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Prevalence of positive rapid plasma reagent tests (RPR) in pregnent women: a real or assumed decrease?

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PREVALENCE OF POSITIVE RAPID PLASMA REAGENT TESTS (RPR) IN PREGNANT WOMEN:

A REAL OR ASSUMED DECREASE?

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Obstetrics and Gynaecology

Johannesburg, 2008

DECLARATION

I, Serasheni Moodley declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Obstetrics and Gynaecology in the University of the Witwatersrand, Johannesburg. It has not previously been submitted for any degree at this or any other university.

_____

Serasheni Moodley

Signed on the 12th day of May, 2008

ABSTRACT

Introduction

The aim of this study was to determine the current RPR positive prevalence rate at the Johannesburg Hospital and to determine whether there has been a significant decrease in the prevalence rate of RPR positive tests.

Patients and Methods

A retrospective analysis of all RPR results within labour ward registers was performed. A sample from 01/08/02 to 31/01/03 was used to determine the current RPR positive prevalence rate. The results from the current period were then compared to the results from a similar study in 1996. Results of two months, six months apart, of each year between these periods were also analyzed in order to determine the trend of RPR positive prevalence rates.

Results

The RPR prevalence rate was 4.4% compared to 19.5% in 1995/96 ($p < 0.0001$). Results obtained from the intervening years showed a statistically significant decrease.

Conclusion

RPR positive prevalence rates at Johannesburg Hospital have decreased significantly in recent years.

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INTRODUCTION

Syphilis is a worldwide disease and is the third most common sexually transmitted bacterial disease in the United States (after gonorrhoea and chlamydia).[1,2] Syphilis infection is normally exclusive to humans and is spread by direct sexual contact, congenital infection or transfusion with infected blood products.[1] Congenital syphilis is now rarely seen in first world countries although the prevalence of syphilis in these countries from 1980 – 1995 was approximately 7%, having peaked at 13% in 1990.[1] In South Africa the average national prevalence rate of syphilis in pregnant women has been stated as 6.6%, being higher in some regions at 10%.[3] Quoted rates include Qolohle et al (6.8%),[4] Cronje et al (12-16%),[5] Mlisana et al (30.7%)[6] and Stewart-Smythe (19-20%).[7]

Recently, the rapid plasma regain (RPR) positive prevalence rate in the high-risk antenatal clinic at Johannesburg hospital seems to have decreased. A large number of the RPR positive patients are HIV negative. High viral loads in HIV positive patients are known to be associated with false negative syphilis serology.[8,9] The aim of this study was to determine the current RPR positive prevalence rate in the Johannesburg Hospital maternity unit and to determine whether any decrease is real or assumed, by correlating the results obtained from pregnant patients admitted to the labour ward with the prevalence of congenital syphilis of infants having presented to the neonatal wards as provided by the Department of Paediatrics. If congenital syphilis rates remain unchanged, the decrease in maternal syphilis would be an assumed one due to false positive results rather than a true decrease. National surveys suggest a decline in the prevalence of syphilis.[10] The methodology in this study includes verification with registers as well as laboratory results to determine whether such a decrease is a real or assumed one.

The specific objectives of this study were:

a. To determine the *past* RPR positive prevalence rate.
b. To determine the *current* RPR positive prevalence rate.
c. To determine an approximate RPR positive prevalence rate for each year from past to current periods.

CHAPTER 1

SYPHILIS IN CONTEXT

1.1 What is syphilis?

1.1.1 Definition

Venereal syphilis, which the broad term syphilis has come to denote, is a sexually transmitted bacterial infection caused by the spirochete *Treponema pallidum*.[11]

1.1.2 Pathophysiology

Untreated, syphilis progresses through three symptomatic stages. Primary and secondary syphilis are highly infectious stages characterized by rapid division of organisms. Since primary syphilis presents with a painless ulcer or chancre, infection may go unnoticed. The mucocutaneous rash of secondary syphilis is transient and may also go unrecognized resulting in lack of treatment and disease progression. Latent syphilis refers to asymptomatic infection which may be early, if within a year of onset of infection, or late, if greater than a year of onset of infection. Early latent syphilis may present with recurrent mucocutaneous rash as the organisms are still in a state of rapid division. During late latent syphilis and tertiary syphilis organisms are thought to be dividing more slowly, necessitating longer duration of therapy. The gummatous lesions of tertiary syphilis are of concern as these result in cardiac, ophthalmic, and auditory abnormalities as well as neurosyphilis which may result in focal ischemia, stroke or psychiatric manifestations.[1, 2, 11]

1.1.3 Incidence

The incidence of the disease has steadily decreased with the advent of penicillin in the early 1940s. The prevalence of syphilis in first world countries from 1980 – 1995 was approximately 7%, having peaked at 13 % in 1990.[1] With time and public health control

measures, rates of primary and secondary syphilis reached a nadir in 2000 in the United States. Since then, despite a continued decline in women and infants, overall rates have begun to increase. However, these are so low that they are now expressed per hundred thousand rather than as a percentage, being between 2-4/100 000 new infections per year from 1997-2004.[12, 13] In South Africa, the average national prevalence rate of syphilis in pregnant women had in 1997 been stated as 6.6%, being higher in some regions at 10%.[3] Quoted rates from 1990 – 1997 include Qolohle et al at 6.8%,[4] Cronje et al at 12 – 16%,[5] Mlisana et al at 30.7%,[6] and Stewart-Smythe at 19-20%.[7] The 'National HIV and Syphilis Antenatal Sero-prevalence Survey in South Africa' showed a graphical decline in syphilis from 10-12% in 1997-1998 to 2-4% in 2002-2004.[10] The quoted South African rates are all from studies of the pregnant population. However, rates from the United States are population based and reflect men, women and infants across all states.

1.2 Why is syphilis of importance in obstetrics and gynaecology?

1.2.1 Congenital syphilis

Congenital syphilis refers to the transplacental passage of spirochetes.[11] The Centers for Disease Control, for the purposes of notification, includes in its definition of congenital syphilis, stillbirths associated with syphilis and the infants of mothers who were inadequately treated or untreated for syphilis, irrespective of the findings in the infant.[14, 15, 16] This definition is of paramount importance as transmission to the fetus approaches 100%. More than 40% of untreated pregnancies will result in perinatal demise. Surviving infants may present with early manifestations (< age 2 years) or late manifestations (> age 2 years). Since the fetus does not mount an inflammatory response prior to 12 weeks gestation, organogenesis is not affected (although treponemes rarely cross the placenta in the first trimester). All organs may however be involved by the infection.[11] Any stage of syphilis occurring during pregnancy may result in an infected fetus and congenital

syphilis usually occurs when treponemes cross the placenta after the 16th-18th week of gestation. Infection may rarely occur from contact with an infectious lesion during delivery.[17] Spirochetaemia results in vasculitis and resultant necrosis and fibrosis in target organs.[18] Fetal manifestations include spontaneous abortion, intrauterine growth restriction, non-immune hydrops fetalis, stillbirth, preterm delivery and perinatal death. Congenital syphilis can present along a broad clinical spectrum with a range of laboratory and radiological findings involving many organs. {See table 1, adapted from *'Sex. Transm. Inf. 2000; 73-79'*}. If adequately detected and treated, these consequences can be avoided.

Table 1: Presentations of congenital syphilis
(Adapted from 'Sex. Transm. Inf. 2000; 73-79')

Clinical findings	**Percentage**
Early	
Abnormal bone X-ray	61
Hepatomegaly	51
Splenomegaly	49
Petechiae	41
Skin lesions	35
Anaemia	34
Lymphadenopathy	32
Jaundice	30
Pseudoparalysis	28
Snuffles	23
Late	
Frontal bossing	30 – 87
Palatal deformation	76
Dental dystrophies*	55
Interstitial Keratitis*	20 – 50
Abnormal bone X-ray	30 – 46
Nasal deformity (saddle deformity)*	10 – 30
Eight nerve deafness	3 – 4
Neurosyphilis	1 – 5
Joint disorder	1 – 3

* Hutchinson Triad

1.2.2 Co-morbid disease and a review of risk factors

Co morbid disease includes HIV infection as well as other sexually transmitted infections (STIs). Cross infection of STIs has been widely recognized and has led to the advent of syndromic management. Mathews et al however found that despite the introduction of syndromic protocols, a fair proportion of STIs and genital tract infections were not being detected and treated due to the high prevalence of multiple syndromes and mixed infections.[19] The complications of inadequate treatment and persistent infection then present to the gynaecologist as advanced disease and sometimes generalized sepsis increasing morbidity, hospital stays and mortality.

