

**THE IMPACT OF PNEUMONIA IN HUMAN IMMUNODEFICIENCY VIRUS (HIV-1)
INFECTED PREGNANT WOMEN ON PERINATAL AND EARLY INFANT
MORTALITY**

by

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DECLARATION

This thesis represents my original work, and has not been submitted previously to this or to any other University. Where assistance has been received, it has been duly acknowledged.

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Signature

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DEDICATION

For Hanna

ETHICAL APPROVAL

Ethical approval for the study of human subjects in this thesis was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu- Natal, Durban, South Africa. Reference number H 163/99. Permission to conduct the study at King Edward VIII hospital and King George V Jubilee Hospital was obtained from the Medical Superintendents, Dr Seedat and Dr Padayatchi respectively.

ABSTRACT

Background: Although the prevalence of pneumonia in pregnancy is reported to be less than 1%, the pregnant state and risk factors associated with the development of pneumonia adversely influence the outcome of pregnancy. KwaZulu-Natal is at the epicenter of the dual epidemics of tuberculosis and HIV-1 and the impact of these diseases occurring concurrently in pregnant women at King Edward VIII hospital (KEH), South Africa have been described previously. The impact of antenatal pneumonia in HIV-1 infected and uninfected women however has not been described in the study population and was investigated.

Methods: Pregnant women with clinical and radiological evidence of pneumonia were recruited from the antenatal clinic and labour ward at KEH. The study was conducted prospectively between January and December 2000. The clinical profile of these women and the causative organisms were determined. In addition the impact of HIV-1 infection, maternal immunosuppression and maternal pneumonia on obstetric and perinatal outcomes were evaluated. Mothers diagnosed with tuberculosis and multi drug resistant tuberculosis were hospitalised at King George V hospital until delivery.

Results: Twenty nine women were diagnosed with antenatal pneumonia (study arm) with *Mycobacterium tuberculosis* the only causative organism isolated. A control arm of 112 pregnant women was also studied. Maternal and perinatal mortality was restricted to the study arm with a maternal mortality ratio of 99 per 100 000 live births and a perinatal mortality rate of 240 per 1000 births.

Pneumonia was significantly associated with a negative overall obstetric outcome in the presence of HIV-1 infection, antenatal care, anaemia and second trimester booking status. In addition, the presence of pneumonia was significantly associated with maternal mortality.

There was a highly significant association between exposure to pneumonia and poor neonatal outcome. Maternal pneumonia, maternal HIV infection and the presence of medical and obstetric conditions were significantly associated with low birth weight and neonatal pneumonia. Further, maternal pneumonia ($p \leq 0.001$) and concurrent HIV infection ($p=0.002$) was significantly associated with neonatal death.

Conclusion: The presence of pneumonia in the antenatal period impacts negatively on maternal and neonatal morbidity and mortality. Health care providers must maintain a high degree of suspicion when managing a pregnant woman with unresolving upper respiratory tract symptoms and refer timeously for further investigation. Pneumonia and in particular pulmonary tuberculosis associated with HIV co- infection in pregnancy is a threat to mother and baby. Therefore in areas endemic for TB and HIV infection, it may be prudent to screen HIV positive pregnant women for symptoms

suggestive of pneumonia and thereby identify women requiring further investigations such as sputum microscopy and cultures, and a screening chest radiograph.

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CHAPTER 1– LITERATURE REVIEW

1.1 Global impact of HIV infection

Twenty six of the forty million people infected with human immunodeficiency virus (HIV) live in Sub Saharan Africa (SSA). Thirteen and half million of those infected are female (Joint United Nations Programme, 2004). South Africa (SA) bears the burden of disease with an estimated 5.3 million South Africans infected (Department of Health, SA, 2005). The epidemic also continues to grow in China, Indonesia, Papua New Guinea, Vietnam, several central Asian republics, the Baltic States and in Northern Africa (Joint United Nations Programme, 2004).

In SSA females are 1.2 times more likely to be infected than their male counterparts. This ratio increases in the 15- 24 year age group with females being 2.5 times more likely to be infected (Joint United Nations Programme, 2004). A national South African household survey conducted found that Kwa Zulu Natal (KZN) had an HIV prevalence of 11.7% (Nelson Mandela/ Human Sciences Research Council, 2002). Furthermore, Connolly *et al* (2004) reported a peak of 24.1% in HIV prevalence in females aged 20- 29 years.

Antenatal prevalence rates are an accepted HIV monitoring tool as it probably reflects the approximate infection rates of both males and females aged 15- 49 years (Walker *et al*, 2003). Six SSA countries (Namibia, Lesotho, Swaziland, Zimbabwe, South Africa and Botswana) have antenatal prevalence rates of 20% or higher (Joint United Nations Programme, 2004). Botswana, Lesotho, Namibia and South Africa have the highest global antenatal prevalence rates exceeding 30% (Joint United Nations Programme, 2004). A steady increase in the South African antenatal prevalence rate has been identified from 1.7% in 1991 to 29.5% in 2004 (figure 1) (Department of Health, SA, 2005). The developing trend reflects a stabilization phase in the epidemic. The province of KZN ranked first with a prevalence rate of 37.5% compared to 32.6% and 13.1% in the provinces of Mpumalanga and Western Cape respectively. The highest prevalence rate (35.4; CI 95%, 33.6- 37.2) was in the age group 25 to 29 years.

The contribution of HIV/ AIDS to morbidity and mortality is well established. There are limited reports of HIV-1 related morbidity in pregnant women. These include post operative complications (Semprini *et al*, 1995), nutritional deficiencies such as anaemia (Burns *et al*, 1999), sexually transmitted diseases (Wawer *et al*, 1999), malaria (Verhoeff *et al*, 1999) and

other infections such as hepatitis C (Michielsen and van Damme, 1999), varicella (De La Cruz Moron *et al*, 1999) and measles (Dao *et al*, 1997). Pulmonary complications are the most common presentation in AIDS defining illnesses. Specific causes include tuberculosis (TB), *Pneumocystis carinii* pneumonia (PCP), acute bacterial infections (such as *Haemophilus influenzae*, *Streptococcus pneumoniae*), fungal infections (such as *Histoplasma capsulatum*, *Cryptococcus neoformans*) and viral infections (such as cytomegalovirus) (Saade, 1997). PCP has been reported to occur mainly in the United States while pulmonary tuberculosis (PTB) occurs mainly in under resourced countries.

HIV/ AIDS is the third leading cause of death among all women aged 25 to 44 years in the United States and is the leading cause of mortality among African- American women in the same age group (Anonymous, 1996b). In Africa it is the leading cause of adult death and disease (World Health Organisation [WHO], 1999a) and studies in Zambia, Uganda, Malawi and Zimbabwe have highlighted the tandem increase in maternal mortality with the HIV/ AIDS epidemic (Ahmed *et al*, 1999; Sewankambo *et al*, 1994; Bicego *et al*, 2002).

In SA, it is estimated that 40% of adult deaths (15- 49 years) are attributable to HIV/ AIDS (Medical Research Council, 2001). In females the mortality rate between 1988 and 1999/ 2000 shows a bimodal pattern with the first peak at 25 to 34 years of age and the second occurring in old age. The confidential enquiry into maternal deaths in South Africa found that HIV/ AIDS was the commonest indirect cause of maternal deaths at all levels of health care (Saving Mothers, Department of Health, SA, 2006). It is likely that the introduction and availability of highly active anti retroviral therapy (HAART) will result in a decline in mortality rates. Current guidelines in South Africa recommend the use of HAART in pregnancy to improve maternal health and the use of single dose nevirapine to mother and baby to decrease the mother to child transmission rates.

The impact of maternal HIV-1 infection on perinatal and neonatal outcomes is more pronounced in under resourced settings. Maternal HIV-1 infection is associated with low birth weight babies (LBW), prematurity (Temmerman *et al*, 1994) and a higher risk of infant death (Brocklehurst and French, 1998), especially in advanced HIV-1 infection.

In summary, due to the negative impact of HIV-1 infection on maternal and neonatal morbidity and mortality, efforts to optimize care must be established.

