SYMPTOMATIC CONGENITAL SYPHILIS IN A TERTIARY NEONATAL UNIT: A RETROSPECTIVE DESCRIPTIVE STUDY

STUDENT: Dr Shakti Pillay

MBChB (Wits)

FCPaeds

University of Cape Town

PLLSHA 011

SUPERVISOR: Dr Lloyd Tooke

MBChB (UCT), MMed (Stel), FCPaeds,

Cert Neonatology

Neonatologist Groote Schuur Hospital,

University of Cape Town

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DECLARATION

I, Shakti Pillay, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Background

Syphilis is a disease that was first described in the 1300s and now 700 years later, despite preventive measures and effective treatment, continues to impact on a global scale, with the burden falling largely on the developing world. We could find no recent published literature looking at predictors of outcomes in neonates born with symptomatic congenital syphilis, especially in the context of a tertiary neonatal setting.

Methodology

The study design was a retrospective descriptive folder review of neonates born with symptomatic congenital syphilis at Groote Schuur Hospital (GSH) from January 2011 to December 2013. One of the primary objectives was to address outcome as well as look at modifiable preventable factors. All neonates treated at GSH (inborn and outborn) who tested serologically positive for syphilis together with clinical signs of syphilis were included. Data was obtained from the National Health Laboratory System (NHLS) database, as well as the notification and death registers at GSH nursery. All data was collected in a Microsoft excel spread sheet and analysed using Microsoft StatPlus.

Results

Fifty of eighty neonates (62.5%) with positive syphilis serology as well as clinical signs of congenital syphilis were included together with their fifty mothers. The majority (98%) of mothers were inadequately untreated. Nineteen neonates demised. There were no statistically significant differences between the deaths and survivors in terms of gestational age ($p = 0.15$), birth weight ($p = 0.08$) or maternal age ($p = 0.51$).

Two significant predictors of mortality were one minute and five minute Apgar scores of less than five ([RR], 3.5; 95% CI 1.6-7.7 and [RR], 2.9; 95% CI 1.5-5.3 respectively). Hydropic neonates, tended to be sicker at birth, requiring intubation and inotropes, which was associated with a poorer outcome (increased risk of mortality).

Conclusion

Despite the introduction of a National Syphilis Screening programme more than twenty years ago together with a large proportion of pregnant women having access to antenatal care, congenital syphilis is still prevalent in South Africa. Failure to access antenatal care, poor partner tracing and a number of modifiable health worker related failures contribute to poor maternal diagnosis and treatment. Many neonates with congenital syphilis require aggressive interventions and there is a high mortality rate. This dissertation adds to the existing body of research particularly with regard to predictors of outcome in tertiary neonatal settings. Certain categories of neonates have a lower survival rate and guidelines about limitation of care may need to be considered in order to optimise resource allocation particularly in resource-constrained settings. Further research is required to elaborate how best to develop protocols in these neonates.

CHAPTER 1: BACKGROUND AND LITERATURE REVIEW

1. BACKGROUND

The word “syphilis” originated in an ancient poem about a shepherd named Syphilis and was first mentioned in 1530. The disease itself however is thought to have precluded its current designation, masquerading previously under the guise of the “Great Pox”, “Morbus Gallicus (French disease)” and “Cupid’s disease” and was thought by some historians to have been present since the 1300s.[1] There are two main theories regarding its origin, the “Colombian” or “New World” theory and the “Pre-Colombian” or “Old World Theory.” In the former, it was postulated that in the 1400s Columbus introduced syphilis into Europe from Haiti where it was endemic. In the latter theory, syphilis was presumed to have originated in Africa and introduced into Europe prior to Columbus’s great voyage.[2] Regardless of its origin, just over 700 years later, syphilis continues to impact on a global scale with the burden falling largely on the developing world.[3,4,5] However, the effects on the developed world are by no means insignificant. In the United States, eradication of syphilis was a genuine possibility, with the declining rates of syphilis observed as the 1990s ended. The increasing trend in syphilis infection rates since 2000 have led to the Centers for Disease Control (CDC) officially ending their syphilis elimination efforts as of December 2013, a mere twenty three years later.[6]

Syphilis is a chronic infectious disease, transmitted both horizontally and vertically by the bacterium *Treponema pallidum* with humans being the only known natural host.[7] Maternal infection is through sexual contact, via abraded skin as well as intact mucous membranes. There exists a high infectivity rate with an estimated thirty percent of individuals who have had sexual contact with a partner becoming infected.[8]

Following exposure and infection, the incubation period is three weeks (10-90 days).[8] Clinical manifestations then proceed through stages: firstly from the painless chancre of primary syphilis at the site of inoculation, followed by the characteristic syphilitic rash affecting the palms and soles of secondary syphilis, transitioning to a latent period and culminating in tertiary syphilis (figure 1). Latent syphilis is largely an asymptomatic period, which typically occurs after resolution of secondary syphilis (skin lesions) until cure or the onset of tertiary syphilis. Forty percent of untreated patients in the latent phase of infection will develop tertiary syphilis.[8] The divisions of early and late latent syphilis are relevant in untreated cases in terms of the risk of relapse to secondary syphilis following infection. Early latent syphilis occurs in the first year following infection and is the period where ninety percent of first relapses occur. Late latent syphilis occurs more than a year after infection.[2,9,10] Tertiary syphilis includes neurological, cardiovascular and gummatous manifestations secondary to a widespread vasculitis.[11] Primary syphilis, secondary syphilis and early latent syphilis mark the periods of greatest infectivity.[12]

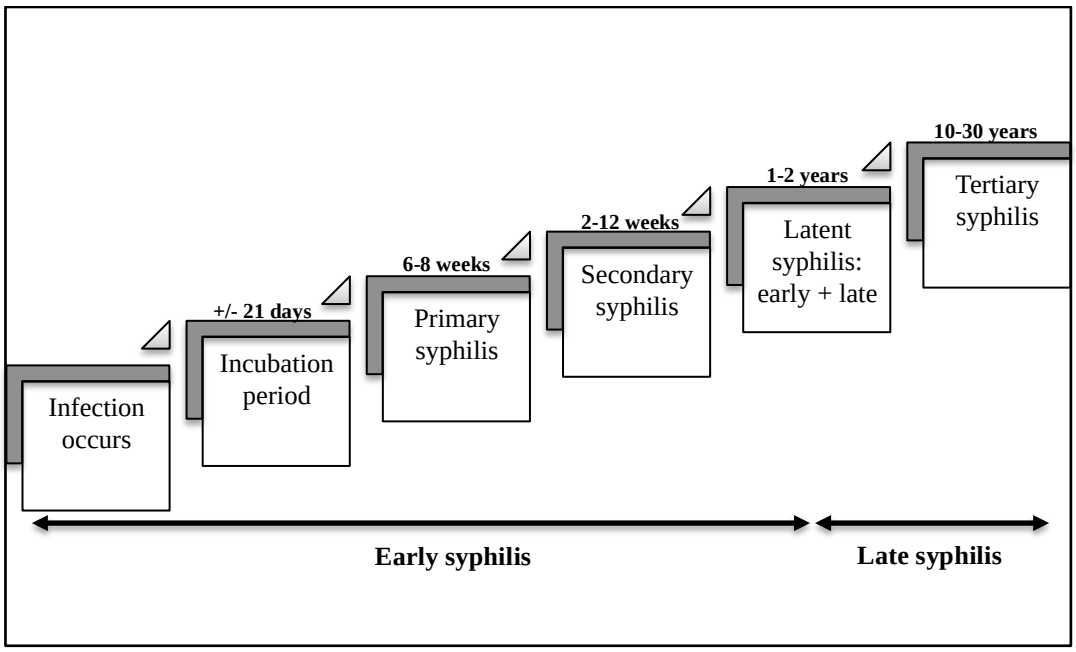


Figure 1: Timeline of syphilis stages

Congenital syphilis occurs through vertical transmission from an infected mother to her baby. The means by which the foetus becomes infected in utero is through haematogenous spread, via the placenta, of an infected mother. In-utero transmission can occur as early as the ninth week of pregnancy, however the most common period of transmission is between the sixteenth and twenty-eighth week of pregnancy.[13] The likelihood of vertical transmission increases with advancing gestation and is dependent on maternal timing of infection and disease stage, with early primary syphilis resulting in significantly higher transmission rates (70-100%) than early latent syphilis (40%) and late latent infection (10%).[14] Furthermore, higher maternal antibody titres during pregnancy and at delivery regardless of treatment status is associated with an increased transmission rate.[15] At least two thirds of neonates born to mothers with untreated primary or secondary syphilis will be infected.[9] Adverse outcomes include foetal demise with spontaneous abortion (often after the first trimester), late-term stillbirths (30-40% of cases), preterm deliver with low birth weight and neonatal deaths.[2,9] The longer the period between maternal infection and pregnancy, the more favourable the neonatal outcome (Kassowitz law) with the risk of infection to the neonate diminishing after four years of maternal infection even in the absence of maternal treatment.[8,15] A single dose of benzathine penicillin is adequate in primary, secondary and early latent syphilis stages with decreasing maternal serological titres acting as an indicator of treatment success. A newborn may rarely be infected perinatally by contact with maternal infectious lesions during delivery. Postnatal transmission, from breastfeeding for example, is also exceedingly rare.[16]

a. Clinical signs

In live born neonates, infection may be clinically recognizable. However two thirds of live born infected neonates are asymptomatic at birth and develop signs and symptoms months to years later, posing a diagnostic dilemma at delivery.[17] Early congenital syphilis refers to symptoms and signs occurring within the first two years of life most often between birth and three months of age. Late congenital syphilis manifests with signs after two years of age.[7,13]

Due to widespread spirochaetal dissemination, symptomatic neonates may have protean clinical signs affecting almost any organ system, explaining why syphilis is often referred to as the "great mimicker" (figure 2).

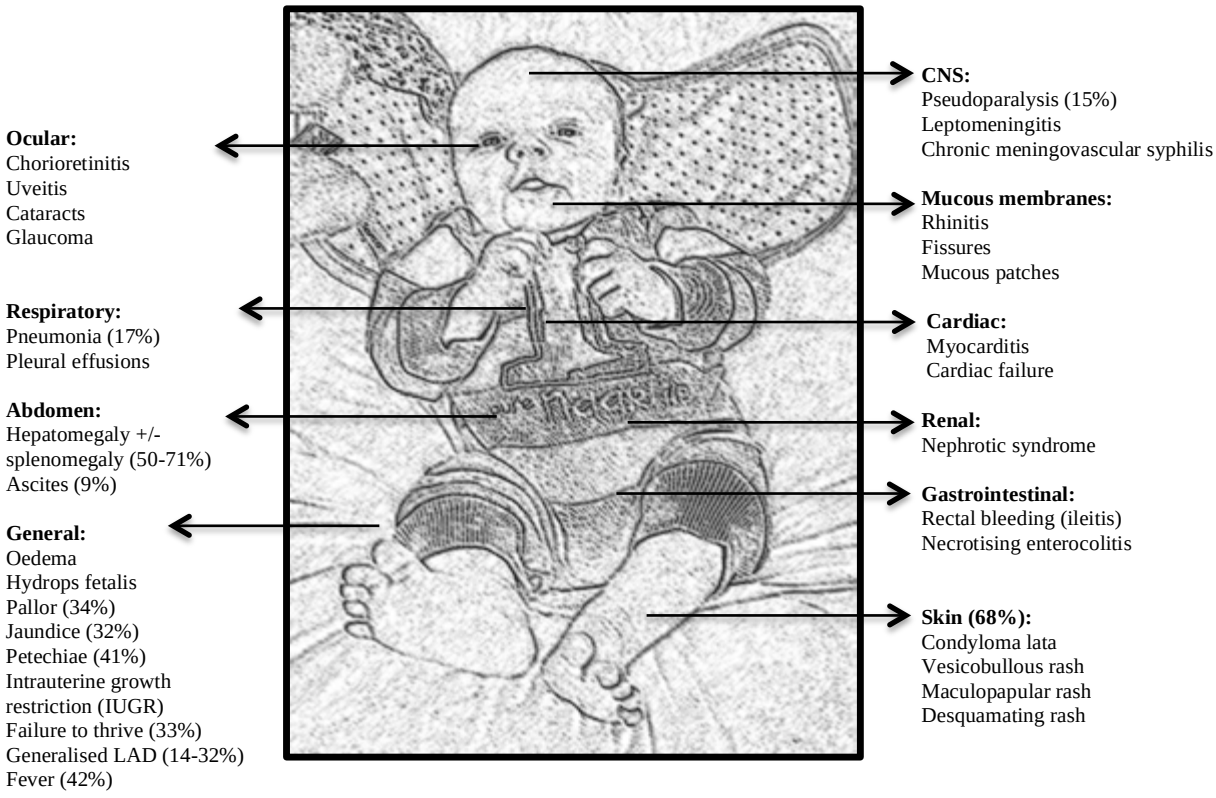


Figure 2. Clinical signs in congenital syphilis [9,17]

The most common clinical findings of early congenital syphilis include, hepatomegaly and/or splenomegaly, skin and mucocutaneous lesions, (maculopapular rash, peeling rash on the palms and soles, vesiculobullous lesions), a watery nasal discharge, pallor, jaundice (commonly cholestatic in nature), pneumonia, and non-tender generalised lymphadenopathy (LAD).[12,14,17,18] The so called "syphilitic snuffles" (watery, occasionally blood tinged nasal discharge), occurs in four to twenty-two percent of neonates and usually within the first two weeks of birth and together with the characteristic syphilitic rash which typically follows it, is highly infectious, teeming with spirochaetes.[9] Early congenital syphilis should be considered in any preterm neonate with unexplained hydrops fetalis or an enlarged placenta with signs of placental infection, as a result of the association of maternal syphilis with preterm delivery in 10-40% of cases.[16,18]

Central nervous system (CNS) manifestations are usually not present at birth or in the immediate neonatal period and tend to occur in untreated neonates as a result of uncontrolled spirochaetal dissemination.

Acute syphilitic leptomeningitis occurs in the first few months of life and presents similarity to bacterial meningitis with fever, irritability and a bulging fontanelle. Chronic meningovascular syphilis has a later presentation toward the end of the first year of year with focal neurologic signs (cranial nerve palsies), neurodevelopmental regression and seizures.[8]

i. Placental weights

As a result of placental inflammatory changes from spirochaetal transmission in-utero the placenta is significantly heavier than expected for weight in neonates with congenital syphilis. In normal pregnancies, the placental weight increases with gestational age but decreases in relation to foetal weight. Malan et al acknowledged the difficulty that this changing ratio of placental weight presented, especially in growth restricted or preterm neonates, as well as the underutilisation of placental weight as a clinical sign in congenital syphilis. They therefore constructed a placental weight chart for birth weight in normal neonates and assessed how this compared to neonates with congenital syphilis. Norms for placental weight were obtained from 13 601 live births generating a graph with corresponding centiles (10^{th}, 50^{th}, 90^{th}). The placental weights for seventy-four live born neonates with congenital syphilis, collected over an eight year period, were then plotted onto this graph (figure 3). These neonates were symptomatic with either clinical or laboratory changes in the face of positive syphilis serological testing. Figure 3 depicts placental weight on the y axis and birth weight on the x axis. Each dot corresponds to placental weight in relation to birth weight in the seventy-four neonates with congenital syphilis, demonstrating that the placentae in neonates with congenital syphilis were significantly heavier than expected for weight ($p < 0.001$). This effect was most marked in those neonates weighing more than two kilograms. Malan et al advocated the routine use of placental weight graphs, especially in neonates who are underweight for gestational age and in areas where syphilis is prevalent.[19]

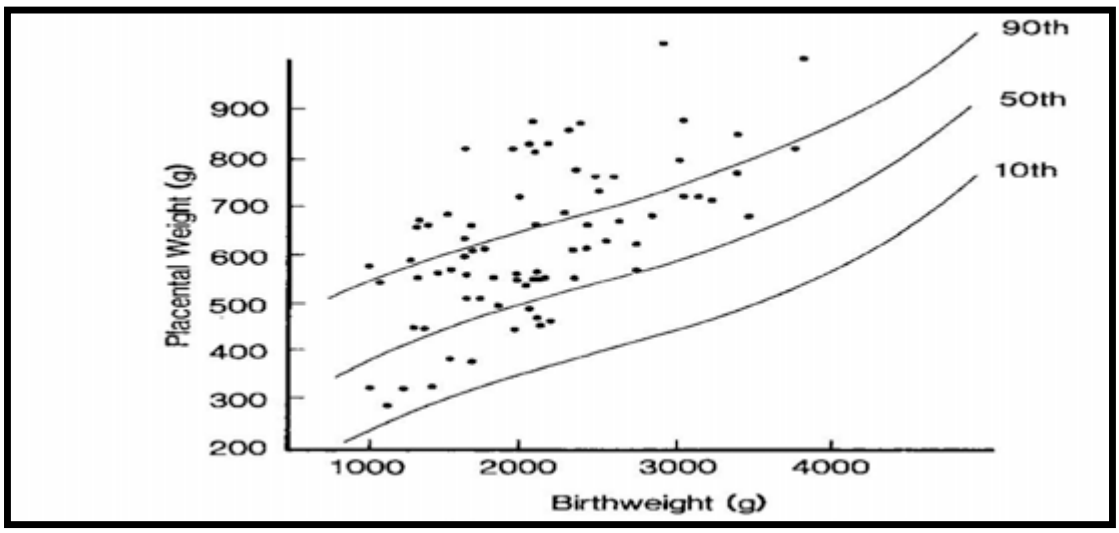


Figure 3. Relative placental weight in congenital syphilis[19]

ii. Long bone changes

Long bone changes, often symmetrical and multiple, are a common manifestation of early congenital syphilis, occurring in sixty to eighty percent of cases, and may be the sole manifestation in neonates born to mothers with untreated syphilis.[20,21] Findings include metaphyseal translucent bands, symmetric localized demineralization, osseous destruction of the medial portion of the proximal tibial metaphysis (Wimberger sign), metaphyseal serration ("sawtooth metaphysis," or Wegener sign) as well as irregular areas of increased density and rarefaction ("moth-eaten" appearance).[22] Periostitis and cortical demineralization occur in the metaphyseal and diaphyseal portions of long bones with epiphyseal sparing. Diaphyseal periostitis is a specific and characteristic radiographic finding of congenital syphilis. Osteochondritis affects the joints of the knees, ankles, wrists, and elbows and may be extremely painful, thereby limiting spontaneous movement and causing "Parrot pseudoparalysis". Bone changes are usually self-limiting showing signs of resolution within six months of treatment.[8,16]

b. Case definition of congenital syphilis

Case definitions of congenital syphilis are not standard and differ by country as well as neonatal unit. Figure 4 depicts the case definitions for congenital syphilis as per the Centers for Disease Control (CDC).

Scenario 1: Proven or highly probable congenital syphilis

- Any neonate with**:**
- Physical examination that is consistent with congenital syphilis OR
- Nontreponemal serologic titre that is fourfold higher than the maternal titre OR
- Positive darkfield test or PCR of lesions or body fluids

Scenario 2: Possible congenital syphilis

- Any neonate with a normal physical examination and a serum quantitative nontreponemal serologic titre equal to or less than fourfold the maternal titre and one of the following:
- Mother was not treated, inadequately treated, or has no documentation of having received treatment OR
- Mother was treated with erythromycin or a regimen not recommended by the CDC OR
- Mother received recommended treatment but less than four weeks before delivery

Scenario 3: Congenital syphilis less likely

- Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titre equal to or less than fourfold the maternal titre and both of the following are true:
- Mother was adequately treated during pregnancy, more than 4 weeks before delivery AND
- Mother has no evidence of reinfection or relapse

Scenario 4: Congenital syphilis unlikely

- Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titre equal to or less than fourfold the maternal titre and both of the following are true:
- Mother was adequately treated before pregnancy AND
- Mother's nontreponemal serologic titre remained low and stable before and during pregnancy and at delivery

Figure 4. Case definitions of congenital syphilis as per the CDC [23]

c. Diagnostic testing

The diagnosis of syphilis relies on serological antibody testing. However, confirming the diagnosis of congenital syphilis poses a diagnostic difficulty due to the effects of maternal transfer of IgG antibodies on both the nontreponemal and treponemal tests together with the absence or subtleness of neonatal clinical signs.[24] Bacteriological confirmation is hindered by failure to culture the elusive *T. pallidum* together with the rarity of skin lesions to provide a medium for darkfield microscopy.[25]

Nontreponemal tests include the rapid plasma reagin (RPR) test, the venereal disease research laboratory (VDRL) test and the automated reagin (ART) test. Treponemal tests include the fluorescent treponemal antibody absorption test (FTA-ab), the *Treponema pallidum* haemagglutination (TPHA) test and most enzyme immunoassay (EIA) tests.

The first group of tests measure antibodies directed against cardiolipin, which is a component of membranes and mammalian tissues. These tests provide quantitative results, and thereby acting as a helpful indicator of disease activity.[8] Non-treponemal tests take up to four to six weeks to become positive following infection and one to three weeks after the onset of the primary lesion.[26] A positive test result is more likely to indicate recent infection as nontreponemal tests do become negative following treatment, within one year in primary syphilis and within two years in the case of secondary syphilis.[8,28] However their usefulness as a screening test is limited by high false negative test results, in the early period of infection, as a result of the prozone phenomenon, as well as in late latent infection, rendering repeat testing necessary. The prozone phenomenon occurs in early infection during the period of seroconversion when high antibody titres inhibit agglutination, resulting in a false negative nontreponemal screening test if undiluted serum is used. This phenomenon can be avoided by serial dilutions of the serum.[8,28,29] A minority of patients will remain “serofast” with low positive titres that persist despite treatment. False positives may also occur in those patients with underlying connective tissue diseases or other chronic inflammatory illnesses as well as pregnancy per se.