Venereal syphilis is a sexually transmitted disease sharing the same risk factors as other sexually transmitted genital tract infections. This includes sexually active females, aged 16-25 years, who do not use contraception and live in areas with a high prevalence of STIs.[20] Age at first intercourse, unmarried status, and the number of sexual partners have all been proven to be risk factors for genital ulcer disease occurring secondary to other STIs. Also, genital ulcerations and inflammation secondary to STIs have been implicated as cofactors for acquisition and transmission of HIV.[21, 22] The increased infection rate in teenagers is thought to be secondary to the lower level of antibodies and the wider area of cervical columnar epithelium allowing colonization with various organisms.[20]

An epidemic in a region is believed to be promoted by multiple factors including the aforementioned high prevalence of STIs,[23] poor access to effective STI treatment, sexual networking patterns prevalent in the area, and the disruptive effects of the migrant labor system.[24, 25, 26] Wilkinson et al attest to South Africa's massive, often unrecognized burden of STIs, having found that although rates were highest in women who engaged in high risk behavior such as sex work, rates were also high amongst women in the general community

considered to be of lower risk. In a study done in rural Kwa-Zulu Natal, they found that 77% of sex workers had at least one STI and 33% had multiple infections. Pregnant women showed corresponding rates of 52% and 18%, and women attending family planning clinics had rates of 27% and 10% respectively. Prevalence of HIV infection in each of these groups was also found to be high at 50%, 16% and 24% respectively. Underlying factors identified by this group included poor quality services, low rates of partner treatment, poor understanding of and response to symptoms, sex work, and high levels of population mobility and migration.[27] STDs and HIV were also found to be frequent along major arterial routes, the communities along these routes having the greatest prevalence of these diseases.[28]

1.3 Diagnostic modalities.

Spirochete visualization by darkfield microscopy and the use of direct fluorescent antibody tests comprise the definitive methods of diagnosing syphilis from a genital ulcer (early syphilis). These are most specific when the chancre or condyloma is present. A microscope with a dark-field condenser or a phase contrast microscope is used to observe motile organisms with a corkscrew appearance. At least 10^4 organisms need to be seen so a negative test does not rule out syphilis unless the exam has been repeated on three consecutive days.[29]

Serological tests for diagnosis may be nonspecific nontreponemal tests, or specific treponemal tests. These are most often only positive from about the fourth week of acquired syphilis, which has an incubation period ranging from 10 to 90 days.

1.3.1 Nonspecific or lipoidal antigen tests:

These include:

- Venereal Disease Research Laboratory (VDRL)
- Rapid Plasma Reagin (RPR)

- Treponemal enzyme assay (ELISA)
- Wasserman Reaction (WR)

These tests are based on antibodies against nontreponemal antigens, for example antigen extracts from beef heart (cardiolipin)[30] and allergy related immunoglobulin E (IgE), which are released by human tissue infected with *Treponema pallidum*. The tests may be positive in other conditions associated with this release. Because they are characterized by the inflammatory response of the primary reaction, these tests often become non-reactive following successful treatment. However, low or negative titres may occur with longstanding disease. The RPR test is used for syphilis detection only. Sensitivity in the primary stage is only 30% after one week of infection in the primary stage, 90% after three weeks as well as in the tertiary stage, and approaches 100% in the second stage of the disease.[31] The VDRL test can be used not only for syphilis detection, but also for quantitative analysis.[32] Some patients demonstrate a serofast reaction where nontreponemal antibodies persist after treatment for a long period of time and sometimes even for the lifespan of the patient. False positives may occur with systemic lupus erythematosus, malaria, infectious mononucleosis, infectious hepatitis, post-vaccination state, leprosy, brucellosis, atypical pneumonia, miliary tuberculosis, typhus, pregnancy, and related treponemal infections such as yaws, pinta and bejel.[30] The specificity of these tests is 75-85% in patients with such pre-existing diseases, but approaches 100% in patients without them.[33] Causes of false negative results are few. Patients with extremely high titres may have false negative results which become positive only after sera dilution. In the advanced stages of HIV infection, patients do not mount an appropriate immune response and hence may have false negative tests.

1.3.2 Specific treponemal antigen tests:

These include:

- Treponema Pallidum Haemagglutination Assay (TPHA)
- Fluorescent Treponemal Antibody Absorbed (FTA-ABS) test
- Micro-Haemagglutination Assay for Treponema Pallidum (MHA-TP)
- Treponemal Enzyme-linked Immunosorbent Assay (ELISA)
- Treponema Pallidum Immobilization Test (TPI)

These tests are only indicated for confirmation of positive syphilis serology.[34] With these tests, specific serum antibodies against treponemal antigens are detected so although fairly specific for syphilis, other treponemal diseases such as yaws, bejel and pinta cannot be excluded. Reactive treponemal tests usually remain reactive for the remainder of the patients' life irrespective of treatment or disease activity. However, up to 25% of patients treated during the primary stage may revert to being serologically non-reactive after two to three years.[35]

Both specific and nonspecific diagnostic tests for syphilis are generally reliable in HIV positive patients, although some may have atypical test results due to deregulation of immune responses. HIV positive patients show a varied immune response. In early infection, there is an abnormal antibody response with loss of clones of antibodies. This may interfere with serology of both specific and nonspecific tests. In advanced stages of the disease there is no longer adequate functioning of the immune system to mount an immune response.[36, 37] If the clinical syndrome is highly suggestive one should the resort to biopsy and direct microscopy.

1.4 Screening

Screening in pregnancy implies measures taken to detect disorders of which the patient has no signs and symptoms, but are likely to have an adverse effect on the well being of mother or fetus, and for which effective intervention is available and necessary.[17, 38]

1.4.1 Recommendations and rationale

Recommendations and the rationale thereof have been instituted by various antenatal screening review committees worldwide and are guided by Centers for Disease Control (CDC), Royal College of Obstetricians and Gynaecologists (RCOG), National Institute of Clinical Excellence (NICE), American College of Obstetricians and Gynaecologists (ACOG) and U.S Preventative Services Task Force (USPSTF) guidelines as well as guidelines from various state departments, pathology groups, paediatric and midwifery committees.[33, 38, 39, 40, 41]

The Three Centre Consensus Guidelines on Antenatal Care issued specific guidelines for the antenatal screening of syphilis with the following levels of evidence.[39]

Table 2: Specific guidelines for the antenatal screening of syphilis
(Adapted from Three Centres Consensus Guidelines on Antenatal Care Project)

Guidelines	Level of Evidence
Early in pregnancy all women should receive appropriate written information about antenatal syphilis testing and be given the opportunity to discuss it with their midwife or doctor.	IV
Antenatal serological screening for syphilis should be offered to all pregnant women	III-2 IV
Screening for syphilis should be undertaken at the first antenatal visit, ideally prior to 16 weeks gestation	IV

III: *"Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies"*
IV: *"Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities."*

Presented below is a summary of recommendations for screening for syphilis infection (antenatal and other) as released by the USPSTF (United States Preventative Services Task Force) in July 2004.[41] These recommendations are deemed necessary for control of antenatal and hence congenital syphilis, and also address a more holistic approach necessary to control the disease within an evidence based framework.

- 'The USPSTF strongly recommends that clinicians screen persons at increased risk for syphilis infection.' **Grade A recommendation**

  Rationale: "Although the potential harms of screening, including false positives, patient anxiety and antibiotic related risks are recognized, the USPSTF feels that benefits of screening high risk persons substantially outweigh the risks as screening tests accurately detect syphilis infection and antibiotics provide cure. However, no

direct evidence was found to prove that screening for syphilis leads to improved health outcomes in such high risk persons."

