In-hospital outcomes of congenital syphilis.

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Thesis presented in fulfilment of the requirements for the degree of Master of Medicine at the Stellenbosch University.

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DECLARATION

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the authorship owner thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Date: .....December 2021.....

Abstract (English)

Introduction. Congenital syphilis remains a leading cause of neonatal morbidity and mortality. Although treatable, a worldwide penicillin shortage has led to a resurgence of this disease. The current state of congenital syphilis in the Western Cape, South Africa is unknown. We aim to describe the mortality and clinical outcomes of congenital syphilis at a resource restricted academic hospital in Cape Town, South Africa.

Methodology. This was a retrospective, descriptive study performed at Tygerberg Hospital, in 2016, of all neonates diagnosed with congenital syphilis. All neonates with a positive rapid plasma reagin (RPR) test, meeting the Centers for Disease Control and Prevention (CDC) criteria for congenital syphilis, admitted to Tygerberg Hospital neonatal service, within the first month of life, were included. Neonates were excluded if clinical data were not available.

Results. Seventy neonates were diagnosed with congenital syphilis. The mean gestational age was 34.8±3.7 weeks and mean birth weight was 2247±717g.The most common clinical findings included respiratory distress (54%), bone abnormalities (43%), thrombocytopaenia (32%) and hepatomegaly (30%). Survival was 89%, with mortality significantly associated with septic shock and prematurity.

Conclusion. We present a cohort, over one year, of congenital syphilis with an 89% survival rate, despite significant morbidities. Prematurity and septic shock were associated with increased mortality. Despite this, most neonates survived and were transferred to other facilities or discharged within 2 weeks of birth.

Opsomming (Afrikaans)

Inleiding. Kongenitale sifilis bly een van die algemeenste oorsake van neonatale morbiditeit en mortaliteit. Alhoewel dit behandelbaar is, het die wêreldwye tekort aan penisillien tot ‘n toename in dié siekte gelei. Die huidige stand van kongenitale sifillis in die Weskaap, Suid Afrika, is onbekend. Ons beskryf die mortaliteit en kliniese uitkomste van kongenitale sifilis in ‘n hulpbronbeperkte hospitaal in Kaapstad, Suid Afrika.

Metodes. Hierdie was ‘n retrospektiewe, beskrywende studie, uitgevoer te Tygerberg Hospitaal in 2016, van alle neonate wat met kongenitale sifillis gediagnoseer is. Alle neonate met ‘n positiewe RPR toets wat in Tygerberg Hospitaal toegelaat is binne die eerste maand van lewe, is in die studie ingesluit. Neonate is uitgesluit indien mediese data onvoldoende was.

Uitslae. Sewentig neonate was toegelaat met kongenitale sifillis, met ‘n gemiddelde gestasie van 34.8±3.7 weke en ‘n gemiddelde geboortegewig van 2247±717g. Die algemeenste kliniese bevindinge was asemhalingsnood (54%), benige abnormaliteite (43%), lae plaatjietelling (32%) and hepatomegalie (30%). Die oorlewing was 89%, en sterfte was geassosieer met prematuriteit en septiese skok.

Opsomming. Ons beskryf ‘n groep neonate wat oor ‘n tydperk van een jaar met kongenitale sifillis gediagnoseer is, met ‘n oorlewing van 89% ondanks ‘n hoë voorkoms van morbiditeit. Bevindinge wat met sterfte verband gehou het, was prematuriteit en septiese skok. Ten spyte hiervan was die meeste neonate binne die eerste 2 weke van lewe na ander fasiliteite oorgeplaas of huis toe ontslaan.

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Most importantly I would like to thank our patients and their caregivers.

Dedication

I dedicate this thesis to Thian and Mieke, my true inspiration.

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List of Abbreviations

BBA: born before arrival
B/C: blood culture
BMV: bag-mask ventilation
BW: birth weight
CDC: The Centers for Disease Control and Prevention
CPAP: continuous positive airway pressure
CPR: cardiopulmonary resuscitation
CRP: c-reactive protein
CSF: cerebrospinal fluid
CXR: chest x-ray
ENT: ear, nose and throat
ETT: endotracheal tube
GA: gestational age
GSH: Groote Schuur Hospital
HIV: human immunodeficiency virus
HREC: Health Research and Ethics Committee
IM: intramuscular
IPPV: intermittent positive pressure ventilation
IV: intravenous
LBW: low birth weight
LOS: late onset sepsis
NICU: neonatal intensive care unit
RDS: respiratory distress syndrome
RPR: rapid plasma reagin
RVD: retroviral disease
SD: standard deviation
SGA: small for gestational age
Stat: immediately
TBH: Tygerberg Hospital
TPHA: treponema pallidum hemagglutination
TTN: transient tachypnoea of the newborn
UK: United Kingdom
USA: United States of America
VDRL: venereal disease research laboratory
WHO: World Health Organization

Chapter 1: Introduction

Congenital syphilis is associated with significant severe morbidities and significant mortality (1). Despite appropriate screening guidelines and effective penicillin therapy, congenital syphilis is showing a global resurgence.

Congenital syphilis is a notifiable disease. It was added to the list of notifiable conditions in South Africa, to increase awareness about the disease and to ensure adequate data capturing, as well as determining the true extent of the disease. Congenital syphilis is a preventable disease. A review at a hospital in Johannesburg in the early 1990's was performed shortly after syphilis was added to the list of notifiable diseases. This review demonstrated that despite meeting the Centers for Disease Control and Prevention (CDC) criteria for congenital syphilis, only 12% of cases were notified that year (2).

During the 2011 National Antenatal Sentinel HIV and Syphilis Prevalence Survey, South Africa, the prevalence of syphilis amongst pregnant women attending public antenatal clinics for the first time during their pregnancies in the Western Cape, was 1,6%. This survey indicated that the prevalence of syphilis in South Africa, for the years 2005 – 2011 had not been declining (3). Even though the numbers were not declining, it was also not accurate, due to poor documentation and difficult auditing processes.

Notification remains a serious concern. In February 2019, the National Institute for Communicable Diseases (NICD) published the latest data. It was noted that only 43,5% of cases were clinical cases notified by health care workers, while positive laboratory alerts made up the largest proportion of notifications. Although it was reported that the City of Cape Town had the highest number of rapid plasma reagin (RPR) positive cases (13.5%) and the Cape Winelands at 8%, only 1,2% of all clinical notifications were from the Western Cape Province (4). Surveillance data from the World Health Organization (WHO) during 2016-2017, indicated that in the African region only 21% of countries reported syphilis prevalence and only 9% of countries were reaching the WHO goal in screening at least 95% of pregnant women and treating at least 95% of these syphilis positive women. During 2016-2017 the

congenital syphilis reporting rate for African countries was 8% with a reported congenital syphilis rate of 4,85%, (5).

