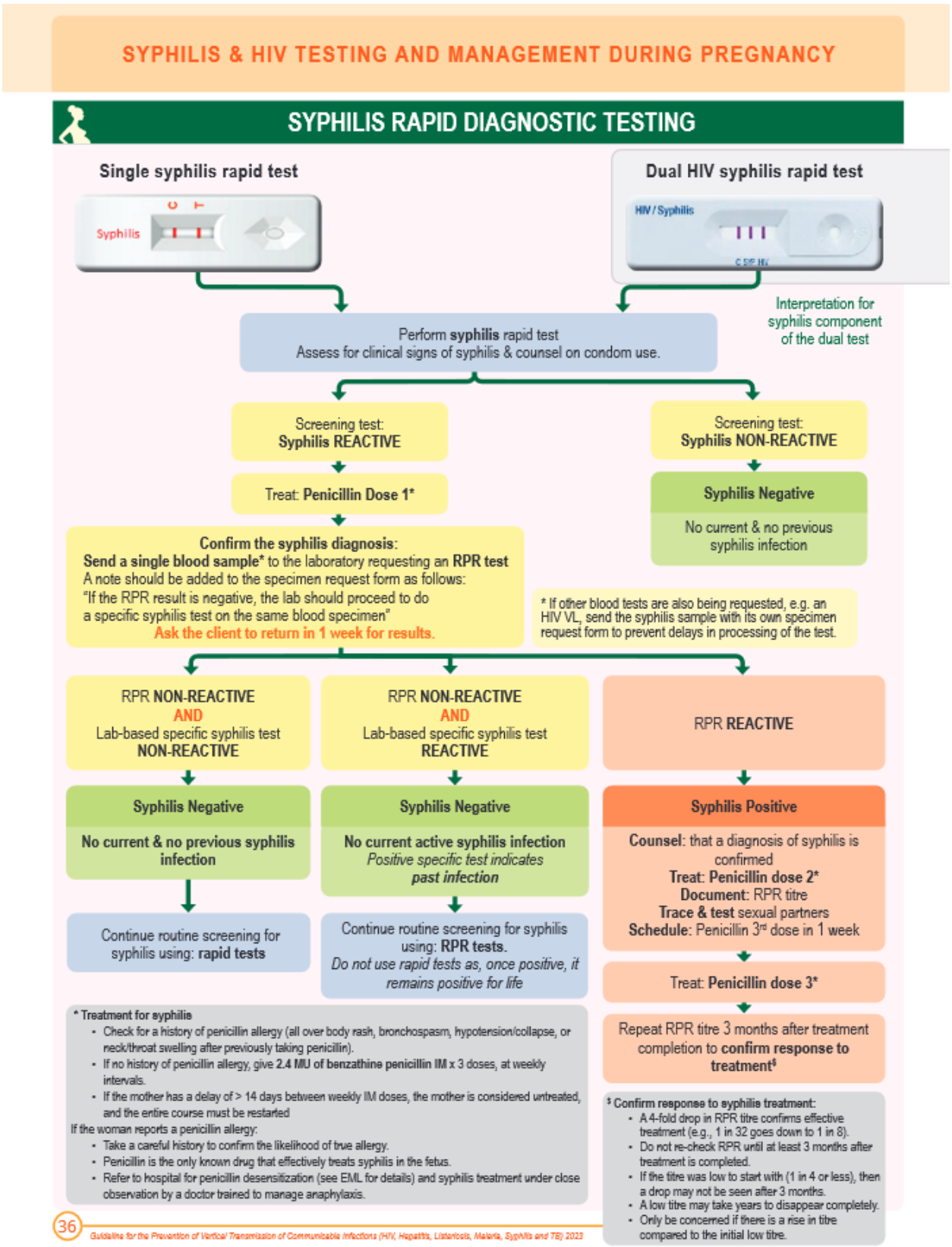
Clients who are already known to be living with HIV should NOT be re-tested for HIV and should therefore not use a **dual** syphilis and HIV rapid test!

HIV & Syphilis Testing Guide for Pregnancy: Which test should be used when?