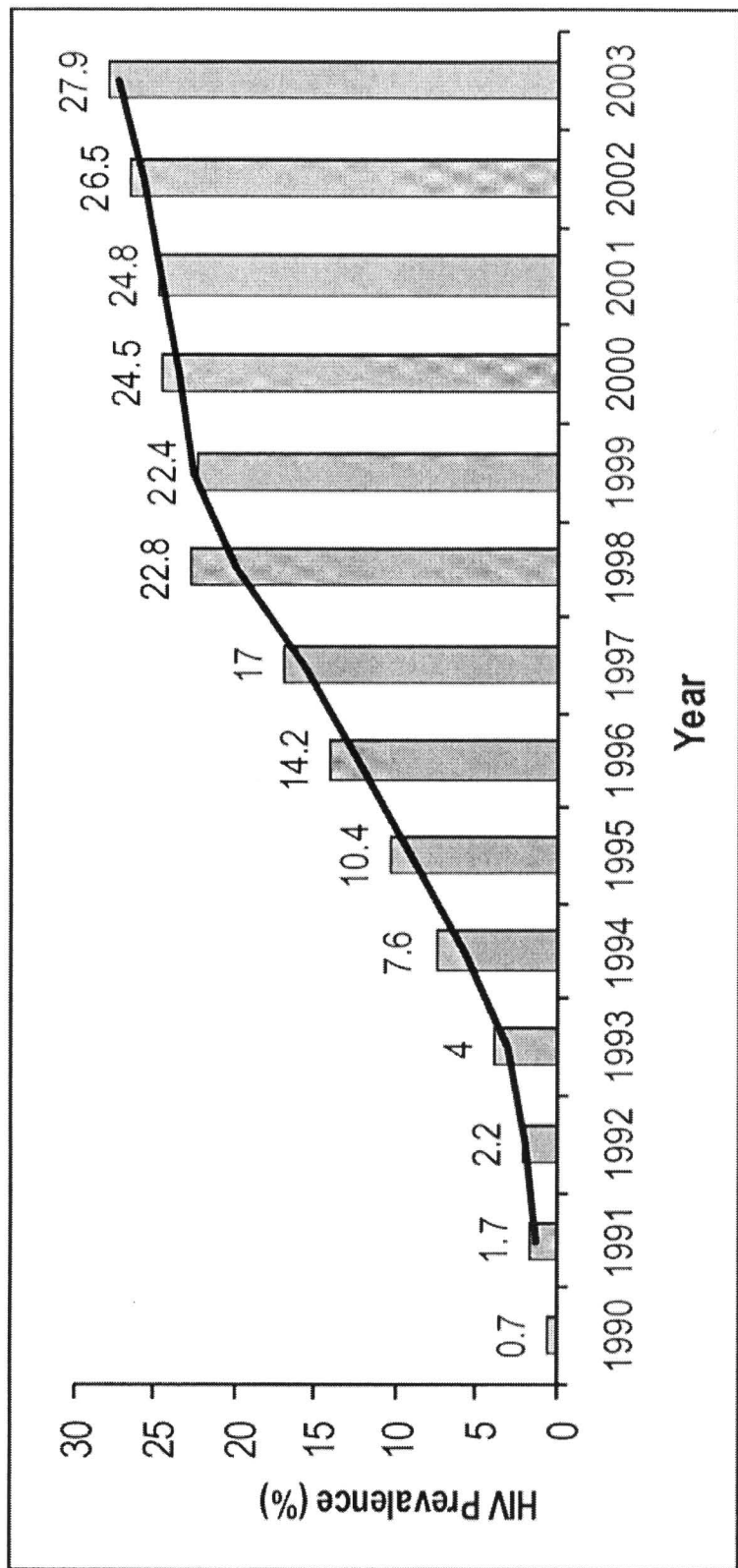


Figure 1: Prevalence of HIV among antenatal care attendees in South Africa, 1990-2003

Courtesy of Department of Health, South Africa (2005). National HIV and syphilis antenatal seroprevalence survey in South Africa 2004. Department of Health, Pretoria.

1.2 Pneumonia in pregnancy

1.2.1 Introduction

Pneumonia in pregnancy occurs in less than 1% of antenatal attendees (Kaunitz *et al*, 1985) which is similar to figures reported for non- pregnant adults. However the pregnant state and risk factors associated with the development of pneumonia adversely influence the outcome of pregnancy. It is the third leading cause of indirect maternal mortality during pregnancy, labour and the puerperium in the United States (Visscher and Visscher, 1971).

Incidence rates depend on patient population, patient characteristics and availability of appropriate treatment. In the pre- antibiotic era, Findland and Dublin (1939) showed a high incidence rate of 1 per 158 deliveries and Hopwood (1965) reported an incidence rate of 1 per 118 deliveries. Subsequently, Benedetti *et al* (1982); Madinger *et al*, (1989) and Berkowitz and LaSala (1990) reported a decrease in incidence rates to 1 per 2288, 1287 and 367 deliveries respectively. Maternal and fetal outcomes were poor with a reported 70% maternal mortality ratio in early reports (refer table 1 for summary of historical findings). The stillbirth rate was high with pregnancy losses experienced in 40 of 64 patients. Seventy one percent of these losses occurred in the third trimester (Ramsdell 1905). Clinical outcomes improved with the advent of antimicrobial therapy and maternal mortality.

1.2.2 Risk factors for the development of pneumonia

Risk factors for the development of antenatal pneumonia include pregnancy and its' associated immunological (Sridama *et al*, 1982; Baley and Schacter, 1985; Hirahara *et al*, 1980; Chardonnens and Jeannet, 1980) and mechanical changes (Fishburne, 1979; Elkus and Popovich, 1992), underlying chronic medical disease, asthma (Munn *et al*, 1999), anaemia, illicit drug use, tobacco use and HIV seropositivity (Benedetti *et al*, 1982; Madinger *et al*, 1989; Berkowitz and LaSala, 1990; Munn *et al*, 1999; Richey *et al*, 1994). The correlation between risk factors and adverse obstetric outcomes was confirmed in studies by Benedetti *et al* (1982), Munn *et al* (1999) and Berkowitz and LaSala (1990) but Richey *et al* (1994) presented evidence that adverse outcomes did not relate to the reported risk factors.

The healthy female generally tolerates the mechanical changes that occur in pregnancy. Pneumonia and acute and chronic lung disease however, diminish the respiratory reserve and respiratory failure can result (Ramsey and Ramin, 2001). Immunological changes that place the mother at risk include the following:

- Decreased lymphocyte proliferative response, especially in the second and third trimester
- Decreased natural killer cell activity
- Change in the T- cell population: a decrease in the total pool with decrease in T- helper cells and increase in T suppressor cells
- Decreased or absent lymphocyte cytotoxic activity
- The production by the trophoblast of a substance that could block maternal recognition of fetal MH compatible antigen
- Hormones in pregnancy (progesterone, human chorionic gonadotropin, alpha feto- protein and cortisol) that may inhibit cell mediated immunity.

(Sridama *et al*, 1982; Baley and Schacter, 1985; Hirahara *et al*, 1980; Chardonnens and Jeannet 1980).

In addition, asthma causes a 5 fold increase in risk for developing pneumonia (Munn *et al*, 1999) and chronic medical conditions known to increase risk include diabetes mellitus, hypertension, cardiac disease and chronic lung disease.

Aside from the above risk factors, other factors that influence outcome include age and parity, gestational age at the time of diagnosis and the extent and distribution of the pneumonia on chest radiograph. Patients under the age of 30 years were found to have better outcomes and the incidence rate of pneumonia was higher in primigravidae (Ramsdell, 1905; Oxorn, 1955) compared to multigravidae (Findland and Dublin, 1939). More recently, a mean parity of 2 was reported by Richey *et al* (1994). Ninety two percent of cases are diagnosed in the 2nd and 3rd trimester (Berkowitz and LaSala, 1990; Richey *et al*, 1994) and Munn *et al* (1999) found that women were diagnosed at a mean gestational age of 29.3 weeks. These latter authors also found that lobar pneumonia was associated with the highest mortality (19.7%) and the greatest fetal loss.

1.2.3 Outcomes of pregnancies complicated by pneumonia

These are dependent on the patient characteristics (as described above) and the measured outcome parameters include:

1.2.3.1 Maternal deaths: Ramsdell (1905) and Findland and Dublin (1939) reported maternal mortality rates of 27.3% and 32% respectively. A marked decline was noted following the introduction of antibiotics and mortality rates ranged between 0% (Benedetti *et al*, 1982; Berkowitz

and LaSala, 1990) to 12.5% (Oxorn, 1955). Factors influencing maternal survival included the lack of severe underlying medical illnesses, initiation of treatment within 7 days of onset of symptoms and the absence of bacteraemia (Benedetti *et al*, 1982).

1.2.3.2 Premature labour and delivery: The pregnant mother tolerates poorly the loss of ventilatory capacity that results from pneumonia. The resultant hypoxaemia and acidosis which may accompany acute pneumonia has a negative effect on the fetus and has been reported to result in preterm labour in 11.1% (Benedetti *et al*, 1982) and 40% (Madinger *et al*, 1989) of mothers. In the group of mothers studied by Madinger *et al* (1989), preterm labours were triggered by multiple maternal complications including bacteraemia (16%), empyema (8%), atrial fibrillation (4%) and respiratory failure requiring ventilation (20%). Richey *et al* (1994) and Berkowitz and LaSala (1990) however did not report higher complication rates of preterm labour in the presence of antenatal pneumonia.

1.2.3.3 Perinatal mortality rate (PMR): The PMR is influenced by maternal characteristics and any delays in diagnosis and implementation of treatment (discussed under 1.2.4). The impact is evident in differing perinatal mortality rates (Benedetti *et al*, 1982; Madinger *et al*, 1989). Mothers studied by Benedetti *et al* (1982) presented within 7 days of onset of illness, were treated immediately and did not develop a bacteraemia. As a result, the PMR in this group was 40/ 1000 deliveries in comparison to the PMR of 115/ 1000 deliveries in the group of ill mothers studied by Madinger *et al* (1989).

1.2.3.4 Neonatal mortality rate/ abortions: An abortion rate of 55% (Findland and Dublin, 1939) and neonatal mortality rate of 41% (Ramsdell, 1905) occurred in the pre antibiotic era. Benedetti *et al* (1982) and Madinger *et al* (1989) reported neonatal death rates of 11% and 12% respectively with the use of antibiotics.

1.2.3.5 Birth weight: Neonates born to mothers with antenatal pneumonia weighed 150 (Yost *et al*, 2000) to 400 grams (Berkowitz and LaSala, 1990) less than neonates from a comparable control group. Munn *et al* (1999) reported a lower average birth weight in pregnancies complicated by pneumonia; 34% of neonates exposed to antenatal pneumonia in comparison to 14% in a control arm were LBW babies.