Syphilis is a sexually transmitted disease, which results in congenital syphilis in neonates if the disease is transmitted to the foetus through the placenta or to the neonate during the birth process, from an untreated or incompletely treated mother. Screening for syphilis is initially performed with non-treponemal tests, either the rapid plasma reagin (RPR) or venereal research laboratory (VDRL) tests. If a non-treponemal screening test is positive, it is advised that a more specific treponemal test, detecting antibodies specific to *Treponema pallidum,* should be performed to confirm the diagnosis. Treponemal tests, *Treponema pallidum* hemagglutination (TPHA), indicate that an infection has occurred in a patient, but does not specify whether the infection was treated or not. During the last five years some laboratories have used a "reversed algorithm", where a treponemal test is done first. If this result is positive, a non-treponemal test (quantitative RPR) is performed. This method, however, has a high false positive rate of 14 – 40%, yet it remains a cost-effective screening method (6). This method will capture all intra-uterine syphilis exposed, even if the mother was treated. The test indicates trans-placental transfer of antibodies to the foetus. The confirmatory RPR test, which provides a titre is then performed to confirm the result of syphilis. In neonates with a positive RPR test the case definition needs to be applied and clinical judgement used to diagnose congenital syphilis and to treat the neonate appropriately (Appendix A).

South African literature on congenital syphilis, as well as the morbidity and mortality associated with the disease, is minimal. We aimed to look at the mortality and morbidity of congenital syphilis in a public hospital in Cape Town, South Africa.

Chapter 2: Literature Review

Congenital syphilis is a life-threatening, vertically transmitted, preventable disease. Mother-to-child transmission occurs in up to 80% of cases if the mother is untreated. Neonatal death (14%) and congenital syphilis (41%) are high in mothers with untreated primary or secondary syphilis, with a very low chance (20%) of delivering an unaffected neonate. Neonatal death (9%) and congenital syphilis (2%) are lower in mothers with untreated late syphilis (more than 1-2 years after infection) and a high chance of delivering a normal neonate (77%) (7). Congenital syphilis occurs in approximately 25-75% of neonates whose mothers are tested positive for *Treponema pallidum*. In Africa, a seropositivity rate of 3-18% in mothers, leads to 1% of neonatal admissions being attributable to congenital syphilis (8).

Syphilis remains a global health issue even in the 21st century (9). Despite adequate screening programmes and effective treatment modalities, there is a worldwide resurgence of this disease (9,10). The prevalence of syphilis in 43 countries over a period of 10 years was reported as 0%-8.3% (11). The USA has shown an 86% increase in adult syphilis cases between 2012-2016 (12), whilst Brazil showed an increase in congenital syphilis incidence from 0.3 to 2.5 per 1000 live births (13,14). *Treponema pallidum* is effectively and exclusively eradicated by penicillin, yet a worldwide shortage of penicillin has been reported by high incidence countries (14,15).

Congenital syphilis is a multi-organ disease with extensive clinical manifestations (tables 1 and 2). It has varying reported case-fatality rates between countries, with up to 38% case fatality reported in South Africa (8). Prematurity, small for gestational age and low birth weight are often encountered (16–18). After intra-uterine exposure, congenital syphilis develops in 15-55% of neonates born prematurely, as compared to 40-70% of term neonates (17).

Syphilis is a preventable disease. The World Health Organization (WHO) provides guidelines for the management of syphilis in pregnancy, as well as the general population (19–21). The notification and treatment of sexual partners should be prioritized (19).

Table 1: Early clinical manifestations of congenital syphilis (<1 year of age)(7)

System	Clinical findings (incidence)
General	Prematurity Small for gestational age Non-immune hydrops
Reticuloendothelial	Generalized, non-tender lymphadenopathy Anaemia Leukopaenia or leukocytosis Thrombocytopaenia (30%) Hepatosplenomegaly (50%-90%)
Mucocutaneous (in 30%-60%)	Snuffles Laryngitis Maculopapular skin rash followed by desquamation, blistering and crusting – prominent on palms and sole Mucous patches (palate, perineum) Condylomata lata (perioral, perianal)
Skeletal (in 70%-80%)	Symmetrical long-bone lesions, more common in lower limbs Metaphyseal osteochondritis with mild to destructive lesions that develop within five weeks of infection Wimberger's sign (demineralization and destruction of the proximal tibial metaphyses) Diaphyseal periostitis Osteitis Dactylitis with involvement of the metacarpals, metatarsals and proximal phalanges
Neurological	Cerebrospinal fluid abnormalities (40-60%) Acute meningitis
Ocular	Salt and pepper chorioretinitis, glaucoma, uveitis
Other organ involvement	Renal involvement: nephrotic syndrome Pulmonary involvement: pneumonia alba Myocarditis Pancreatitis Gastrointestinal inflammation and fibrosis

The WHO recommends that all pregnant women should be screened for syphilis at the first contact with a healthcare facility, preferably within the first 12 weeks of the pregnancy. The syphilis screening test should be repeated at 28-32 weeks gestation, as well as at the time of delivery (10). The CDC, as well as WHO, suggest that a non-treponemal test should be followed by a confirmatory treponemal test (7). The current South African guidelines suggest that all pregnant women should be screened for syphilis at their first contact with a healthcare

provider, as well as retested at 32 – 34 weeks gestation, if they tested negative during the first trimester of their pregnancy. There are currently different screening options, depending on which initial test was performed – RPR test (rapid test or laboratory test), laboratory treponema pallidum (TPHA) test (table 3) (22).

Table 2: Late clinical manifestations of congenital syphilis (>1 year of age)(7)

System	Clinical findings
Dental	Hutchinson's teeth, hypoplastic enamel, mulberry molars
Ear	Sensorineural hearing loss due to osteochondritis of otic capsule and cochlear degeneration
Cutaneous	Rhagades
Skeletal	Frontal bossing, square cranium Short maxilla, high palatal arch and saddle nose deformity Saber shins (anterior tibial bowing) Higoumenaki's sign (sternoclavicular thickening) Clutton's joints
Neurological	Mental retardation, hydrocephalus, seizures, cranial nerve palsies, paresis Untreated neurosyphilis may lead to chronic meningovascular syphilis with hydrocephalus, cerebral infarctions and cranial nerve palsies
Ocular	Interstitial keratitis
Other organ involvement	Renal involvement: paroxysmal cold haemoglubinuria
Hutchinson's triad	Interstitial keratitis Hutchinson's teeth Sensorineural hearing loss

A positive RPR test during the neonatal period is suggestive of congenital syphilis; however, it should not be the only marker used to diagnose congenital syphilis. The sensitivity of this method was estimated at 4 – 13% with a specificity of 99%. If this method is used to diagnose congenital syphilis, an RPR-titre of at least four-fold the maternal titre at birth is required to demonstrate fetal antibody synthesis (25).

In neonates born to mothers with a positive RPR and Treponemal test, the management protocol will depend on several factors, including maternal antenatal treatment, the maternal

titre and the neonatal clinical examination (7). All neonates with symptomatic congenital syphilis require 10 days of parenteral penicillin (14) (Appendix A)

Table 3: Serological tests in the diagnosis of syphilis according to the stage of syphilis (23,24).