The second group of tests measure specific treponemal antibodies, and do become positive earlier in the period of infection. However, titres correlate poorly with disease activity and as they tend to remain positive for life, monitoring of treatment response is not possible. A positive test result indicates past or current infection and is intepreted in light of the RPR (non-treponemal test) titre. These tests are positive in 75-85% of patients with primary syphilis and 100% of patients with secondary syphilis.[28,30]

Testing algorithms differ between countries as well as neonatal units. Testing involves a single test from either group or combination testing with a screening test followed by a confirmatory test. The current WHO recommendation is for combination testing with a nontreponemal test followed by a treponemal test for screening and monitoring of therapy and establishing a presumptive diagnosis respectively. Some centres consider the gold standard to be the treponemal FTA-ab test. Because IgM antibodies become evident in the serum toward the end of the second week of infection and do not cross the placenta, a positive FTA-ab IgM indicates active neonatal disease and can be used to stage infection and provides a baseline for treatment monitoring; however false positives do occur.[8,29]

Rapid tests are cost effective, simple to use, point of care devices, with a rapid turnaround time for results. They utilize blood, serum or plasma to test for syphilis antibodies with a specificity of eighty-five to ninety-eight percent and a sensitivity of ninety-three to ninety-eight percent. Their usefulness in resource limited settings cannot be emphasized enough.[27] Results obtained on the same day ensures that maternal treatment can be instituted immediately which is an approach that has proven cost effective in countries with a syphilis prevalence of more than 0.15%.[30] In the interim a formal laboratory syphilis test should be sent for confirmation. However, this formal result will not influence the commencement of maternal treatment, which is an approach essential to the prevention of congenital syphilis.

d. Supportive investigations

i. Blood investigations

Haematological findings of early congenital syphilis include anaemia (coombs negative haemolytic anaemia usually in the neonatal period), thrombocytopenia, leucopenia or leucocytosis, with or without a leukaemoid reaction. Hepatic derangements include cholestatic jaundice with or without a syphilitic hepatitis picture (elevated alkaline phosphatase (ALP) and transminases). There may be evidence of a disseminated intravascular coagulopathy (DIC).[22]

ii. Cerebrospinal fluid findings

The CDC recommends a lumbar puncture for cases of proven or highly probably congenital syphilis as well as cases of possible congenital syphilis. CSF findings in acute syphilitic leptomeningitis is usually in keeping with an aseptic process. A raised protein count (>150mg/dl) and raised white cell count (>25mm^3) are suggestion but not diagnostic of neurosyphilis. A positive CSF VDRL test generally confirms the diagnosis, however false positives may occur.[23]

iii. Other investigations

Chest x-rays may be useful in those neonates with respiratory distress. “Pneumonia alba” is the classical term for the fibrosing alveolitis in congenital syphilis but this is largely a post-mortem diagnosis. Radiologically there may be evidence of a diffuse pulmonic infiltrate but no chest x-ray findings are completely diagnostic of congenital syphilis.[8]

e. Treatment

Penicillin is effective in all stages of syphilis and remains the drug of choice for treatment of neurosyphilis, maternal as well as congenital syphilis, with T. *pallidum* having yet to demonstrate resistance toward this drug.[31] The risk of infection is terminated within twenty-four to forty-eight hours of treatment.[30]

Treatment in the neonate depends on two factors:

- Maternal treatment status i.e. fully treated, untreated or partially treated
- Neonatal clinical status i.e. symptomatic or not

Single doses of penicillin may be effective in the early stages of syphilis; however it is often clinically difficult to ascertain the maternal stage of syphilis. By definition, a fully treated mother should receive three doses of intramuscular penicillin weekly for three weeks with the last dose received more than one month prior to delivery, which would be more than adequate in the majority of mothers. Penicillin allergic mothers should be referred for penicillin desensitization. In situations where this is not feasible, mothers may be treated with fourteen days of a macrolide (erythromycin).[32,33] It is important to note that erythromycin is not nearly as efficacious as penicillin and is unreliable in curing maternal infection or preventing congenital syphilis. Mothers treated with erythromycin should be presumed partially treated and neonates born to these mothers should be assumed to have possible congenital syphilis even in the absence of clinical signs.[23,34] Partially treated mothers may have commenced treatment antenatally but it was incorrect in terms of dosing, duration or timing prior to delivery. An untreated mother would have received no treatment at all. Figure 5 demonstrates the suggested neonatal treatment algorithm as per the CDC.

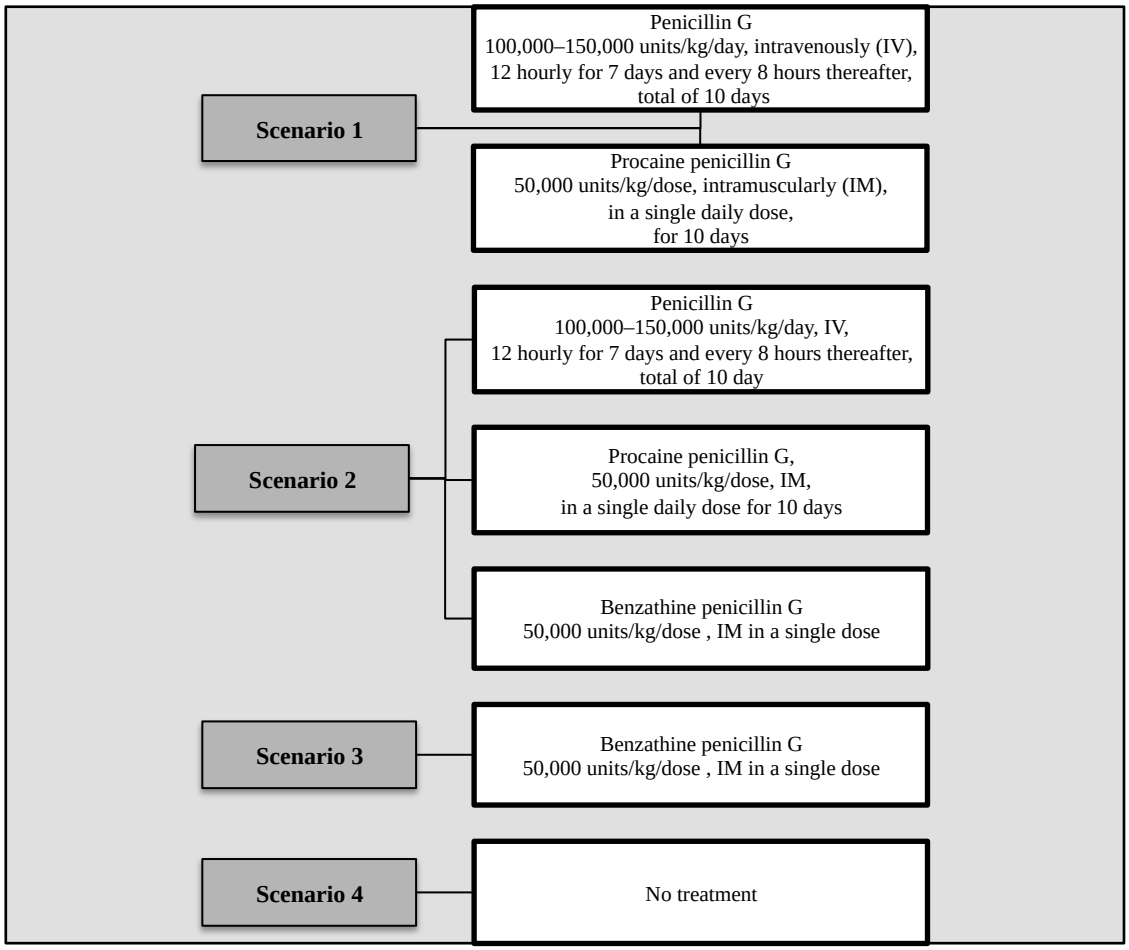


Figure 5. CDC treatment algorithm for neonates (scenario numbering corresponds to case definition numbering as per figure 4)[23]

f. Follow up

In some centres recommendation for follow-up of infants diagnosed with congenital syphilis includes repeat serological testing performed at one, two, three, six and twelve months of age depending on the likelihood of neonatal infection post delivery. In neonates where congenital syphilis was considered less likely or unlikely, nontreponemal tests should be repeated until they become non-reactive or titres demonstrate a fourfold reduction.[8] Maternal transfer of nontreponemal antibodies may take up to six months to disappear. Evidence of stable or rising nontreponemal titres after six to twelve months of age, in fully treated neonates, warrants re-investigation and treatment of syphilis (figure 6).[8,23]

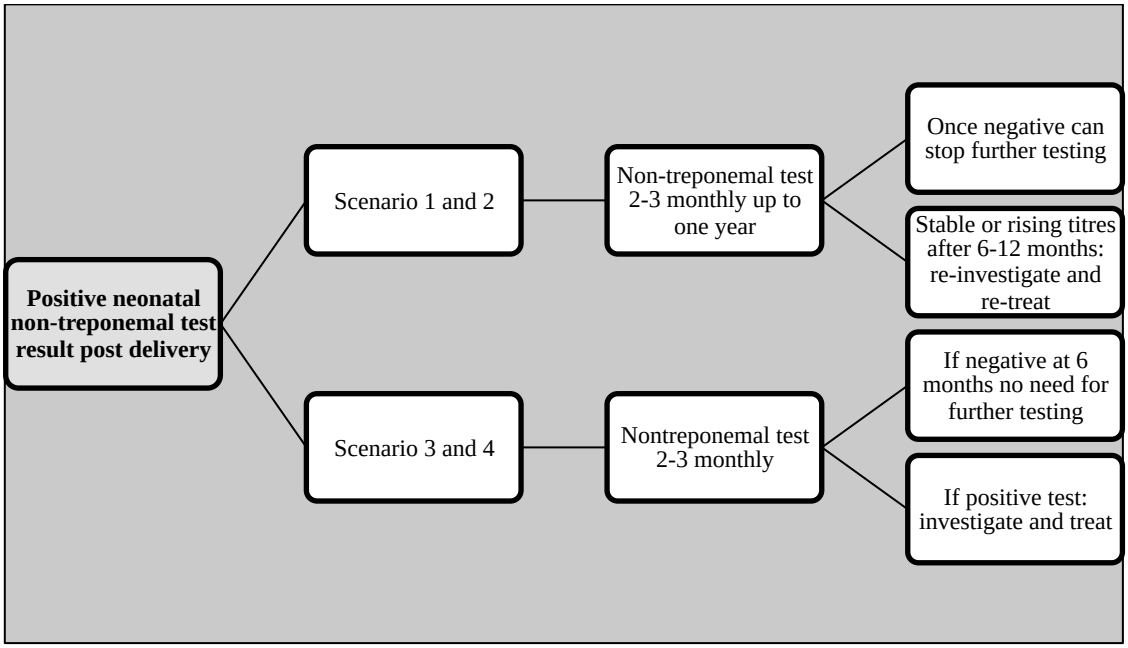


Figure 6: CDC algorithm for follow-up testing (scenario numbering corresponds to case definition numbering as per figure 4)[23]

2. GROOTE SCHUUR HOSPITAL NEONATAL UNIT PROTOCOL

a. Maternal syphilis

The most common congenital infection in our setting is congenital syphilis. As per National Department of Health protocol, maternal syphilis screening should be routinely performed in all pregnant women at booking and if non-reactive, retesting should occur after thirty-two weeks.[35] The National Health Laboratory Service (NHLS) is a public health laboratory providing diagnostic services to national and provincial health departments, including Groote Schuur Hospital (GSH). During the study period, the NHLS changed their serological testing algorithm for the diagnosis of syphilis. Prior to March 2013, a nontreponemal test such as RPR acted as a screening tool, followed by a confirmatory treponemal test (TPHA). The current practice (from March 2013- present) consists of performing an automated treponemal screening test (TPHA) at first, followed by a nontreponemal test (RPR) to determine disease activity. The advantages of this new testing algorithm are that it offers increased sensitivity and specificity, as well as reduction in time required for testing. FTA-ab testing is not utilised at GSH as a result of high false negative and positive results in our laboratory. Darkfield microscopy is not available in South Africa.

b. Neonatal syphilis

GSH neonatal unit protocol does not require nor utilize maternal or neonatal titres in order to make a diagnosis of congenital syphilis. The presence of clinical signs, as mentioned above, in a neonate born to a mother with syphilis whether treated or not, implies symptomatic congenital syphilis and is an indication for neonatal treatment. However, it is important to note that those neonates who are born to untreated or partially treated mothers who are asymptomatic at birth nevertheless receive an intramuscular dose of benzathine penicillin, to cover those two thirds of infected neonates that are asymptomatic at birth. We do not use intramuscular procaine penicillin as an alternate option as per the CDC guidelines (figure 7).

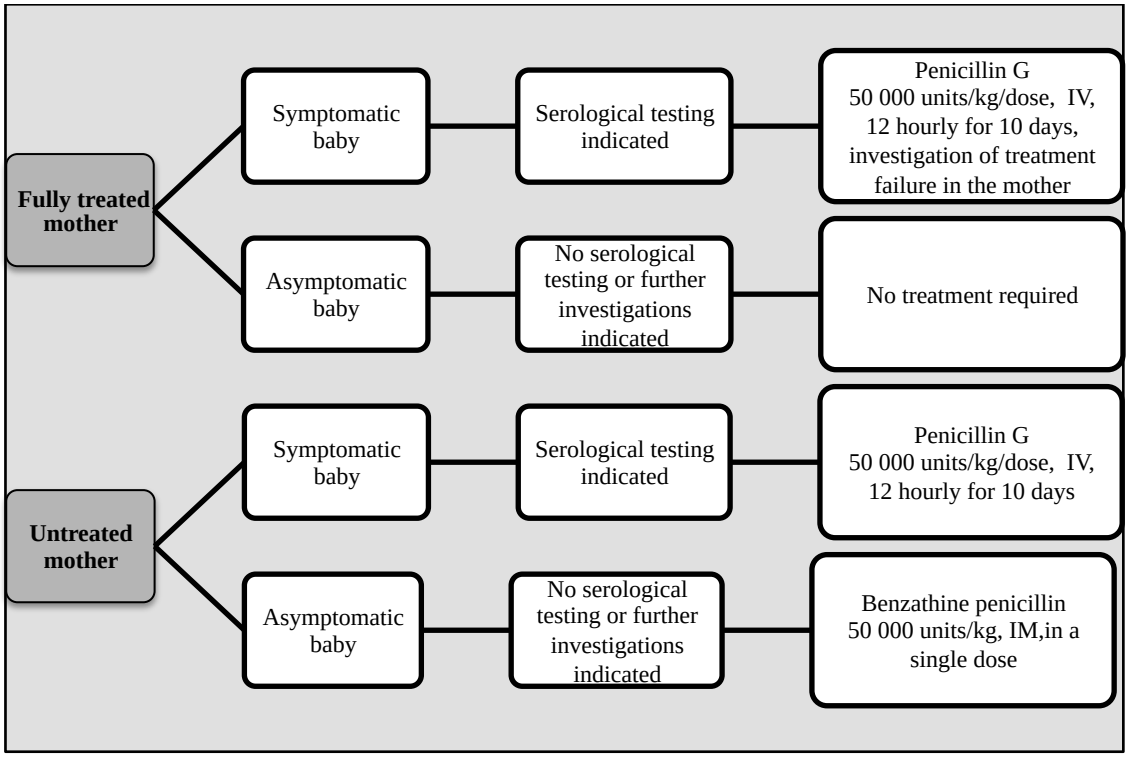


Figure 7. GSH protocol for management of syphilis exposed neonates

In our unit, lumbar punctures are not routinely indicated in all neonates with congenital syphilis, as an abnormal result will not change management outcome nor treatment duration. Long bone x-rays are also not routinely performed in all exposed neonates. They may be requested in the event of a neonate requiring radiological imaging for another indication for e.g. in those intubated neonates requiring chest x-rays to assess endotracheal tube placement or review for underlying lung pathology.

Congenital syphilis is a notifiable condition. Our unit protocol dictates that notification of congenital syphilis occurs and that maternal sexual contacts be traced and treated. It also requires repeat nontreponemal serological testing in all infected neonates at three months of age to ensure that the test has become negative and/or the titre is decreasing.

3. STUDY MOTIVATION

The World Development Report cites antenatal screening and treatment of syphilis as one of the most cost effective public health interventions.[36] Preventative tools for congenital syphilis have being available for more than fifty years with a cost of less than $1, yet symptomatic congenital syphilis remains one of the leading causes of neonatal deaths.[37] Even after treatment, women who contract syphilis during pregnancy have a 2.5 fold higher risk of adverse outcomes than uninfected women.[38] In fact, excluding morbidity, the global perinatal mortality rate from congenital syphilis is similar to or exceeds the perinatal deaths estimated for HIV, malaria or tetanus, which is a significant for a disease which is largely preventable.[3] Interestingly, advocacy and donor funds are being shunted toward Prevention of Mother to Child Transmission (PMTCT) programmes, yet many of the infants in whom HIV is prevented may die of syphilis.[37] Despite these alarming facts, a survey of twenty-two Sub-Saharan African countries found that although universal screening of syphilis in pregnancy was recommended policy in seventeen countries, only thirty-eight percent of women attending antenatal clinics were actually screened and treated. None of the countries surveyed had national targets or indicators for monitoring the progress of antenatal syphilis screening, suggesting that it was not seen as a priority.[39] Kuznik et al reviewed the public health burden associated with untreated maternal syphilis in forty-three Sub-Saharan African countries. They demonstrated significant mortality and morbidity (in terms of stillbirths, neonatal deaths, low birth weight and congenital syphilis infection) in infants born to mothers with syphilis across Sub-Saharan African. In fact, the public health burden associated with adverse pregnancy outcomes from maternal syphilis, if included, would be comparable to that of combined pertussis, diphtheria, measles and tetanus or combined neonatal infection and sepsis in the Sub-Saharan African region.[40]

South Africa was found to be one of the few African countries with access to antenatal care (ANC), where ninety-seven percent of pregnant women had access to at least one ANC visit with 74.5 percent of those women being screened for syphilis infection at that visit.

Despite this, the total disability adjusted life year (DALY), a measure of years of life lost due to disability, ill health and death, due to adverse pregnancy outcomes resulting from maternal syphilis infection was one hundred and ten thousand, worse than those countries with higher syphilis prevalence rates and poorer antenatal care and screening.[41] The implication is that in South Africa, there are other factors at play accounting for the higher DALY, which may be related to inadequate treatment or follow-up.

The above factors demonstrate that in developing countries such as ours, syphilis remains a public health concern with congenital syphilis impacting significantly on neonatal as well as infant morbidity and mortality, with the resultant impact on resources and cost. A number of South African studies, spanning more than twenty years, by Pieper et al[42], Ballot et al[43], Delport et al[44] and Saloojee et al[45] have highlighted the burden associated with syphilis and yet despite these implications, syphilis as well as preventative measures against it does not appear to be a flagged as a health priority.

Anecdotal evidence seemed to indicate an increasing number of neonates treated at GSH who were diagnosed with symptomatic congenital syphilis. The apparent increase in numbers may have been due to changes in referral pathways. Since April 2012, Khayelithsha District Hospital opened its doors resulting in neonates from outside the drainage area being referred into GSH. Furthermore, policy changes resulted in all mothers less than thirty weeks pregnant with threatened preterm labour being referred directly to GSH for tocoloysis or delivery. The resultant overall increase in complicated deliveries at GSH may have contributed to the higher numbers of neonates being seen with syphilis. Nevertheless, these neonates were often extremely ill with an associated increased risk of morbidity and mortality.

The motivation for this study was to describe the clinical features of these symptomatic neonates with congenital syphilis particularly pertaining to the maximum level of care required as well as their outcome in terms of morbidity and mortality. One of the primary objectives was to identify factors associated with symptomatic neonates, with the hope of identifying those, which may be avoidable.

Furthermore, the demonstration of adverse outcomes in symptomatic neonates assists in strengthening the argument for improving preventative measures antenatally by advocating early booking and therefore timeous diagnosis and appropriate treatment of maternal syphilis infection.