1.2.3.6 Transmission of common viral pathogens from mother to fetus/ newborn:

Goodrum (1997) reported that:

- a. Influenza virus crosses the placenta and can cause neonatal infection but it does not however have a teratogenic effect. Further short or long term sequelae were not noted in infected neonates.
- b. If *Varicella zoster* infection occurs before 20 weeks gestation, a 2% risk of developing congenital malformation exists. In addition, premature labour and the development of varicella infection in the neonate can occur.

1.2.4 Diagnosis and management

Worsening or persistent symptoms following an upper respiratory tract illness during pregnancy should alert health care givers to perform investigations to exclude an underlying pneumonia. Further investigation should be prompted by the symptoms and signs outlined in appendix C. The overall approach to antenatal pneumonia is to admit, manage any underlying medical illness, investigate and prescribe appropriate antimicrobial or antiviral therapy for the pneumonia. If respiratory function is compromised, supportive management includes an arterial blood gas with appropriate oxygen support and ventilation if indicated.

Physical examination is only 47- 69% sensitive and 58- 75% specific for the diagnosis of pneumonia. Therefore all suspected cases require chest radiographs as an additional diagnostic tool (appendix D). Other diagnostic aids include microscopy, cytology, staining and culture of sputum samples and bronchoscopy specimens and culture, and serologic testing of blood samples.

Causative organisms cannot be isolated in 40- 61% of community acquired pneumonia (Madinger *et al*, 1989; Panting- Kemp *et al*, 2000; American Thoracic Society, 1994) due to varying the diagnostic methods that have been described above. They are similar however, to causative organisms in non pregnant females of reproductive age. Approximately two- thirds of infections are bacterial, two thirds of which are caused by *Streptococcus pneumoniae* (Nolan and Hankins, 1995). Pneumococcal pneumonia is characterised by the abrupt onset of fever and chills which is accompanied by pleuritic chest pain, blood tinged or purulent sputum and dyspnoea. Bacteraemia occurs in 25- 70% of patients and causes higher mortality rates despite intensive care (Brandenberg *et al*, 2000; Phair *et al*, 1983). The second commonest bacterial cause is *Haemophilus influenzae*. Therefore if bacterial pneumonia is suspected, antibiotic treatment active against these 2 organisms need to be prescribed. Additional concerns with regards to emerging antibiotic resistance profiles, the possibility of atypical pneumonia caused by *Mycoplasma*, *Legionella* or *Chlamydia* and nosocomial infections must also to be considered. The contribution of TB and its combined impact

with the HIV epidemic on the antenatal population cannot be underestimated and will be discussed later in the chapter.

Viruses are the second most common cause of antenatal pneumonia. Viral pneumonia has a worse prognosis in pregnancy and complications include bacterial super infection, acute respiratory distress syndrome and respiratory failure (Rigby and Paternak, 1996). Influenza virus and varicella are the two common viral causative organisms. Influenza infection typically has a short incubation period characterised by an abrupt onset of symptoms which include a high fever, malaise and myalgia, sore throat, headache and a productive cough (Ramsey and Ramin, 2001). These symptoms usually resolve within 3 days and the complications described earlier arise after five days (Kort *et al*, 1986; Ramsey and Ramin, 2001). Varicella pneumonia is more common in the pregnant population compared to the non pregnant population. Within 3- 5 days of developing a rash, symptoms and signs of pneumonia develop. It is usually accompanied by dyspnoea, malaise, pleurisy and sputum tinged with blood. Viral pneumonia therefore requires prompt identification and aggressive management to prevent morbidity and mortality.

Pneumonia in the immunocompromised population is caused by a number of organisms and include bacterial (*Mycobacterium* and *Mycoplasma*), parasitic (*Pneumocystis carinii*), viral, fungal and protozoal (*Cryptococcus neoformans*, *Histoplasma capsulatum* and *Coccidioides immitis*) organisms. Pneumonia due to fungal and protozoal causes is usually part of widespread disease and presentation is dependent on organ involvement.

Pneumocystis carinii pneumonia (PCP) is the most common cause of AIDS related deaths in pregnancy (Ahmad *et al*, 2001). Twenty two cases of PCP in pregnancy were described by Ahmad *et al* (2001) with a 50% maternal mortality, 5 intra uterine deaths and 4 neonatal deaths reported. The diagnosis of PCP is prompted by a high index of suspicion as the presenting symptoms of tachypnoea, dyspnoea, non productive cough and fever are often dismissed as the symptoms of pregnancy. Typically PCP has an insidious onset with a normal chest radiograph that can proceed to progressive deterioration with bilateral alveolar disease in the perihilar and lower lung fields (Minkoff *et al*, 1986).

In summary, although pneumonia in pregnancy has a low incidence rate, it results in significant morbidity and mortality in mother and baby if poorly managed. Therefore any pregnant female with a non resolving upper respiratory tract infection and pyrexia must be closely monitored and investigated further.

Table 1: Historical perspective of pneumonia in pregnancy

Author	Antenatal cases	Outcome
Ramsdell (1905)	350	144 diagnosed in 1 st 6 months, 70% aborted. Overall maternal mortality: 70% 41% of newborns born at a viable age died
Findland and Dublin (1939)	212	55% aborted 32% maternal mortality
DeLee and Greenhill (1943)		66% spontaneous abortions

1.3 Tuberculosis in pregnancy

1.3.1 Introduction

Tuberculosis was declared a global emergency by the World Health Organization (WHO) in 1993. It affects over a third of the world's population and accounts for 2- 4% of burden of disease; 7% of all deaths and 26% of all preventable deaths (Castelo *et al*, 1995). Twenty two high burden of disease countries were identified at the end of 2002 (WHO, 2002). There are 7.1 million new cases and 2.5 million deaths occurring annually in under resourced countries, 95% of which is confined to South East Asia and Sub Saharan Africa (Murray *et al*, 1990). The TB epidemic was mirrored by a concomitant explosion of HIV infection. Tuberculosis rates per capita in Africa averaged at 259/ 100 000 population with an average HIV infection rate of 32% (Dye *et al*, 1999). Co infection rates range between 50- 70% (Margono *et al*, 1994). Factors other than HIV that affect the incidence of TB include poor socio-economic conditions, homelessness, immigration patterns and drug addiction. Tuberculosis is the leading infectious cause of death in females worldwide and the third leading cause of morbidity and mortality in the reproductive age group in the developing world (Connolly and Nunn, 1996). Tuberculosis in pregnancy is uncommon in the United States but an incidence rate of 0.1% has been noted in TB endemic areas. The rate of progression of infection to disease in pregnancy has been poorly documented. It has been established however that the prevalence in the pregnant population is comparable to that in the non pregnant population (Pridie and Stradling, 1961; Murray *et al*, 1999; de Cock *et al*, 1992; Nunn *et al*, 1994). Schaefer *et al* (1975) reported prevalence rates of 18- 29 / 100 000 compared to 94.8/ 100 000 (in pregnancy) reported by Nunn *et al* (1994). In rural SA, TB amongst females with a mean age of 33.4 years increased from 28% to 37% between 1991 and 1995 (Wilkinson and Davies, 1997b). An increase in TB related deaths to 157.5% and 400% in that age group was reported by Connolly *et al* (1998) and Kleinschmidt (1999) respectively. In pregnancy an 8.6 fold increase in antenatal TB was noted at a tertiary centre (Pillay *et al*, 2001).

1.3.2 Impact of pregnancy on tuberculosis

This has been debated since the time of Hippocrates when TB was thought to be beneficial to the course of pregnancy. By the mid 19th century this view changed as TB was reported to worsen during pregnancy and termination of pregnancy was recommended by the early 20th century (Vallejo and Starke, 1992; Hedvall, 1953). The relapse and reactivation of TB as well as the impact of pregnancy on TB has also been argued.

Good *et al* (1981) performed a retrospective study on activation and relapse of TB disease in pregnancy. A total of 27 cases were reported and of those, six cases occurred during pregnancy and 21 occurred in the year post delivery. Snider (1984) reported that postpartum relapses were higher and Good *et al* (1981) described a 65% relapse rate one year post delivery in otherwise asymptomatic patients. Some investigators contradict these findings and report a lower relapse rate of 10- 15% one year postpartum, as well as reporting no evidence of an increased risk post partum (Pridie and Stradling, 1961; Hedvall, 1953; Good *et al*, 1981; de March, 1975; Cohen *et al*, 1952; Lane, 1957). It was also thought that the weakened immunological state related to pregnancy could reactivate TB (Seegers, 1954). In addition, studies have failed to show pregnancy to have adverse effects on the course of adequately treated TB (Schaefer *et al*, 1957; Flanagan and Hensler, 1959; Wilson *et al*, 1973).

1.3.3 Impact of tuberculosis on pregnancy

Early reports on the effect of TB on the course of pregnancy were also contradictory. Recently significant adverse outcomes have been documented. It is the extent of clinical and radiographic disease and individual susceptibility to TB acquisition that determines the course of the disease rather than the interaction between TB and pregnancy (Cohen *et al*, 1952, Lane, 1957).