Test	**Primary Syphilis**	**Secondary Syphilis**	**Latent Syphilis**	**Late Syphilis**	**All stages**	**All stages**	**All stages**
	Sensitivity (%)				**Specificity (%)**	**PPV**	**NPV**
RPR	86 (77-99)	100	98 (95-100)	73	98 (93-99)	73.2	100
VDRL	78 (74-87)	100	96 (88-100)	71 (34-94)	98 (96-99)		
TPHA	88 (86-100)	100	100		96 (95-100)	80.4	100

NPV: negative predictive value; PPV positive predictive value; RPR: rapid plasma reagin; TPHA: *Treponema pallidum* particle agglutination assay. VDRL: venereal disease research laboratory

Widespread shortages of benzathine penicillin G have compromised the prevention of congenital syphilis. The global supply, demand and use of benzathine penicillin G should be prioritized in maternal syphilis, as well as congenital syphilis, to meet the WHO goal of eliminating congenital syphilis (19,21).

The aim of our study was to describe the mortality and clinical outcomes of neonates with congenital syphilis, born or admitted to a tertiary level hospital in Cape Town, South Africa, within the first 30 days of life.

Chapter 3: Method

This was a retrospective, descriptive study performed at Tygerberg Hospital of all neonates diagnosed with congenital syphilis, within the first month of life, during 2016. All the neonates, included into the study population, had a positive TPHA test, followed by a quantitative RPR test.

Neonates were included if they had a positive RPR test and met one of the CCDC criteria for congenital syphilis (table 4).

Neonates were included if they met the criteria for confirmed or probable congenital syphilis. Evidence of congenital syphilis on physical examination that was used for inclusion was: Small for gestational age (SGA), hydrops fetalis, petechiae or skin lesions suggestive of congenital syphilis, hepatosplenomegaly, bone abnormalities on X-ray, conjugated hyperbilirubinemia, anemia and thrombocytopenia (see definitions below).

Neonates were excluded if they met the CDC criteria of less likely or unlikely congenital syphilis. Neonates with missing medical records were also excluded.

Setting

This study was conducted at Tygerberg Hospital. Tygerberg Hospital is a tertiary referral hospital in the Western Cape, South Africa as well as the academic hospital of Stellenbosch University. Tygerberg Hospital provides secondary level healthcare to children in the surrounding geographical areas as well as tertiary care to all paediatric patients in the Metro East, Northern and Eastern rural districts of the Western Cape. Approximately 4500 neonates are admitted to the Tygerberg Neonatal Service annually. Approximately 10% of neonates admitted to the Neonatal Service at Tygerberg Hospital, are outborn.

Table 4: Case definition of congenital syphilis by the CDC(2015)(6)

Probable congenital syphilis

A condition affecting an infant whose mother had untreated or inadequately treated* syphilis at delivery, regardless of signs in the infant, or an infant or child who has a reactive non-treponemal test for syphilis (Venereal Disease Research Laboratory [VDRL], rapid plasma reagin [RPR], or equivalent serologic methods) **AND** any one of the following:

- Any evidence of congenital syphilis on physical examination (see Clinical description)
- Any evidence of congenital syphilis on radiographs of long bones
- A reactive cerebrospinal fluid (CSF) VDRL test
- In a nontraumatic lumbar puncture, an elevated CSF leukocyte (white blood cell, WBC) count or protein (without other cause):
  Suggested parameters for abnormal CSF WBC and protein values:
  1. During the first 30 days of life, a CSF WBC count of >15 WBC/mm3 or a CSF protein >120 mg/dL.
  2. After the first 30 days of life, a CSF WBC count of >5 WBC/mm3 or a CSF protein >40 mg/dL, regardless of CSF serology.
     The treating clinician should be consulted to interpret the CSF values for the specific patient.

*Adequate treatment is defined as completion of a penicillin-based regimen, in accordance with CDC treatment guidelines, appropriate for stage of infection, initiated 30 or more days before delivery.

Confirmed congenital syphilis

A case that is laboratory confirmed.

Less likely congenital syphilis

Neonate with normal physical examination and a serum quantitative non-treponemal serological titre equal to or less than fourfold the maternal titre and BOTH the following are true:

1. Mother appropriately treated during pregnancy, treatment appropriate for stage of infection, treatment administered for > 4 weeks before delivery AND
2. no signs of relapse or reinfection

Unlikely congenital syphilis

Neonate with normal physical examination and a serum quantitative non-treponemal serological titre equal to or less than fourfold the maternal titre and BOTH the following are true:

1. mother's treatment was adequate before pregnancy AND
2. mother's non-treponemal serological titre remained low and stable (ie serofast) before and during pregnancy and at delivery (VDRL<1:2, RPR <1:4))

Study Population

The study population included all neonates (under the age of 28 days) with a positive RPR, test performed at Tygerberg Hospital between 1 January 2016 and 31 December 2016, meeting CDC criteria for probable or confirmed congenital syphilis (table 4).

Sources of Data

Neonates were identified from results obtained from the National Health Laboratory Service (NHLS) database, as well as from admission records of the neonatal service. Neonatal and maternal details were reviewed. The relevant X-rays were reviewed on the digital Tygerberg Hospital Radiology System.

Data Collection Methods

Data were collected from the clinical notes using a case report form (appendix B). Maternal demographic data included antenatal booking status, human immunodeficiency virus (HIV) status, and a viral load if the HIV status was positive. HIV viral suppression was defined as less than 100 viral copies per milliliter. The maternal RPR titre value was obtained from the National Health Laboratory Service (NHLS) database.

The neonatal demographic data included in the case report form were sex, delivery details, birth weight, gestational age (in completed weeks, as determined by foot length or early antenatal ultrasound) and growth appropriateness. Birth before arrival at a medical facility, multiple pregnancy and a diagnosis of congenital syphilis after one week of life was also documented. Prematurity was defined as a gestational age of less than 37 weeks at birth. A birth weight of less than 2500 grams was defined as low birth weight; very low birth weight was defined as a birth weight between 1500 grams and 1000 grams and a birth weight of less than 1000 grams was defined as an extremely low birth weight. Neonates were considered to be small for gestational age if they had a birth weight below the 10th for gestational age.

The following clinical manifestations were documented:

1. Hypoglycaemia, defined as a serum glucose value of less than 2,6mmol/l;
2. Conjugated hyperbilirubinemia, defined as a conjugated fraction of the total serum bilirubin of more than 20%;
3. Hydrops foetalis, defined as fluid collection in two or more body compartments, which included a pleural effusion, pericardial effusion, ascites or skin edema;
4. Shock, defined as a combination of clinical findings that included low blood pressure, poor perfusion, tachycardia or bradycardia, tachypnoea or apnea, hypothermia and oliguria;
5. Hepatosplenomegaly was defined as a liver or a spleen palpable more than 2cm below the costal margin;
6. Any cardiac abnormalities confirmed on echocardiography;
7. Renal abnormalities on renal sonar or abnormally raised urea and creatinine laboratory values;
8. Respiratory distress was defined as tachypnea (>60 breaths/min), alar flaring, intercostal or subcostal recessions, tracheal tug and grunting. The origin of respiratory distress was categorized as transient tachypnea of the newborn, pneumonia or respiratory distress syndrome, according to CXR performed in the first 12-24 hours of life, if clinically indicated as per TBH standard operating protocols;
9. Convulsions, clinically detected or electrically diagnosed on an amplitude-integrated electroencephalogram;
10. Hydrocephalus, defined as a head circumference of more than two standard deviations above the mean (>97th percentile) for age or ventriculomegaly on cranial sonar or computed tomography scan of the brain;
11. Meningitis, defined by abnormal cerebrospinal fluid(CSF) findings (Appendix C);
12. Bony changes in keeping with congenital syphilis - periosteal reaction, demineralization or under mineralization and cortical irregularity of the bony structures;
13. Anaemia in the neonate was defined as a hemoglobin < 10g/dl;
14. Thrombocytopaenia as a platelet count < 150 x10 ^{9} /l;
15. Sepsis, defined as a positive blood culture (B/C) or a C - reactive protein (CRP) > 10mg/l, with associated clinical concerns indicative of new sepsis

All records were reviewed for any other significant complications, including surgical complications, neonatal intensive care unit (NICU) admissions or invasive ventilation requirements.