- 'The USPSTF strongly recommends that clinicians screen all pregnant women for syphilis infection.' **Grade A recommendation**

  *Rationale: "*Benefits of such screening substantially outweigh potential harms since the proportion of infants with clinical manifestations of syphilis infection and with positive serologies is reduced as a result."

- 'The USPSTF recommends against routine screening of asymptomatic persons who are not at increased risk for syphilis infection.' **Grade D recommendation**

  Rationale: "Harms of screening in the low risk population outweigh risks as the incidence of syphilis in the general population is low."

1.4.2 Standards for screening

In South Africa, although antenatal screening for syphilis is advocated, no guidelines exist as to the standards for such screening. Patients are at most told that they are being tested for syphilis and at follow up visits they may be informed of their results. Often patients only get to know their results if they require treatment. The figure below illustrates an example of minimum standards that apply in first world countries for the antenatal screening of syphilis.[38]

Figure 1: Minimum standards for the antenatal screening of syphilis

(Adapted from Making decisions: Standards Protocols and the Performance Management Framework to support the provision of Antenatal Screening in Wales: A Consultation Document; 2004)

Minimum standards for antenatal screening for syphilis

5.4.1 The woman's informed verbal consent is required and a record of her consent must be made in the maternity notes.

5.4.2 Whenever possible screening should be offered and undertaken before 13 weeks of pregnancy to enable treatment to start promptly and reduce the risk of fetal damage.

5.4.3 A record of the serum test being taken must be made in the maternity notes.

5.4.4 The laboratory request form must require the identification of the sample as 'antenatal screening'. If a single request form is used for multiple screening tests, the form must contain a clear indication of the screening tests which the woman has given consent.

5.4.5 All relevant clinical information must be included on the request form.

5.4.6 The test should normally be undertaken by a laboratory which is accredited or approved by CPA UK Ltd.

5.4.7 It is recommended that the screening test assay has a high sensitivity ideally at least 99% and a high specificity (99.95%).

5.4.8 The test result must be provided by the laboratory to the Trust Powys LHB within 7 working days.

5.4.9 All women must be informed by the Trust Powys LHB of the result within 15 working days.

5.4.10 If the screening test is negative the woman should be informed that she has a low chance of having the condition at present.

5.4.11 Confirmed syphilis positive test results indicating current infection should be telephoned to the consultant, screening midwife or named deputy so urgent arrangements can be made for the woman to return to the clinic for the result. The result should not be electronically be transferred from the laboratory to the maternity or other services unless appropriate security arrangements are in place to ensure the result can only be accessed by locally agreed named individuals.

5.4.12 As syphilis is a rare condition in the UK, all women testing positive should be referred to a specialist in Genitourinary Medicine (GUM) for assessment and counselling.

5.4.13 The woman's suspected or confirmed syphilis positive result should not be:

- recorded on the maternity information system without the woman's informed consent
- written in an appropriate way in the hospital maternity notes
- on blood request forms or other request forms where hospital staff unconnected to the woman's care will have unnecessary access to this information

It becomes clear from the above minimum criteria that we in South Africa are sadly deficient in our approach to antenatal screening for syphilis. At a bare minimum, one should follow the CDC recommendation that 'no infant should leave the hospital if maternal serologic status has not been determined at least once during pregnancy and preferably again at delivery' with reference to syphilis serology.[2]

1.4.3 On-site screening

The rationale for on-site screening for syphilis is based on the premise that in a third world country such as our own, pregnant women often initiate antenatal care late in pregnancy. Since between 2 weeks and a month may elapse prior to the follow-up visit, appropriate management of a positive test is delayed. This may result in women giving birth before being treated for syphilis and does not effectively prevent congenital syphilis. On-site screening would enable immediate diagnosis and initiation of treatment of these patients.[42] A South African study investigated the RPR card test as a screening test to diagnose the presence of syphilis as well as titres. The on-site RPR test had a sensitivity of 92.8%, a negative predictive value of 99.5%, a specificity of 96.3% and a positive predictive value of 64.7% showing that maternal syphilis could be diagnosed in the majority of cases screened on-site at their initial visit.[42] Although active syphilis is denoted by an RPR titre of 1:8 or greater, the risk of fetal infection becomes more likely if the RPR titre is greater than 1:16.[43] For RPR titres greater than or equal to 1:8 the on-site RPR card had a sensitivity of 90.5% although for titres greater than or equal to 1:16 the sensitivity approached 100% implying that all patients at risk for congenital syphilis could be identified and treatment initiated on-site.[3] This does compare with the sensitivity and specificity of conventional RPR testing. This has far reaching consequences in a South African setting where patients present late and minimum standards for screening are poorly defined. The CDC has recognized this and hence

recommends that where prenatal care is not optimal, such card screening and treatment be performed.[2]

1.4.4 Re-screening

The CDC recommends that in areas of high prevalence, screening should be done in early pregnancy, in the third trimester and at delivery.[2] The rationale for this is to lower the incidence of congenital syphilis by decreasing the prevalence of maternal syphilis. In the South African context, Opai-Tetteh et al made a case for re-screening in areas of high prevalence, having identified a higher seroconversion rate at King Edward VIII Hospital in KwaZulu Natal as compared to Tygerberg Hospital in Cape Town.[44]

1.4.5 Screening Considerations

The stage of infection may well complicate screening. Women tested too early (less than three weeks from onset of infection) may show false negatives.[31, 45] This would be more likely in areas of high prevalence than in the general population. The syphilitic ulcer is generally painless and transient and may be missed by the patient herself, as well as the health care worker who does not do a vulval and vaginal examination.

Also, any woman who has a stillbirth after 20 weeks gestation should be screened for syphilis.[2]

1.5 Treatment

1.5.1 Patient

When determining appropriate therapy, many factors need consideration. These include the stage of maternal infection, the physiological changes of pregnancy which alter drug pharmacokinetics, the effect of the drugs on the fetus, penicillin allergy and HIV co-infection.[45]

For this reason, patients with titres of above 1:8 should receive standard treatment as outlined below. Patients with titres of 1:8 and below should ideally be re-screened with one of the specific treponemal tests and only be treated in the event of this being positive. This would prevent unnecessary treatment of the false-positive patient. South African National Maternity Guidelines are however to treat all patients who are RPR positive, irrespective of titre. This is due to problems with follow-up, cost and the possibility that a specific test is very likely to come back positive as a result of old infections.

Penicillin is the treatment of choice for the treatment of syphilis and is also safe in pregnancy and during breastfeeding.[46] The CDC recommends that treatment during pregnancy should comprise a stage-appropriate penicillin regimen. Women with primary, secondary or early latent syphilis should receive a second dose of benzathine penicillin one week following the initial dose.[2,46] The policy in South Africa is to treat maternal syphilis with Benzathine benzylpenicillin, IMI, 2,4 MU weekly for three doses.[47] In the South Africa context patients often present late and the health care worker is unable to ascertain the stage of syphilis making this recommendation appropriate. This is supported by clinical microbiology guidelines for treatment of syphilis in pregnancy of unknown duration.[48]

Some patients may display an acute febrile reaction accompanied by flu-like symptoms within the first 24 hours of any therapy for syphilis. This is known as the Jarisch-Herxheimer reaction and should not deter therapy. Patients should however be informed of the risk thereof and that such reaction may result in fetal distress or preterm labor.[2, 46] Therefore, although no guidelines exist as to prevention of such risk, it would be better to admit patients with such flu-like symptoms for observation for 24 hours.