Poor outcomes are found if TB is diagnosed at an advanced gestational age or in the puerperium and in those untreated in pregnancy. The late diagnosis of TB results in a four fold increase in obstetric morbidity and a nine fold increase in preterm labour (Figuroa- Damian and Arredondo- Garcia, 1998). Increased incidence of spontaneous abortions, post partum haemorrhage, toxemia, labour difficulties (Bjerkedal, 1975) and oligohydramnios have also been reported (Margono *et al*, 1994).

The site of TB is another factor which influences the outcome. Extra pulmonary tuberculosis (EPTB) accounts for 5- 10% of antenatal TB cases with bone, meninges, lymph nodes, genital tract and the placenta being affected. Between 1983 and 1993, EPTB accounted for 20% of the antenatal TB cases in India (Jana *et al*, 1999). Cases of EPTB without lymph node involvement were associated with higher antenatal hospitalization and adverse perinatal outcome as a result of advanced maternal disease. In a recent retrospective review, EPTB accounted for 53% of TB in pregnancy with involvement of the abdomen, lymph nodes (cervical, intra thoracic, parasternal and axillary) and ischio rectal fossa (Kothari *et al*, 2006). Although women sought medical attention late in the disease due to the sites involved, there were no maternal or perinatal deaths.

1.3.4 Tuberculosis and HIV co infection

Few reports of TB and HIV co-infection in pregnancy exist despite the greatest impact occurring in females in the reproductive age group. Possible dynamics in co infected cases include pregnancy as a risk factor for the development of TB in HIV infection (Gilks *et al*, 1990), the increased risk post partum of TB in HIV infected females (Leroy *et al*, 1995) and whether pregnancy poses any additional risk to the development of TB (Espinal *et al*, 1996). Reports on the combined impact of TB and HIV have been limited (Margono *et al*, 1994; Brost and Newman, 1997; Mofenson *et al*, 1995). Margono *et al* (1994) reported on eleven women with pulmonary TB (PTB) who had agreed to HIV testing. Seven of these women were HIV-1 co infected. In comparison, Llewelyn *et al*, (2000) described 10 of 13 PTB patients to be HIV uninfected. The incidence of TB HIV co infection was reflective of the impact of HIV on TB incidence in New York (Margono *et al*, 1994) and this finding was not evident in the United Kingdom (Llewelyn *et al*, 2000).

Reports from Africa have shown an increased risk of the development of TB in HIV infected women post delivery (Gilks *et al*, 1990; Leroy *et al*, 1995). In 215 HIV infected pregnant women followed up for a 4 year period post delivery, the incidence of TB was 2.9 per 100 women- years and in HIV uninfected women this incidence was 0.2 per 100 women-years (Leroy *et al*, 1995). Gilks *et al* (1990) reported the development of active TB in six women six months post delivery. Five of these women were HIV infected compared to one HIV uninfected woman. Almost 79% of women attending a tertiary centre in SA had PTB and 63% of the women were diagnosed in the third trimester (Pillay *et al*, 2001). There was no statistical difference in the rate of sputum smear microscopy positivity and diagnosis of PTB between the HIV infected and uninfected women. The prevalence of TB in HIV uninfected mothers was $72.9/10^5$ compared to a prevalence of $774.5/10^5$ in co infected mothers. The attributable fraction of TB related to HIV infection was 71.7%.

1.3.5 Maternal mortality

Well recognized direct causes of maternal mortality include hypertensive disorders of pregnancy, obstetric haemorrhage and sepsis (Moodley *et al*, 1996; Melrose, 1984). The contribution of TB to maternal mortality varies. Tuberculosis accounted for 25% of the 58% of non- obstetric related mortality in Zambia (Ahmed *et al*, 1999). Tuberculosis- HIV-1 co- infection was present in 92% of the patients. Tuberculosis contributed between 6.3- 10% of maternal deaths in India (Juneja *et al*, 1994) and 6.6% in Mexico (Figueroa- Damian and Arredondo- Garcia, 1998). Tuberculosis was established as the third leading cause of death following sepsis and hypertensive disorders of

pregnancy in South Africa (Khan *et al*, 2001). In the latter study, the combined impact of dual infection was evident as 93% of TB related mortalities occurred in HIV-1 co infected mothers. The mortality rate in such cases was 121/ 1 000 live births compared to 38.5/ 1 000 live births in women with TB infection alone. Parameters that reached statistical significance in co infected women were earlier time to death and less likelihood to be ventilated. There were no significant differences identified in age, parity, previous abortion and booking status between the TB -infected and uninfected women (Khan *et al*, 2001).

1.3.6 Presentation, diagnosis and treatment of tuberculosis in pregnancy

Delays in the diagnosis of TB in pregnancy are multifold. The presentation of TB in pregnancy is non specific with symptoms similar to that in non pregnant females and often early disease and symptoms mimic the physiologic changes of pregnancy (Llewelyn *et al*, 2000; Doveren and Block, 1998). Between 19 - 75% of patients diagnosed with TB are asymptomatic (Good *et al*, 1981; Bjerkedal *et al*, 1975; Cantwell *et al*, 1994). Carter and Mates (1994) matched a group of pregnant women with PTB to non pregnant women with PTB and found pregnant women to be significantly more likely to be asymptomatic at the time of diagnosis. Other factors for delayed diagnosis include EPTB with few symptoms and late presentation (Kothari *et al*, 2006), the deference of the CXR in pregnancy, smear negative sputum samples in TB transmitting mothers, delay in sputum culture results for *M tuberculosis* and cases where the neonate is the index case (Pillay *et al*, 2004b).

The key to the diagnosis of PTB is for the care giver to maintain a high index of suspicion and refer for comprehensive investigations. Ideally samples for acid fast bacilli (AFB) detection are needed. As PTB is the commonest form of TB in pregnancy, sputa samples are required but lymph node biopsies, cerebrospinal fluid samples and endometrial/ placental sampling post delivery can also assist in diagnosis. Other tools used include chest radiographs with abdominal shielding and tuberculin skin tests. The value of skin tests in endemic areas however is limited as it does not distinguish between infection and activity nor can it indicate the extent of the disease.

The initiation of anti-TB medication in pregnancy is based on the benefit to the mother, fetus, family and community. A delay in treatment results in higher mortality rates (Pablos- Mendez *et al*, 1996) and transmission to the neonate (Pillay *et al*, 2004b). In the United States, treatment is recommended for 9 months with Rifampicin (RIF), Isoniazid (INH) and Ethambutol (EMB) (Centre for Disease Control and Prevention, 1993), with changes to therapy based on susceptibility results. Treatment is continued for 3 months following sputum culture negativity. In the United Kingdom

treatment regimens include Pyrazinamide (PZA) (Llewelyn *et al*, 2000). National guidelines for South Africa are based on weight bands and recommend 2 months treatment with RIF, INH, PZA and EMB and a continuation phase of 4 months with RIF and INH only (Department of Health, SA, 2000a) (appendices E.1 and E. 2).

In HIV co infected patients 9 to 12 months of initial TB treatment is followed by 6 months of follow up therapy. Human immunodeficiency virus infected pregnant women with a positive tuberculin skin test in absence of active disease (Brost and Newman, 1997) are offered prophylaxis with INH and PZA for 12 months.

1. 3.7 Perinatal outcomes

Adverse perinatal outcomes are more pronounced if (maternal) pulmonary lesions are advanced, if treatment is delayed or remains incomplete late in pregnancy. Active PTB poses an increased risk of prematurity, acute fetal distress, intra uterine growth restriction (IUGR), LBW and perinatal mortality (Jana *et al*, 1994). The frequency of acute fetal distress in TB exposed neonates was 15.2% compared to 6.3% in controls ($p < 0.01$). Jana *et al* (1994) reported a 2 fold increase in prematurity, SGA and LBW and a 6 fold increase in perinatal deaths in TB exposed neonates. Extranodal TB also influenced perinatal outcome resulting in apgars below 6 and a 3 fold increase in LBW babies as compared to controls (Jana *et al*, 1999). This was comparable to results from Mexico of a 2 fold increase in perinatal morbidity in TB exposed neonates (Figueroa- Damian and Arredondo- Garcia, 1998). Ratner *et al* (1951) reported prematurity in 23- 64% of cases depending on severity of disease. Locally, the perinatal mortality rate (PMR) associated with maternal TB-HIV co infection is 1.6 fold higher than the general figure for the province of KwaZulu-Natal. Prematurity, LBW and IUGR occurred in 46%, 66% and 49% of these exposed neonates respectively (Pillay *et al*, 2004b).

Despite advances in treatment options, perinatal outcomes have not improved. In 1975, a 10 fold increase in fetal loss between 16- 28 weeks was reported by Bjerkedal *et al* (1975). Some studies however report good fetal outcomes (Kothari *et al*, 2006; Deshmukh *et al*, 1964; Selikoff and Dorfmann, 1965).

Concern over increased congenital abnormalities was raised with the introduction of anti tuberculous therapy (appendix E.3). RIF, INH, Streptomycin (S), EMB, Kanamycin (KAN) and Cycloserine (CYC) cross the placenta. Safe use of RIF, INH and EMB in pregnancy has been established. Streptomycin is associated with 8th nerve damage in 1 of 6 fetuses resulting in mild vestibular damage to profound bilateral deafness (Holdiness, 1987a; Jacobs and Abernathy, 1988).