Data management and Statistical analysis

Data Collection

All data collected in this study were managed according to Good Clinical Practice requirements and ethical standards. Case report forms were used to collect data. These forms were stored securely.

Data Analysis

Descriptive statistics (means and standard deviation and number and percentage, as appropriate) were used to analyze data. Chi2 and Student t-test were used to compare data for survivors and non-survivors.

Ethical considerations

The study was approved by the Health Research Ethics Committee of Stellenbosch University (S18/07/141) (Appendix D).

All patient data were anonymized. Patient identifiers and study numbers were kept in separate databases and were only accessible to researchers directly involved in the study.

Consent was obtained from the medical superintendent of Tygerberg Hospital, as custodian of patient records (Appendix E).

The neonates involved in this study did not benefit directly from it, but this study will hopefully be beneficial to future neonates at risk of congenital syphilis.

Chapter 4: RESULTS

Demographics

A total of 453 neonates were screened for congenital syphilis with an RPR test at Tygerberg Hospital during the one-year study period. The "reverse algorithm" for syphilis testing was used at TBH during 2016. Of these neonates, 95 (20.9%) tested serologically positive; 86 (90.5%) of these neonates had medical data available. Seventy of the 86 (81.4%) neonates had symptomatic congenital syphilis. The mortality of congenital syphilis cases was 8 (11%) (fig 1).

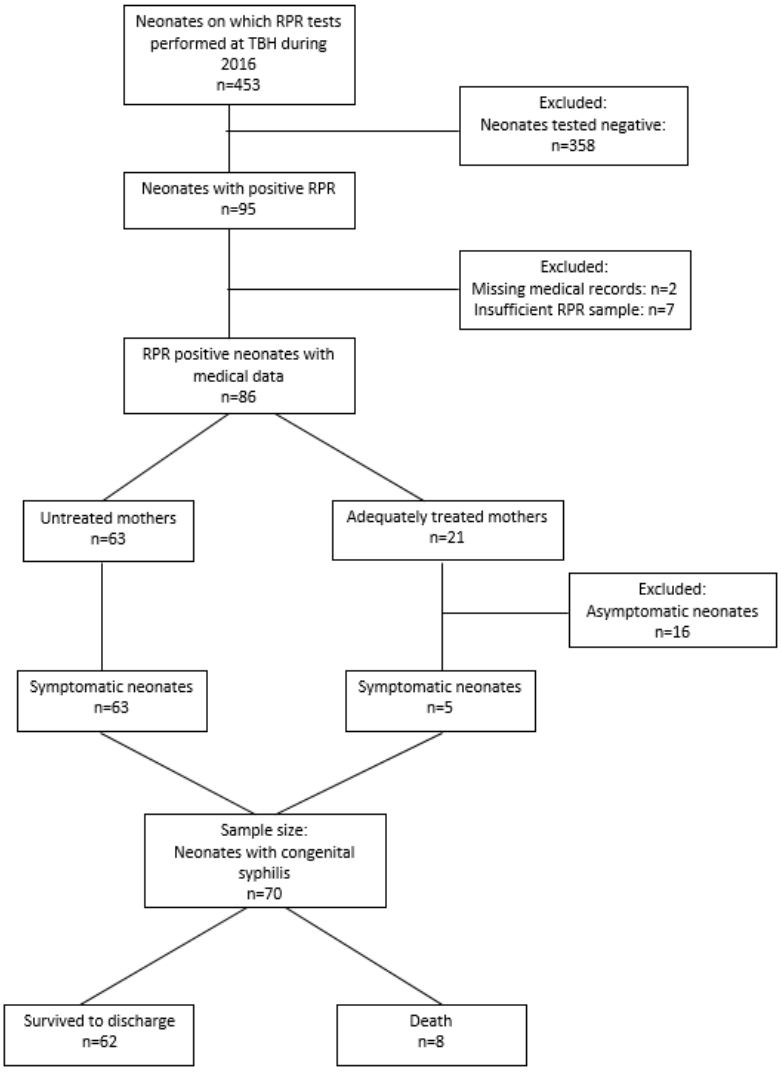


Figure 1: Flow diagram for neonates with congenital syphilis included in study

Of the 70 neonates with congenital syphilis, only 46 (66%) of the mothers had attended antenatal clinics. Of these mothers, 18 (25%) were HIV-positive of which 8 (44%) were virally suppressed. All mothers tested TPHA positive prior to RPR positive tests. Maternal RPR varied widely with 80% of titres being ≥1:4 (fig 2). Maternal and neonatal demographics and neonatal clinical characteristics are shown in table 4.

Table 5: Maternal and neonatal demographics of study cohort

Variable		Results (n=70)
Maternal Demographics		
Maternal antenatal clinic attendance, n (%)		46 (66)
Maternal HIV positive, n (%)		18 (26)
Maternal HIV suppressed viral load, n (%)		8(44)
Maternal drug abuse, n(%)		14 (20)
Neonatal Demographics		
Male, n (%)		31 (44)
Gestational age (weeks), mean±SD		34.8± 3.7
Prematurity (<37 weeks gestational age), n(%)		20 (29)
Birth weight (g), mean±SD		2247±717
VLBW (<1500g), n(%)		14 (20)
SGA[*], n (%)		17 (24)
Born before arrival, n (%)		14 (15)
Apgar 1 minute, mean±SD		7.4± 2.2
Apgar 5 minute, mean±SD		8.7± 1.7
Apgar 10 minute, mean±SD		9.2± 1.3
Perinatal asphyxia[*], n (%)		5 (8)
Resuscitation at delivery, n (%)	None CPAP only Mask ventilation ETT/IPPV CPR/Adrenaline	37 (53) 18 (26) 4 (6) 9 (13) 2 (2)
Neonate HIV positive, n (%)		1 (3)

CPAP – continuous positive airway pressure; CPR – cardio-pulmonary resuscitation; ETT – endotracheal tube; HIV – human immunodeficiency virus; IPPV – intermittent positive pressure ventilation; SD – standard deviation; SGA – small-for-gestational age; VLBW – very low birth weight

**SGA – defined as weight below 10th centile for gestational age

*Perinatal asphyxia defined as a 5-minute apgar < 7

The majority of neonates were born at term (71%) and 24% of neonates were small for gestational age (SGA). Resuscitation at delivery was required in 47% of the neonates, mostly CPAP only (table 5). All neonates initially screened positive by TPHA testing followed by RPR testing, as per TBH protocol. The neonatal RPR titres ranged from 1 – 256 (figure 2). Only 8 (12%) of neonates had RPR titres above those of their mothers and only 1 (1%) infant had an

RPR titre more than 4 times that of the maternal titre. There was a poor correlation between maternal and neonatal RPR values (fig 2). Only 1 (1%) neonate was diagnosed with congenital syphilis after the first week of life. All babies of HIV-positive mothers were screened for HIV by PCR, with 1 (1%) neonate being confirmed HIV positive.