1.5.2 Fetus

Treatment of the mother prior to the 16th week of gestation completely eradicates the infection and its sequelae. It is thought that treponemes cannot cross the Langhans cell layer of the placenta which only begins to atrophy at 16 weeks of gestation. Treatment from 16 weeks of gestation does cure infection but may not prevent stigmata of congenital syphilis. Kassowitz's law is that pregnancy in a woman with early syphilis generally ends in fetal demise, subsequent pregnancies result in fetuses with congenital syphilis and still subsequent pregnancies may not be affected. This is due to bacteraemia which may persist as long as 8 years untreated.[48]

Fetal infection may still occur in up to 14% of appropriately treated cases.[45] Ultrasound signs of fetal syphilis include signs such as hepatomegaly or hydrops fetalis and may indicate fetuses at increased risk of treatment failure even before commencing therapy. Such fetuses will need close follow-up and a second course of therapy may well be warranted. If the fetus is severely infected prior to initiating therapy, the Jarisch-Herxheimer reaction may result in preterm labor or fetal death.[48]

1.5.3 Partner

To prevent the spread of sexually transmitted disease, treatment of the partner has always been advocated. With syphilis, sexual transmission only occurs when there are mucocutaneous lesions and these are rare after one year of infection. Sexual partners however still warrant evaluation. South African guidelines mandate examination and treatment of the sexual partner.[47] The CDC recommends treatment of partners presumptively in persons exposed to the patient within 90 days of the diagnosis of primary, secondary or early latent syphilis, as a serological test may be falsely negative within this time. For those exposed for a period of longer than 90 days, treatment should be given if loss to follow up is a problem or if test results are not available immediately. Otherwise, the partner should be tested and treated depending on their result although a titer of greater than 1:16 may not necessarily mean early syphilis and response therefore should ideally be monitored by subsequent follow up and serological titers.[2] The recommended regimen for treatment is Benzathine penicillin 2.4 million units IMI as a single dose.

1.5.4 HIV co-infection

Aberrant serological responses may occur in the patient infected with HIV. These range from higher serological titers to false negative results and a longer time span to seropositive results. Since these occur more as exceptions to the rule and are not regular occurrences, specialists feel normal interpretation of serological tests should apply.[2] If clinical suspicion is high and the test result does not concur, repeat testing or biopsy of lesions present can be done and sent for darkfield microscopy. Although the CDC recommends treatment of these patients with a single dose of benzathine penicillin, they also acknowledge that in these patients some specialists recommend repeat doses weekly for a total of three doses.[2] This is the recommendation adhered to in pregnancy and is no different from that in the patient without HIV co-infection.

1.5.5 Penicillin-allergic patient

Doxycycline or tetracycline are alternative therapies to penicillin in the non-pregnant patient.[2] These drugs are not safe for use in pregnancy and hence not recommended for the treatment of maternal syphilis. The policy for the treatment of maternal syphilis from the South African Department of Health is to treat the penicillin sensitive patient with erythromycin, oral, 500mg, 6 hourly for 28 days and to give penicillin to the baby after delivery.[47] Although erythromycin, azithromycin or ceftriaxone can be used in pregnancy; the treatment of syphilis in pregnant patient who is allergic to penicillin poses a problem since no alternative to penicillin has proved effective in the treatment of syphilis during pregnancy. Erythromycin does not reliably cure an infected fetus as it does not reliably cross the placenta, and no adequate data exist for the use of azithromycin and ceftriaxone in this regard.[2,48]

It is essential therefore, for the penicillin allergic mother, to consider desensitization. Most patients reporting penicillin allergy may not display hypersensitivity because the hypersensitivity has faded or they were never allergic to penicillin.[46] Although between 3 and 10% of studied populations have experienced urticaria, angioedema or anaphylaxis following penicillin therapy, only 10% of patients who report severe allergic reactions actually remain allergic. In these however, re-administration could cause acute severe and fatal anaphylaxis.[2] Skin testing (90% -97% sensitivity) with major and minor determinants is therefore necessary in patients with a history of penicillin sensitivity. Patients who no longer express IgE antibodies will not elicit a reaction and can be safely treated with penicillin. For patients proven to be sensitive or for whom the full battery of skin tests is not available, desensitization in a hospital setting must be done. This can be either oral or IVI and takes approximately 4 hours to complete (see figure 2). Maintenance on penicillin is then necessary until the full course of therapy is completed.[2]

Figure 2: Suggested penicillin desensitization protocol
(Adapted from Sexually Transmitted Diseases Treatment Guidelines; 2002)

Penicillin V suspension dose		Amount (units/mL)	
	mL	Units	Cumulative dose (units)
1	1,000	0.1	100 100
2	1,000	0.2	200 300
3	1,000	0.4	400 700
4	1,000	0.8	800 1,500
5	1,000	1.6	1,600 3,100
6	1,000	3.2	3,200 6,300
7	1,000	6.4	6,400 12,700
8	10,000	1.2	12,000 24,700
9	10,000	2.4	24,000 48,700
10	10,000	4.8	48,000 96,700
11	80,000	1.0	80,000 176,700
12	80,000	2.0	160,000 336,700
13	80,000	4.0	320,000 656,700
14	80,000	8.0	640,000 1,296,700

NOTE: Observation period: 30 minutes before parenteral administration of penicillin. * Reprinted with permission from the *New England Journal of Medicine*(Wendel GO, Jr, Stark BJ, Jamison RB, Melina RD, Sullivan TJ. Penicillin allergy and desensitization in serious infections during pregnancy. N Engl J Med 1985;312: 1229–32.).
† Interval between doses, 15 minutes; elapsed time, 3 hours and 45 minutes; cumulative dose, 1.3 million units.
§ The specific amount of drug was diluted in approximately 30 mL of water and then administered orally.

1.5.6 Congenital syphilis

Congenital syphilis may result in stillbirth, hydrops fetalis or prematurity.[48] Much of detection and prevention of congenital syphilis is dependent on antenatal screening. Routine screening of newborn sera is inadvisable since these can be negative depending on the pre-delivery maternal titer or if the mother was infected late in pregnancy. Also passage of

maternal IgG antibodies across the placenta further complicates diagnosis in the newborn. Currently no commercially available IgM antibody test can be recommended.[2] If the maternal RPR result is unknown at delivery, it should still be tested in preference to that of the newborn.

Clinical microbiological and CDC guidelines concur on the assessment and treatment of infants who fit the definition of congenital syphilis and are displayed below.[2,48]

Figure 3: Guideline for the management of the infant born to a mother with reactive treponemal serology in pregnancy

(Adapted from Clinical Microbiology Guidelines; January 2005)

Management of the infant

All infants of mothers who were treated for syphilis before or during pregnancy, should be fully examined clinically at birth and at six weeks, 3, 6 and 12 months of age. Serological testing with quantitative RPR should be performed at birth and at 3, 6 and 12 months.

- If the mother was treated with an appropriate course of penicillin and has shown reduction in three, the infant should be monitored serologically as above. Full evaluation and treatment for congenital syphilis will be necessary in such cases only if there is a rise or persistence of titre and/or clinical or radiological evidence of disease.

An infant should be evaluated for congenital syphilis if he/she was born to a mother with a positive specific treponemal test and one or more of the following conditions are operative :

1. The mother received no treatment.
2. The treatment given to the mother is not known.
3. The treatment given to the mother is inadequate.
4. The probability of follow-up is uncertain.
5. The mother was treated with an antibiotic other than penicillin (erythromycin usually)
6. Treatment was with penicillin but the expected decrease in nontreponemal antibody titre after treatment did not occur.
7. Appropriate treatment was given but there was insufficient serological follow-up to assess the response to the treatment and the current infection status.
8. Treatment was less than one month before delivery.

- In each of these cases above, the infant should be admitted for evaluation for congenital syphilis. Treatment should commence with minimal delay in each of the above scenarios regardless of the findings (see Table and Algorithm).

- In addition, any infant with physical or laboratory findings consistent with a diagnosis of congenital syphilis should be treated without delay.