These adverse events are unrelated to the dose or gestational age at which S was received. A comparison of incidence rates (IR) in congenital abnormalities between TB exposed neonates whose mothers were offered different treatment combinations was conducted by Varpela (1964). An IR of 9.8% in neonates exposed to para amino salicylic acid (PAS), INH and S was documented in contrast to an IR of 3.6% in unexposed neonates. Lowe (1964) reported an IR of 2.8% in neonates exposed to PAS and INH compared to an IR of 4.1% in unexposed neonates. Snider *et al* (1984) reviewed 1480 pregnant women who received anti TB drugs during pregnancy. Ninety four percent of mothers progressed to full term pregnancies and 2.9% of neonates exposed to anti tuberculosis drugs in utero developed birth defects. With the exclusion of neonates born to mothers who received streptomycin, the risk of an adverse pregnancy outcome was no greater than in healthy pregnant females.

1.3.8 Vertical transmission and congenital tuberculosis

The modes of transmission from mother to child include haematogenous spread from placenta to umbilical vein resulting in one or more primary complexes in the liver and lung, or aspiration or ingestion of amniotic fluid contaminated by placental or genital tract infection resulting in primary complex formation in the lung, gastro intestinal tract or middle ear (Smith and Teele, 1990). Infection through the umbilical cord is rare with fewer than 300 cases reported (Selikoff and Dorfmann, 1965; Smith and Teele, 1990). Mortality from congenital TB can exceed 50% (Mofenson *et al*, 1995) although the rate of vertical transmission is very low at 0- 3% (Ratner *et al*, 1951; Blackall, 1969; Hageman *et al*, 1980; Nemir and o'Hare, 1985). Recently, Cantwell *et al* (1994) reviewed 29 cases of congenital TB and reported a mortality rate of 22% in the neonates on anti TB treatment.

Risk factors that influence the transmission of TB include untreated maternal TB, miliary TB, pleural effusion, TB meningitis and maternal AFB smear positive sputum (Hageman *et al*, 1980; Nemir and o'Hare, 1985; Golditch, 1971; Myers *et al*, 1981). HIV as an additional independent risk factor for the vertical transmission of TB has also been established (Pillay *et al*, 2004b). A 16% materno- fetal transmission rate of TB was reported in bacteriologically proven and suspected maternal TB. Seven neonates were born to mothers with bacteriologically proven TB in pregnancy and 9 neonates were born to mothers who were sputum and culture negative for *Mycobacterium tuberculosis*. Eleven of these 16 neonates were HIV exposed and the 7 who were HIV infected, rapidly progressed to death between 3- 10 months of age.

Symptoms and signs of congenital TB are non specific (appendix F) with median age at presentation of 24 days (Deshmukh *et al*, 1964). These symptoms and signs encompass other acute and chronic intra uterine infections including HIV, cytomegalovirus infection and syphilis. Investigation of a neonate for TB is therefore driven by maternal history or investigator suspicion.

The diagnosis of congenital TB is guided by Cantwells criteria which is a modification of Beitzke's criteria (appendix G). Investigation of a neonate is similar to that of the mother with smear, microscopy and culture of 3 early morning gastric washing samples for AFB. On collection, the samples are buffered in equivalent volumes of 1% sodium bicarbonate solution. Other tests that can assist with diagnosis are directed by the clinical picture. These include chest radiographs, cerebrospinal fluid for smear and culture of AFB despite the low yield (Hageman *et al*, 1980; Nemir and o'Hare, 1985), middle ear fluid, bone marrow aspirate, tracheal aspirate and tissue biopsy (either lymph node or liver). Nearly all infants infected with congenital TB have an abnormal radiograph which may initially be normal but can rapidly progress to cavitation (Miller and Miller, 1996).

Treatment with a four drug regimen is commenced upon diagnosis of TB. Prophylaxis is offered for 3 months to a well neonate whose mother was treated antenatally for TB (doses for prophylaxis and treatment are outlined in appendix E.5). A chest radiograph and tuberculin skin test is performed on the infant following completion of treatment. Prophylaxis is stopped if both are non reactive but re-investigation for TB is recommended if abnormal (Pillay *et al*, 2004a).

In the past, the newborn and the mother were separated until the mother was AFB sputum culture negative (Good *et al*, 1981; Cunningham *et al*, 1982). Currently this is advocated if the mother is non-compliant, if a family member is infectious or if the neonate is at risk of contact with multi drug resistant strains of TB. This option is impractical in under resourced countries. Bacillus Calmette Guérin (BCG) vaccination, appropriate prophylaxis and treatment and close monitoring of the neonate following discharge from the centre are more feasible options.

The protective efficacy of BCG vaccine in the prevention of pulmonary TB in adults and adolescents remains controversial (MacGregor, 1980; Anonymous, 1972; Anonymous, 1980). However two recent meta analyses of published literature by Colditz *et al* (1994) and Rodrigues *et al* (1993) showed a 64- 86% protective efficacy against miliary TB and TB meningitis in clinical trials in children. In addition a 75% efficacy in case control studies and 71% protective efficacy against death was documented (Colditz *et al*, 1994). Therefore in endemic TB areas where contact

with an untreated, infectious person is high, the BCG vaccine is advocated by the WHO as part of the Extended Program for Immunization for Infants (von Reyn *et al*, 1987).

In countries with a low TB incidence, the use of BCG is not practical as it could affect the early detection and treatment of new cases of TB. This is due to the inability of the tuberculin skin test reaction to distinguish between a response due to BCG vaccination and active disease (Menzies *et al*, 1992).

1.3.9 Breast feeding

Despite anti tuberculosis drugs being expressed in breast milk, breast feeding can still occur under the following conditions:

1.3.9.1 To breast feed prior to ingestion of medication and to bottle feed for the period that follows immediately after medication.

1.3.9.2 If neonate is receiving INH, to be aware of possible toxicity as 20% of the therapeutic level is reached through breast feeding.

1.3.9.3 Limited data on PzA and PAS indicate that these drugs are safe to use in breastfeeding mothers. However the combination of PAS and INH increases the half life and concentration of INH thereby affecting INH levels in the breast milk (Snider and Powell, 1984; Tran and Montakantikul, 1998; Holdiness, 1984) (appendix E.4).

In summary, an increasing incidence of TB in pregnancy has been reported. Maternal mortality is accentuated in dual infection (TB and HIV-1) with the risk of transmission to the neonate higher in untreated cases of (maternal) TB. With early diagnosis and treatment, TB in pregnancy can be successfully managed with improved outcomes for both mother and baby.

1.4 The global threat of multi drug resistant tuberculosis

1.4.1 Background

The advent of chemotherapeutic agents for TB resulted in the emergence of drug resistance mainly due to the improper use of regimens and lack of compliance (Medical Research Council, 1948). Historically resistance initially developed to Streptomycin (S), which led to the development and use of short course regimens involving Rifampicin (RIF). The success of short course treatment was short lived and sporadic multi drug resistant TB (MDR TB) outbreaks occurred in patients receiving prolonged inadequate anti TB chemotherapy. Defined as resistance to at least RIF and Isoniazid [INH] with or without resistance to other TB drugs, MDR TB was described in prisons and hospitals in the eastern United States, Europe and Latin America in the early 1990s (Kent, 1993; Centre for Disease control, 1996; Drobniewski, 1995).

Multi drug resistant TB is now a global threat with 50 million people infected worldwide. Primary resistance is usually 5% or less in countries with stringent TB control programmes compared to 15% in countries with newer programmes that have replaced previous less comprehensive ones. Between 1996 and 1999, the WHO and the International Union against Tubercle and Lung Disease (IUATLD) surveyed and identified MDR TB in 58 countries (Pablos- Mendez *et al*, 1998). An estimated 70% of cases are limited to just 10 countries, highlighting local shortcomings in TB and MDR TB management. The availability of anti tuberculosis drugs within poor TB control programmes in the well resourced countries has resulted in a higher prevalence rate of MDR TB compared to poor countries where access to Rifampicin is limited. "Hotspots" are described in Estonia (14.1%), the Henan province [China] (10.8%), Latvia (9%), Ivanovo- oblast (9%) and Tomsk- oblast [Russia] (6.5%), Iran (5%) and Zhejiang province [China] (4.5%) [Appendix H]. The median prevalence for resistance to one drug and multidrug is 10.7% and 1.0% respectively in *newly diagnosed* cases and in *previously treated* cases, is 23.3% and 9.3% respectively (for the same variables).

Levels of MDR TB in Africa are generally low as a result of the 61% coverage by directly observed therapy short course (DOTS) programmes as compared to the global average of 42.6% (WHO, 2000; WHO, 1997a). The Medical Research Council of South Africa's National Tuberculosis Research Programme of South Africa indicated a 1% and 4% MDR TB rate in new and previously treated cases respectively for 3 provinces in SA. The 2 year case fatality rates of between 30- 50%, are higher in HIV infected individuals (Medical Research Council, 1999) and single drug resistance

is highest to INH at 14.1% (Weyer and Kleeberg, 1992). KwaZulu-Natal has the highest MDR TB rate of 10.2% (Anastasis *et al*, 1997) in South Africa. A six fold increase in MDR TB was reported by Davies *et al* (1999) between 1994 and 1996 in rural KwaZulu-Natal.

MDR TB is well documented in South African gold miners with an HIV prevalence in approximately 50% of all cases (Churchyard *et al*, 1999). The background TB incidence in these gold miners is 2000/ 100 000 (Snider and Roper, 1992). Resistance was found to be more common in previously treated TB cases and there was no significant association with HIV status and sputum smear status (Churchyard *et al*, 2000).