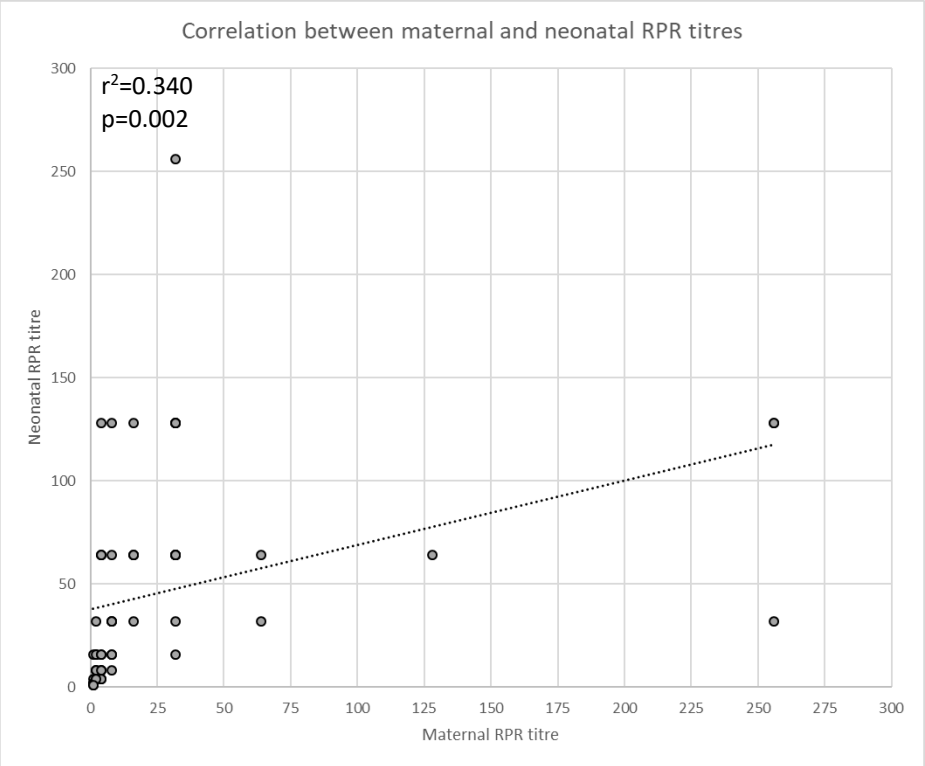


Figure 2: Correlation between maternal and neonatal RPR titres

Clinical manifestations of the neonates

A wide spectrum of clinical manifestations associated with congenital syphilis was observed (table 6). Overall, the most common findings in our cohort were respiratory distress (54%), bone abnormalities (44%), hepatosplenomegaly (30%) and thrombocytopaenia (31%). No eye abnormalities were observed.

NICU admission was necessary for 13 (19%) of these neonates. The average stay in the NICU was 7.0± 7.8 days.

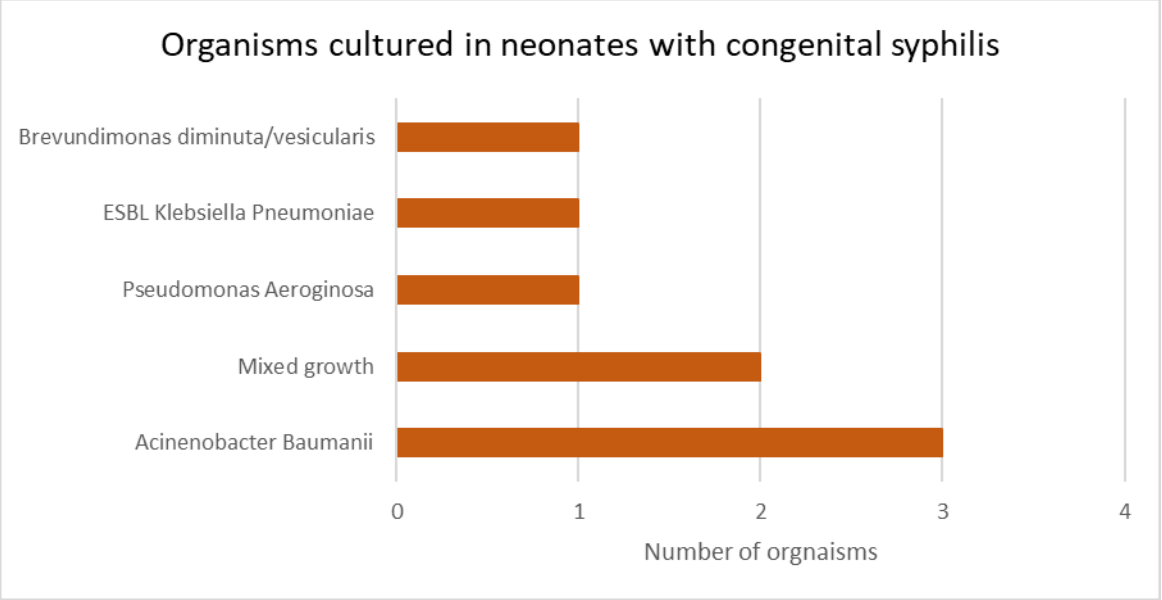
Table 6: Clinical manifestations of neonates presenting with symptomatic congenital syphilis

System affected	Specific abnormality	Results (n=70)
Respiratory abnormalities	TTN, n (%) RDS, n (%) Pneumonia, n (%)	4 (6) 20 (29) 14 (20)
Cardiovascular abnormalities	Shock, n (%)	4 (6)
	Septic shock, n (%)	6 (9)
	Cardiac abnormalities, n (%)	3 (4)
Central nervous system abnormalities	Hydrocephalus, n (%)	1 (1)
	Meningitis, n (%)	3 (4)
	Convulsions, n (%)	6 (9)
Gastro-intestinal abnormalities	Jaundice, n (%)	13 (19)
	Hepatomegaly, n (%)	21 (30)
	Splenomegaly, n (%)	15 (21)
	Hepatosplenomegaly, n(%)	21 (30)
	Renal abnormalities, n (%)	4 (6)
Other abnormalities	Hypoglycaemia, n (%)	10 (14)
	Hydrops fetalis, n (%)	4 (6)
	Skin lesions, n (%)	13 (19)
	Bone abnormalities, n (%)*	25 (44)
Hematological abnormalities	Anaemia, n (%)	13 (19)
	Hemoglobin (g/dl), mean±SD	15.2±4.4
	Thrombocytopaenia, n (%)	22 (31)
	Platelet count (cells/mm3), mean±SD	202±148
Late onset sepsis	All, n (%) Suspected, n (%) B/C positive, n (%) Urine culture positive, n (%)	26 (37) 18 (26) 7 (10) 1 (1)
	Age at late onset sepsis (days), mean±SD	3.8 ±5.4
	LOS CRP value (mg/L), mean±SD	37.0±43.0
NICU admission	NICU admission, n (%)	13 (19)
	Duration of NICU admission in days, mean±SD	7.0±7.8
	Duration of ventilation in days, mean±SD	4.9±6.0
Length of stay (days),	Home, mean±SD 46	18.0±16.9
	Transfer, mean±SD	10.8±13.3
	Demised, mean±SD	13.6±16.1