What to do when a facility does not have syphilis rapid tests in stock




SYPHILIS & HIV TESTING AND MANAGEMENT DURING PREGNANCY
SYPHILIS RAPID DIAGNOSTIC TESTING
Single syphilis rapid test
Syphilis
Dual HIV syphilis rapid test
HIV / Syphilis
Interpretation for syphilis component of the dual test
Perform syphilis rapid test
Assess for clinical signs of syphilis & counsel on condom use.
Screening test: Syphilis REACTIVE
Treat: Penicillin Dose 1*
Confirm the syphilis diagnosis:
Send a single blood sample* to the laboratory requesting an RPR test
A note should be added to the specimen request form as follows:
"If the RPR result is negative, the lab should proceed to do a specific syphilis test on the same blood specimen"
Ask the client to return in 1 week for results.
Screening test: Syphilis NON-REACTIVE
Syphilis Negative
No current & no previous syphilis infection
* If other blood tests are also being requested, e.g. an HIV VL, send the syphilis sample with its own specimen request form to prevent delays in processing of the test.
RPR NON-REACTIVE AND Lab-based specific syphilis test NON-REACTIVE
Syphilis Negative
No current & no previous syphilis infection
Continue routine screening for syphilis using: rapid tests
RPR NON-REACTIVE AND Lab-based specific syphilis test REACTIVE
Syphilis Negative
No current active syphilis infection
Positive specific test indicates past infection
Continue routine screening for syphilis using: RPR tests.
Do not use rapid tests as, once positive, it remains positive for life
RPR REACTIVE
Syphilis Positive
Counsel: that a diagnosis of syphilis is confirmed
Treat: Penicillin dose 2*
Document: RPR titre
Trace & test sexual partners
Schedule: Penicillin 3rd dose in 1 week
Treat: Penicillin dose 3*
Repeat RPR titre 3 months after treatment completion to confirm response to treatment$
* Treatment for syphilis
Check for a history of penicillin allergy (all over body rash, bronchospasm, hypotension/collapse, or neck/throat swelling after previously taking penicillin).
If no history of penicillin allergy, give 2.4 MU of benzathine penicillin IM x 3 doses, at weekly intervals.
If the mother has a delay of > 14 days between weekly IM doses, the mother is considered untreated, and the entire course must be restarted
If the woman reports a penicillin allergy:
Take a careful history to confirm the likelihood of true allergy.
Penicillin is the only known drug that effectively treats syphilis in the fetus.
Refer to hospital for penicillin desensitization (see EML for details) and syphilis treatment under close observation by a doctor trained to manage anaphylaxis.
$ Confirm response to syphilis treatment:
A 4-fold drop in RPR titre confirms effective treatment (e.g., 1 in 32 goes down to 1 in 8).
Do not re-check RPR until at least 3 months after treatment is completed.
If the titre was low to start with (1 in 4 or less), then a drop may not be seen after 3 months.
A low titre may take years to disappear completely.
Only be concerned if there is a rise in titre compared to the initial low titre.
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Guideline for the Prevention of Vertical Transmission of Communicable Infections (HIV, Hepatitis, Listeriosis, Malaria, Syphilis and TB) 2023

SYPHILIS & HIV TESTING AND MANAGEMENT DURING PREGNANCY

LABORATORY-BASED TESTING WHEN RAPID TESTS ARE UNAVAILABLE OR INAPPROPRIATE

Send a single blood sample* to the laboratory requesting an RPR test
A note should be added to the specimen request form as follows:
If the RPR titre result is **1:4 or less**, the lab should proceed to do a **specific syphilis test** on the same blood specimen

Assess for clinical signs of syphilis & counsel on condom use.
Ask the client to return in 1 week for results.

* If other blood tests are also being requested, e.g. an HIV VL, send the syphilis sample with its own specimen request form to prevent delays in processing of the test

RPR REACTIVE titre 1:8 or greater	RPR **REACTIVE** titre 1:4 or less **AND** Specific syphilis test **REACTIVE**	RPR **REACTIVE** titre 1:4 or less **AND** Specific syphilis test **NON-REACTIVE**	RPR **NON-REACTIVE**

Syphilis Positive

Counsel: that a diagnosis of syphilis is confirmed
Treat: Penicillin dose 1*
Document: RPR titre
Trace & test sexual partners
Schedule: Penicillin 2nd dose in 1 week

Treat: **Penicillin dose 2*** / Schedule: Penicillin 3rd dose in 1 week

Treat: **Penicillin dose 3***

Repeat RPR titre 3 months after treatment completion to **confirm response to treatment**[§]

Syphilis Negative

No current syphilis infection
Continue routine follow-up screening for syphilis.