4. LITERATURE REVIEW

The aim of the literature review was to identify the relevant literature pertaining to congenital syphilis with particular reference to maternal factors, neonatal clinical parameters, including outcomes in terms of morbidity and mortality as well as modifiable factors in terms of preventative strategies. Evidence with particular relevance to the developing world was sought.

a. Literature search strategy, inclusion and exclusion criteria

A search of major online medical databases (Pubmed/Medline) and an internet search using Google scholar was performed. The following Medical Subject Headings and Boolean operators were used: “congenital syphilis” AND “clinical signs” AND “outcomes”. Search filters were used to include all studies published in the period from 1990 to the present, in English only and available online with access to an abstract at least. Eighteen studies met inclusion criteria. The articles that were excluded included case reports of congenital syphilis, articles pertaining to maternal syphilis infection predominantly, articles with a focus on diagnosis and treatment of congenital syphilis and articles concerning syphilis epidemiology. An article that reviewed congenital syphilis rates in relation to an outbreak in British Columbia was also excluded. The following table provides a summary of the ten international studies. Following on from that, is a discussion of a meta-analysis and seven studies set in an Africa context, particularly Sub-Saharan Africa and South Africa.

b. Summary and interpretation of literature

Table 1: Summary of ten international studies identified by search strategies	
1. The Incidence of Congenital Syphilis in the United Kingdom (UK): February 2010 to January 2015[46]	
Study objective	To estimate the incidence of congenital syphilis in the UK.
Study design	Prospective, descriptive study between February 2010 and January 2015.
Population and setting	UK
Congenital syphilis case definition	Confirmed, presumptive and possible diagnoses as per CDC criteria.
Results	
Number of cases	17 of 175 reports (9.7%) identified as cases (3 confirmed, 13 presumptive, 1 possible).
Neonatal factors (n=17)	12 male. 5 female. 8 premature. Median birth weight 2000g (865g-2170g). 7 asymptomatic.
Clinical findings	Severe anaemia, hepatosplenomegaly, rhinitis, oedema, thrombocytopaenia, skeletal damage, neurosyphilis. One child was blind and deaf.
Number of deaths	1 intrauterine death (IUD).
Maternal factors (n=17)	13 white mothers. Age range 17-31 years. 2 diagnosed between 20 and 30 weeks gestation. 5 late diagnoses; 2 diagnosed 1 month before delivery, 3 diagnosed in last month of pregnancy. 5 diagnosed at delivery. 5 post delivery. Social concerns included drug use, prostitution, incarceration and improper health seeking behaviours.
Conclusions	UK incidence of congenital syphilis below the WHO threshold for elimination (< 0.5/1000 live births), which was related to effective surveillance monitoring.
Comments	Primary focus was on the importance of effective and reliable surveillance programmes together with adequate health care services as means of achieving a low congenital syphilis incidence rate. Detail in terms of the individual congenital syphilis cases itself was therefore not a core aspect of this article. Despite the developed world setting as well as the lack of racial diversity in this cohort, study was recent and social factors were similar to those seen in the current South African context.
2. Gestational and Congenital Syphilis Epidemic in the Colombian Pacific Coast[47]	
Study objective	To determine contributing factors to the failure of congenital syphilis prevention programmes. To determine clinical aspects and outcomes of infected neonates.
Study design	Retrospective electronic health record review between January to July 2011.
Population and setting	Buenaventura, Colombian Pacific Coast
Congenital syphilis case definition	"Newborn, stillborn or abortion product born to a mother with untreated or inadequately treated gestational syphilis."
Results	
Number of cases	89 neonates and 92 mothers.
Neonatal factors (n=89)	Almost equal numbers of males and females. 16.3% were preterm and low birth weight. More than half were vaginal deliveries. Most were asymptomatic at the initial clinical examination.
Clinical findings	11.2% had mucocutaneous involvement; skin lesions 2.2% and snuffles in 9%. 2 (2.2%) had poor weight gain. 15 (16.8%) were jaundiced. 26.5% were anaemic. 31.3% had features of a transaminitis.
Number of deaths	7 demised (5 stillbirths, 2 early neonatal deaths). 5 were premature infants; 4 of 5 had a gestational age (GA) < 29 wks.
Neonatal test results (n=81) (VDRL with titres)	Non reactive 16 (19.8%) < 1:4 46 (56.8%) > 1:8 10 (12.3%) > 1:16 9 (11.1%)
Maternal factors (n=92)	None known to be HIV positive. 30.4% sought no antenatal care. 26% had inadequate perinatal care. 39% untreated. Of those who received penicillin 5 were appropriately treated. Partner tracing poorly documented.
Maternal test results (n=92) (VDRL and TPHA)	**VDRL** < 1:4 40 (43.5%) > 1:8 20 (21.8 %) > 1:16 30 (32.6 %) Not done 1 (1.1%) **TPHA** Yes 48 (52.2%) No 29 (31.5%)
Conclusion	The incidence of congenital syphilis in the 7 month time period was 6%, higher than the WHO threshold for elimination. Avoidable factors included poor maternal health seeking behaviour, as a result of logistical, financial and geographical limitations as well as delay in testing turn around times.
Comments	Study population was a developing country with socio-economic limitations similar to those faced in South Africa. Of note 20% met the case definition for congenital syphilis but were in fact VDRL negative.
3. Congenital Syphilis in Switzerland: Gone, Forgotten, on the Return[48]	
Study objective	To evaluate the total number of pregnant women with positive syphilis serology together with the neonatal outcomes and clinical features.
Study design	Retrospective study between 2000 and 2009.
Population and setting	Zurich, Switzerland

Results	Out of 13,968 deliveries, positive syphilis serology was present in 9 of the mothers. 1 neonate had signs and symptoms of congenital syphilis.
Conclusion	The absence of routine antenatal syphilis screening programmes may lead to an increase in congenital syphilis incidence rates as a result of emerging infection in young women of childbearing age.
Comments	Small cohort of positive maternal cases in the 9 year study period.
4. Pregnancy and Neonatal Outcomes of Women With Reactive Syphilis Serology in Alberta, 2002 to 2006[49]	
Study objective	To describe the maternal characteristics and the neonatal outcomes of pregnant women with positive syphilis serology.
Study design	Retrospective chart review of pregnant women in Alberta with reactive syphilis serology between 2002 and 2006.
Population and setting	Alberta, Canada
Congenital syphilis case definition	Probable and definitive syphilis cases as per the provincial and national case definitions.
Results	
Number of cases	60 confirmed cases of maternal syphilis (75 pregnancies and 80 births).
Neonatal factors (n=80)	Of the 30 appropriately treated pregnancies pre-conception (32 neonates), 31 neonates unaffected and 1 presumed to be unaffected (lost to follow-up). Of the 45 untreated mothers before conception (48 neonates), 7 neonates had confirmed congenital syphilis, 1 had probable congenital syphilis, 3 were lost to follow-up and 37 were asymptomatic and unaffected. All 7 confirmed congenital syphilis cases were preterm, with a median gestational age of twenty-nine weeks (range 23 to 36).
Neonatal outcomes based on maternal diagnosis and treatment	
Syphilis diagnosed prenatally (39 pregnancies; 42 births)	41 live born infants • 37 had no evidence of congenital syphilis • 2 had evidence of congenital syphilis (One confirmed, one probable) Median gestational age of maternal treatment 20 weeks (8 -36 weeks) • Confirmed case: untreated mother diagnosed at 21 weeks who defaulted follow-up until delivery (29 weeks) • Probable case: mother treated at 42 weeks gestational, 3 weeks < delivery
Syphilis diagnosed perinatally (6 pregnancies; 6 births)	6 live births • All symptomatic neonates Maternal treatment: • 5 mothers treated post- partum only • 1 untreated and died before treatment commenced
Clinical findings	Anaemia (n=3). Long bone changes (n=3). Hepatosplenomegaly (n=5). Rash in 3. 2 hydropic. Long-term effects at age 1 to 5 years included death (n=1), microcephaly and seizures (n=1), microcephaly and visual impairment (n=1), visual impairment alone (n =1).
Number of deaths	Stillborn at 27 weeks GA born to a mother diagnosed prenatally.1 early neonatal death (day 1) in mother diagnosed perinatally.
Maternal factors (n=60)	Median age 23 years (19-29 years). 57 non-Caucasian (80.2%). 10 Caucasian (14.1%). 30 pregnancies appropriately treated. 45 pregnancies no treatment or antenatal care. No statistically significant differences in demographics (age, ethnicity, immigrant status) between women delivering infants with congenital syphilis, those with uninfected children, and those treated before conception. Of the 7 neonates with confirmed congenital syphilis, 4 mothers accessed no prenatal care, 2 had inadequate prenatal care, 1 mother inappropriately labelled as having a false positive RPR whose baby was then born with signs of congenital syphilis.
Conclusions	Syphilis rates seem to be increasing in a setting previously thought to have low rates. Inadequate pre-natal care listed as a contributing factor to this increasing rate.
Comments	Of the 42 neonates born to fully treated mothers, only 1 had confirmed congenital syphilis, which supports importance of early diagnosis and effective treatment in mothers. One of the few studies that looked at long term outcome. Majority of neonates were asymptomatic.
5. Outcome of Maternal Syphilis at Rajavithi Hospital on Offsprings[50]	
Study objective	To assess whether maternal syphilis treatment is appropriate in preventing congenital syphilis and to review the outcomes of infants born to mothers with untreated syphilis.
Study design	Prospective surveillance study from September 2002 to December 2003. Follow up was at 1,2,4,6 months.
Population and setting	Bangkok, Thailand
Congenital syphilis case definition	All offsprings born to mothers with syphilis.
Results	
Number of cases	63 mothers and 64 infants.
Neonatal factors (n=64)	Mean birth weight 3034 +/- 495 grams. 9 infants (14.06%) identified with presumptive congenital syphilis. 50 infants (78.13%) including the 9 presumptive cases were followed up; all had appropriate growth parameters. 34 (68%) were seronegative on follow-up VDRL tests.
Clinical findings	Hepatomegaly (55.56%), desquamation of palms and soles (44.44%), radiological changes (33.33%) and abnormal cerebrospinal fluid (25%).
Number of deaths	No stillbirths or deaths.
Neonatal and maternal test results	Maternal and neonatal VDRL titres were between weakly reactive to 1:32 and nonreactive to 1:32 respectively.
Maternal factors (n=63)	84.13% had adequate prenatal care. Mean maternal age, mean gestation age at treatment for syphilis and at delivery were 30.31 (+/- 5.60 years), 32.75 (+/- 6. 73 weeks) and 38.60 (+/- 1.57) weeks respectively. 23 cases (36.51%) were appropriately treated with penicillin, inadequate penicillin treatment in 5 cases (7.94%), erythromycin treatment in 9 cases (14.29%). 26 mothers (41.27%) received no treatment at all.
Conclusion	Congenital syphilis rates associated with untreated or inadequately treated maternal syphilis.

Comments	Follow-up with assessment for serological testing was done which was not a common feature in other studies.
6. Clinical Features and Follow-up of Congenital Syphilis[51]	
Study objective	To evaluate clinical features and outcomes of children treated for congenital syphilis
Study design	Prospective case control study from May 1997 to December 2004. Follow-up was from birth to 5 years of age.
Population and setting	Porto Alegre, Brazil
Congenital syphilis case definition	Infant whose mother had untreated syphilis or inappropriately treated syphilis. Clinical findings consistent with congenital syphilis or a serum nontreponemal test titre 4-fold > than the mothers.
Results	
Number of cases	379 of 24920 inborn live births (1.5%) and 19 outborn neonates met the case definition. (Total number = 398). Compared with 120 infants whose mothers were appropriately treated for syphilis.
Neonatal factors (n=398)	38 (9.5%) were symptomatic. 21 (5.5%) of 379 inborn infants were symptomatic (95% CI, 3.5%- 8.5%) which was more common in preterm infants: 21% versus 3% in full-term infants ([RR], 4.5; 95% CI, 2.6 - 7.7). 30 % evaluated between 6 months and 5 year; most had a favourable outcome.
Clinical findings	292 (77%) had a lab/x-ray evaluation; 85 (29%) had a physical or lab/x-ray abnormality, more common in preterm (51%) than in full-term (26%) infants (RR, 1.97; 95% CI, 1.35-2.87). 4 most common clinical signs were hepatomegaly (71.1%), splenomegaly (60.5%), pallor (42.1%) and cholestatic jaundice (28.9%). Symptom risk found to be higher in untreated/inadequately treated mothers.
Number of deaths	37 foetal deaths due to congenital syphilis occurred in this time period but were excluded. 11 of 398 died (2.8%). 1 out of 120 died.
Neonatal test results	Serum VDRL was positive at birth in 328 (82.5%) neonates who met the case definition; negative in 70 (17.5%) cases.
Maternal factors (n=398)	499 neonates out of 24 920 deliveries born to mothers who tested positive for syphilis. 120 (24%) born to fully treated mothers. 379 neonates (76%) born to inadequately treated mothers. Maternal factors associated with congenital syphilis – untreated mothers with negative VDRL during pregnancy with positive test result at delivery (64.3%), inadequate treatment in terms of duration, drug choice, doses in relation to delivery and failure of titre improvement.
Conclusion	Congenital syphilis associated with a number of negative sequelae, some irreversible. Largely due to inadequate maternal treatment.
Comments	Detailed descriptive study. Some abnormality was detected by lab/x-ray evaluation in 25% of asymptomatic infants indicating the importance of a through clinical assessment in neonates where suspicion for congenital syphilis is high. Majority of cases were asymptomatic. One of the few studies that elaborated on individual clinical signs and that had a control population.
7. Maternal / Congenital Syphilis in a Large Tertiary-Care Urban Hospital [52]	
Study objective	To report the clinical, laboratory and serological findings of neonates and their mothers with syphilis.
Study design	Retrospective folder review for one year in 1990.
Population and setting	Michigan, Detroit
Congenital syphilis case definition	All babies born to mothers with both a positive RPR and FTA-ab test.
Results	
Number of cases	Out of 9 591 deliveries, 148 pregnant women (1.5%) had positive RPR and FTA-ABS tests. Control was the entire obstetric population.
Neonatal factors (n=148)	80 (54.1%) male. Mean gestational age of live-born infants was 37.3 weeks (28-42 weeks) with a birth weight range from 750 to 4050 g. Both the mean gestational age and the mean birth weight of the live-born study infants were significantly < than figures for infants born to entire obstetric population (P = 0.0001). 75% of infants both to untreated or inappropriately treated mothers were asymptomatic.
Clinical findings	3 infants born to untreated mothers had clinical signs of syphilis (hepatosplenomegaly, rash and anaemia) as compared to none in the inappropriately treated group.
Number of deaths	6 infants were stillborn.
Maternal factors (n=148)	Mean age 25.83 years. 72 mothers (48.6%) were untreated. 31 mothers (21%) received inadequate treatment. 45 mothers (30.4%) received adequate treatment. One third had history of substance use. Majority were black, multiparous women.
Conclusion	The findings in this study suggested a resurgence of syphilis in both mothers and infants.
Comment	Despite the study being more than twenty years old in a first world setting, the social implications of substance abuse on maternal syphilis diagnosis and treatment is still very relevant today. One of the few studies with a control group.
8. Congenital and Maternal Syphilis in the Capital of Brazil[53]	
Study objective	To describe the epidemiology of congenital and maternal syphilis.
Study design	Retrospective descriptive study in 2010.
Population and setting	Brazilian Federal District
Congenital syphilis case definition	Not defined in article.
Results	
Number of cases	137 congenital syphilis cases. 133 neonates and their mothers included (4 had inconsistent records).
Neonatal factors (n=133)	113 (84.9%) were reported as live births. Age (average ± standard deviation) at diagnosis was 1.72 ± 12.9 days (range 0-148 days). 116 (87.3%) were diagnosed in the first two days of life. 87 (791%) were adequately treated.
Clinical findings	12 (9%) exhibited clinical signs (jaundice 4 (3%); anaemia 1 (3%); hepatomegaly 1 (3%).

	3 (2.3 %) had long bone changes. Treatment was administered to 119 children, 79.1% (n=87) were treated appropriately.
Number of deaths	3.8% (n=5) stillbirths, 3.8% (n=5) deaths, 2.3% (n=3) deaths specifically from congenital syphilis, 3% (n=4) as abortions.
Neonatal test results	106 (79.7%) tested with a nontreponemal test; 78 (63%) tested positive.
Maternal factors (n=133)	Of the 133 mothers of children with congenital syphilis, highest rates (per 1,000 live births) were in mothers who were black (11.3/1,000 live births) or ≥40 years old (4.0/1,000 live births). 28,6% (n=38) had < than 9 years of education; majority (54.9%, n=73) were homemakers. 116 (52.6%) mothers received prenatal care; 70 (60.4%) diagnosed with syphilis during pregnancy. Only 1 mother was adequately treated. 100 (75.2%) of partners untreated. Treatment inadequate for 88% of mothers (n=117).
Maternal test results (n=133)	125 mothers had positive nontreponemal tests; 49 mothers had positive treponemal tests.
Conclusion	Although mothers received prenatal care, maternal diagnosis and treatment of syphilis was inadequate due to poor partner tracing. Factors associated with higher rates of congenital syphilis included black/brown skin, low socioeconomic status as well as maternal age between 20-30 years.
Comments	Brazil is a developing country with a similar socioeconomic structure to South Africa. This study acknowledges the public health concerns associated with rising syphilis rates and highlights the inadequacies in maternal prenatal care and therefore maternal treatment of syphilis.
9. Maternal and Congenital Syphilis Under-reported and Difficult to Control[54]	
Study objective	To identify and to describe reported and unreported cases of congenital and maternal syphilis.
Study design	Retrospective descriptive study from January 2007 to July 2013.
Population and setting	Brazil
Congenital syphilis case definition	Every child, miscarriage, or stillbirth with clinical or serologic or microbiological evidence of syphilis born to a mother with syphilis that had not been treated or had received inadequate treatment.
Results	
Number of cases	54 cases of congenital syphilis. 93 cases of maternal syphilis.
Neonatal factors (n=54)	88.9% asymptomatic. No cases of co-infection with HIV/AIDS recorded. 51.8% treated as directed. Follow-up was poor.
Clinical findings	4 (7.4%) had clinical signs. 77.8% maintained adequate weight for gestational age.
Number of deaths	16.1% progressed to abortion or stillbirth.
Neonatal test results	24 (25.8%) were not tested for syphilis. 26 (27.9%) were positive. 22 (23.7%) were negative.
Maternal factors (n=93)	Predominantly mulatto, between 21 and 30 years; single marital status. 43% attended minimum number of 6 appointments; however, mostly late diagnoses (62.4%). No cases adequately treated. 33.3% of pregnant women received no treatment. 6.5% of syphilis in pregnant women notified. 98% of partners untreated.
Maternal test results	Not provided.
Conclusion	Vertical transmission of syphilis is largely a product of inadequate maternal antenatal care, poor reporting of syphilis and lack of effective partner tracing.
Comments	This is the most recently published study (2016). Six years after the study by Muricy et al also from Brazil, published in 2015, but based on data from 2010, the same modifiable inadequacies concerning maternal syphilis infection are showcased.[54] This is unreasonable for a largely preventative disease where neonatal outcomes are known to be unfavourable.
10. Congenital Syphilis at Goroka Base Hospital: Incidence, Clinical Features and Risk Factors for Mortality[55]	
Study objective	To describe the clinical features, incidence of congenital syphilis and risk factors for death.
Study design	Prospective study design from January 1998 to December 1999.
Population and setting	Papua New Guinea.
Congenital syphilis case definition	Symptoms of congenital syphilis in the presence of a positive VDRL test.
Results	
Number of cases	67 affected neonates and children.
Neonatal factors (n=67)	55% were male. Median birth weight 2.4 kg (interquartile range 1.7-3.1 kg). 18 were < 2 kg; 9 weighed < 1.5 kg.
Clinical findings	Common clinical findings were anaemia, splenomegaly, hepatomegaly, jaundice and anaemia. Mortality in first admission was lower in babies whose mothers received hospital antenatal care: 3 of 18 died, compared with 14 deaths in 31 children of mothers not receiving hospital antenatal care (Fisher's exact test = 0.06).
Number of deaths	19 deaths (first admission). 3 deaths (follow-up period). Total mortality rate 33%. Relative risk for death from syphilis in babies weighing < 2 kg was 3.35 (95% confidence interval 2.39-4.71).
Neonatal test results	Not elaborated on.
Maternal factors (n=67)	Antenatal care attendance recorded for 49 of the 67 mothers. 25 (51%) had at least 1 antenatal visit; 24 (49%) did not receive any antenatal care. 25 booked mothers.
Maternal test results	15 babies with congenital syphilis born to 69 mothers with a positive VDRL and TPHA. 1 of the 18 mothers who was treated delivered an affected baby; 14 affected babies born to mothers who did not receive treatment.
Conclusion	Syphilis contributed substantially to mortality in low birth weight babies which was statistically significant.
Comments	Older study but one of the only ones assessing risk factors for mortality. Case definition for syphilis same as out study.

Pooled estimates across six studies from a systematic review and meta-analysis of adverse pregnancy outcomes among untreated women with syphilis and women without syphilis demonstrated foetal loss and stillbirth being twenty-one percent more frequent, neonatal deaths being 9.3% more frequent and prematurity or low birth weight being 5.8% more frequent among women with syphilis. Mortality was higher (10%) in the single study that estimated infant death among infants of mothers with syphilis. Data from three of the six studies was from an African context.[56] Further insight into the African perspective of congenital syphilis was provided by Kruger et al in the form of a retrospective folder review of all cases diagnosed with congenital syphilis over a thirty month period in a single centre in rural Tanzania. Despite the small number of cases (14), the study was important in identifying two factors; the difficulty in diagnosing congenital syphilis in resource poor settings as clinical signs were not always overt at birth as well as the value of maternal screening in pregnancy to ensure timeous treatment of maternal syphilis, a recurring theme in many of the studies mentioned above.[4]

Pertaining to a South African context, a cross sectional study by Bam et al in the early nineties in Bloemfontein assessed the prevalence of syphilis in both mothers and their babies. The study found a fifteen percent maternal seroprevalence rate and similar to the studies mentioned above failure of maternal treatment was listed as a contributory factor to congenital syphilis.[57] A study performed in a large tertiary urban hospital in Gauteng in the early nineties, reviewing notification of congenital syphilis over a one-year period, found that two hundred and nine (4.7 %) deliveries were in syphilis positive mothers. Two hundred neonates met the CDC case definition of congenital syphilis; twelve pregnancies resulted in stillbirths, eight in incomplete abortions and two in early neonatal deaths.[43] An additional study from a tertiary neonatal unit in the Western Cape that looked specifically at chest radiograph features of congenital syphilis, described twenty cases of congenital syphilis over a two year period. Hepatomegaly, jaundice and anaemia were the commonest clinical signs; radiographic changes (extensive periositis, increased density of the rib cage, scapula, clavicles and humerus) were found to have a positive predictive value of more than seventy percent.[42]

Insight into the rural impact of syphilis was from a South African study by Wilkinson et al, which demonstrated that adverse pregnancy outcomes were almost twelve times more likely in woman with syphilis than in seronegative woman.[58] Neonates with symptomatic congenital syphilis often require longer hospital admissions and are more likely to require neonatal intensive care admissions.[59] In one large South African referral hospital, it was noted that on average, one neonatal ICU bed out of a total of twelve is occupied by an infant with syphilis.[45]

c. Identification of gaps and need for further research

The above literature suggests that syphilis is on the rise in both developed as well as developing countries. Alarmingly, studies more than twenty years ago noted the resurgence of syphilis that, at present, remains unyielding. Untreated or inadequately treated maternal syphilis is a product of deficient prenatal care and is compounded by poor socioeconomic conditions. Despite the rising trend as well as case fatality rates of symptomatic syphilis in South Africa as high as thirty-eight percent, we could find no recent published literature looking at predictors of outcomes in neonates born with symptomatic congenital syphilis, especially in the context of a tertiary neonatal setting.[45] This study is therefore valuable in that it would not only add new information about an age-old disease, but it may act as an important source for development of guidelines regarding limitation of care in certain categories of neonates with congenital syphilis who have a low survival rate. This is turn may have implications on resource allocation and protocol development in the future.

CHAPTER 2: OBJECTIVES AND METHODS

1. OBJECTIVES

a. Primary objectives

i. What was the outcome for symptomatic neonates in terms of mortality and morbidity?