Recommended regimens for treatment of infants who fit the criteria for congenital syphilis include:[2]

- Aqueous crystalline penicillin G; 100000–150000 units/kg/day *10 days in divided doses
- Procaine penicillin G; 50000 units/kg/dose IMI once daily *10 days
- Benzathine penicillin G; 50000 units/kg/dose IMI stat

1.6 Psychosocial issues

Epidemiological studies have shown that a major contributor to the increased risk of congenital syphilis was a lack of antenatal care. Women most likely to infect their fetuses with syphilis often have complex dilemmas impeding their access to screening and treatment. Psychosocial issues that make medical treatment goals difficult to achieve and that have been associated with syphilis include low education levels, teenage pregnancy, HIV infection, cocaine use and underutilization of health infrastructure.[45] Training of health care workers addressing such communities centers on reducing sexual prejudices and adopting an attitude toward reproductive health which allows for the sexual lifestyle of the user within their own context. Health service reform stresses a rights-centered approach providing free and informed consent to these patients and respecting their rights especially with regard to prenatal, antenatal and postnatal care, as well as STD treatment and family planning. For this to be successful, a community orientated approach, coordinated with a base institution is necessary. Accessibility needs to be facilitated.[49]

1.7 Follow-up

Although treatment of maternal syphilis is usually highly effective, treatment in the third trimester is more likely to fail. Treatment failure can occur but is less likely in earlier trimesters. Monthly serological follow-up for the remainder of the pregnancy is therefore recommended. High titer syphilis should show up to a four fold drop and low titer syphilis should remain stable. The persistent of ultrasound markers of fetal syphilis following therapy may also indicate treatment failure.[48] In either of these scenarios re-treatment is necessary. In the United Kingdom such patients should also be referred to genitourinary medicine (GUM) clinics for counseling, postpartum follow up and screening for other STDs. All infants who are treated following positive maternal serology should ideally be followed up at 6 weeks, and have repeat serology at 3, 6 and 12 months of age.[48] HIV infected patients should be followed up at 3, 6, 9, 12 and 24 months following therapy to assess for treatment failure. Those who meet criteria for treatment failure should be referred appropriately for re-treatment and investigation for neurosyphilis.[2] Infrastructure for such follow-up is the ideal to adequately manage these patients and prevent further spread of the disease but is largely unavailable in the third world context.

1.8 The concept of prevention and elimination

Syphilis infection is normally exclusive to humans and is spread by direct sexual contact, congenital infection or transfusion with blood products.[1] Any disease that is exclusive to humans can potentially be eradicated not unlike the worldwide effort with poliomyelitis. This concept has been addressed by the syphilis elimination effort in the United States.

1.8.1 Worldwide

In 1999, the CDC initiated 'The National Plan to Eliminate Syphilis' from the United States. The rationale for this was the declining rates of syphilis in the United States in the preceding decade. The plan focused on populations having the highest prevalence of syphilis and has to date shown a decline in these populations. However an increase was noticed in a group not focused on; that being the 'men who have sex with men' group.[13]

Syphilis elimination has been defined by the CDC as the absence of sustained transmission of the disease.[50] The burden of disease, including increased HIV transmission and congenital syphilis was appropriately highlighted. Recognition that a conscious effort to eliminate syphilis would result in decreasing such comorbidities is central to such an effort. The presence of genitourinary medicine clinics is part of the essential infrastructure for the success of such an effort. It is not surprising then, that the three goals guiding this plan include:

- Investing in and enhancing public health services and interventions
- Prioritising and targeting populations at risk
- Improving accountability of prevention efforts

The above goals highlight improved surveillance, recognition, treatment and prevention of the disease. The importance of adequate interaction with laboratory and testing sevices as well as the private health care sector is recognized. Integral to the process is staff training, ongoing research and data or research driven planning and integration.[50] The CDC has been implementing the above plan with a prospective five year timetable of activities dictating progress. Such a timetable is integral to the success of such an initiative.

1.8.2 The South African context

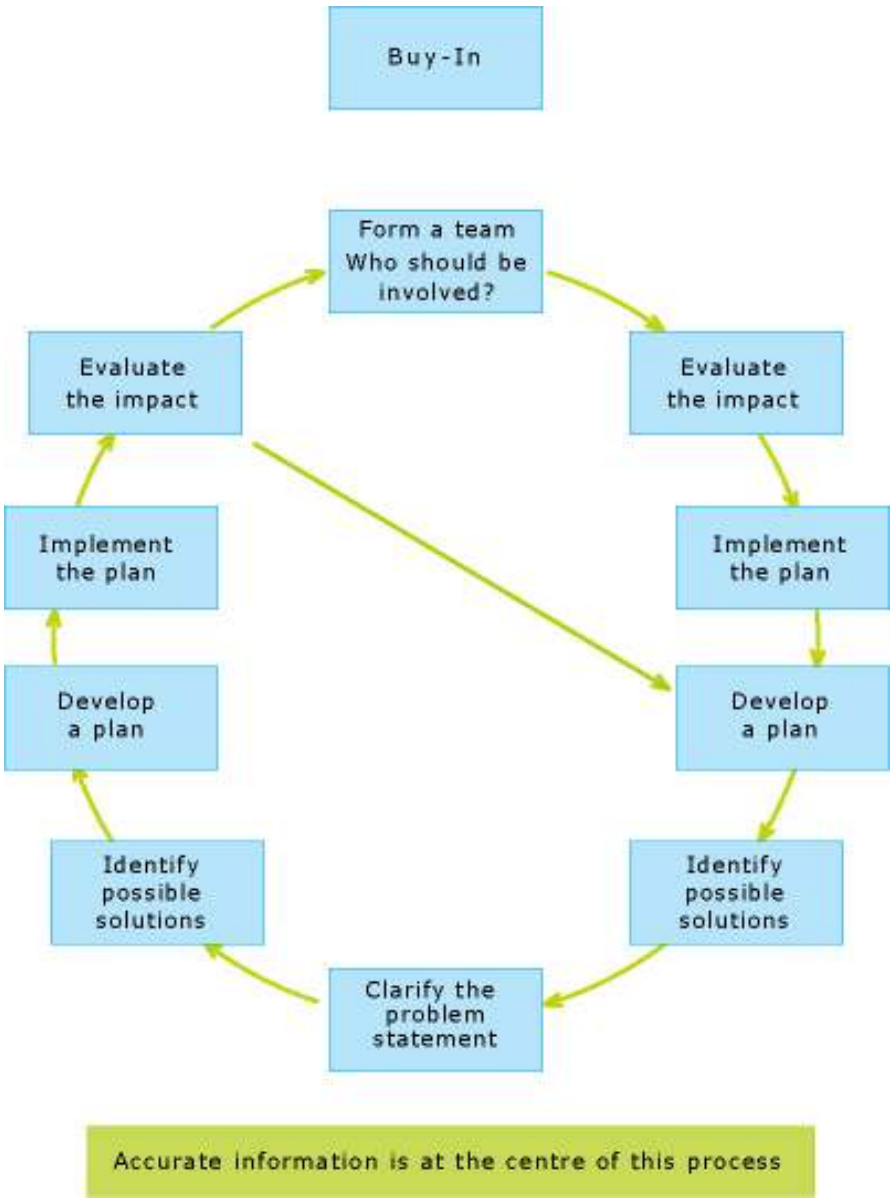
The burden of sexually transmitted disease including syphilis in a third world country is even more apparent, paving the way for comorbidities and HIV infection. Stabilisation of prevalence rates of syphilis is essential for a syphilis elimination effort, hence the need for ongoing research into syphilis prevalence trends. The lack of specified genitourinary medicine clinics serves as a drawback in infrastructure. Primary health care facilities, excellent research units and support networks such as Thetha Junction can however assist in the initiation of this much needed infrastructure within a cost-effective strategic plan.

Integration of services encompasses creation of health facilities in order to optimize prevention and care strategies, hence saving time and providing quality health care. In Latin America 'Maternal-child health and sexually transmitted diseases and HIV/AIDS integration' is one of the integrations related to reproductive health. It promotes testing for HIV and syphilis in order to decrease mother to child transmission of these diseases. Similarly, 'New populations and available family planning or STD and HIV/AIDS services integration' was aimed at addressing other populations at risk of sexually transmitted diseases in the Latin American context.[49]

In South Africa, the National STI initiative has addressed similar issues. STIs were recognized as a major health priority in South Africa because of their associated morbidity and mortality. Four sites were selected as pilot sites for intervention, focusing on STI management and prevention within the public health sector through monitoring and evaluation, training and support. Guidelines were then issued based on the successes and failures at the four selected sites.[51]

Figure 4 summarizes the approach that was used by the Reproductive Health and Research Unit (RHRU) in the STI initiative.