B/C – blood culture; CRP – C-reactive protein; HMD – hyaline membrane disease; GIT – gastro-intestinal tract; LOS – late onset sepsis; NICU – neonatal intensive care unit; RDS – respiratory distress syndrome; SD – standard deviation; TTN – transient tachypnea of the newborn
* 57/70 neonates were screened

Twenty-six (37%) neonates developed new symptoms during their admission to the neonatal wards and hospital-acquired bacterial infection was suspected. Blood culture, urine culture and C-reactive protein (CRP) were performed. Of the infants who developed sepsis (26), blood cultures were positive in 7 (27%) and urine culture was positive in 1(1%) of neonates. The other 18 (69%) of neonates had a raised CRP only. *Acinetobacter baumannii* was the most common organism on blood and *Candida albicans* was the only organism cultured on urine

cultures. Two blood cultures were positive for different pathogens. An *Acinetobacter baumannii* with an *Enterococcus faecalis* on the one and an *Acinetobacter baumannii* with an *Enterobacter Cloacae* on the other. The other positive blood cultures had a single organism only (figure 3).



Mixed growth organisms were Actinobacteria Baumanii/ Enterococcus Faecalis (n=1) and Acinetobacter Baumanii/ Enterobacter Cloacae (n=1)

Figure 3: Positive cultures and the organisms cultured (n=7)

Comparison of survivors and non-survivors of neonates with symptomatic congenital syphilis

During the study period, a total of 8 (11%) neonates died due to symptomatic congenital syphilis. Forty-six of the 62 survivors (74%) were discharged home and the other 16 (26%) neonates were transferred to stepdown facilities for further care and growth (table 7).

Table 7: Comparison of survivors and non-survivors of neonates with symptomatic congenital syphilis

Variable	All n=70	Survivors n=62	Non-survivors n=8	p-value
MATERNAL DEMOGRAPHICS				
Unbooked, n (%)	24 (34)	22 (35)	2 (25)	0.576
Mum HIV pos, n (%)	18 (26)	16 (26)	2 (25)	0.951
Mum HIV not suppressed, n (%)	8 (11)	7 (11)	1 (13)	0.867
Maternal drug abuse, n (%)	14 (20)	11 (18)	3 (38)	0.188
NEONATAL DEMOGRAPHICS				
Gestational Age (weeks), mean±SD	34.8 ±3.7	34.7±3.7	35.8±4.3	0.439
Prematurity, n(%)	20 (29)	15 (24)	5 (63)	**0.022**
Birth Weight (grams), mean±SD	2247±717	2218±716	2471±728	0.351
VLBW, n(%)	13 (19)	12 (19)	1 (13)	0.681
Male, n (%)	31 (44)	27 (44)	4 (50)	0.749
Diagnosed more than one week of age, n(%)	17 (24)	15 (24)	2 (25)	0.950
Born before arrival n (%)	14 (20)	14 (23)	0 (0)	0.131
SGA, n(%)	17 (24)	15 (24)	2 (25)	0.950
Apgar1 minute, mean±SD	7.4±2.2	7.2±2.3	8.7±0.4	0.071
Apgar5 minute, mean±SD	8.7±1.7	8.6±1.8	9.5±0.7	0.168
Apgar 10 minute, mean±SD	9.2±1.3	9.1±1.4	9.8±0.3	0.165
Perinatal Asphyxia*, n(%)	5 (7)	5 (8)	0 (0)	0.409
Delivery Room resuscitation (any), n(%)	33 (47)	29 (47)	4 (50)	0.873
NEONATAL CLINICAL MANIFESTATION				
NICU admission, n(%)	13 (19)	13 (21)	0 (0)	0.153
Hypoglycaemia, n(%)	10 (14)	10 (16)	0 (0)	0.225
Jaundice, n(%)	13 (19)	13 (21)	0 (0)	0.153
Hydrops, n(%)	4 (6)	4 (6)	0 (0)	0.479
Skin lesions, n(%)	13 (19)	12 (19)	1 (13)	0.681
Hepatomegaly, n(%)	21 (30)	20 (32)	1 (13)	0.272
Splenomegaly, n(%)	10 (14)	15 (24)	0 (0)	0.121
Respiratory distress, n(%)	37 (53)	33 (53)	4 (50)	0.873
Convulsions, n(%)	6 (9)	6 (10)	0 (0)	0.352
Meningitis, n(%)	3 (4)	3 (5)	0 (0)	0.520
Hydrocephalus, n(%)	1 (1)	1 (2)	0 (0)	0.688
Renal abnormality, n(%)	4 (6)	4 (6)	0 (0)	0.479
Cardiac abnormality, n(%)	3 (3)	3 (5)	0 (0)	0.520
Bone abnormality, n(%)	25 (36)	22 (35)	3 (38)	0.868
Shock, n(%)	6 (9)	0 (0)	6 (75)	**<0.001**
Anaemia (Hb<10), n(%)	13 (19)	13 (21)	0 (0)	0.153
Hemoglobin (g/dl), mean±SD	15.2±4.4	14.8±4.5	18.1±1.8	**0.045**
Thrombocytopaenia <150cells/mm^3, n(%)	22 (29)	22 (35)	0 (0)	**0.045**
Platelet count, mean±SD	202±148	195±153	259±80	0.251
BC positive sepsis, n(%)	8 (11)	8 (13)	0 (0)	0.281

B/C – blood culture; CRP – C-reactive protein; HIV – human immunodeficiency virus; NICU – neonatal intensive care unit; SD – standard deviation; SGA – small-for gestational age (<10th centile); RPR – rapid plasma reagin

Prematurity, septic shock, anaemia and thrombocytopaenia differed between survivors and non-survivors.

Congenital syphilis treatment

All neonates received either a 10-day course of penicillin G intravenously or a single dose of intramuscular Bicillin at birth, as per the Tygerberg treatment protocol (appendix A). The treatment regimen was based on history, clinical and serological findings. Forty-three (61%) neonates received intravenous treatment regimen and 27 (39%) neonates received intramuscular Bicillin.