Morbidity will be assessed as:

- Need for respiratory support (Intermittent positive pressure ventilation (IPPV), high frequency oscillation and ventilation (HFOV), continuous positive pressure ventilation (CPAP)
- Level of care required (intensive care unit [ICU], high care, low level unit)
- Associated haematological abnormalities necessitating blood products
- Seizures /neurological deficits

ii. Were there identifiable modifiable factors, which resulted in neonates being born with congenital syphilis?

- Patient factors: Unbooked mothers, mothers who defaulted follow-up visits
- Clinical/personnel factors: failure by health care provider to act on positive results or syphilis testing not done
- Health facility factors: no rapid tests (out of stock etc.)

b. Secondary objectives

i. What is the incidence of symptomatic congenital syphilis per number of total deliveries at GSH nursery and how does this compare to regional, national and international figures, taking into account that GSH is a referral centre?

ii. What were the clinical signs (including placental weights), radiological signs as well as laboratory findings in neonates born with congenital syphilis?

iii. What was the short and medium term neurodevelopmental outcome of these neonates?

- Ultrasound scans acted as proxy for short-term neurodevelopmental outcome, assessing presence of intraventricular hemorrhages (IVH) or periventricular leukomalacia (PVL)
- Twenty week infant neurodevelopmental assessment (INA) assessed medium term neurodevelopmental outcome
- Follow-up admissions

iv. Was serological syphilis testing repeated at three months of age as per the GSH neonatal unit protocol?

2. METHODOLOGY

a. Study design and setting

The study design was a retrospective descriptive folder review of neonates with symptomatic congenital syphilis admitted to GSH from the 1st January 2011, to the 31st December 2013. GSH is a tertiary neonatal unit with an average of five thousand five hundred live births per annum and acts as the primary referral centre for the Metrowest Area of Cape Town. The Metro West geographical service area includes the sub-districts of Klipfontein, Mitchell's Plain, Southern and Western with a total of approximately forty-thousand deliveries per annum.[60]

b. Sample

i. Inclusion criteria

All neonates treated at GSH (inborn and outborn) who tested serologically positive for syphilis together with clinical signs of syphilis were included. As per our unit protocol, serological testing for syphilis is always performed in symptomatic neonates (i.e. those with hepatosplenomegaly, pallor, hydrops etc.).

ii. Exclusion criteria

We have excluded those neonates with absent clinical signs of congenital syphilis in the face of positive syphilis serology (non-treponemal and treponemal tests). As it is not routine unit practice to test these neonates, some reasons may include incorrect application of the protocol or misinterpretation of clinical signs.

c. Methods

All syphilis serological tests (RPR, TPHA, FTA-Ab) performed at GSH in the paediatric population between 1st January 2011 and 31st December 2013 were obtained from the NHLS database in the form of a Microsoft excel spread sheet. This included all children tested for syphilis at GSH from birth up to and including 4 months of age for whom age was recorded. Permission, as well as the serological test result spreadsheet, was obtained from the clinical head of microbiology. All neonates with positive syphilis serology were identified. As congenital syphilis is a notifiable condition in South Africa, the notification register at GSH nursery (GW17/5) as well as the death register were used to supplement the laboratory results in order to ensure comprehensiveness and inclusivity of all congenital syphilis cases. The folders of all neonates who tested serologically positive for syphilis together with all neonates notified for congenital syphilis as well as those neonates whose cause of death was recorded as congenital syphilis as per the death register were then obtained from hospital records and the relevant data captured.

d. Data collection

i. Data collection sheet

Each neonate had a standardized data collection sheet onto which the relevant information was captured, as documented by the attending physician (see appendix 1). The assumption was that undocumented information was not asked or performed by the attending physician.

ii. Data sources

Patient folders acted as the primary means of obtaining data. In instances where results were undocumented, the NHLS database, via patient folder numbers, was utilised to locate those missing results. Similarly, this database was used to assess whether placental histology was sent as well as to follow-up six-week HIV PCR results and syphilis serological testing at three months of age.

Information regarding neurodevelopmental outcome, was obtained through the high-risk clinic register. High-risk clinic is where the first neurodevelopmental screening occurs at twenty weeks corrected gestational age (GA) in those neonates who had a protracted and complicated clinical cause (intubation for prolonged periods, extreme prematurity, recurrent apnoeas, seizures, encephalopathy). The high-risk register identified those neonates who defaulted neurodevelopmental follow-up and in those who did follow-up the resultant neurodevelopmental outcome was documented. The electronic Clinicom system, which provides information regarding admissions, discharges and deaths in the Western Cape hospitals, was used to identify those neonates who had subsequent admissions to hospital following discharge, utilizing folder numbers and dates of birth. Their relevant folders were then sought and their development as assessed at that admission was documented.

e. Statistical analysis

Data collected was transferred from each information sheet onto a Microsoft excel database, which was identical for each neonate. Names were omitted and information was linked via patient initials.

All data was analysed descriptively which included means and standard deviations for normally distributed data and medians and inter-quartile ranges for non-normally distributed continuous data.

Descriptive statistics and graphical representation in the form of bar graphs, pie charts and box and whiskers plots were used to explore data and results using Microsoft excel. Microsoft StatPlus was used for statistical calculations. In terms of statistical analysis, relative risks with 95% confidence intervals and p values were used to compare outcomes between deaths and survivors. Bivariate analysis was used to compare differences in the death and survivor groups; Chi-squared tests for categorical data, T-tests for normally distributed numeric data and the Mann Whitney U test for non-parametric numeric data.

f. Ethical considerations

Folders were reviewed at GSH and never removed from the premises. No written parental consent was obtained as this was a retrospective study and all identifying data was removed. Approval from the Health Sciences Faculty Human Research Ethics Committee (HREC) was obtained (HREC 263/2014).

CHAPTER 3: RESULTS

1. RESULTS

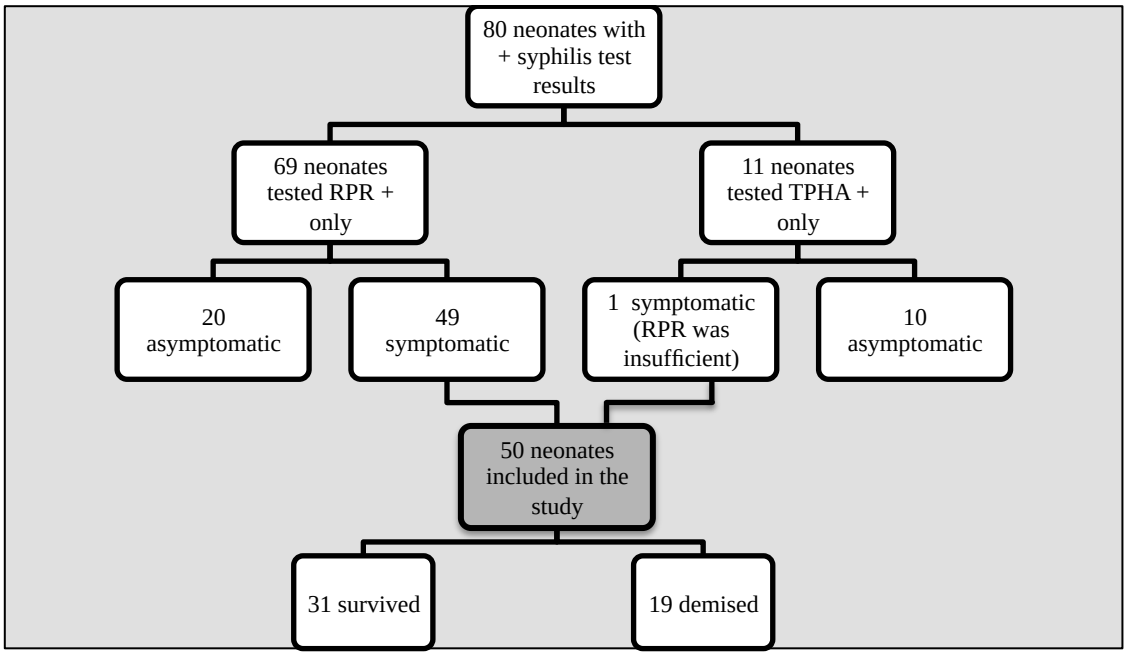


Figure 1. Summary of results

Eighty neonates tested serologically positive for syphilis with either a nontreponemal or treponemal test. The notification and death registers did not yield any additional cases. The folders of all eighty neonates were reviewed which included a set of dichorionic diamniotic twins.

Included neonates: Fifty neonates with positive syphilis serology as well as clinical signs of congenital syphilis were included together with their fifty mothers. Nineteen (38%) of the symptomatic neonates demised (figure 1).

Excluded neonates: Thirty neonates who were noted to be asymptomatic without clinical signs of congenital syphilis, did not meet the case definition, and were therefore excluded. This included one of the twins (the other twin was symptomatic). All thirty neonates did receive a single intramuscular dose of penicillin at delivery.

a. Maternal characteristics

Mothers resided in a wide variety of suburbs with no particular residential area or geographical location demonstrating a higher number of cases. However, forty-five (90%) mothers were coloured and five (10%) were black. The mean maternal age was 24.78 years (+/- 5.5 years). Forty-three (86%) mothers were under the age of thirty. The majority of mothers (60%) were multiparous (figure 2).

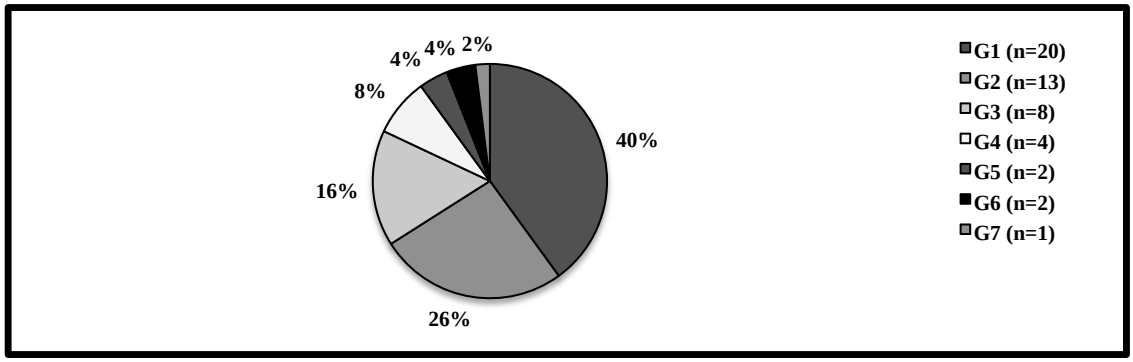


Figure 2. Maternal gravidity (G) (n=50)

Twenty-eight (56%) mothers were unbooked and therefore received no antenatal care. The mean age of the unbooked mothers was 24.8 years (+/- 4.5 years). Ten unbooked mothers were primiparous. One twenty-three year old mother whose current pregnancy was her sixth, and who delivered a term infant, was unbooked. The reasons for being unbooked were not documented for any of the twenty-eight mothers.

Twenty-two (44%) mothers did book. Fifteen of the sixteen mothers who booked and whose gestation at booking was known, booked in the second trimester or later with only one mother booking early at seven weeks gestation (figure 3). The median gestation at booking for these sixteen mothers was thirty weeks (IQR 23.5-31.5 weeks).

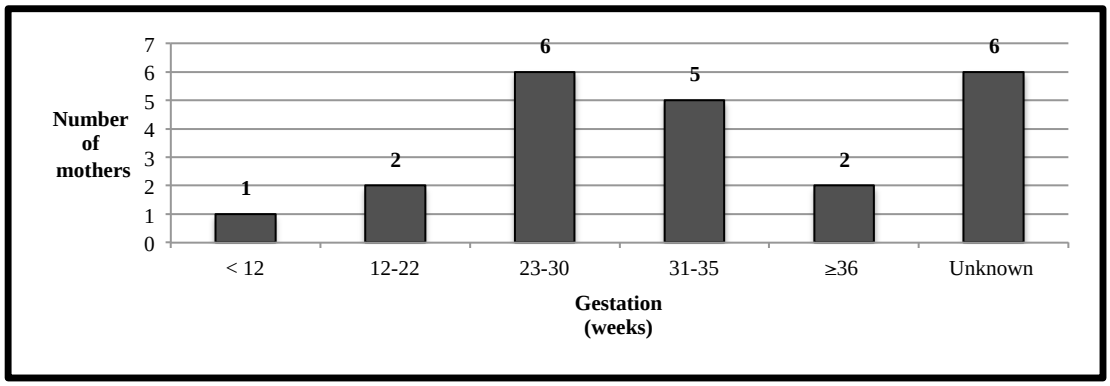


Figure 3. Gestation at booking (n=22)

Twelve mothers (24%) were substance users. Ten used methamphetamines; one was a regular ethanol user and one smoked heroine. All twelve of these mothers were unbooked with the mean age of twenty-five years old (+/- 5.7 years).

Seven mothers were HIV positive with two on recommended antiretroviral therapy (ART) as per protocol at that time. All seven mothers were diagnosed with the current pregnancy. Four of the seven mothers were unbooked. Two mothers, who did book at twenty-two and thirty-one weeks respectively, with CD_4 counts of 422 cells/μL and 298 cells/μL respectively, were on prophylaxis in the form of zidovudine as per the National Department of Health protocol at that time. The third mother with a CD_4 count of 601 cells/μL who did book had an unknown gestation at booking. However it was known to be late and close to the timing of delivery, explaining why neither maternal prophylaxis nor ART was initiated. No other CD_4 or viral load results were known.

i. Maternal test results

Figure 4 summarises the maternal syphilis serological test results.

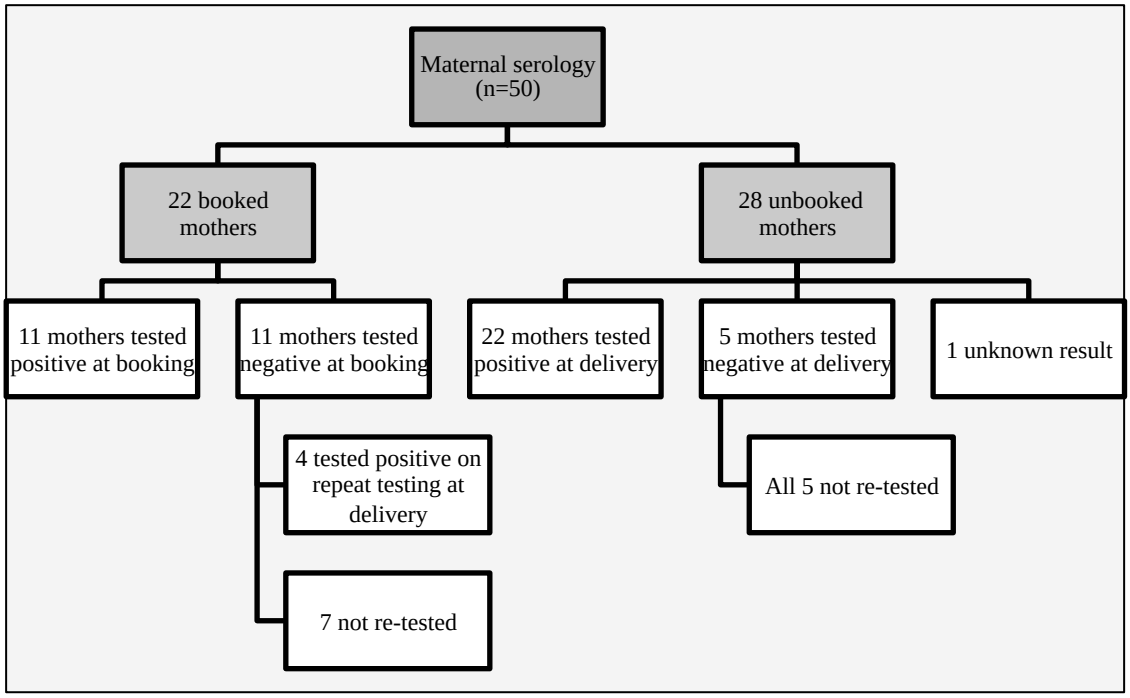


Figure 4: Summary of maternal serological test results

The following table depicts the syphilis serological test results of the twenty-eight unbooked mothers (table 1). One unbooked mother had no syphilis testing performed. In the remaining twenty-seven mothers, testing was performed at the time of delivery.

Tests and titres	**Number (n=28)**
Nontreponemal test	
RPR positive	22
RPR negative	5
RPR unknown	1
RPR titres	
Rapid test (no titre)	13
1:256	1
1:64	5
1:32	1
1:16	2
Treponemal test	
TPHA positive	2
TPHA negative	0
TPHA not done	26
RPR and TPHA positive	2

Table 1. Results of the twenty-eight unbooked mothers

The following table depicts the syphilis serological test results of the twenty-two booked mothers (table 2).

Tests and titres	Number (n=22)
Nontreponemal test	
RPR positive	11
RPR negative	11
RPR titres	
Rapid test (no titre)	2
1:256	4
1:64	2
1:16	2
1:1	1
Treponemal test	
TPHA positive	0
TPHA not done	22

Table 2. Results of the twenty-two booked mothers during pregnancy

Of the eleven mothers who tested negative antenatally, four tested positive on subsequent test results - three at delivery and one post-delivery (figure 4). The duration between negative and positive test results was known for two of the mothers, two and half months between testing for one mother and two weeks for the other. The remaining seven mothers, who tested negative during pregnancy, were presumed infected through the screening of their symptomatic babies who tested positive for syphilis as part of the investigative work up for congenital infection. The gestation at which syphilis testing was negative was known for seven of the eleven mothers with six of the seven testing negative before thirty-two weeks gestation with only one mother undergoing retesting after thirty-two weeks (table 3). In the remaining four booked mothers who tested negative at an unknown gestation antenatally, two had repeat tests at delivery; one was positive on a rapid test and the other mother was positive on a RPR test with a titre of 1:64. The GA of their babies was twenty-eight and thirty-six weeks respectively. Another mother had a documented “possible syphilitic rash” on her antenatal card- however, her test was neither repeated, nor was she treated with penicillin.

Gestation at negative testing in weeks	Was repeat testing performed after 32 weeks gestation?	Result if repeated
7 (n=1)	No	
22 (n=1)	No	
23 (n=1)	Yes at delivery at 33 weeks (Titre 1:16)	Positive
23 (n=1)	No	
24 (n=1)	No	
31 (n=1)	No	
33 (n=1)	Yes at delivery at 35 weeks (Titre 1:64)	Positive

Table 3. Gestation at which maternal syphilis serology was negative (n=7)

Therefore, syphilis was serologically confirmed in thirty-seven (74%) of mothers. However, more than seventy percent of these mothers were diagnosed at delivery with 24% being diagnosed within two weeks of delivery (figure 5).

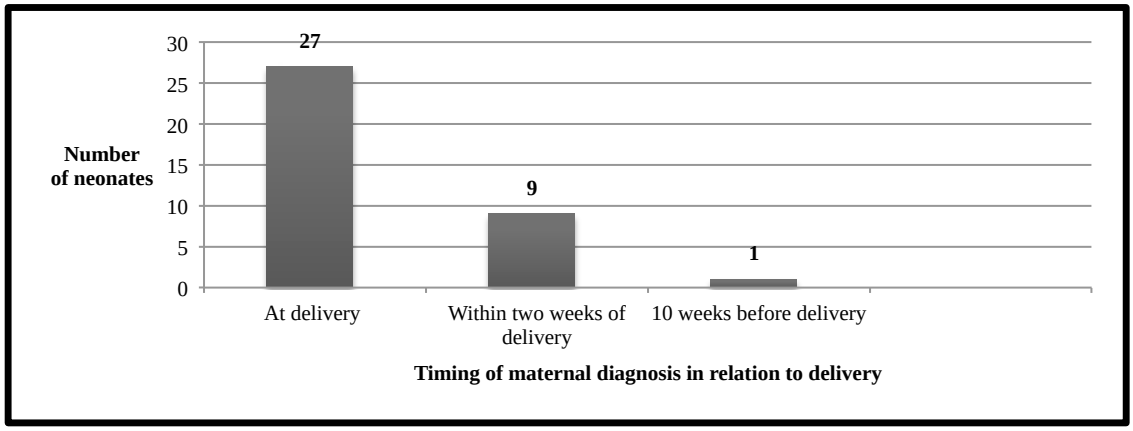


Figure 5. Relationship of positive maternal syphilis diagnosis to delivery (n=37)

ii. Maternal treatment

The overall maternal treatment rate was poor with just one mother being fully treated (figures 6, 7, 8).