§ Confirm response to syphilis treatment:
- A 4-fold drop in RPR titre confirms effective treatment (e.g., 1 in 32 goes down to 1 in 8).
- Do not re-check RPR until at least 3 months after treatment is completed.
- If the titre was low to start with (1 in 4 or less), then a drop may not be seen after 3 months.
- A low titre may take years to disappear completely.
- Only be concerned if there is a rise in titre compared to the initial low titre.

*** Treatment for syphilis**
- Check for a history of penicillin allergy (all over body rash, bronchospasm, hypotension/collapse, or neck/throat swelling after previously taking penicillin).
- If no history of penicillin allergy, give **2.4 MU of benzathine penicillin IM** x 3 doses, at weekly intervals.
- If the mother has a delay of > 14 days between weekly IM doses, the mother is considered untreated, and the entire course must be restarted

If the woman reports a penicillin allergy:
- Take a careful history to confirm the likelihood of true allergy.
- Penicillin is the only known drug that effectively treats syphilis in the fetus.
- Refer to hospital for penicillin desensitization (see EML for details) and syphilis treatment under close observation by a doctor trained to manage anaphylaxis.

TREATING PARTNERS

- Trace and test partners of women with confirmed syphilis
- Test the partner using a rapid syphilis test if available and assess for symptoms and signs of a genital ulcer or secondary syphilis.
- If the rapid test is positive, and symptoms or signs of syphilis are present, treat the partner for early syphilis using one of the following options:
  - A single immediate dose of benzathine penicillin 2.4 MU IM, if stock levels are sufficient
  - If penicillin stock levels are insufficient, give Doxycycline 100mg 12-hourly orally for 14 days
- If the rapid test is positive and there are NO symptoms or signs of syphilis, send a confirmatory blood sample to the laboratory for an RPR. Do not wait for the results before treating the partner, but be sure to check the results 1 week later. Treat the partner for latent syphilis using one of the following options:
  - Benzathine penicillin 2.4 MU IM, once weekly for 3 weeks, if stock levels are sufficient
  - If penicillin stock levels are insufficient, give Doxycycline 100mg 12-hourly orally for 30 days

MANDATORY NOTIFICATION FOR CONGENITAL SYPHILIS

- **CS is a Category 2 Notifiable Medical Condition (NMC)**: Health care workers must notify all cases of congenital syphilis through paper-based or electronic case notification forms (CNF) to the National Institute for Communicable Disease (NICD) within 7 days of diagnosis.
- Refer to link: https://www.nicd.ac.za/nmc-overview/notification-forms/
- Stillbirths due to syphilis should also be notified.

Appendix G: Calculations for attributable proportions

Calculations for attributable proportions were limited to the cohort of patients who had a perinatal outcome (stillbirth, neonate survived, early neonatal death, late neonatal death). Pregnancies with early pregnancy outcomes (ectopic pregnancy, miscarriage and termination) were excluded as 71% of them did not have a laboratory test and it is suspected that the testing procedure for those with early outcomes may be different to those with late outcomes. Pregnancies for which the neonatal outcome was unknown were also excluded from these calculations (2.9% of all outcomes).

Attributable Proportion in Exposed :

APe = [(Risk of outcome in exposed – Risk of outcome in unexposed) / Risk in exposed]

Attributable Prop in Population:

APt=(Risk of outcome in the population – Risk outcome in the unexposed) / Risk of outcome in population

*Exposed (RPR positive) : Defined as those syphilis positive (RPR positive)

* Unexposed (No RPR positive) : Defined as those who did not screen syphilis positive (not tested, syphilis negative, previous syphilis, test error).

StillBirth:

	Stillbirth +	Stillbirth -	
RPR positive	314	6120	6434
No RPR positive result	6206	364411	370617
	6520	370531	377051

APe = 0.645 ~ 65% (95% CI 60.4% - 68.3%)

APt = 3% (95% CI 2.47% - 3.46%)

Neonatal Death

	Early Neonatal Death +	Early Neonatal Death -	
RPR +	83	6351	6434
No RPR positive result	2458	368159	370617
	2541	374510	377051

Ape = 49% (95% CI 36.1%- 58.6%)

APt = 1.59% (95% CI 0.88% - 2.28%)