Chapter 5: Discussion

We describe a cohort of neonates with symptomatic congenital syphilis presenting over a period of one year at a single referral hospital with a survival rate of 89% despite significant morbidities. Multiple clinical manifestations were associated with mortality. Despite this, most neonates were discharged or transferred within 2 weeks of birth.

Our study showed that fewer mothers were unbooked, compared to more than half of the mothers from a similar study performed at another tertiary referral hospital (Groote Schuur Hospital (GSH)) in Cape Town. Despite this, the portion of unbooked mothers remained high. The same study showed a large proportion of mothers abused illicit substances (26), although our study, substance abuse could be documented in 20% of the mothers. However, it may have been significantly under-reported in our study due to the retrospective nature of this study. This may have contributed to the significant differences in mortality between these two studies.

A quarter of the mothers in our study were HIV positive, with less than half being virally suppressed. However, the neonatal HIV infection was very low. In the GSH study, only 14% of syphilis positive mothers were HIV positive (26). Syphilis is known to interfere with epithelial barriers, to cause a reduction in T-cells and to increase the HIV viral load, thus increasing the risk of HIV infection transmission (27).

Our study population had a gestational age and birth weight similar to an Indian study (28). Contrary to our study, a review performed in 24 countries from 1990 to 2009, documented a significantly higher number of premature and low birth weight neonates born to mothers with syphilis, compared to mothers who tested negative (18). Similar to our study, a study performed in Thailand, showed that most infants with congenital syphilis were born at term. The Thailand study demonstrated a birth weight appropriate for gestational age, where our study had a significant proportion of neonates that were small for gestational age (29).

Similar to our study, the GSH study found low Apgar scores to be associated with an increased risk for mortality (26). In our study none of the neonates with hydrops fetalis demised, contrary to a study in Harare (30) and GSH (26), where hydrops fetalis was documented to be a significant risk factor for mortality.

The high occurrence of respiratory distress in our study population could possibly be attributed to prematurity, rather than the congenital syphilis, similar to The Red Cross War Memorial Children's Hospital study (31).

Clinical manifestations in our study that resemble those found in international studies from China (32), Thailand (29) and Zimbabwe (30), included hepatosplenomegaly, obstructive jaundice and thrombocytopaenia. A literature review from 1917 to 2000, showed similar incidences of clinical abnormalities and also demonstrated minimal eye abnormalities in the neonatal period (33), in keeping with our and a Brazilian study (32).

Our study population, similar to a Brazilian study (32) and the GSH study (26), demonstrated hypoglycaemia as a complication of congenital syphilis, but contrary to an Indian study (28).

Hepatosplenomegaly, bony lesions and skin lesions were common in our study, similar to multiple other studies: GSH study(26), Thailand study (29), UK study (34), Harare study (30) and study from Shanghai, China (32).

We did not document any lymphadenopathy in our study population, contrary to studies performed in the UK (9) and India (28).

None of the neonates in the present study had any surgical complications. This is contrary to The Red Cross War Memorial Children's Hospital study, where four neonates with congenital syphilis, had small bowel complications. Exocrine pancreatic insufficiency, due to syphilitic pancreatitis, may be a contributing factor in the development of intestinal dysmotility, meconium ileus or a meconium plug. Stenosis and atresia of the bowel are thought to be secondary to an ischemic intestinal insult in syphilitic arteritis (31). A similar case was reported on in 1998, where a neonate developed ileal ulceration and intestinal perforation (35).

In this study, only one infant had a VDRL requested on cerebrospinal fluid (CSF). Previous studies have highlighted the controversial aspect of CSF findings in congenital syphilis due to a high specificity (99.8%), but low sensitivity (50%) (36). A negative VDRL on CSF does not exclude the possibility of neurosyphilis. Despite a CSF VDRL stated as standard of care in the literature, its value in terms of treatment and long term management, remain questionable (7,8). The CSF should be repeated at 6 months age and if the findings persists, a repeat course of penicillin G has been advised (7). It has been found that 40-60% of children with congenital syphilis, aged less than one year, have CSF changes. The true incidence of congenital neurosyphilis has not yet been established. However, neurosyphilis has been stated to be a late complication of missed or untreated congenital syphilis (7). Previous studies have demonstrated asymptomatic neurosyphilis in 25-33% of children by the age of 2 years (9). Follow-up is recommended in all patients with congenital syphilis with repeat serology tests at one, two, four, six and twelve months.

More than one-third of neonates in our study developed late-onset sepsis. A previous University of Cape Town study looked at the immune function of neonates with congenital syphilis. The findings suggested that, although these neonates had a normal quantitative immune response, functional (including cytotoxic and killing) abnormalities could account for the increased susceptibility to develop secondary bacterial infections (37). Neonates with congenital syphilis have a significantly increased amount of circulating immune complexes, compared to the control groups. These complexes are thought to be an important factor in immune modulation and tissue damage in these neonates (37).

Our study showed a low overall mortality, contrary to the recent publication from GSH, which showed a high mortality. Our study included only symptomatic infants, similar to the GSH study. The differences may be attributable to various factors. Patient profiles differed - we had fewer unbooked pregnancies and substance abuse amongst the mothers. Timing of the diagnosis and commencement of specific treatment also differed.

Neonates exposed to syphilis are considered high risk if they are symptomatic, their titre is fourfold the maternal titre, the mother received no treatment or inadequate treatment, or if

her titre did not decrease as expected post treatment. If the mother was commenced on treatment within one month pre-delivery or if she was treated with a non-penicillin antibiotic it is also considered as a high risk exposure (9). Only one of the neonates in our study had a titre fourfold that of the maternal titre.

Our study has several limitations. Due to the retrospective nature of the study, not all clinical manifestations of congenital syphilis could be accurately captured, e.g. the duration and degree of hypoglycaemia and conjugated hyperbilirubinemia. Several neonates were discharged with their mothers after receiving intramuscular therapy and were not available for inclusion in the study as they were never admitted to the neonatal service. An accurate incidence of congenital syphilis could not be calculated as congenital syphilis neonates were also admitted from outside Tygerberg Hospital for NICU care. The long-term sequelae of congenital syphilis were not included in this study. This is an important clinical consideration, especially in asymptomatic neonates, born to mothers fully and appropriately treated for syphilis, who are being discharged from hospital.

Chapter 6: Conclusion

We present a cohort of neonates with symptomatic congenital syphilis, presenting over a period of one year, with an 89% survival rate. Congenital syphilis still causes significant morbidity and mortality in neonates, despite being a preventable disease. Maternal screening, partner tracing and ante-natal maternal treatment prioritization may reduce the morbidity and mortality of exposed neonates. In doing so, it may reduce the burden on neonatal units and decrease the cost of neonatal care (8). Even in areas of lower prevalence, it remains cost effective and cost saving to screen for syphilis in the ante-natal period (17). It is considerably more difficult, expensive and an added burden to the health system if a neonate is born with congenital syphilis (38).