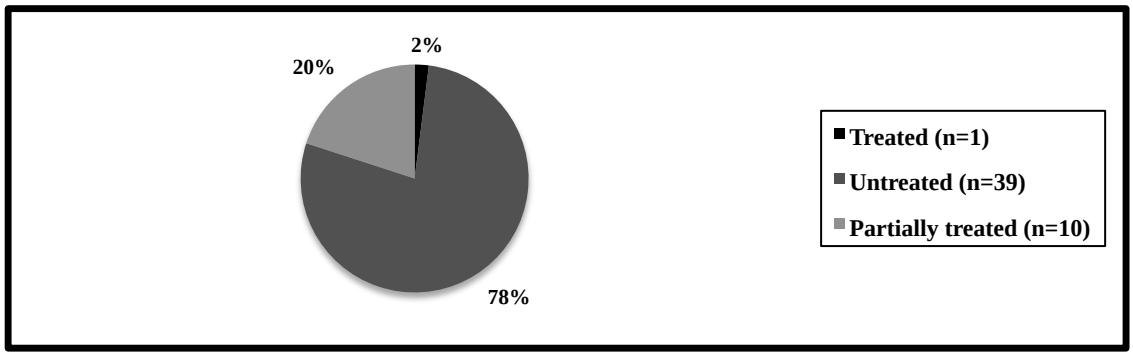


Figure 6. Maternal treatment outcomes (n=50)

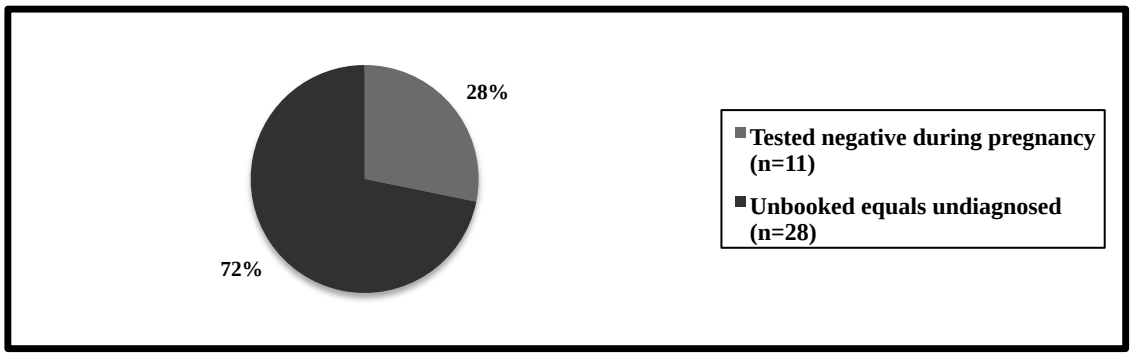


Figure 7. Maternal reasons for being untreated (n=39)

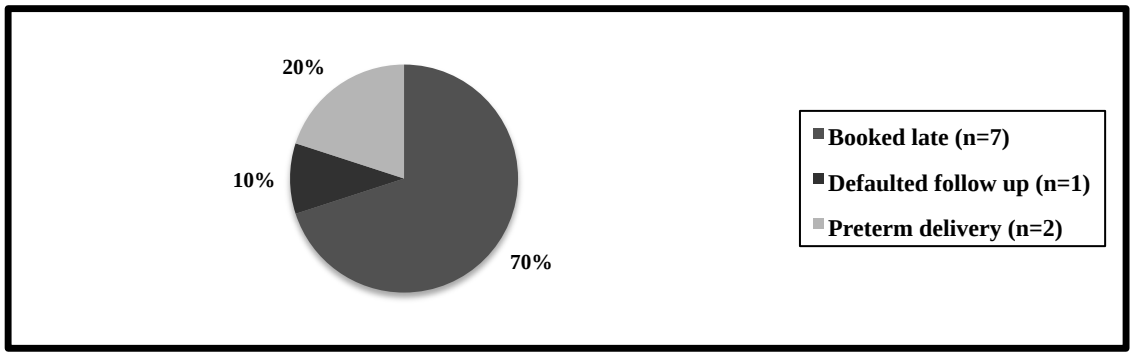


Figure 8. Maternal reasons for being partially treated (n=10)

The seven mothers who booked late were partially treated as they delivered before treatment was completed; two booked at thirty-one weeks gestation and delivered at thirty-three and thirty-four weeks respectively. Two mothers who booked at thirty-two and thirty-three weeks respectively both delivered two weeks later and two mothers who booked at thirty-six and thirty-seven weeks respectively both delivered a week later. The exact gestation at booking was unknown for the seventh mother but it was known to be late in pregnancy as the baby's gestational age was thirty-eight weeks and maternal treatment was not yet completed. The two partially treated mothers with preterm deliveries booked at twenty-four and twenty eight weeks gestation respectively and delivered within a week.

Despite syphilis being serologically confirmed in more than seventy percent of mothers, the inadequate maternal treatment rate can be explained by the timing of maternal diagnosis in relation to delivery (figure 5).

The only mother who tested serologically positive for syphilis and was fully treated was in turn the only mother who booked more than one month before delivery at twenty-two weeks, ten weeks prior to delivery. However her partner was not treated. Unfortunately the other two mothers who booked at seven weeks and twenty-two weeks respectively tested negative for syphilis and did not have repeat testing performed and were therefore untreated.

Partner tracing information was poorly documented. Four partners (8%) were traced and referred for treatment with the rest undocumented.

b. Neonatal characteristics

Twenty-two (44%) neonates were born at GSH (inborn). Of the twenty-eight (56%) outborn neonates three were born at home. The remaining twenty-five were born in district and regional hospitals as well as midwifery obstetric units (MOUs) and referred into GSH. Being outborn had no statistically significant effect on neonatal mortality ($p = 0.83$). Twenty-nine (58%) were male neonates and twenty-one (42%) were female. Thirty-one neonates (62%) were born via normal vertex deliveries with caesarean sections comprising the remaining thirty eight percent.

The median gestational age was thirty-four weeks based on Ballard scoring performed at birth (IQR 31-36.5 weeks) (figure 9). Forty-two (84%) neonates were less than thirty-eight weeks gestational age at birth. The mean birth weight was 1933 grams (+/- 685g) (figure 10).

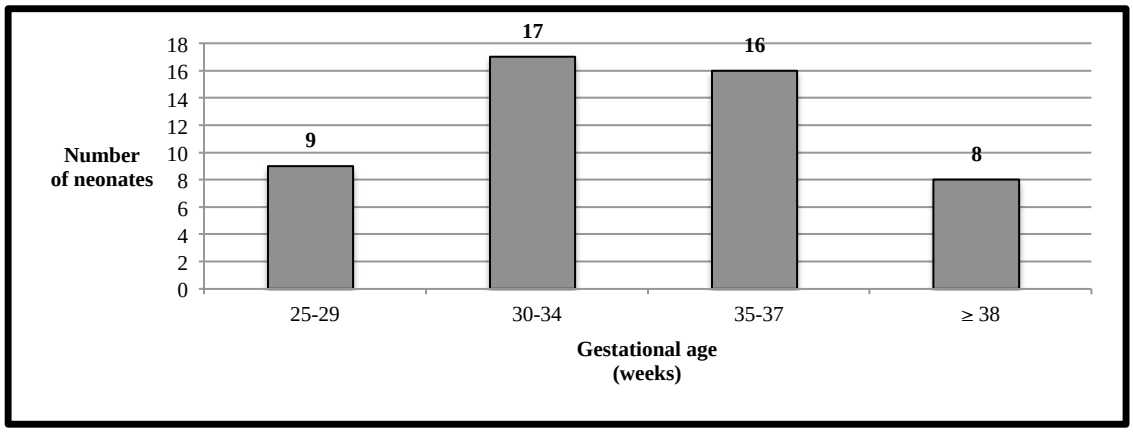


Figure 9. Gestational age (n=50)

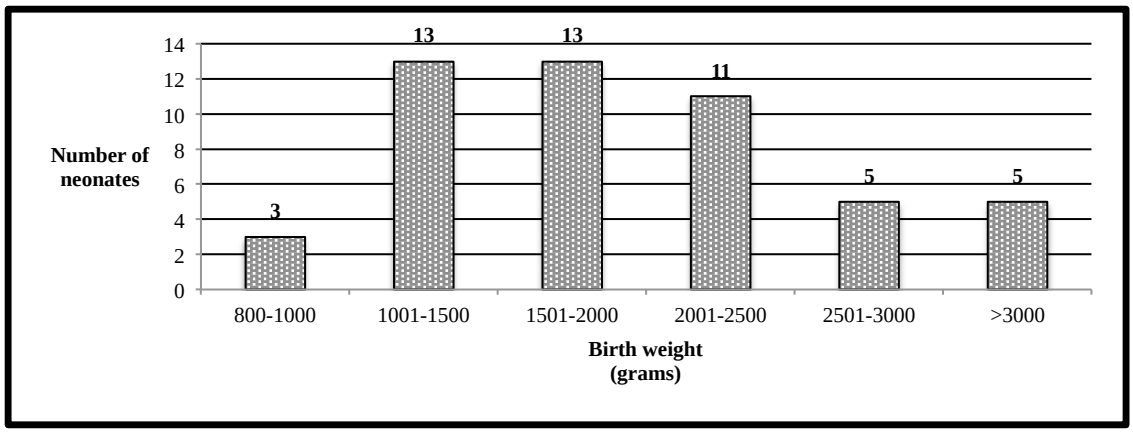


Figure 10. Birth weight (n=50)

Twenty-five neonates (50%) required resuscitation at birth. Ten required basic resuscitation in the form of stimulation and CPAP. Twelve required intubation and seven needed cardiorespiratory resuscitation (CPR). Two neonates, who required intubation and CPR, also required adrenaline. These twenty-five neonates had a mean one minute Apgar score of 3 (+/- 2) and a mean five minute Apgar score of 6 (+/- 2).

i. HIV exposure

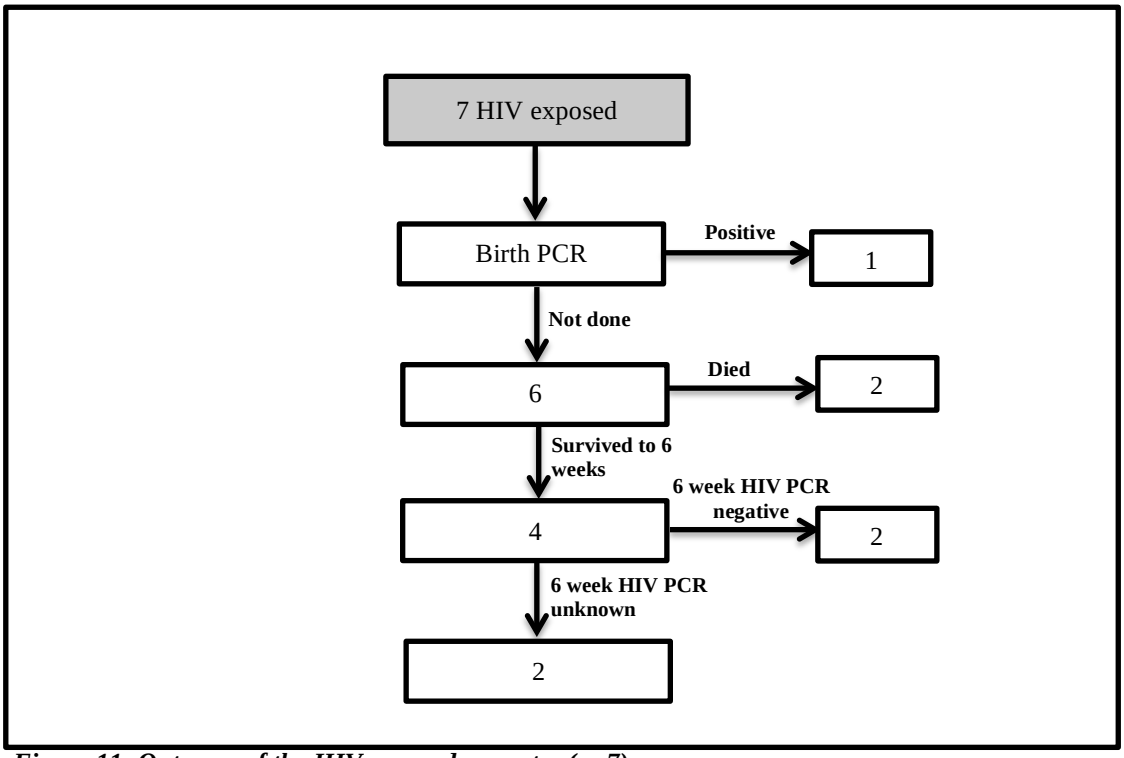


Figure 11: Outcome of the HIV exposed neonates (n=7)

The mean birth weight for the seven HIV exposed neonates was 2154 grams (+/- 893g) with a median gestational age of 33 weeks (IQR 32-36.5 weeks). Gestational age and birth weight were similar in the HIV exposed and HIV unexposed groups (p = 0.9 and p = 0.36 respectively) (figure 12).

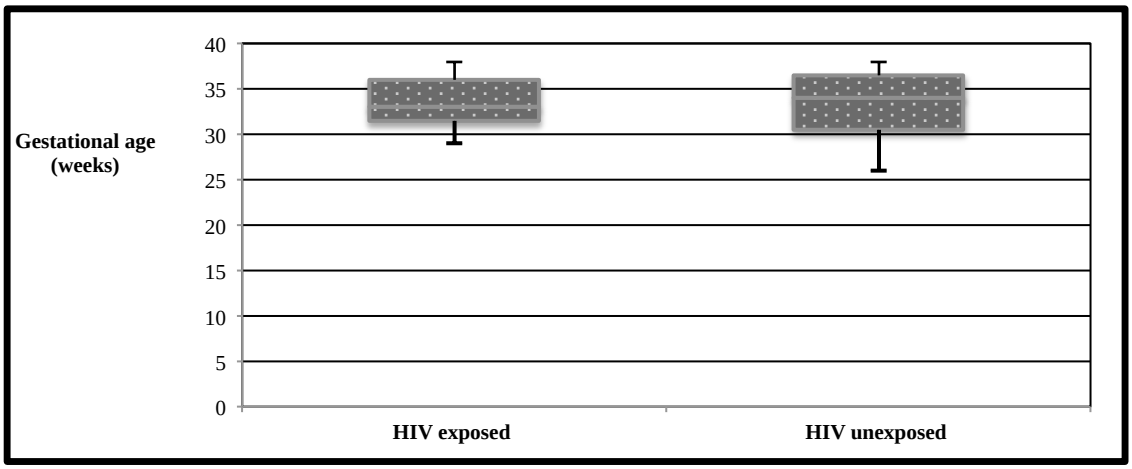


Figure 12. Gestational age comparison between HIV exposed and HIV unexposed neonates

Of the seven HIV exposed neonates, two who were born to unbooked mothers with no maternal ART exposure antenatally, demised on day two and day nine of life respectively. The first neonate was extremely unwell from birth; she was outborn at a MOU with low Apgars of one and three requiring extensive resuscitation. She was premature at thirty-six weeks GA, anaemic (Hb= 9g/dl) and thrombocytopenic (platelets = 44 x 10^9/l) with signs of marked respiratory distress requiring HFOV and inotropes until the day of demise on day two. The second neonate was premature at thirty-three weeks GA born via a caesarean section for cord prolapse; she had a birth CRP of 154 mg/l with signs of respiratory distress and also required HFOV and inotropes until the day of demise. All seven neonates received prophylaxis either in the form of single dose nevirapine (n=2) or dual prophylaxis with nevirapine and zidovudine (n=5) as per the unit protocol at the time. One neonate, born to an unbooked mother with no ART exposure antenatally was infected, diagnosed on a forty eight hour HIV PCR test and initiated on ART nineteen days post delivery. Based on the timing of diagnosis this was likely an in-utero transmission. Two neonates were known to be negative on a six week HIV PCR and two had unknown HIV PCR results at six weeks (figure 11).

ii. Clinical signs

Figure 13 demonstrates the clinical signs present in the symptomatic neonates as documented, by the attending physician, on initial presentation. Oedema was presumed to denote body swelling with interstitial fluid accumulation in the absence of compartmental fluid collections. Hydrops fetalis implied fluid collection in two or more sites such as pleural effusions, pericardial effusions or ascites and was by definition non-immune in origin. Petechiae, jaundice and pallor were clinical assessments of presumed thrombocytopenia, elevated bilirubin levels and anaemia respectively. Intrauterine growth restriction (IUGR) referred to those neonates whose birth weight and/or length and head circumference plotted below the third centile for gestational age. Hepatosplenomegaly (HSM) referred to any documented palpable liver AND spleen. Respiratory distress was defined as clinical signs of distress such as tachypnoea and inter/subcostal recessions together with the need for supplemental oxygen in any form within twenty-four hours of birth.

Shock was a clinical assessment based on signs of poor perfusion with supporting evidence from blood pressure measurements and arterial blood gases. Murmurs presumed to be a patent ductus arteriosus (PDA) were usually clinical assessments. Persistent pulmonary hypertension of the newborn (PPHN) was defined as pre and post ductal oxygen saturation differentials of more than ten percent. Four neonates had seizures; two were term neonates with electrical seizures diagnosed on a cerebral function monitor (one demised and one survived). The remaining two neonates with clinical and electrical seizures both demised; one was term with severe meconium aspiration syndrome and the other was a septic preterm neonate with birth asphyxia, requiring intubation and CPR at delivery. None of the four neonates had a lumbar puncture performed.

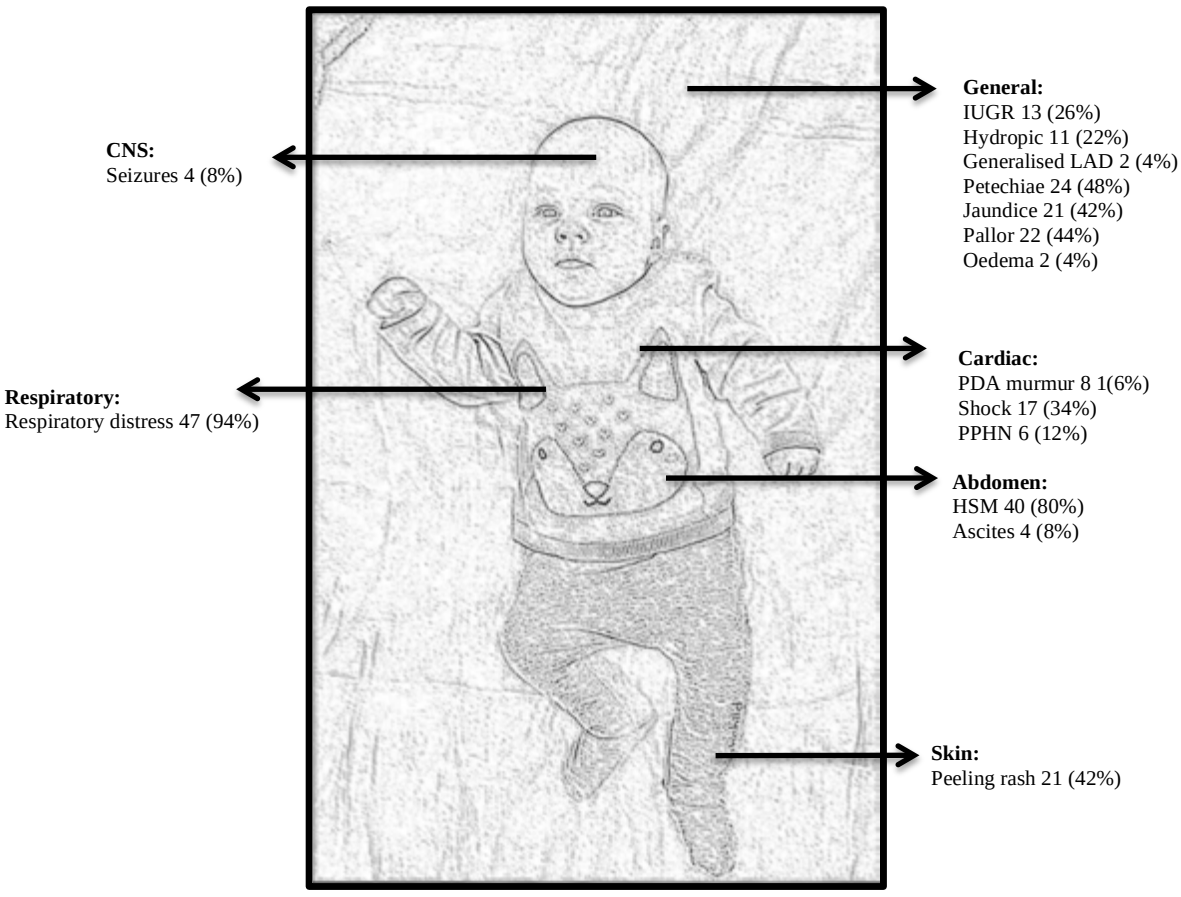


Figure 13. Clinical signs in the fifty symptomatic neonates

Respiratory distress was the commonest clinical sign. Figure 14 depicts the outcome in these neonates comparing premature neonates and term neonates.

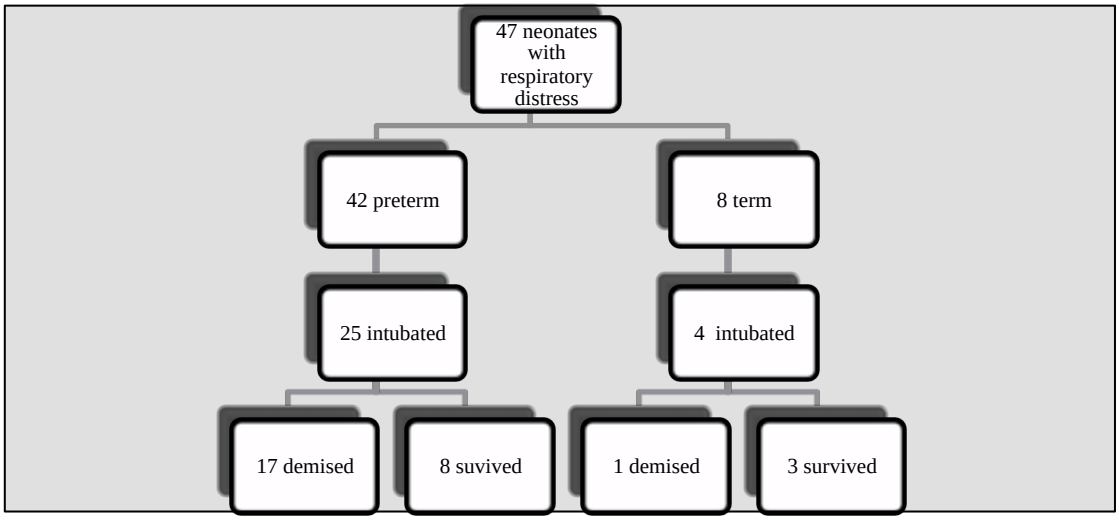


Figure 14. Outcome of neonates with respiratory distress (n=47)

There were more preterm neonates with respiratory distress than term neonates. Premature neonates were not significantly more likely to be intubated than term neonates ([RR], 1.2; 95% CI 0.5-2.5). However the need for intubation in preterm neonates had a statistically significant effect on mortality ([RR], 11.6; 95% CI 1.7-78.9).

Placental weights were known for thirty-seven (74%) of the fifty symptomatic neonates and were plotted on the placenta for birth weight graph created by Malan et al (figure 15).[19] A large number of placentae were noted to be relatively heavier than birth weight and plotted on or above the 90th centile (n=27). Of the neonates weighing more than 2 kg, all but two plotted above the 90th centile, in keeping with the findings of Malan et al.