Figure 4: STI Initiative to Improve STI care at a District Level: The Quality Assurance Cycle.
(Adapted from Guidelines for Improving Quality of STI Management in a Health District, RHRU)



From this project, it was found to be essential to identify a team of people committed to improving the quality of STI care. The teams involved in this circumstance were motivated enough to undertake a number of initiatives, some of which became implemented at a

national level. The initiatives included compiling a workbook to support clinical training, encouraging STI contact tracing in local languages, monitoring performance at a clinic as well as a sub-district level and contacting the relevant centers to alleviate drug shortages. Key officials were mobilized in order to achieve goals. This entailed co-operation between officials of local and provincial authorities.[51]

Another initiative by the RHRU which shows progress and initiative in the South African context is the 'National Survey of HIV and Sexual Behavior among Young South Africans'. This survey comprised of comprehensive analysis of sexual and behavioral information and HIV testing in the 15 – 24 year old age group.[52] The survey shows that the youth of South Africa are indeed at risk of HIV infection with one in ten of them currently being infected. More than two thirds changed their sexual behavior once aware of their risk and many increased their use of condoms. Many however underestimated their personal risk of infection.[52] Much literature regards age 16 – 25 as being the age group at highest risk of STI's, including syphilis. Such a survey is therefore integral in approaching the burden of STI's in the South African context and can be used to positive effect in the initiation of a syphilis elimination effort in this country.

'The National STI/HIV Baseline Assessment 2002/2003' consisted of telephonic surveys of prmary health care facilities throughout South Africa, looking at facility description, staff allocation, numbers of STI patients, knowledge of drugs used in syndromic management, drug availability for syndromic management, antenatal syphilis screening, staff training in the management of STI's, HIV management and condom distribution.[53] The initiative found that only half of professional nurses working within primary health care facilities were trained in syndromic management of STI's. As a result treatment quality was compromised by insufficiently trained staff and inappropriate use of antibiotics available. Clinical assessment, counseling and record keeping were also compromised. As a result less than 50% of facilities provided appropriate treatment for vaginal discharge, urethral discharge and genital ulcers.[53]

Such an initiative is key to providing the infrastructure and training necessary for syphilis elimination.

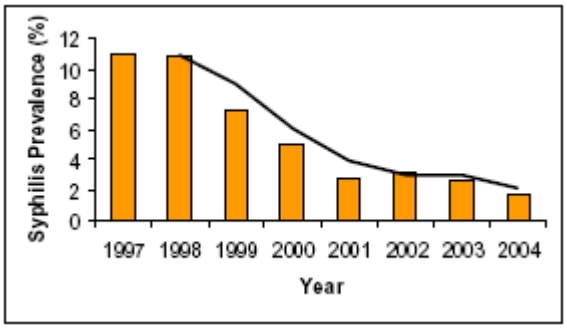
The RHRU has therefore contributed with excellent surveys to the improvement of STI care within South Africa and such care, if optimally initiated can be used in designing an approach to the elimination of Syphilis within a South African context.

1.8.3 Is syphilis declining in South Africa?

In October 2004, the National Department of Health conducted the fifteenth National HIV and Syphilis Antenatal Sero-prevalence Survey. The primary objective of this survey was to provide information on the prevalence of HIV and syphilis among pregnant females attending antenatal care in the public sector. The study design was a cross-sectional, anonymous unlinked survey among women attending antenatal care at selected sites in the nine provinces across South Africa. All pregnant women attending antenatal care for the first time in the index pregnancy were eligible for inclusion. The survey was conducted in October 2004. Blood, labeled with barcodes that were used on data collection sheets, was collected from the women. HIV ELISA tests were done and RPR tests were performed to identify syphilis. Results were compared with similar surveys from past years. Results show a definite trend toward declining syphilis rates from 1998 to 2004. A decline from approximately 12% to 2% was seen spanning this time period. (See figure 5.)[10]

Figure 5: Syphilis prevalence trends among antenatal clinic attendees: 1997 – 2004

(Adapted from the National HIV and Syphilis Antenatal Sero-prevalence Survey in South Africa 2004)



Such studies show the progress made by our health facilities in the decline of syphilis. Despite spanning the nine provinces, such surveys do however have limitations, as testing is done in one month only and only incorporates patients who seek antenatal care. They don't include miscarriages due to syphilis and the un-booked patient, who may, for social reasons, be at greater risk of the disease. Laboratory statistics may hence prove more valuable as access to all such results is possible.

CHAPTER 2:

RPR SEROPREVALENCE RESEARCH

2.1 METHODOLOGY

This study was a retrospective record review conducted at Johannesburg Hospital, Gauteng. The patients delivered at Johannesburg Hospital include high risk antenatal clinic patients as well as referrals from feeder clinics and secondary level hospitals. All positive RPR tests, irrespective of titre were included. The current prevalence was determined by a sample of RPR results of patients delivered at Johannesburg Hospital from 1 August 2002 to 31 January 2003. In addition, period samples were used and the RPR positive prevalence was determined for each of these periods. The approximate prevalence for each year from past to current periods was determined for two months of each year, six months apart from 1996 to 2002. In order to be representative, February (1 to 28/29) and August (1 to 31) of each of these years was chosen. January was avoided as a large number of patients travel in January and do not necessarily give birth where they attend antenatal clinic.

The control group, referred to as 'past prevalence' was the patients from the Stewart-Smythe study[7], which had been conducted on similar lines at the same hospital from 1 January 1995 to 31 March 1996. Although unpublished, a sample size of 15147 patients was used, these patients having given birth at Johannesburg Hospital.

Since data collection was done from labour ward registers, and all patients with available results for each specified period were used, bias during data collection was unlikely. Laboratory statistics of reactive syphilis serology of pregnant patients who presented to the Johannesburg Hospital, including booked and unbooked patients, were analysed in order to

confirm trends in RPR seroprevalence. This served to verify the results collected from the current period, as laboratory results from prior to the year 2000 could not be obtained. These results were not computerized.

Labour ward register reviews were done with the help of collation sheets using the following headings:

- Age
- Booked/ unbooked
- Hospital number/ date of delivery
- RPR 'positive'/ RPR 'negative'/ RPR 'unknown'
- HIV 'positive'/ HIV 'negative'/ HIV 'unknown'

This information was added so that any relevance to the change in RPR positive prevalence rate could be determined. Also, congenital syphilis data from 1995-1996 and 2000-2002 was collected in order to help identify whether the proposed decrease in RPR positive prevalence was indeed a true one (if proven) or if it was likely to be due to a large number of false negatives. This information was collected from the records of the Department of Peadiatrics at Johannesburg Hospital. The Centers for Disease Control, for the purposes of notification, includes in its definition of congenital syphilis, stillbirths associated with syphilis and the infants of mothers who were inadequately treated or untreated for syphilis, irrespective of the findings in the infant. This was the definition adhered to in this study.[14,15,16]

The results of the current study period and each prior year were collated separately to determine the trend in RPR positive prevalence. Microsoft Excel software was used to aid data entry. Statistical analysis of results of the current period as compared to the 1995 – 1996

control group was achieved using EPi-Info 6 statistical software. This analysis was then applied to each year between the 2 study periods. The contribution of other factors referred to in the collation sheets was also analysed. Comparison of prevalence rates was done using the chi-squared test (with statistical significance accepted at $p < 0.05$) and odds ratios with 95% confidence intervals.

Ethics approval was obtained for our study. (Annexure 1)

2.2 RESULTS

The records of 3832 patients were obtained for the current period (August 2002 – January 2003). Two thousand, nine hundred and five (75.8%) patients were RPR negative; 134 (3.5%) were RPR positive and 793 (20.7%) did not have RPR results available.