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Appendix A: Congenital syphilis treatment regimen at Tygerberg Hospital Neonatal Unit

Maternal RPR status		
	Reactive	Non-reactive
Neonate with signs of congenital syphilis	Penicillin G 50 000u/kg/dose IVI 12 hourly for 10 days OR Procaine Penicillin 50 000u/kg daily IM for 10 days	Repeat test on mother and neonate
Neonate without signs of congenital syphilis	Bicillin 50 000u/kg stat IM	No treatment
Exceptions: 1) HIV positive mother who is RPR reactive and untreated for syphilis with an asymptomatic baby; 2) If clinician is uncertain: Perform RPR titre in baby: If RPR titre ≥4 times the mother – 10 days of Penicillin If RPR titre ≤4 times the mother – Bicillin 50 000u/kg stat IM		

Stat: immediately; IVI: intravenous; IMI: intramuscular

Appendix B: Clinical record form

Study number	

Personal Information

Study number	
Name	
Surname	
Date of birth	
Sex	
Folder number	
Maternal Folder number	
Suburb (Address)	

Demographic information

Date of birth		
Sex		
Suburb		

1) Maternal screening

Booked □ Unbooked □

2) HIV

Reactive □ Non-reactive □

3) TPHA

Reactive □ Non-reactive □

4) **RPR**

Reactive □ Non-reactive □

5) Gestational age

< 28 weeks □ 28 – 32 weeks □ 33-37 weeks □ ≥38 weeks

6) Birth weight

< 1000g □ 1000 – 1500g □ 1500 – 2500g □

>2500g □

7) Resuscitation at birth

a) IPPV Yes □ No □
b) CPR Yes □ No □
c) Fluid bolus Yes □ No □

d) Adrenaline Yes □ No □
e) Other:

8) Clinical findings

a) Fever Yes □ No □
b) Hypoglycaemia Yes □ No □
c) Cholestatic jaundice Yes □ No □
d) Hydrops fetalis Yes □ No □
e) Septic Shock Yes □ No □
f) Skin lesions Yes □ No □
g) Hepatomegaly Yes □ No □
h) Splenomegaly Yes □ No □
i) Respiratory distress (Support required) Yes □ No □
j) Keratitis/Uveitis/Scleritis Yes □ No □
k) Convulsions Yes □ No □
l) Meningitis Yes □ No □
m) Hydrocephalus Yes □ No □
n) Other:

9) Special investigations

a) RPR Reactive □ Non-Reactive □
b) Titre -> Mother: Neonate

>1:4 □ <1:4 □

c) Symmetrical long bone lesions Yes □ No □
d) Other:

10) Treatment

Stat dose Bicillin IMI □ 10 days Parenteral Penicillin G □

Other:

11) Outcome

Discharged □ Transfer □ Death □

Appendix C: Cerebro-spinal fluid values used to diagnose meningitis at Tygerberg Hospital

Normal CSF white cell count(cells/mm³) values in term infants:

	0-24 hours	Day 1	Day 7
Polymorphs	3 (0-70)	7 (0-26)	2 (0-5)
Lymphocytes	2 (0-20)	5 (0-16)	1 (0-4)

Normal CSF white cell count(cells/mm³) values in premature infants:

	Weight	Day 0-7	Day 8-28	Day 29-84
White cells	≤ 1000g	3 (1-8)	4 (0-14)	4 (0-11)
White cells	1 – 1.5kg	4 (1-10)	7 (0-44)	8 (0-23)
Polymorphs	≤1000g	11% (0-50%)	8% (0-66%)	2% (0-36%)
Polymorphs	1 – 1.5kg	4% (0-28%)	10% (0-60%)	11% (0-48%)

Appendix D: HREC approval letter

UNIVERSITEIT
STELLENBOSCH
UNIVERSITY

Health Research Ethics Committee (HREC)

Approval Notice

New Application

29/08/2018

Project ID :7701

HREC Reference #: S18/07/141

Title: A descriptive analysis of the incidence, morbidity and mortality associated with congenital syphilis in neonates under 28 days of age at Tygerberg Hospital, South Africa: A retrospective cross-sectional study

Dear Dr Carien Bekker,

The **Response to Stipulations** received on 29/08/2018 10:05 was reviewed by members of **Health Research Ethics Committee 2 (HREC2)** via **expedited** review procedures on 29/08/2018 and was approved.

Please note the following information about your approved research protocol:

Protocol Approval Period: **This project has approval for 12 months from the date of this letter.**

Please remember to use your **Project ID [7701]** on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review

Please note you can submit your progress report through the online ethics application process, available at: Links Application Form Direct Link and the application should be submitted to the HREC before the year has expired. Please see *Forms and Instructions* on our HREC website (www.sun.ac.za/healthresearchethics) for guidance on how to submit a progress report.

The HREC will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility, permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Please consult the Western Cape Government website for access to the online Health Research Approval Process, see: https://www.westerncape.gov.za/general-publication/health-researchapproval-process. Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and instructions, please visit: Forms and Instructions on our HREC website
https://applyethics.sun.ac.za/ProjectView/Index/7701

If you have any questions or need further assistance, please contact the HREC office at 021 938 9677.

Yours sincerely,

Francis Masiye,

HREC Coordinator,

Health Research Ethics Committee 2 (HREC2).

National Health Research Ethics Council (NHREC) Registration Number:

REC-130408-012 (HREC1·REC-230208-010 (HREC2)

Federal Wide Assurance Number: 00001372
Office of Human Research Protections (OHRP) Institutional Review Board
(IRB) Number: IRB0005240 (HREC1·IRB0005239 (HREC2)

The Health Research Ethics Committee (HREC) complies with the SA National Health Act No. 61 of 2003 as it pertains to health research. The HREC abides by the ethical norms and principles for research, established by the World Medical Association (2013). Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects; *The South African Department of Health (2006). Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa (2nd edition)*; as well as the Department of Health (2015). Ethics in Health Research: Principles, Processes and Structures (2nd edition).

The Health Research Ethics Committee reviews research involving human subjects conducted or supported by the Department of Health and
Human Services, or other federal departments or agencies that apply the Federal Policy for the Protection of Human Subjects to such research (United States Code of Federal Regulations Title 45 Part 46); and/or clinical investigations regulated by the Food and Drug Administration (FDA) of the Department of Health and Human Services.

Appendix E: Tygerberg Hospital Consent to perform research

TYGERBERG HOSPITAL
Research Projects
ENQUIRIES: Dr GG Marinus
TELEPHONE:021 938 5752

Ethics Reference: S18/07/141

TITLE: A descriptive analysis of the incidence, morbidity and mortality associated with congenital syphilis in neonates under 28 days of age at
Tygerberg Hospital, South Africa: A retrospective cross-sectional study

Dear Dr Carien Bekker

PERMISSION TO CONDUCT YOUR RESEARCH AT TYGERBERG HOSPITAL.

1. In accordance with the Provincial Research Policy and Tygerberg Hospital Notice No 40/2009, permission is hereby granted for you to conduct the above-mentioned research here at Tygerberg Hospital.
2. Researchers, in accessing Provincial health facilities, are expressing consent to provide the Department with an electronic copy of the final feedback within six months of completion of research. This can be submitted to the Provincial Research Co-Ordinator (Health.Research@westerncape.gov.za).

DR GG MARINUS **MANAGER: MEDICAL SERVICES**