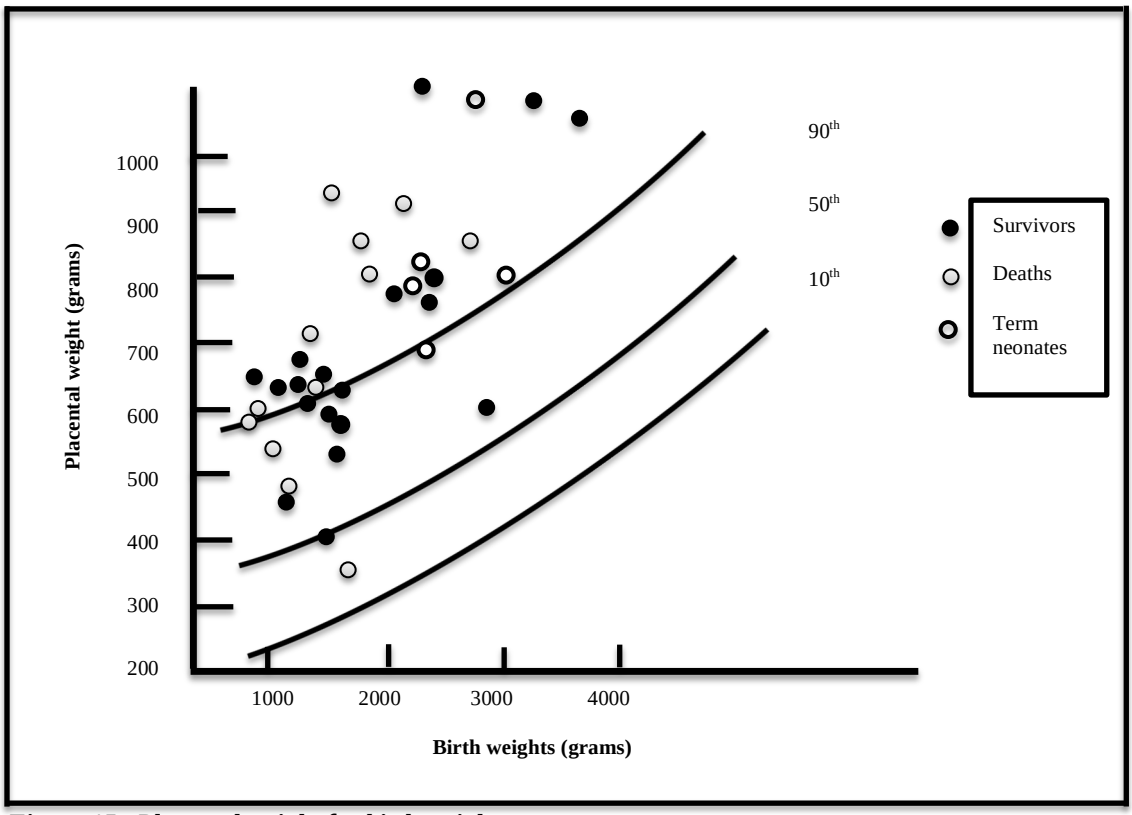
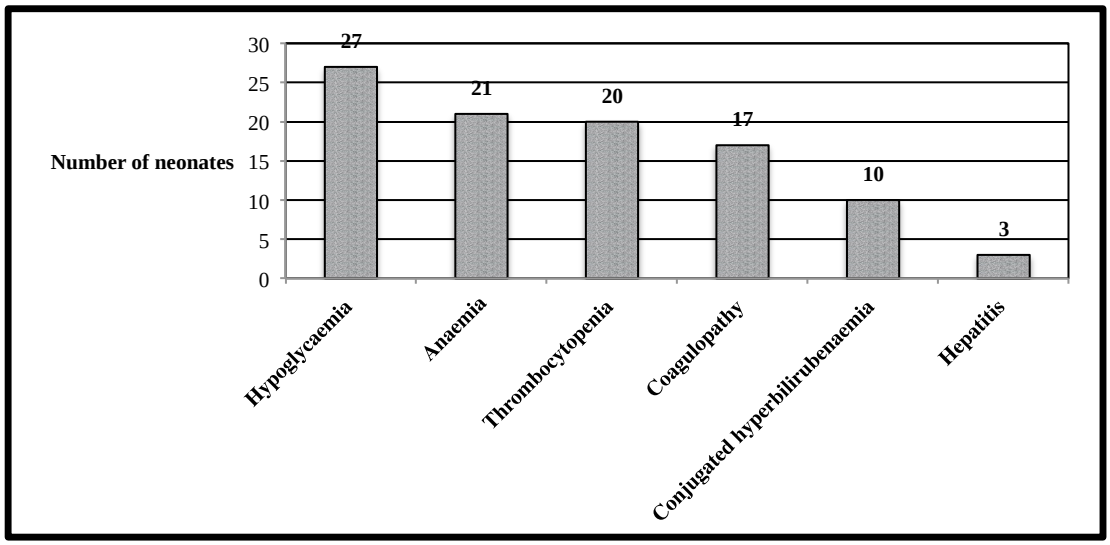


Figure 15. Placental weight for birth weight

iii. Laboratory investigations

One acutely unwell neonate had no serological test results other than a positive RPR for syphilis. Other blood tests taken were insufficient, and due to demise on day one of life, repeat testing could not be performed. All other forty-nine neonates had a FBC and CRP performed. Twenty-one neonates were anaemic and the median haemoglobin at birth for these neonates was 9.5 g/dl (IQR 1.8-10.5 g/dl). Twenty neonates were thrombocytopenic at birth and the median platelet count for these neonates was 27 x 10^9/l (IQR 16-37.5 x10^9/l). Figure 16 depicts the commonest laboratory derangements noted.



Definitions (pertaining to figure 16)	
Hypoglycaemia (within 24 hours of birth)	HGT < 2.6 g/dl
Anaemia (within 24 hours of birth)	Hb < 11 g/dl
Thrombocytopenia (within 24 hours of birth)	Platelets < 150 $x10^9$/L
Coagulopathy (within 24 hours of birth)	Deranged clotting profile (Prolonged INR/PTT/ low fibrinogen)
Conjugated hyperbilirubenaemia	Conjugated bilirubin > 20% of total bilirubin
Hepatitis	Transaminitis (AST /ALT > 40 U/l)

Figure 16. Abnormal laboratory investigations

The commonest laboratory derangement was hypoglycaemia (54%). Of these twenty-seven neonates, twelve had a single hypoglycaemic episode post delivery, which resolved following a ten percent dextrose bolus. Fifteen neonates had severe hypoglycaemia: four were managed with a single dose of glucagon and hydrocortisone and eleven required a dextrose cocktail to maintain euglycaemia. Six of these eleven neonates required a 12.5% cocktail, two required a 15% cocktail and three required a 20% cocktail.

iv. Radiological and other special investigations

Thirty-three (66%) neonates had long bone x-rays performed. Of these thirty-three, eighteen neonates (55%) had long bone changes in keeping with congenital syphilis. These included metaphyseal translucent bands, periosteal reactions, and the "ratbitten" appearance of "Wimberger sign". The bones commonly affected were the tibia, femur and the humerus.

Thirty-two neonates had cranial ultrasound scans performed of which twenty-three (72%) where abnormal in varying degrees (table 4). Abnormalities in the neonates who demised were all noted within the first three days of life. Cranial ultrasound scan findings in the eight neonates who survived were all noted in the first week of life. "Cerebral oedema" is often overcalled or misdiagnosed. Periventricular flares (PV) and Grade 1 and 2 IVH's are considered insignificant and all surviving neonates with these abnormalities had no neurological sequelae on discharge.

Findings	Total number (n=23)	Survivors (n=8)	Deaths (n=15)
Mild changes	**9**	**5**	**4**
PV flares only	1	1	0
Grade 1 or 2 IVH's	8	4	4
Moderate/uncertain changes	**7**	**3**	**4**
Grade 3 IVH (unilateral)	2	2	0
"Cerebral oedema" only	5	1	4
Severe changes	**7**	**0**	**7**
Bleeds with PVL	1	0	1
Bleeds with cortical infarcts and PVL	1	0	1
Bilateral grade 4 IVH's with hydrocephalus and PVL	2	0	2
Bleeds with dilated ventricles	3	0	3

Table 4: Cranial ultrasound scan findings

No placentae were sent for histology.

v. Sepsis

Forty-nine neonates (98%) who were treated with antibiotics at birth had a septic screen performed, including a blood culture. Forty of these forty-nine neonates (82%) had a raised CRP of more than ten within forty-eight hours of birth. The median CRP was 62.95 mg/l (IQR 38.2 - 106.6 mg/l). Six neonates (12%) had culture positive sepsis, more than seventy-two hours after birth, and therefore presumed to have hospital acquired infections. One neonate who subsequently demised on day nineteen of life had two positive blood cultures: Extended spectrum beta-lactamase (ESBL) Klebsiella pneumonia on day six and Candida parapsilosis on day 12. One neonate with ESBL Klebsiella pneumonia sepsis demised on day twenty-one of life (figure 17).

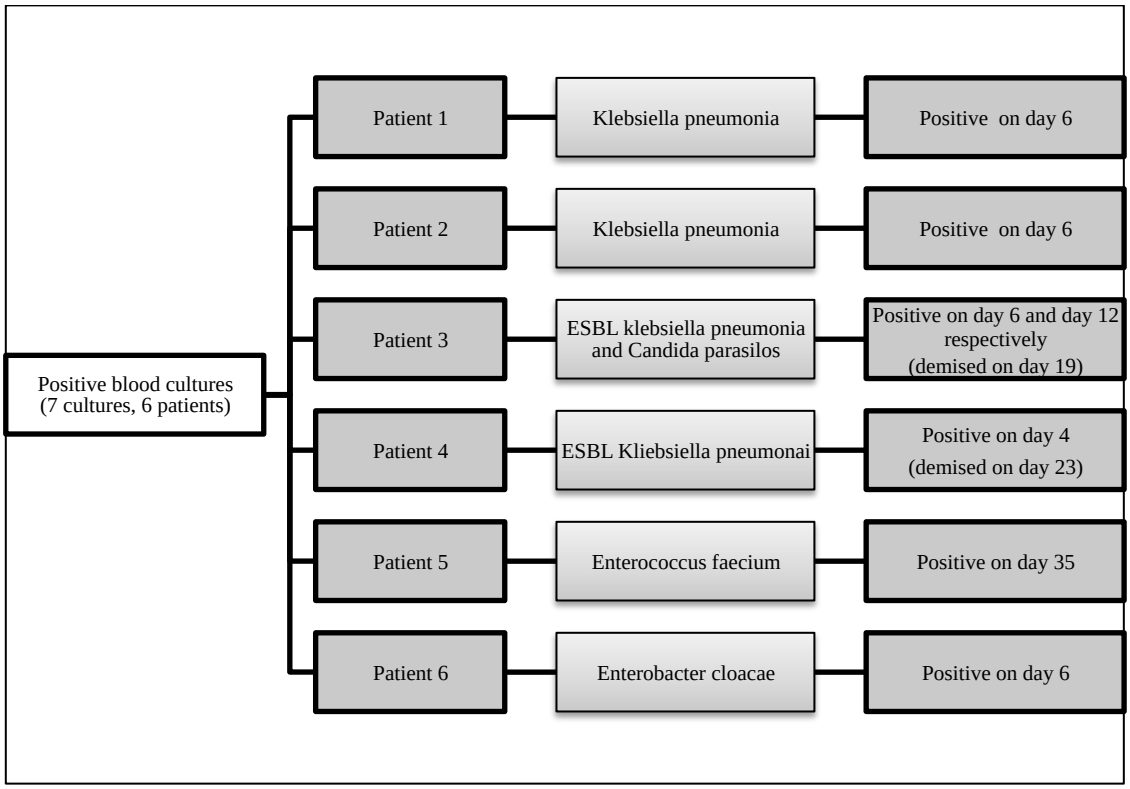


Figure 17. Positive blood cultures

vi. Neonatal serology

The following table depicts the neonatal serologic test results (table 5).

Tests and titres	Number (n=50)
Nontreponemal test	
RPR positive	49
RPR insufficient	1
RPR titres	
1:256	6
1:128	1
1:64	17
1:16	13
1:4	8
1:1	3
Unknown	1
Treponemal tests	
TPHA positive	16
TPHA not done	34
RPR and TPHA positive	15

Table 5. Results of neonatal serology

RPR titres were known in twenty mothers and their babies. Five (25%) of these neonates had titres at least four times or more than their mothers (figure 18).

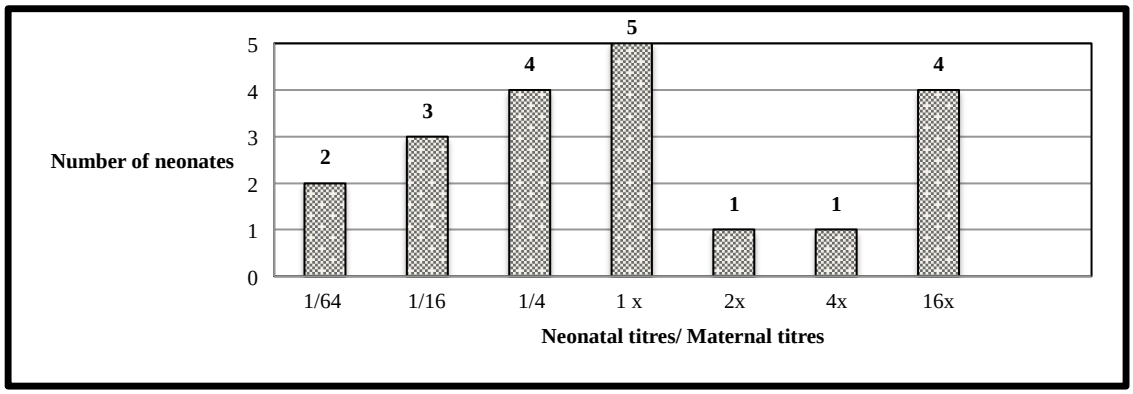


Figure 18. Relationship of neonatal titres to maternal titres (n=20)

vii. Level of care required

The sickest neonates i.e. those requiring intubation and/or inotropes were admitted into ICU. High care was reserved for those unwell neonates who required support in the form of CPAP but had no other features of severity warranting ICU admission. The low intensity unit was for well neonates who required admission for monitoring, observation and/or antibiotics (figure 19).

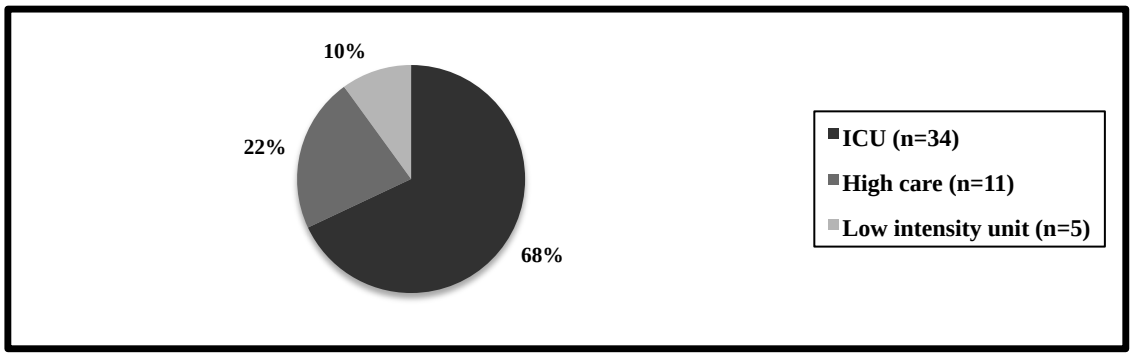


Figure 19. Admission area after delivery (n=50)

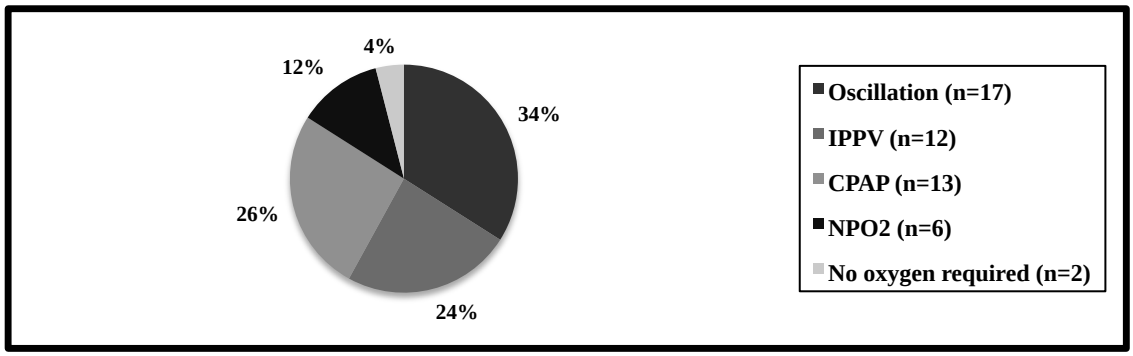


Figure 20. Maximum mode of respiratory support required from birth (n=50)

Figure 20 depicts the maximum mode of respiration support required from birth. The median duration of ventilation for the eleven survivors was 4.5 days (IQR 4-6.5 days). Nineteen neonates (38%) required inotropes; sixteen for more than twenty-four hours and three for less than twenty-four hours.

Twenty-five neonates (50%) required blood products with eighteen of these twenty-five neonates requiring multiple products (figure 21). One neonate did not receive products due to limitation of care.

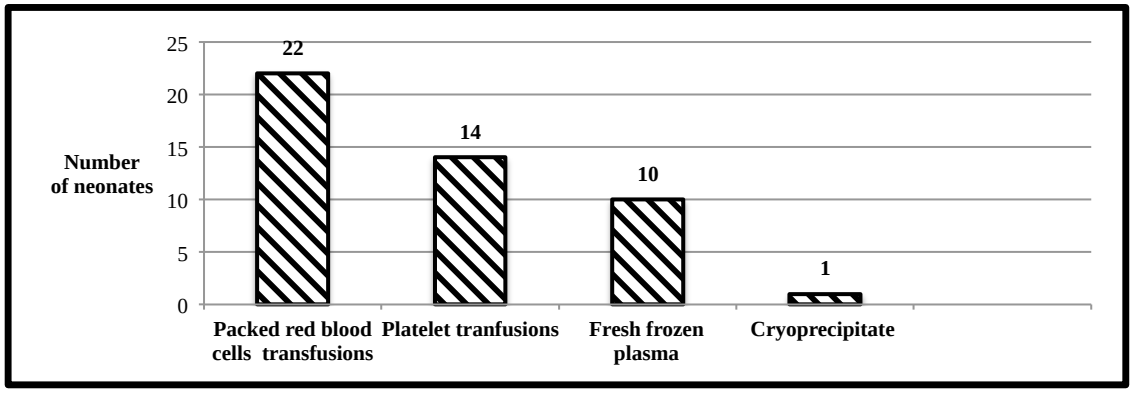


Figure 21. Blood products transfused (n=25)

Three neonates were referred to district hospitals for ongoing care when they were stable and off respiratory support. The mean duration of hospital stay for the seven term neonates who survived and were discharged from GSH was 18.5 days (+/-7.5 days).

viii. Antibiotics

Forty-eight neonates (96%) were treated appropriately. All neonates who survived for more than ten days received a full ten day course of intravenous penicillin as per the unit protocol. One symptomatic neonate who demised on day twenty of life, with a RPR titre equal to the maternal titre of 1:64, was inappropriately treated with a single dose of intramuscular penicillin. This neonate's mother had clinical signs of secondary syphilis at delivery (condylomata lata). Another symptomatic neonate was treated with only seven days of penicillin. The course was written up for ten days but inadvertently stopped on the prescription chart after seven days. The fifteen neonates who survived for less than ten days were treated with penicillin until the day of demise.

Twenty-seven neonates (54%) were notified.

ix. Outcomes and follow-up

Figure 22 depicts the outcome of the fifty cases.

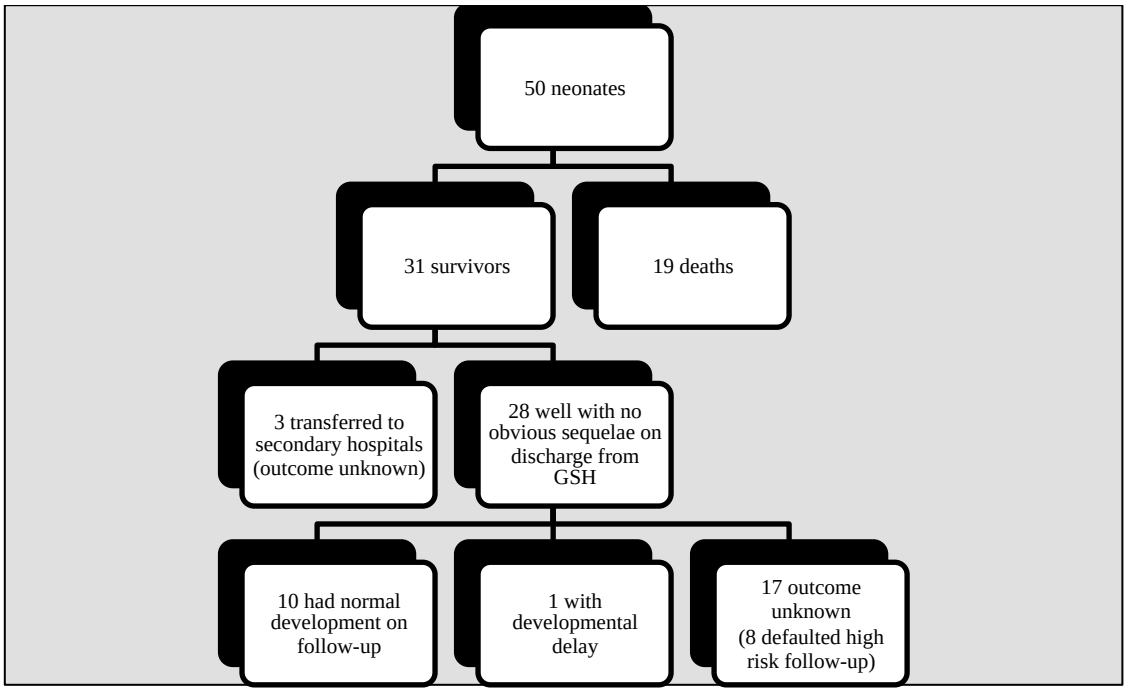


Figure 22: Outcome of the fifty cases

Medium term neurodevelopmental outcome was known for eleven of the thirty-one survivors:

1. Ten had documented normal development:
    - Three neonates on formal infant neurodevelopmental assessments at twenty weeks corrected GA
        - One of which had a unilateral grade 3 IVH during admission
    - One at two months
    - One at three months
    - Two at four months
    - One at thirteen months
    - One at twenty months
    - One at thirty one months

2. The neonate who was diagnosed HIV positive on a birth PCR had development delay on follow-up at three months.

The second neonate with a unilateral grade three IVH was transferred to a secondary level hospital on day eight of life and lost to follow-up. The term neonate with seizures was also lost to follow-up.