Using known results only, the current prevalence was determined at 4.4%, a statistically significant difference being observed when compared to the past prevalence of 19.5% in 1995/96 (Table 3). Similarly, a statistically significant decrease in rates of congenital syphilis was noted (Table 4).

Table 3: Comparison of RPR seroprevalence rates in 2002/03 compared with a similar sample taken in 1995/96

Sample	RPR seropositivity	Percent	Odds ratio = 0.19: (95%CI 0.16-0.23) (P< 0.0001)
2002/2003	134/3039	4.4	
1995/1996	2960/15147	19.5	

Table 4: Comparison of congenital syphilis prevalence rates in 2002/03 compared with those of 1995/96

Sample	Congenital syphilis	Percent	Odds ratio = 0 24. 95%CI (0.21-0.33) (P< 0.0001)
2002/2003	102/3089	3.3	
1995/1996	151/1195	12.64	

Verification of results using the laboratory statistics of seropositive pregnant women attending Johannesburg hospital for the study period revealed a prevalence rate of 4.8% (46/961 patients). This included 34 RPR positive tests and 12 Wasserman Reaction (WR) positive tests, which were all charted as RPR positive on the patients' booking cards. Booking results for the whole of 2002 were collected and revealed a seroprevalence rate of 4.6% (68/1467 patients) of which 66 were RPR positive and 2 were WR positive. From 1 January 2003 to 22 April 2003 (date when results were collected from the laboratory) the seroprevalence was noted to be lower at 3.4% (30/551 patients) of which 11 were RPR positive and 19 WR positive. Table 5 illustrates the availability of results for the period intervening the past and current study samples.

Table 5: Prevalence rates of RPR negative, RPR positive and RPR unknown patients in 1-month period samples from August 1999 to August 2002

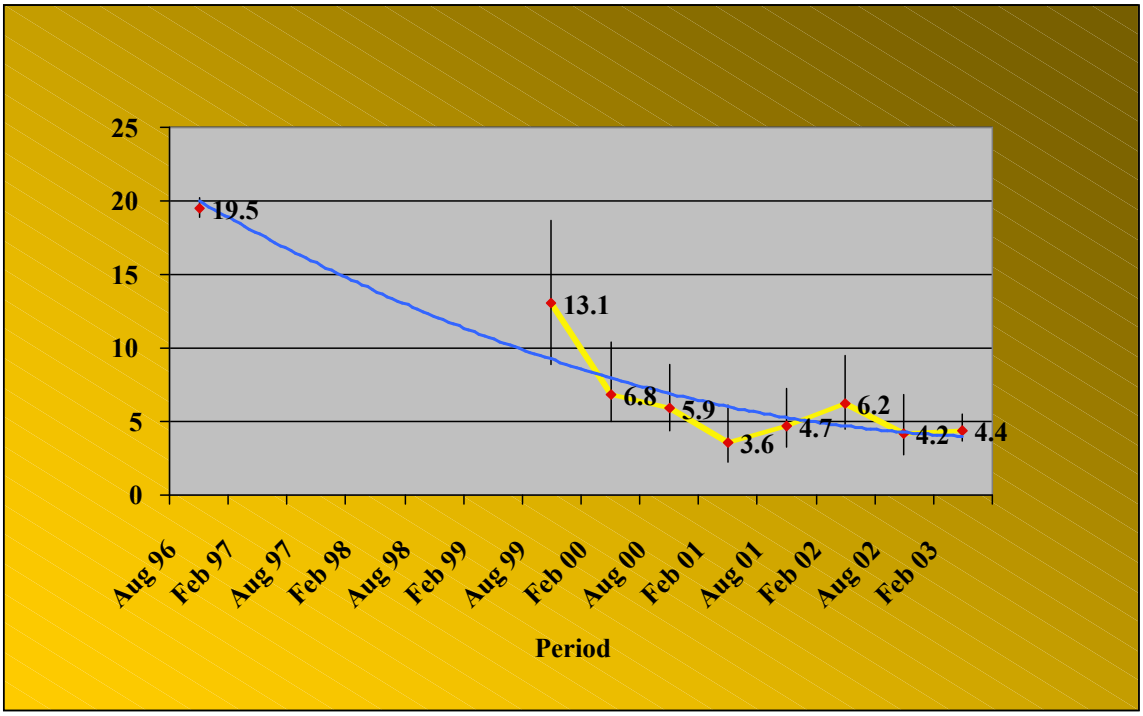
Results		Aug 1999	Feb 2000	Aug 2000	Feb 2001	Aug 2001	Feb 2002	Aug 2002
RPR negative	No.	173	397	493	433	530	426	476
	%	36.7	68.5	73.5	80.8	82.0	76.9	74.7
RPR positive	No.	26	29	31	16	26	28	21
	%	5.5	5.0	4.6	3.0	4.0	5.1	3.3
RPR unknown	No.	272	157	147	87	90	100	140
	%	57.8	26.6	21.9	16.2	13.9	18.1	21.9
Total results		471	583	671	536	646	554	637
Total known results		199	426	524	449	556	454	497
Known RPR prevalence		**13.1%**	**6.8%**	**5.9%**	**3.6%**	**4.7%**	**6.2%**	**4.2%**

Aug=August, Feb=February.

2.3 DISCUSSION

The observed decrease in the prevalence of positive RPR tests was statistically significant, the past period (1995 -1996) having had a RPR seropositivity rate of 19.5% as opposed to the current period (2002 – 2003) having a rate of 4.4%.

Figure 6: RPR seroprevalence rate progression from 1995/96 to 2002/03



The prevalence each year, from past to current periods, initially showed a statistically significant decrease followed by a stabilization in the prevalence, showing that the decrease is not linear but rather hyperbolic (Figure 6). This is extremely important as the RPR test is used as a marker for syphilis and, being an infectious disease, one needs to exclude the possibility of the decrease frequently observed during a 'seasonal' low. The fact that the decline in prevalence has been consistent and now stabilized makes this phenomenon unlikely with syphilis since the study in its comparison has spanned a period of seven years.

Also, since this study has dealt with the RPR seroprevalence rate, irrespective of titre, the true syphilis rate is likely to be even lower, as it is known that a large number of low-titre RPR positive results are false positives.[2,3,42]

With the decrease in the prevalence of RPR seropositivity it was important to assess whether there was a concomitant decrease in the rate of congenital syphilis. This was also noted with the prevalence decreasing from 12.6% in the past period (1995-1996) to a prevalence rate of 3.3% in the current period (2002 – 2003).

Although these results were obtained from the Johannesburg Hospital, statistics from another large local centre, Chris Hani Baragwanath Hospital, revealed 70 deaths from congenital syphilis in 1995, 11 in the year 2000, 8 in 2001 and just 6 in 2002, thus also showing a progressive decline in prevalence.

The concurrent and progressive decrease in the prevalence of congenital syphilis suggests that there has indeed been a true decrease in RPR seroprevalence from 1995 to 2003. The rates appear to have stabilized at between 4 and 6 %. If this is true nationwide, retesting in the third trimester, as previously suggested in areas of high prevalence[44], may no longer be an issue. Potential causes of the observed decrease in this study are many, including:

- Changes in the test characteristics with possible impaired sensitivity
- Changes in patient profile
- Potentially incorrect statistics in 1995
- A type 1 statistical error
- HIV effects on test characteristics
- Widespread antibiotic use

- Termination of pregnancy
- Miscarriages
- Sampling technique

The laboratory servicing the Johannesburg Hospital denies any changes in the test characteristics since 1995. Patients may well differ with education, improved psychosocial support structures, socio-economic upliftment, better nutrition and a greater awareness of safe sexual practices; although there is no obvious evidence that sexual practices have changed or usage of condoms has increased to such a degree to substantiate the decline in prevalence of syphilis. A type 1 error is improbable as the p values are extremely low. In HIV infected individuals, serological tests such as the RPR tests, which are based on the immune response of the individual, may well be falsely negative in both early and late stages of the disease due to deregulation of the immune responses.[36,37]

Widespread antibiotic use, especially with the high prevalence of HIV in the general population, and with the advent of syndromic management for sexually transmitted infections, may well account for the decrease in the prevalence of syphilis and hence RPR positive tests in the general population as well as the pregnant population.[2,19] In the penicillin-allergic, non-pregnant patient, syphilis can be treated with doxycycline, tetracycline, ceftriaxone and azithromycin.[2] These are all commonly used antibiotics so patients may well be treated unwittingly before they fall pregnant.