Factors related to the development of drug resistant TB are:

1.4.1.1 Poor or unsupervised *TB control programmes*: Directly observed therapy (DOT) is an effective tool used in TB control programmes to curb the TB epidemic. The prevalence of MDR TB is 2.5 fold higher in countries with poorly controlled programmes compared to those with programmes that are well controlled (Iseman *et al*, 1993). The DOTS and DOTS plus frameworks are outlined in appendix I.

Ivanovo- oblast and Cameroon are examples of countries lacking efficient DOT structures resulting in an MDR TB rate of 9% in new cases (Espinal *et al*, 2000) and an overall proportion of 51.1% of acquired drug resistance in previously treated cases (Kuaban *et al*, 2000). In comparison, countries with successful national control programmes achieve higher cure rates and lower levels of resistance. Benin, Cuba, the Czech Republic and Kenya achieve cure rates around or greater than 80% with MDR TB rates under 1% (Espinal *et al*, 2000; Cohn *et al*, 1997).

1.4.1.2 Problems with *treatment* include poor availability, lack of accessibility or irregular supply of treatment, lack of standardised treatment protocols, poor quality of drugs, and the cost of second line therapy used (Mwinga, 2001; Mohapatra *et al*, 2002). Mahmoudi and Iseman (1993) described an average of 3.9 errors per patient treated by physicians. These included the addition of a single drug to a failing regimen, failure to identify drug resistance, prescription of a previous inadequate regime, inadequate duration of therapy and the inability to identify or manage patient non- compliance. Inappropriate schedules are still being prescribed despite guidelines (Liu *et al*, 1998).

1.4.1.3 *Patient factors* include poor compliance to current drug regimens, past history of TB with exposure to TB therapy and social factors like homelessness and unemployment (Kuaban *et al*, 2000, Espinal *et al*, 1999; Espinal *et al*, 2001a; Pleumpanupat *et al*, 2003). Twenty percent of patients with TB default or fail to respond to treatment but less than 2% have MDR TB even in “hot

spots". This is an indication of the poor supervision that results in the development of MDR TB (Dye *et al*, 1999).

1.4.1.4 The link with the *HIV epidemic* that has been established in some countries is a reflection of nosocomial transmission and the rapid progression to disease in an HIV infected individual (Frieden *et al*, 1993; Bradford *et al*, 1996). HIV has not been identified as an independent risk factor for the development of MDR TB (Kuaban *et al*, 2000, Espinal *et al*, 2001a; Deivanayagam *et al*, 2001; Putong *et al*, 2002; Noeske and Nguenke, 2002). HIV- 1 co infected patients do however have higher case fatality rates and lower cure rates (Medical Research Council, 1999; Putong *et al*, 2002), and are more likely to have a prior history of treatment (Mac-Arthur *et al*, 2001).

1.4.2 Emergence of drug resistance

Spontaneous unlinked chromosomal mutation results in single anti TB drug resistance. The rate at which this occurs to S and INH in an unselected population is 10^{-6} organisms, to Ethionamide (ETH) and PzA 10^{-5} organisms and to RIF, 10^{-8} organisms (David, 1970). Therefore development of *spontaneous* resistance to rifampicin and isoniazid is 10^{-14} . Populations of resistant bacilli accumulate with inappropriate or incomplete anti tuberculosis regimens (Mitchison and Nunn, 1986) which then require multiple bactericidal drugs for successful treatment outcomes.

Acquired drug resistance results from the selection of resistant mutants in the bacterial population that remains following the destruction of susceptible bacilli by TB drugs. This selection is exaggerated by inadequate or incomplete therapy. The susceptible bacilli are killed and resistant strains multiply. The speed at which resistance develops to S is 45 days and to RIF, between 2-5 months (Medical Research Council, 1999).

1.4.3 Management of MDR TB:

The approach is multi-sectoral with each country adapting the 'DOTS plus' framework to available resources. Additional resources identified include the involvement of non- governmental organisations, primary health and community health care givers (Nachega and Chaisson, 2003) and providing health services in informal settings in poor countries (Wilkinson, 1994). In rural Northern KwaZulu- Natal, patients supervised by community health workers and volunteers achieved completion rates of 88% and 85% respectively compared to 79% achieved through clinic supervision (Wilkinson, 1997a). Community based therapy in Peru was successful despite all patients initially being exposed to a median of 7 anti TB drugs and a median resistance to 6 drugs (Mitnick *et al*, 2003). Patients were treated with a median of 6 drugs for a median period of 23

months (range 0.4- 35.9) using the DOT strategy and 83% were cured at the end of treatment. Self supervised therapy was also reported to be more successful in the first randomized trial in retreatment cases than directly observed therapy (Zwarenstein *et al*, 1998).

1.4.3.1 Diagnosis of MDR TB

It is a laboratory based diagnosis and is suspected under the following conditions:

1. Close contact history with known MDR TB patient,
2. Patient remains sputum culture positive after 2 months of anti TB treatment despite adherence,
3. Patient smear negative at 2 months but lacks clinical improvement or
4. Patient smear negative at 2 months and smear positive at 5 months.

New diagnostic methods are outlined in appendix J.

1.4.3.2 Choice and duration of treatment

The choice of drugs and the duration of treatment used in (susceptible) TB regimens are inadequate for MDR TB treatment as cure rates of less than 60% are achieved (Espinal *et al*, 2000; Coninx *et al*, 1999). The median time to relapse using first line therapy for MDR TB is 8 months (Migliori *et al*, 2002). The range, type of activity, side effect profile and parameters monitored during usage of second line therapy is outlined in appendix E.4 (Medical Research Council, 1999; Bastian and Colebunders, 1999).

Treatment of MDR TB is complicated and requires therapy for at least 24 months. This includes an initial 4 month intensive phase followed by a 12-18 month continuation phase determined by initial sputum culture reversion (Nachega and Chaisson, 2003). A 12 month alternative is an option if fully supervised treatment with 4 agents at maximum dose to which the isolate is susceptible, is provided (Medical Research Council, 1999; Perez- Guzman *et al*, 2002). Treatment should be given 7 days a week for hospitalized patients and 5 days a week for outpatients (Medical Research Council, 1999).

Two approaches are available for the treatment of MDR TB. One approach is the use of a standard combination of drugs irrespective of the susceptibility results. Five drugs are prescribed for the intensive phase (usually Kanamycin, Ethionamide, PzA, Ofloxacin, Cycloserine or EMB) with reduction to 3 drugs for the continuation phase (ethionamide, ofloxacin and cycloserine or EMB).

The second approach is an individualized approach based on susceptibility results. Treatment with at least 4 drugs to which the isolate is susceptible is commenced (Nachega and Chaisson, 2003). At

least 3 of the drugs should not have been previously administered for a period of 3 or more months. In addition, not more than 1 drug from each category should be chosen and an aminoglycoside should be prescribed during the intensive phase.

Although the use of second line therapy is advocated for the treatment of MDR TB, this intervention might create additional resistance to second line agents in countries with poor cure rates using short course chemotherapy (Raviglione *et al*, 2001).

1.4.3.3 Monitoring response to therapy

Monthly sputum smear microscopy and culture are the most sensitive indicators of response to treatment (WHO 1997b). They are repeated until 3 consecutive culture negative results are obtained. Culture conversion time is usually 4 months after commencing therapy although this can sometimes take up to 8 months (Goble *et al*, 1993). The recommendation of the American Thoracic Society and the Centres for Disease Control is to then withdraw the more toxic, weaker drugs and to continue with the remaining 2- 3 drugs under supervised conditions for another 18- 24 months (1994). Quarterly microbiological examinations are then performed until completion of treatment.

1.4.4 Cost of treatment

The cost involved in the treatment of MDR TB is prohibitively high for under resourced countries. In South Africa the cost of treating a case of MDR TB is 10- 20 times the cost of treating an uncomplicated drug- susceptible case at roughly 30 000 SAR (Medical Research council, 1999). Studies in the United States (Mahmoudi and Iseman, 1993), Cape Town (SA) (Dick and Henchie, 1998), United Kingdom (White and Moore- Gillon, 2000) and Netherlands (Geerligs *et al*, 2001) support these reported high costs of managing MDR TB. Mahmoudi and Iseman (1993) found that \$4.8 million was used in the United States in the treatment of 28 patients previously mismanaged by physicians. The estimated mean cost of treatment excluding additional multidisciplinary input was 60 000 British sterling compared to 6040 used to treat drug susceptible TB (White and Moore- Gillon, 2000).

1.4.5 Prognosis

Outcomes in MDR TB have improved with prompt investigation, availability of appropriate treatment and efficient TB control programmes (Turret *et al*, 1995; Tahaoglu *et al*, 2001). Five year follow up of 343 TB patients in the Western Cape (SA) revealed 70% to have MDR TB by Schaaf *et al* (1996). A cure rate of 27% and a mortality rate of 48% were reported. Cure and mortality rates in

patients with strains resistant to INH or Rifampicin, and/ or to other first line anti TB drugs, were 49% and 27% respectively. Only 33% of all patients were cured after 5 years.

Surgical intervention is considered in selected patients with persistently positive sputum samples following 4 months of therapy, persistent cavitations, destruction of one lobe or one lung, previous relapses and a high or potential risk of relapse (Iseman *et al*, 1990; Muthusamy *et al*, 1992; Pomerantz and Brown, 1997). Cure rates over 90% can be achieved under these conditions (Pomerantz and Brown, 1997).