Despite the recommendation for repeat testing at three months, no documentation or lab evidence of follow up serological testing for syphilis was found.

c. Deaths

i. General characteristics

Nineteen neonates demised (38%). In this group, thirteen mothers (68%) were unbooked and eleven mothers (58%) were under the age of twenty-five. However, neonates born to unbooked mothers, did not have a statistically significant increased risk for death although there was a trend towards this ([RR], 1.7; CI 0.7-3.8). No mother in this group of nineteen was fully treated with sixteen (84%) mothers untreated; thirteen as a result of being unbooked and three who tested negative at booking and had no repeat testing performed after thirty-two weeks. Three mothers were partially treated as a result of preterm delivery (n=1) and late booking (n=2). One twenty-eight year old, unbooked mother, who delivered a preterm baby at thirty-two weeks GA, had a previous intra-uterine death (IUD) secondary to syphilis confirmed on histology two years prior to the current pregnancy. Her baby subsequently demised on day three of life. It was unknown whether she or her partner was treated in the previous pregnancy. Higher maternal serological titres of more than 1:64 were not associated with a significantly increased risk of neonatal mortality ([RR], 1.1; 95% CI 0.4-3.1). No partner tracing was documented in this group.

There were no statistically significant differences between the deaths and survivors in terms of gestational age ($p = 0.15$), birth weight ($p = 0.08$) or maternal age ($p = 0.51$). The median gestational age of the neonates who demised was thirty-three weeks (IQR 30-36 weeks) and the mean birth weight was 1717 grams (+/- 608 grams) (figures 23, 24). Prematurity (GA < 38 weeks) had no statistically significant effect on mortality ([RR], 3.4; 95% CI, 0.5-22); neither did a low birth weight (< 2kg) ([RR], 1.6; 95% CI 0.7-4.4). Our study population had more male than female neonates; however gender had no statistically significant effect on mortality ([RR], 1.2; 95% CI 0.5-2.6).

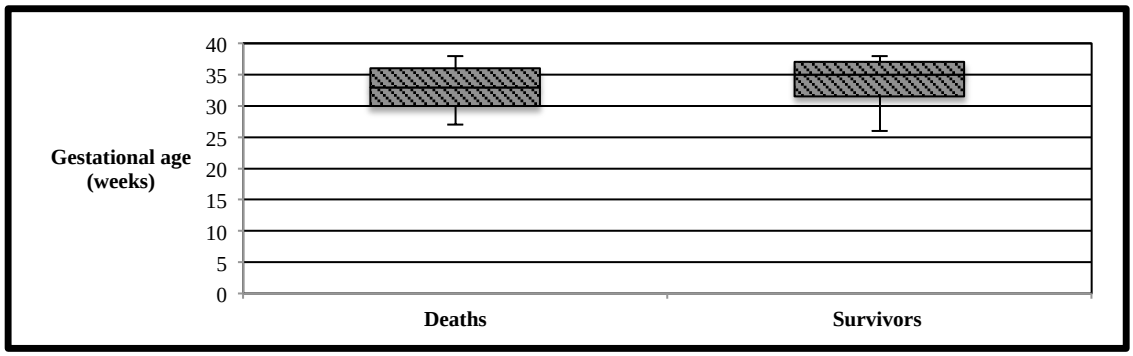


Figure 23. Box and whiskers plot showing gestational age comparison between deaths and survivors

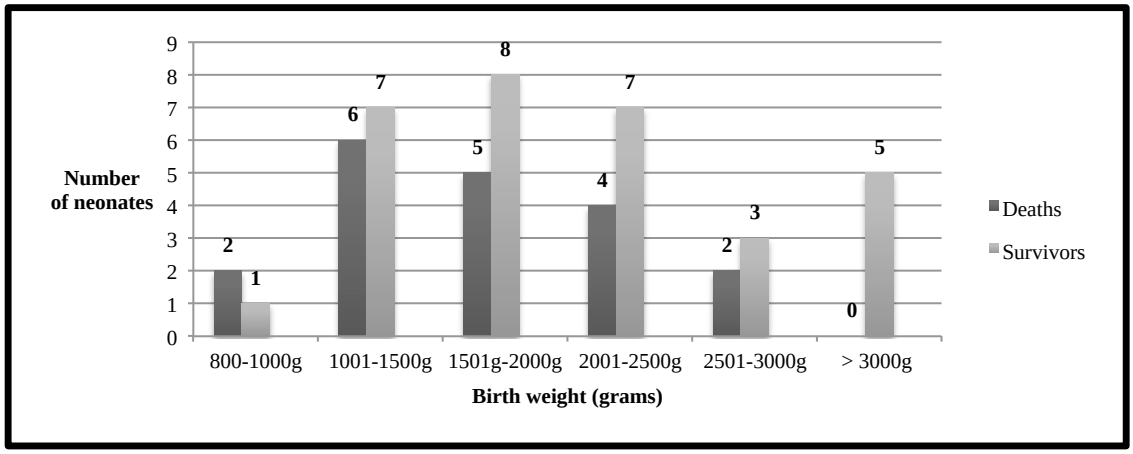


Figure 24. Comparison of birth weights in deaths and survivors

ii. Clinical signs

The five most common clinical signs in the neonates who demised were:

1. Respiratory distress 19 (100%)
2. HSM 15 (79%)
3. Petechiae 13 (68%)
4. Pallor 12 (63%)
5. Shock (58%)

Overall, the neonates who demised had lower median platelet and haemoglobin counts at delivery together with a higher median birth CRP. However these were not statistically significant (p=0.91 and p=0.45 p = 0.87 respectively) (figures 25, 26, 27). Eleven (58%) of the nineteen neonates who demised had a haemoglobin level less than 11 g/dl at birth, however although there was a strong trend toward mortality, it too was not statistically significant (p = 0.07).

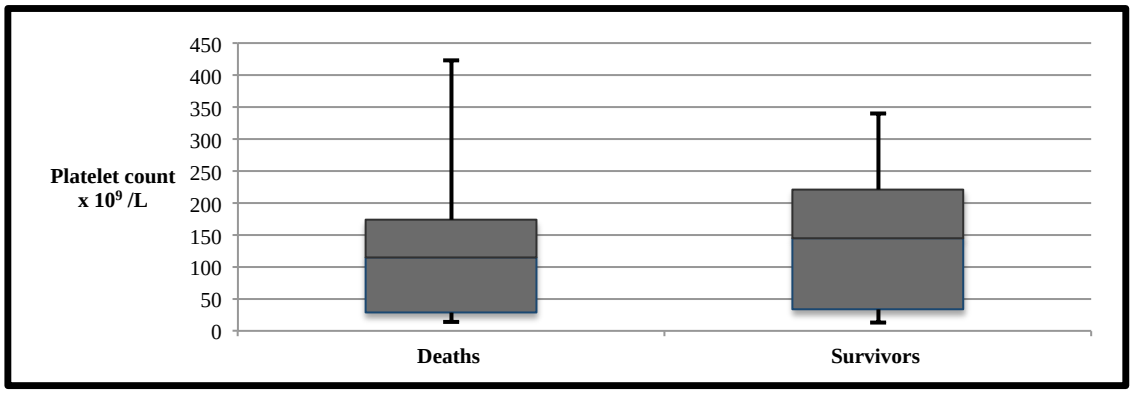


Figure 25: Platelet counts at birth in deaths (n=18) and survivors (n=31

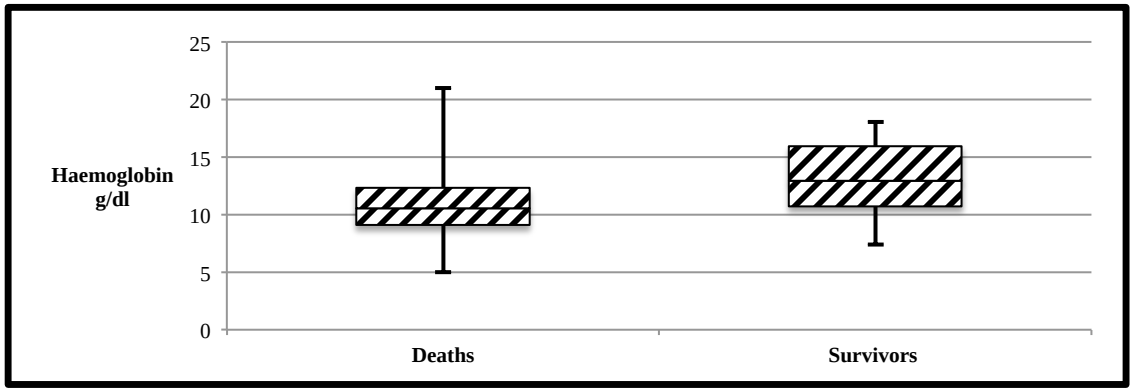


Figure 26: Haemoglobin levels at birth in deaths (n=18) and survivors (n=31)

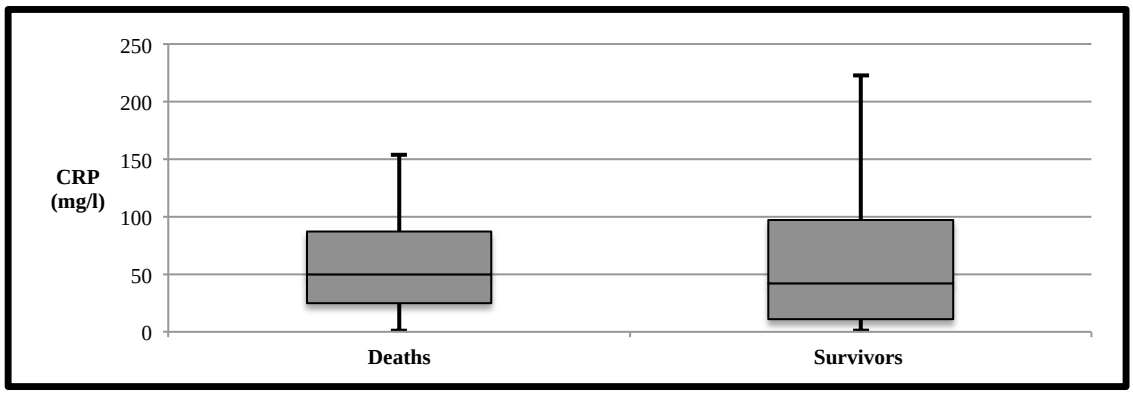


Figure 27: CRP results within 48 hours of birth in deaths (n=18) and survivors (n=31)

iii. Level of care and risk factors for death

Blood gases obtained from the umbilical cord at delivery were known for eleven of the neonates who demised; the mean pH of which was 7.0 (+/-SD 0.16). All nineteen neonates who demised required resuscitation at birth. Thirteen neonates (68%) required intubation. Five in addition, required CPR and two required CPR and adrenaline. Neonates with a low one minute Apgar score of less than five were 3.5 times more likely to demise than neonates with a one minute Apgar score of five or more ([RR], 3.5; 95% CI 1.6-7.7). Following resuscitation, a five minute Apgar score that remained at five or less than five was associated with an increased risk of mortality (table 6).

Figure 28 demonstrates the comparative level of care required in the deaths and survivors. Eighteen out of nineteen neonates who demised, required admission to ICU. The need for intubation within twenty-four hours of birth was associated with an increased risk of mortality (p=0.009) as was the need for inotropes (p=0.006). In the eighteen neonates who demised, the median duration of ventilation was three days (IQR 2-5 days). The median day of death was 4.5 days (Range 1-24 days).

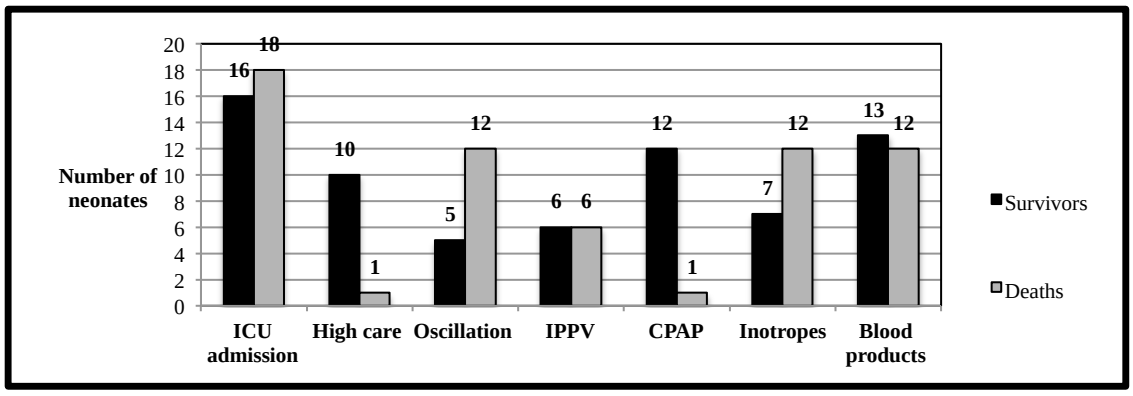


Figure 28. Level of care in deaths and survivors

Hypoglycaemia was a common clinical finding amongst the neonates who demised (63%); however the relative risk of death was not statistically significant. Coagulopathy at birth, requiring blood products was associated with a statistically significant increased risk of mortality as were moderate to severely abnormal cranial ultrasound scan findings (table 6).

Investigation	Relative risk of death	Significance	
Hydrops fetalis	2.6	95% CI 1.4-4.8	P=0.003
Low 1 minute Apgar score < 5	3.4	95% CI 1.6-7.7	P=0.001
Low 5 minute Apgar ≤ 5	2.9	95% CI 1.5-5.3	P= 0.001
Coagulopathy	2.2	95% CI 1.1-4.3	P= 0.03
Abnormal cranial ultrasound scan (excludes PV flares and mild IVH's)	3.5	95% CI 1.8-6.9	P = 0.0002
Hypoglycaemia (HGT < 2.6 g/dl)	1.4	95% CI 0.7-3.1	P= 0.32
Thrombocytopenia (Platelet count < 150 x 10^9/l)	1.1	95% CI 0.5-2.2	P= 0.81
Raised CRP > 10mg/l	1.5	95% CI 0.5-2.3	P=0.43

Table 6. Risk factors for death

Hydropic neonates

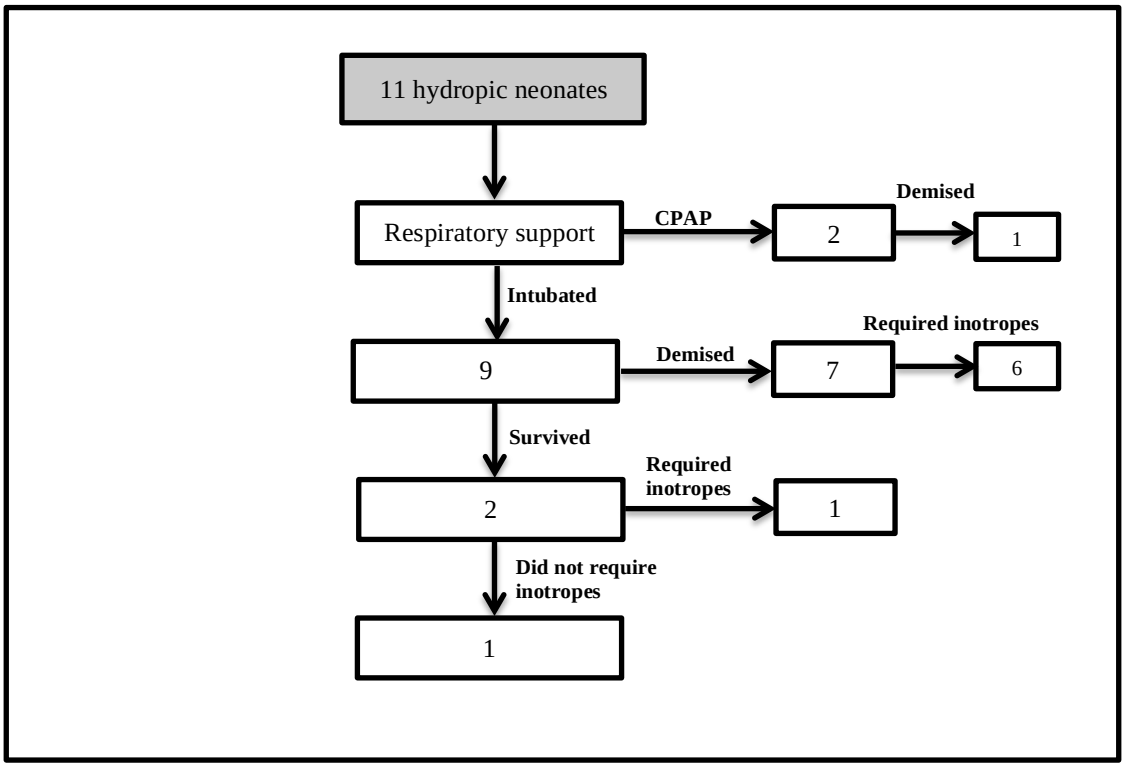


Figure 29. Management of the eleven hydropic neonates

There were a total of eleven hydropic neonates of which eight demised. Hydropic neonates had an increased risk of mortality ([RR], 2.6; 95% CI 1.4-4.8), requiring intubation and inotropes. All eight neonates who demised required resuscitation at birth. Seven of these eight neonates were intubated, six of which also required inotropes with only one hydropic neonate who demised managed with CPAP (figure 29). One extremely unwell hydropic neonate was ventilated for nineteen days until the day of demise.

CHAPTER 4: DISCUSSION

1. DISCUSSION

a. Incidence

In 1999, the World Health Organization (WHO) approximated that 12 million new cases of syphilis occur worldwide each year with one third of new cases occurring in Africa alone.[61] Almost a decade later, in 2008, the WHO estimated that globally, 1.86 million pregnant women per year are infected with syphilis and that a large proportion are inadequately or poorly treated.[56] With a presumed 45-70% probability of vertical transmission, the estimated number of cases of congenital syphilis ranges between 700 000 and 1.5 million annually accounting for an estimated 420 000 to 600 000 perinatal deaths through stillbirths and neonatal deaths.[4] Developing countries bear the brunt of the infections with 3-15% of women in their reproductive age infected with syphilis.[62] In Sub-Saharan Africa a figure of 10% is quoted, with congenital syphilis being the most common cause of perinatal mortality, accounting for 26% of stillbirths and 11% of neonatal deaths.[5,63]

Despite the initiation and funding of a South African National Syphilis Screening Programme by the Department of Health in the early 1980s, syphilis prevalence in South Africa is not declining. According to the 2011 National Antenatal Sentinel HIV & Syphilis Prevalence Survey, South Africa's syphilis prevalence rate has shown a 0.1 % increase from 1.5 % (95% CI 1.4-1.7) in 2010 to 1.6% (95% CI 1.5-1.8) in 2011. Among pregnant women attending antenatal clinics, there has been an overall decrease in syphilis prevalence from 11.2% in 1997 to 1.6% in 2011.[5,64] However, the syphilis prevalence rate among antenatal women in the Western Cape has increased from 1.2% in 2010 to 1.6% in 2011.[64]

Data from the Perinatal Problem Identification Programme (PPIP) parallels this, showing a steady increase in the percentage of births in serologically positive pregnant mothers in the Metro West area of the Western Cape (GSH, Mowbray Maternity Hospital, New Somerset Hospital and MOUs to these drainage areas) with 0.8% of births occurring in serologically positive mothers in 2011, 0.9 % in 2012, and 1.2% in 2013. Perinatal deaths from congenital syphilis in the Metro West area also showed an increase between 2011 and 2013, of 3% to 3.5 % respectively.[65]

Our study showed a symptomatic congenital syphilis incidence rate of 0.13% (1.3 per 1000 live births), taking into account inborn deliveries only and the 5500 deliveries per annum at GSH. Compared to international studies in developed countries, this incidence rate is more than double the WHO threshold for elimination of congenital syphilis of 0.5 per 1000 live births.[46,48] However, compared to studies in other socioeconomically disadvantaged countries such as Brazil and the Colombian Pacific Coast, our rate is lower.[43,49] Recent South African statistics pertaining to congenital syphilis is limited. One South African study quoted a congenital syphilis rate of 10% amongst stillbirths.[44] Taking into account the number of notified cases of congenital syphilis cases per annum in the Western Cape, a decreasing trend is noted: 127 in 1998, 66 in 1999 and 47 in 2000.[66] Considering that there were 60 313 recorded live births in the Western Cape in 2000, the congenital syphilis incidence rate was 0.08%, which is lower than our study rate. However, as only 27 neonates (54%) in our study were notified, underreporting, rather than an actual reduction in congenital syphilis cases, may be a contributing factor to the lower congenital syphilis rate in 2000. Provincial rates for congenital syphilis are lacking; a prevalence rate of 0.7% was quoted in both Baragwanath and Kalafong Hospitals in the province of Gauteng in the early nineties.[43]

b. Mothers

i. General characteristics

In our study the majority of mothers with syphilis were young and primiparous. Coloured mothers were predominant (n=45) with a small number of black mothers (n=5) and no Caucasian mothers. This finding of predominantly Coloured mothers was unexpected and could not be fully explained by the geographical locations or drainage areas that GSH serves, as the percentage of Coloured and Black mothers utilizing these services are almost equal (fifty-two percent are Black and forty-six percent are Coloured). The absence of Caucasian mothers may be explained by the small percentage (2%) that utilize GSH services.[67] Study populations of predominantly young, non-Caucasian mothers was noted in Canada, USA and Brazil and may be a consequence of lower socio-economic status in these population groups.[49,52,53] However there were no studies identified, either internationally or in South Africa, which commented on a higher prevalence of syphilis in the Coloured population specifically. Similarly the 2011 South African National Antenatal Sentinel HIV & Syphilis Prevalence Survey does not elaborate on individual population groups with syphilis.[64] In our study, there were no apparent explanations for why this maternal population group had a higher rate of syphilis infection with no identifiable unifying characteristics in these mothers.

ii. Modifiable factors: Patient

There have been no large reported case-series of congenital syphilis following appropriate maternal treatment.[15,46,50,51,49-51] This is supported by our study finding of congenital syphilis in predominantly untreated or inadequately treated mothers. Access to antenatal care, including syphilis screening, during pregnancy is generally poor in developing countries, with only 68% of pregnant women receiving antenatal care and often only after the first trimester.