Termination of pregnancy and miscarriages may also mask the prevalence of positive RPR tests as many of these patients are not tested for syphilis and syphilis may itself be a causative factor in miscarriages after the first trimester and these patients would not reach the labour ward and be included in the RPR positive statistics. Frequent unprotected sexual intercourse

is a recognized risk factor for both STIs, unwanted pregnancies and termination of pregnancy.

Sampling technique problems are unlikely to have caused bias in this study. A number of verification exercises were undertaken as described above.

Limitations

The discussion has highlighted a number of limitations inherent in a study of this nature. The potential causes of a decrease in the prevalence of RPR positive tests as mentioned above could not be fully investigated.

Sampling of all patients delivered in the Johannesburg Hospital labour ward necessitated inclusion of patients referred to this tertiary labour ward from other institutions. All referral letters however did not come with the RPR and/or HIV results of these patients.

A number of verification procedures were done to obviate the above limitations where possible. The results of these procedures correlated well with the results of the study. The study however could not be based purely on laboratory results, as results from the laboratory were only available after the year 2000 on computer and previous results could not be obtained as laboratory registers are only kept for three months now that all results are charted on computer. The advantage of laboratory results though is that they include the results of blood tests of unbooked patients that were not in labour ward registers at the time of delivery but had been sent to the laboratory on admission.

Implications

Current practice dictated by our national guidelines includes routine testing for syphilis in the pregnant population with non-specific tests and treatment of all positive results irrespective of titre. This has implications to both the patient and the health system. Treatment of a possible false positive test result may negatively affect the patient's morale and relationship with her partner, as syphilis is a sexually transmitted disease and benzathine penicillin injections are extremely painful. However, specific serological tests for syphilis are expensive, results take longer and the longer a patient is left untreated, the greater the chance of repeated exposure, mid-trimester miscarriages, stillbirths and congenital syphilis.

For this reason as well as the fact that the decrease in congenital syphilis is indeed a positive outcome measure, I recommend that current practice still be continued until further studies are conducted in the different regions of South Africa. A similar study from Addington Hospital, KwaZulu Natal showed similar results.[54]

In the long term, it is reassuring to know that the RPR positive rate and hence the syphilis rate is approaching that of first world countries.[1] Natural syphilis is a disease exclusive to humans[1], not unlike poliomyelitis, and hence has the potential of being eradicated. It is possible that the current national guidelines of treatment irrespective of titre may have contributed to the decreasing prevalence rates of the condition in South Africa. Contact tracing is essential if male partners involved in spread of the disease are to be identified and treated. Perhaps testing for syphilis with RPR tests should be done at all consultations for sexually transmitted disease as well as all termination of pregnancy sites.[12,19] If this is done as an active attempt to eradicate the disease, prevalence rates could drop further. Routine treatment of a positive result irrespective of titre could become unnecessary as fewer specific

tests would be needed and patients would no longer need to be treated for false positive results.

CONCLUSION

RPR positive prevalence rates at the Johannesburg hospital have decreased significantly since 1995. The concurrent drop in the prevalence rate of congenital syphilis suggests that this is a true rather than an assumed decrease. The prevalence seems to have stabilized over the last few years. The implications of this lower RPR positive prevalence rate and the causes thereof are numerous and warrant further investigation.

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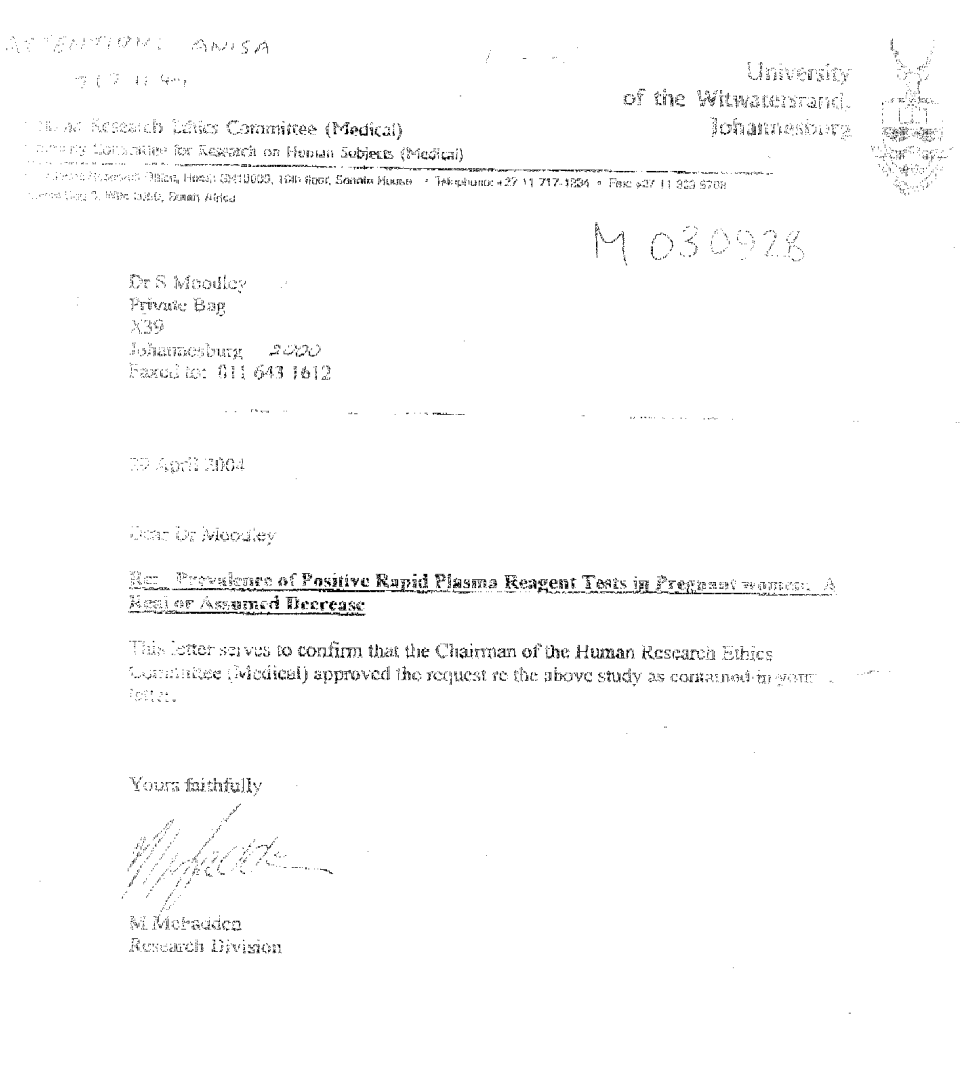
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ANNEXURE 1: ETHICS APPROVAL



ATTENTION: ANISA

University of the Witwatersrand, Johannesburg

Human Research Ethics Committee (Medical)
Faculty Committee for Research on Human Subjects (Medical)
Postal Address: Private Bag, Wits, 2050, 10th floor, Senate House • Telephone +27 11 717-1234 • Fax +27 11 339-8709
Website: http://, Wits Cable, South Africa

M 030928

Dr S Moodley
Private Bag
X39
Johannesburg 2000
Faxed to: 011 643 1612

29 April 2004

Dear Dr Moodley

Re: Prevalence of Positive Rapid Plasma Reagent Tests in Pregnant women: A Result of Assumed Decrease

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) approved the request re the above study as contained in your letter.

Yours faithfully

M Mehtaden
Research Division