Initial reports show poor outcomes in HIV uninfected patients with MDR TB. Eight patients were reported on in the British Medical Research Council trials and 5 failed treatment and 2 relapsed (Mitchison and Nunn, 1986). In Denver, 47 of 134 patients failed to respond to therapy and 12 relapsed (44% failure rate) (Goble *et al*, 1993). A more recent report showed a 96% clinical improvement with culture conversion in all patients on whom data was available (Telzak *et al*, 1995).

1.4.6 Control of MDR TB

The key to curbing the MDR TB threat is a successful TB control programme. A multifaceted approach using DOTS can achieve cure rates exceeding 90% (Chaulk and Kazandjian, 1998). New York City accounted for 3.5% of US burden of disease and 61.4% of cases had MDR TB (Bloch *et al*, 1994). Strategies implemented to curb this escalation included a DOTS programme, better infection control in hospitals, reduction in capacity of homeless shelters, improved screening and isolation facilities in prisons (Bradford *et al*, 1996). These interventions reduced the prevalence from 2.8% in 1993 to 1.6% in 1996 (Moore *et al*, 1997).

The WHO DOTS strategy was introduced in Tomsk oblast (Russia) in 1994 (Mawer *et al*, 2001) and success rates between existing Russian policy and WHO short course chemotherapy (SCC) were compared. Treatment success rates and smear conversion rates at 6 months in smear positive groups at 6 months were comparable. However, 6 month culture conversion rates were significantly better in the SCC group (p value equal to 0.0001). Culture conversion occurred in 40% of MDR TB cases compared to 86% of non resistant cases. The drawbacks identified in this study were the exclusion of those who had relapsed and were being retreated following default, and those who were chronic cases.

The DOT strategy can also reduce the rate of MDR TB. This was evident from studies performed in Burkino Faso (Ledru *et al*, 1996), Hong Kong (Kam and Yip, 2001), Chile, Sierra Leone and

Uruguay (Medical Research Council, 1999). The frequency of drug resistance decreased from 13% to 6.7% over a 13 year period in Tarrant County, Texas following the implementation of DOTS. The frequency of acquired resistance also decreased from 14% to 2.1% (Weis *et al*, 1994).

Best practice SCC can also eliminate MDR epidemics. In Hong Kong, the proportion of resistance to any drug has been steadily declining at an average of 3% per year for the last 15 years, with the MDR rate falling at an average of 7.5% per year (Kam and Yip, 2001). The republic of Korea has documented an MDR TB rate persistently under 2.5% since 1980 (Hong *et al*, 2000).

In summary, MDR TB is mainly due to patient, administrative and health service provider failings and its' control lies in successful TB control programmes that achieve high cure rates. Various strategies to lower TB transmission and implement successful DOT programmes have been documented and can be adapted to improve existing TB control frameworks.

1.5 HIV-1 and MDR TB in pregnancy

As discussed in the previous chapters, the incidence and impact of TB and HIV infections and co-infection in pregnancy has been documented globally. Reports of MDR TB in pregnancy have been limited to 12 cases (Nitta *et al*, 1999; Shin *et al*, 2003; Lessnau and Qarrah, 2003; Gach *et al*, 1999) (Table 2), with no reports of HIV-1 co-infection.

These cases pose multiple challenges in investigation, diagnosis and treatment of dual HIV-1 and MDR TB disease in perinatal health care. Management dilemmas include the choice of continuation or termination of pregnancy, to use or withhold potentially teratogenic drugs, choice of anti TB drugs in the exposed, symptomatic neonate and infant and the use of BCG (which has been addressed in section 1.3.8 and appendix L).

In the few reported cases, one mother chose to terminate her pregnancy for social reasons and not for the further management of the infection (Nitta *et al*, 1999) and one experienced pre term labour (Lessnau and Qarrah, 2003). Of twelve MDR TB complicated pregnancies, 9 mothers delivered at term with no evidence of congenital or neonatal abnormalities (Nitta *et al*, 1999; Shin *et al*, 2003).

The withholding of MDR TB treatment during pregnancy has been described by Nitta *et al* (1999) and Shin *et al* (2003). However, the risk of dissemination and progression of disease in the mother and transmission to the fetus far outweighs the potential teratogenic risk (Vallejo and Starke, 1992; Miller and Miller, 1996).

The dilemma posed is whether to offer (neonatal) anti TB drugs based on the maternal profile of multidrug resistance or conventional therapy if the neonate displays symptoms of TB disease. Routine prophylaxis was not offered in other studies (Nitta *et al*, 1999; Shin *et al*, 2003; Lessnau and Qarrah, 2003). Treatment based on maternal resistance profile was commenced in one child due to a positive (infectious) contact history with clinical symptoms and signs (Lessnau and Qarrah, 2003) and preventative therapy with PZA and EMB was initiated in another as the mother remained infectious at delivery (Nitta *et al*, 1999). Isoniazid prophylaxis was offered to two infants due to positive tuberculin skin tests (Nitta *et al*, 1999).

The local experience with MDR TB in pregnancy is limited to 4 cases (unpublished data, Department of Obstetrics and Gynaecology and Paediatrics and Child Health). This is the first report of HIV-1 and MDR TB co-infection in pregnancy with two women HIV-1 co-infected. The mean age, parity and gravidity was 32 years, 2 and 3 respectively. Three patients did not seek antenatal care with the remaining one having only attended the antenatal clinic once in the second trimester.

Syphilis serology was negative in three of the four cases. All 4 patients had received prior first line treatment for PTB. At the time of diagnosis of pregnancy, all mothers were *Mycobacterium tuberculosis* sputum and culture positive. Three mothers were diagnosed prior to conception at a mean time to diagnosis of 13 months prior to pregnancy. One mother was diagnosed at 14 weeks gestation. These mothers were resistant to a median of 4 drugs (range 3-6) [table 11]. Sputum cultures were processed monthly to assess response to treatment and the median time to first sputum culture conversion was 11 months (range 10- 14). Non- adherence to the current regimen occurred in case 3. Patient 4 was discharged as a treatment failure after 18 months of second line anti TB drugs. Three mothers experienced drug related complications (table 12): case 2 and 3 developed significant sensorineural deafness and case 1 developed drug induced hepatitis.

Two mothers remained smear positive and three were culture positive at the time of delivery. One mother (case 3) elected to terminate her pregnancy at 20 weeks and another experienced preterm labour at 34 weeks. One year post delivery, case 1 had a pneumonectomy for a destroyed lung. One month thereafter she developed haemoptysis which required bronchial artery embolization.

Overt teratogenicity was not observed in the 3 live births and *M tuberculosis* was not cultured from their gastric aspirates, cerebrospinal fluid or (maternal) endometrial scraping. However the HIV-1 exposed infant was symptomatic at follow up with pulmonary infiltrates and progressive hepatosplenomegaly. *M tuberculosis* was not cultured from the gastric washings and liver biopsy showed non specific changes on histology. A nine month course of R, I and PZA was initiated as possible TB was a consideration. In the absence of culture evidence of an MDR pattern in the infant, it was elected not to commence this infant on anti-tuberculous therapy based on the profile of the maternal sputa as the mother was culture negative at birth and the infant responded to the regimen chosen.

Of the two HIV-1 exposed neonates, one was uninfected and liver and lung biopsies in the second case (the aborted fetus) confirmed prematurity with evidence of extramedullary haematopoiesis. HIV-1 PCR was not undertaken on biopsy samples.

In summary, successful management of MDR TB during pregnancy is possible with appropriate and early interventions as evidenced in the few reported cases.

Table 2: Global experience of MDR TB in pregnancy

Author	Institute	Number of cases	MDR TB treatment during pregnancy	Maternal outcome at the time of report	Gestational age at delivery, mode of delivery	Neonatal outcome
Shin <i>et al</i> (2003)	Harvard Medical School	7	2 diagnosed prior to pregnancy, treatment started in 2 nd trimester 1 continued and 4 stopped treatment until after delivery	1 treatment failure, 1 defaulted, 2 on treatment, 3 cured	Term vaginal deliveries	No congenital or neonatal abnormalities, no evidence of TB disease
Lessnau and Qarrah (2003)	Weill Medical School	1	Commenced at 26 weeks gestation	Cured	Preterm (35 weeks) vaginal delivery	No congenital or neonatal abnormality, no evidence of TB disease
Nitta <i>et al</i> (1999)	Los Angeles TB control unit	4 (1 with <i>M Bovis</i>)	Of 3 cases, 1 treatment withheld, 1 continued during pregnancy, 1 therapeutic abortion	Cured	Term deliveries	No congenital or neonatal abnormalities, no evidence of TB disease

* All MDR TB treatment schedules based on individual susceptibility results

CHAPTER 2 – METHODOLOGY

2.1 Justification for study

The incidence of pneumonia in pregnancy is similar to that in the non pregnant state. It is the pregnant state itself and risk factors for the development of pneumonia that adversely influence the outcome of pregnancies complicated by antenatal pneumonia. Risk factors for and causative organisms for the development of pneumonia as well as various outcome measures have been documented in the literature.

Pulmonary complications are the commonest presentation in HIV/ AIDS. Females in the reproductive age group bear the burden of the HIV epidemic and the impact of HIV on maternal morbidity and mortality has been documented. There are limited reports on the impact of pneumonia and HIV co infection on the course of pregnancy and on maternal and neonatal outcomes. Recent reports have shown an increase in PTB in pregnant women in resource constrained settings.