However, South Africa is one of the few African countries where this is not the case, as more than 90% of pregnant women have at least one antenatal care visit with 74.5% of these women being tested for syphilis during their pregnancies.[41,69] In our study, despite serological confirmation of syphilis in more than three quarters of mothers, the overall maternal treatment rate was extremely poor – this was a dominant feature from other studies too.[47,49,50,] This may be explained by the timing of maternal diagnosis in relation to delivery, with more than 70% of mothers being diagnosed at delivery. This was largely a product of failure to access antenatal care on the part of mothers, as evidenced by the high percentage that were unbooked and late booking beyond the first trimester in those mothers who did book. This phenomenon of poor health seeking behaviour in pregnancy contributing to congenital syphilis rates was noted in other developing countries.[47,49,54] A Ugandan study identified some of the reasons why women choose to not access antenatal care. This was influenced by parity where primigravida mothers were less likely to seek health care. Other factors included perceived high cost and disillusionment with the health system. Furthermore, some women failed to understand the relevance of antenatal care.[70] In our study population, documentation for why mothers were unbooked was poor. Access to health care was unlikely a factor as all mothers lived in urban areas close to health facilities. Lack of education and insight may have played a role, as the unbooked mothers tended to be younger and primiparous, which were findings from other studies too.[45,48] However this was not supported by the Ugandan study which found that marital status, religion and education had no effect on health seeking behaviour.[71] Substance use was a likely contributing factor, as all mothers who used substances were unbooked and of a younger age. Taking into account that multiparous women with term deliveries were also unbooked, there were possible underlying unidentified socio-cultural factors at play. The influence of social factors on maternal antenatal care, syphilis diagnosis and treatment was noted in studies from both the developing and developed world with incarceration, substance use and prostitution mentioned as possible contributing factors. [46,71] However these social factors may be more complex and multi-faceted as Almeida et al identified married women with a single sexual partner and more than eight years of education as having higher rates of infection.[54]

iii. Modifiable factors: Clinical/personnel

In terms of health-worker related failures, our study highlighted numerous modifiable elements. Failure to repeat syphilis serological tests after thirty-two weeks gestation in those mothers who booked early and tested negative at booking, as per National Department of Health Protocol, resulted in those mothers being untreated. An initial negative test may have been a true negative where an uninfected mother in early pregnancy was infected at a later gestation. A more plausible explanation is a false negative test result, which occurs in very early infection before seroconversion and the production of antibodies ("window period") or as a result of the prozone phenomenon during the period of seroconversion. High antibody titres in undiluted maternal serum inhibit agglutination and the formation of antigen-antibody complexes causing a false negative test result. Liu et al demonstrated that there was an increased odds of the prozone phenomenon occurring during pregnancy ([OR], 4.123; p= 0.015).[72] Serial dilutions of serum will prevent this phenomenon and is in fact recommended practise in areas of high syphilis prevalence.[73] However, cost limits its routine use in our setting. This is the rationale behind repeat testing after thirty–two weeks gestation or in those situations where clinical suspicion of maternal syphilis is high. This means that, in our study, failure to repeat serology, perform a dilution test or empirically treat the mother with a 'possible syphilitic rash' were modifiable health worker related errors. These factors need to be addressed in order to attain the WHO target for syphilis elimination of more than 95% coverage of syphilis testing for pregnant women.[74] More importantly, maternal syphilis is an independent risk factor for mortality in neonates and infants.[75]

Partner tracing and treatment of partners was extremely poor; this was a finding from a number of other studies too.[53,54] Maternal re-infection was the likely reason for symptomatic congenital syphilis in the baby born to the only fully treated mother, and possibly the reason for the mother with a previous IUD secondary to syphilis delivering another symptomatic baby (early neonatal death).

It was unknown whether the second mother or her partner was treated after the delivery of an IUD; if either was untreated this was a modifiable health-worker related failure. Partner tracing has been associated with a threefold improvement in the outcome of pregnancy.[76]

iv. Modifiable factors: Health system

Possible health system factors that may have contributed to mothers not being re-tested for syphilis or not booking include resource limitations such as stock shortages (e.g. of rapid testing kits) or overburdened health workers and health systems (e.g. lack of antenatal sisters or long waiting times). However, in our study due to absent documentation these health system factors were unknown.

The introduction of rapid syphilis serological tests in antenatal clinics is a novel health system factor. In our study, 16 (43%) of the 37 mothers who tested positive, were diagnosed on rapid tests with the remaining 21 mothers confirmed positive on formal serological testing. In areas where laboratory access is readily available such as in urban tertiary centres, rapid testing is less frequently performed explaining why the majority of booked mothers, receiving antenatal care at GSH, were diagnosed on formal testing. Fourteen of the rapid tests performed were at delivery largely in the unbooked mothers to facilitate rapid diagnosis and dictate immediate neonatal management. A South Africa rural study in KZN demonstrated that the addition of on-site syphilis testing in areas with laboratory access, did not offer additional benefit; it did not lead to improvement in treatment rates or a reduction in perinatal mortality. However in light of their cost-effectiveness, rapid turn-around time of results as well as their high sensitivity (85-98%) and specificity (93-98%) rapid tests are invaluable in resource constrained settings such as rural areas with no access to laboratory services.[27,77]

c. Neonates

i. General characteristics

There is a well known association between untreated maternal syphilis and preterm delivery with an incidence of between 10-40%.[2,5] Annually, according to the WHO, 270 000 premature and low birth weigh neonates are born as a result of maternal syphilis infection.[5]

In our study, prematurity was a dominant feature with forty-two out of the fifty neonates born with a GA of less than 38 weeks at birth. Spontaneous vertex deliveries were the most common delivery mode in premature neonates (n=25); however in the case of caesarean sections not all mothers who delivered premature neonates were in spontaneous labour with indications for the caesarean sections including foetal distress, umbilical cord prolapse and placental abruption. In some of these cases preterm delivery may have been unrelated to congenital syphilis. The mean birth weight in our study population was less than 2kg. This was lower than findings from other studies in the USA, UK, Thailand and Papua New Guinea.[46,50,52,55] However both the birth weight and GA findings were similar to those from another South African study performed at Tygerberg Hospital in the early nineties.[42]

Our study finding of only one twin being symptomatic for congenital syphilis was noted in a number of older studies.[78]

ii. HIV exposure

The complex interaction between adult HIV and syphilis infection has been extensively studied with HIV impacting on syphilis transmission rates as well as clinical presentation.[79] There were only seven HIV exposed neonates in our study with one confirmed infected case via in-utero transmission out of the three tested.

This small percentage of HIV exposed neonates is likely a product of the political commitment and advocacy toward HIV prevention and treatment in the recent years at both a global and national level. This rate of 14% is similar to the background rate of HIV positive mothers at GSH.[60] This differs from the findings of a study in Johannesburg from more than twenty years ago before access to ART where the incidence of HIV infection in mothers with syphilis was 3 times greater than that of the total obstetric population at the time.[43]

iii. Clinical signs

The commonest clinical sign in our study was respiratory distress. More preterm neonates, with respiratory distress at birth, were intubated as compared to term neonates although this was not statistically significant. In the face of a largely unbooked maternal population with poor antenatal care, it is likely that most premature neonates were steroid immature and therefore at increased risk for hyaline membrane disease (HMD). However, differentiating between HMD and pneumonia secondary to syphilis poses diagnostic difficulties and they are often indistinguishable on chest x-ray.[42] It is possible that those neonates treated for HMD may have had a congenital pneumonia secondary to syphilis.

Our study findings of HSM, petechiae, pallor and jaundice were common clinical signs in symptomatic groups of neonates from other study populations.[46,47,55] However, none of our cases had rhinitis or the “syphilitic snuffles” which is quoted to be in the range of 4-22% of neonates, and may be the earliest presenting sign.[2,47] Radiological abnormalities, despite being noted in more than half of neonates who had long bone x-rays performed, were lower than rates of 75-100% quoted in the literature.[2,21] Long bone x-rays are not a routine investigation in our protocol and 17 of our study neonates did not have one performed; this may be a reason for the lower rate of abnormalities detected in our study.

Our study was one of the few that reviewed placental weight in relation to birth weight. The placentae overall were noted to be heavier, more so in those neonates with a birth weight of more than 2 kg in keeping with the findings of Malan et al.[19] The value of placental weight as a clinical sign is largely unrecognised by clinicians, as evident by the poor documentation in the medical notes. Its more routine use should therefore be advocated especially in neonates weighting more than 2kg at birth.

iv. Laboratory derangements

Hypoglycaemia was one of the commonest laboratory derangements noted in more than half of our study population. Fifteen of these twenty-seven neonates (55%) had severe hypoglycaemia requiring glucagon and hydrocortisone or higher dextrose containing cocktails. The greatest risk period was within the first twenty-four hours of birth, usually the period soon after delivery, on an initial glucose check. Based on the longer duration and more aggressive intervention required in those neonates with severe hypoglycaemia, the aetiology was likely multi-factorial. Possible reasons may be related to increased metabolic demands compounded by the complications of prematurity such as hypothermia, reduced glucose stores as well as delay in initiation of feeds or fluids. There have been case reports of hypopituitarism as a result of early congenital syphilis which may a cause for prolonged hypoglycaemia in these neonates; however, this was unlikely in our study population as a result of eventual resolution of hypoglycaemia with no other systemic features suggestive of hypopituitarism.[80] Our findings indicate that despite hypoglycaemia not being a statistically significant risk factor for death, it should be anticipated in neonates with congenital syphilis. Preventative strategies such as intravenous fluids and early feeding should be instituted timeously together with regular dextrose monitoring in the first twenty-four hours of life. The finding of hypoglycaemia has not previously been noted in other case series and this requires further interrogation.

v. Serological testing

A number of studies that assessed the neonatal effects of inadequate maternal treatment found that clinical, radiological and laboratory evidence of congenital syphilis was uncommon with some studies quoting rates of asymptomatic neonates in the range of 75-90%. The diagnosis of neonatal syphilis hinged on maternal serological testing and treatment history.[4,43,49,51]

Current CDC guidelines recommend testing of all exposed neonates and consider titres that are fourfold higher than the maternal titres as significant. Lower titres may be considered significant in the face of clinical signs or inadequate maternal treatment. As per CDC guidelines, our study population were all "proven/highly probably congenital syphilis" based on clinical signs alone. All our study cases were immediately initiated on penicillin without awaiting serological test results. Our findings suggest that a symptomatic neonate together with a maternal history suggestive of untreated syphilis is likely to have a positive test result. Taking into account that one of the major difficulties in confirming congenital syphilis in resource poor settings is the absence of sophisticated laboratory tests, our findings suggest that serological testing for syphilis is not essential in making the diagnosis when clinical signs are overt and maternal history is highly suggestive.[45,23] Even in areas where serological testing is easily accessible, diagnosis is not always confirmed, with some studies quoting negative nontreponemal test results between 20-30% in those neonates who met the case definition for congenital syphilis.[44,51,49]

We found that in those cases where both maternal and neonatal titres were known, three quarters of neonates had titres less than fourfold the maternal titres despite being symptomatic. This is why serological syphilis tests and titres are not routinely performed in all exposed neonates in our unit. The focus is rather on a thorough clinical examination and immediate initiation of empiric treatment in symptomatic neonates, without awaiting serological test results. In asymptomatic neonates, the identification of those born to poorly treated mothers is paramount to ensure a single dose of intramuscular penicillin is given, in order to treat the two thirds of potentially infected cases. A study by Paryani et al demonstrated that this single penicillin dose as treatment was as efficacious as a ten day course in asymptomatic neonates; this is supported by current WHO recommendations, especially in a resource poor setting.[81]

vi. Morbidity and predictors of mortality

In our study, the majority of neonates required aggressive intervention and care. A total of 34 (68%) neonates required admission into ICU, 29 of which were intubated and 19 of which required inotropes. Eighteen of the ICU admissions demised, with all 18 deaths requiring intubation (12 requiring HFOV and 6 requiring IPPV) and 12 neonates requiring inotropes. The cost implications of caring for neonates with congenital syphilis are well known. In addition to preventing significant neonatal morbidity and mortality, this is the rationale behind screening for syphilis even in areas with a low syphilis prevalence.[82] One study quoted adjusted costs of caring for an infant with syphilis of more than three times that of caring for an infant without syphilis.[83] This is compounded by the extended duration of hospital stay, which is noted on average to be more than 7.5 days longer than that of an infant without syphilis.[82] Overall term neonates without congenital syphilis admitted to our unit tend to have a shorter admission time than premature neonates. Our study findings however demonstrated that the term neonates with congenital syphilis had a mean duration hospital stay of 18 days. Other than the resultant cost implications, there is an associated psychological component of prolonged hospital stay with both maternal and neonatal implications pertaining to establishment of maternal-infant bonding.

A study that was most closely related to ours was from the latter part of the 1990s in Papua New Guinea. Their case definition for congenital syphilis was identical and they too addressed risk factors for death. Their sample size was larger than ours with a comparative control group of neonates without syphilis; however detail regarding the level of care required (ICU/intubation etc.) in those that demised was lacking. Low birth weight less than 2 kg was a statistically significant risk factor for death.[55] This finding was not supported by our study. This may be accounted for by the study time period, which was more than fifteen years ago in the largely developing country of Papua New Guinea. It is possible that the low birth weight neonates with congenital syphilis were sicker at birth and born at a time when resources available for low birth weight neonates may have been lacking.

We found that two strong predictors of mortality were one and five minute Apgar scores of less than five with the need for intubation and inotropes within the first twenty-four hours of life associated with a statistically significant increased risk of death. The mean cord gas pH of 7 in those neonates who demised was suggestive of intrapartum compromise with all neonates being unwell from birth. The lack of improvement in the five minute Apgar score suggests need for prolonged resuscitation. These findings of low Apgar scores in neonates with congenital syphilis was noted in an older study from a large tertiary hospital in the Western Cape where a mean one minute Apgar score of 4 (range 1-9) and a mean 5 min Apgar score of 6 (range 4-10) was recorded. None of the twenty neonates in this study demised.[42]

We noted that just under half of our study population were anaemic at birth with the neonates who demised having a lower median haemoglobin level at delivery. However this difference was not statistically significant with anaemia not being a significant risk factor for mortality. This finding was supported by the study from Papua New Guinea.[55] However, we did find that neonates who were coagulopathic at birth had a statistically significant increased risk of death. There were no other studies that specifically mentioned this complication. Our study was also one of the only studies that reviewed cranial ultrasound scan findings in neonates with congenital syphilis. Severe abnormalities were noted in the group that demised which was associated with a statistically significant increase in mortality. However there were likely confounding variables associated with these abnormalities, related to prematurity and birth asphyxia. Due to our small sample size we did not correct for these confounders.

We noted that hydrops fetalis was a statistically significant independent risk factor for mortality. Eight of eleven hydropic neonates demised with seven of these requiring intubation and six requiring inotropes within twenty-four hours of birth. In light of the high mortality of hydropic neonates (72%), limitation of care may be considered in those that are critically unwell who require aggressive management in the first twenty-four hours of life. This may be particularly relevant in resource-constrained settings.

vii. Treatment and Notification

Disease notification is a vital public health initiative; its use as a monitoring tool helps to evaluate the extent of the problem and aims to reduce the number of congenital syphilis cases. In our study, notification of congenital syphilis was extremely poor with just over half of our study population being notified. The identification of poor notification by health workers was demonstrated by Ballot et al in the early 1990s in Johannesburg and yet more than twenty years later we are still failing in this regard.[43]

A positive finding was that the majority of our study population was appropriately treated. Both incorrectly treated cases involved modifiable health worker failures. The first case involved failure to adhere to the unit protocol where a symptomatic neonate was treated with a single dose of intramuscular penicillin. It is possible that in the second case in the face of an elevated CRP, the attending physician overlooked the diagnosis of syphilis and stopped antibiotics after a course of treatment for sepsis.

viii. Follow-up

Outcome was known for 11 of the surviving neonates with 10 having documented normal development and only one neonatal with signs of developmental delay (HIV infected). There are no large studies evaluating ultimate outcome in neonates with congenital syphilis.[82]

One small study with a five-year follow-up period demonstrated more adverse outcomes than our study such as seizures, visual impairment and death.[49] An additional study from Brazil found that most of the neonates evaluated up to five years had a favourable outcome.[51]

We failed to locate any repeat serological testing performed in our thirty-one survivors, which again is a health worker related factor with failure to adhere to the unit protocol. A single study found that 68% of their study population was negative on repeat serological testing

CHAPTER 5: STUDY LIMITATIONS AND CONCLUSION

1. STUDY LIMITATIONS

In view of maternal syphilis serological testing not being the focus of this study, not all neonates born to mothers with syphilis were included. From the literature, it is known that two thirds of live born infected neonates are asymptomatic at birth and develop signs months to years later. Therefore, we acknowledge that we may have overlooked those neonates with later presentations. However, for the purpose of this folder review, the symptomatic neonates at birth were of interest. It was also possible, although unlikely, that we overlooked those outborn surviving neonates who were not notified and had syphilis testing at their delivery hospital; likewise those neonates who demised before syphilis serology could be performed.

Being a retrospective folder review, not all relevant questions were answerable. This was mainly due to poor documentation specifically regarding why mothers were unbooked and whether partner tracing was sought. Furthermore, because neonates were registered at birth under their mothers names, follow-up of HIV PCR or serological syphilis testing may have been performed under different names and possibly even different folder numbers, explaining the difficulty in tracing these results. For this same reason, there was difficulty in tracing neurodevelopmental outcome, as some children defaulted follow-up and possibly presented to other drainage areas where no record keeping existed.

Our small sample size and the lack of a control group meant that our study was not powered to detect small differences between deaths and survivors. This also meant that we could not correct for confounding variables using logistical regression analysis.

2. CONCLUSION

Despite the introduction of a National Syphilis Screening programme more than twenty years ago together with a large proportion of pregnant women having access to antenatal care, congenital syphilis is still prevalent in South Africa. Failure to access antenatal care, poor partner tracing and a number of modifiable health worker related failures contributed to poor maternal diagnosis and treatment. Maternal syphilis is an independent risk factor for neonatal mortality. Many neonates with congenital syphilis require aggressive interventions and maximum levels of care. This dissertation adds to the existing body of research particularly with regard to predictors of outcome in tertiary neonatal settings. Hypoglycaemia and hydrops fetalis in particular have not been addressed previously. Certain categories of neonates have a lower survival rate and guidelines about limitation of care may need to be considered in order to optimise resource allocation particularly in resource-constrained settings. Further research is required to elaborate how best to develop protocols in these neonates.

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APPENDICES

Appendix 1: Data Sheet

Maternal Factors	
Residential area	
Ethnicity	
Age	
Gravidity and parity	
Booked	Yes
	No
Gestational age at booking	
RVD positive	Yes
	No
Haart (including duration)	Yes
	No
Syphilis test results	
If syphilis positive: at what gestational age was diagnosis made?	
Fully treated *	Yes
	No
Partially treated *	Yes
	No
Untreated *	Yes
	No
Reasons for being untreated	Lost to follow-up
	Booked late therefore delievered before completing treatment
	Preterm labour
	Unbooked
	Clinical/personel factors
Partner tracing	Yes
	No

* **Fully treated:** 3 IM doses of benzathine penicillin weekly for three weeks with the last dose being given more than one month before delivery
* **Partially treated:** incomplete doses of penicllin or last dose given less than one month before delivery
* **Untreated:** no penicillin received

Neonatal Factors	
Gestational age	
Sex	
Birth weight	
IUGR	Yes
	No
Apgar scores	
Need for resusitation	Yes
	No
If resusitated	Neopuff only
	Intubation
	CPR
	Adrenaline
Clinical signs	
None	
General signs	Oedema/hydropic
	Pallor
	Jaundice
	Petechiae
	Placental weight
CNS	Seizures
	Intra-ventricular haemorrages/hydrocephalus
	Meningitis
Respiratory	Respiratory distress/pneumonia
	Pleural effusions
CVS	Shock
	Pericardial effusions
Abdomen	Hepatosplenomegaly
Skin/mucous membranes	Bullae
	Rhinitis
	Fissures/scars
	Maculo-papular rash over palms and soles
	Desquamation
Haematological	Anaemia
	Thromobocytopenia
	DIC

Anaemia: low haemoglobin level < 11g/dl. Transfusions dictated by GSH unit protocol.
Thrombocytopenia: platelet count less than 150 x 10^9/l

Neonatal Factors	
Diagnosis	
Serological tests for syphilus	
Xrays of long bones	
Additional investigations	
CRP	
Positive cultures	
Cranial ultrasound scan	
Management	
Level of care	ICU
	High care
	Low level care
Maximum mode of respiratory support	NPO_2
	$CPAP/HFO_2$
	IPPV
	HFOV
Need for iontropes	Yes
	No
Duration and type of ionotrope	
Need for blood products	Yes
	No
Type of blood product used	
Antibiotic used	
Duration of antibiotic	
Length of hospital stay	
Outcome	Death
	Morbidity
	Well with no obvious sequelae
Notified	Yes
	No
Follow-up given	
Neurodevelopmental outcome	