Kwa Zulu Natal is at the epicenter of both the TB and HIV epidemics with females in the reproductive age group most commonly affected. There is no data on the impact of pneumonia and HIV co infection in women attending the antenatal clinic at our centre. The study was designed to establish the extent to which pneumonia in pregnancy was due to primary bacterial infections or a secondary infection associated with HIV co infection. In addition, the impact of pneumonia on maternal and perinatal morbidity and mortality was evaluated.

2.2 Aim

To determine the clinical profile of mothers with pneumonia during pregnancy at King Edward VIII hospital and to evaluate the association with HIV-1 infection, maternal immunosuppression and maternal and perinatal outcome.

2.3 Hypothesis

Mothers with pneumonia during pregnancy are more likely to be HIV-1 infected; the detection of maternal pneumonia is associated with adverse clinical, obstetric and perinatal outcome.

2.4 Objectives

2.4.1 To assess the effects of pneumonia in pregnancy on maternal mortality, duration of hospitalization and obstetric outcome in HIV-1 infected and uninfected mothers.

2.4.2 To assess the impact of pneumonia in pregnancy on neonatal morbidity and mortality.

2.4.3 To determine the causative organisms of pneumonia in HIV-1 infected and HIV-1 uninfected pregnant women at KEH.

2.5 Study design

The study design is two fold. The first is a case control study in which pregnant women with pneumonia attending the antenatal clinic and labour wards were identified. The study arm consisted of HIV-1 infected and uninfected pregnant women with pneumonia and the control arm consisted of HIV-1 infected and uninfected pregnant women without pneumonia. Risk factors for the development of pneumonia, the causative organisms of pneumonia and the extent of HIV-1 and pulmonary disease were assessed.

The second is a cohort study wherein maternal and neonatal outcomes were recorded for the two arms.

If approximately 10- 15 000 women deliver at the hospital per year, 20- 30 000 would deliver over the 24 month period. Based on this number of deliveries, the prevalence of pneumonia in this population can be estimated to within 0.15% with a confidence level of 95% and assuming an estimated prevalence of 1%. Approximately 200- 300 mothers will be detected during this time period.

For both comparisons, viz between the (a) HIV-1 infected pregnant women with pneumonia (study) and HIV-1 uninfected women with pneumonia (study) and between (b) pregnant women with pneumonia (study) and women without pneumonia (control), the outcome measure will be low birth weight rate.

For comparisons between HIV-infected pregnant women with pneumonia and HIV infected women without pneumonia, with a sample size of 114 women in each group, a 19% difference between the two groups could be detected with a confidence of 95% and power of 80% assuming a ratio of 1:1 between cases and controls assuming a 42% prevalence in women HIV-1 infected without pneumonia, estimated from the rate in women HIV-infected without TB from a previous study conducted at the site.

If a ratio of 1:2 cases and controls is assumed, then with a sample of 114 cases and 228 controls, a difference of 16% could be detected. This is a similar difference in low birth weight to that observed in the study of TB/HIV co infected mothers conducted at the site.

The initial statistical projection was for a 3 year period. However with poor accrual and other constraints, women were only recruited over a one year period. With the advice of a statistician, the study to control number of cases was increased to a 1:4 ratio of cases.

2.6 Study site and patients

2.6.1 Inclusion criteria and recruitment

Mothers presenting between January and December 2000 to the antenatal clinic and labour ward facilities at King Edward VIII hospital with clinical symptoms and signs indicative of pneumonia were investigated. Clinical symptoms included cough for more than 3 weeks, loss of appetite, loss of weight, fever, night sweats, haemoptysis, malaise and fatigue and difficulty breathing (refer appendix C).

Chest radiographs were performed with abdominal shielding. All radiographs were requested by the primary investigator and commented on by a single radiologist. Women with pneumonia were informed of the study and written informed consent was obtained if they were agreeable. All women were offered voluntary counseling and testing for HIV-1 as standard of care.

Women with TB and MDR TB were hospitalized at King George V but continued to receive antenatal care at KEH until delivery. Their KGV records were reviewed at each antenatal visit to monitor their response to TB and MDR TB treatment.

For each mother recruited into the study, a control mother who did not have clinical evidence for pneumonia was recruited. All controls gave informed consent and pneumonia was excluded by taking a screening history for symptoms suggestive of an upper respiratory or chest infection; physical examination and sputum examination if appropriate, as pneumonia may often mimic symptoms and signs associated with the physiologic state of pregnancy (Llewelyn *et al*, 2000; Doveren and Block, 1998). All asymptomatic mothers with clinical signs were excluded from the study but the clinical details were recorded. The control arm was selected as a measure against firstly, the impact of antenatal pneumonia on obstetric and neonatal outcomes and secondly, to identify possible risk factors associated with the development of pneumonia. The selection of HIV infected and uninfected women from the same antenatal clinic provided an appropriate control arm.

2.6.2 Observed parameters and investigations for both groups of women

The clinical history, physical state, gestational age, clinical and radiological extent of the pneumonia was recorded at entry into the study. In the case of all HIV-1 infected mothers, the stage of HIV infection was documented (CDC revised criteria 1993, WHO clinical staging for HIV infection- refer appendices A and B). Treatment instituted in women with pneumonia was recorded. This was determined by the attending obstetrician, and was no different from the standard of care provided for women with pneumonia at the hospital. A follow up chest radiograph was undertaken where there was persistence of clinical signs following two weeks of therapy.

At recruitment, a full blood count, liver function test, T lymphocyte subset analysis (CD4 and CD8) and confirmation of HIV-1 infection by HIV-1 ELISA (Abbott, Wiesbaden) were performed. Sputum samples were sent for microbiological and cytological analysis. Samples were also analysed for *Mycobacterium tuberculosis*.

2.6.3 At delivery

Mothers were re evaluated at the time of delivery. In view of the outcome of the Nevirapine 012 trial in Uganda, it was considered standard of care to offer all HIV-1 infected mothers single dose Nevirapine 200mg orally at the onset of labour, and all neonates received 2mg/ kg within 72 hours of birth. The following parameters were documented (during and following delivery):

- Obstetric progress,
- Mode of delivery,
- Perinatal outcome viz stillbirths, abortions, premature births, intra uterine growth restriction,
- Neonatal anthropometry and early neonatal deaths

2.6.4 Follow up:

Within the first 48 hours of life, a T lymphocyte assay (CD4 and CD8 count) was performed. HIV-1 exposed neonates were followed up at one week, six weeks and three months of age. Morbidity and mortality, especially within the first week of life was recorded. All neonates with clinical features of pneumonia were investigated. If maternal TB was present during gestation, investigation was as for the mother with smear, microscopy and culture of 3 early morning gastric washing samples for AFB.

Continued follow up and standard care was offered to HIV-1 infected babies and their mothers after the three month study period. HIV-1 uninfected babies were referred to their nearest clinic for normal infant care as is standard practice. All mothers and their babies wishing to retain follow up at the clinic were managed accordingly.

2.7 Consent

Informed consent was obtained from all participants prior to any information being collected or study procedures being initiated in accordance with the institutional ethical guidelines. The informed consent administered to all participants is attached (appendix M).

2.8 Ethical approval

Ethical approval for the study of human research participants in this thesis was obtained from the Ethics Committee of the University of Natal, Nelson R Mandela Medical School, Durban, South Africa. Reference number H 163/99. Permission to conduct the study at King Edward VIII hospital and King George V Jubilee Hospital was obtained from the medical superintendents, Dr Seedat and Dr Padayatchi respectively.

2.9 Statistical analysis

Data was analysed using the statistical package SAS version 6.0 (SAS institute, USA).

A combination of descriptive statistics and chi squared tests were used in the analysis. Comparisons between the groups was analyzed using a chi-square test for categorical data such as proportion premature, outcome, mode of delivery and multivariate analysis of variance (MANOVA) for risk factors measured on a quantitative scale such as haemoglobin, cd4 counts. Specifically a 2 tailed Pearson chi squared test, (at $\alpha = 0.05$) was used. Nonparametric tests or log transformations were used where the data was not normally distributed between the study and control groups. A multiple logistic model was used to identify independent risk factors and to adjust for confounders.

The Kaplan Meier survival function was not used to analyze time until death nor were the log rank tests used to compare survival between groups due to the distribution of data as all the deaths were confined to the study arm where the mothers had pneumonia.

2.10 Case definitions

2.10.1 Diagnosis of maternal tuberculosis (WHO, 2001)

2.10.1.1 Pulmonary TB- sputum smear positive:

- One or more initial sputum smear examinations positive for AFB, or
- One sputum smear examination positive for AFB plus radiographic abnormalities consistent with active pulmonary TB as determined by a clinician, or
- One sputum smear positive for AFB plus sputum culture positive for *M tuberculosis*

2.10.1.2 Pulmonary TB- sputum smear negative:

A case of PTB that does not meet the above definition for smear positive TB but does meet the following:

- At least 3 sputum specimens negative for AFB, and
- Radiographic abnormalities consistent with active PTB, and
- No response to a course of broad spectrum antibiotics, and
- Decision by a clinician to treat with a full course of anti- TB chemotherapy.

2.10.1.3 Suspected pulmonary tuberculosis:

Mycobacterium tuberculosis was isolated on sputum smear microscopy.

2.10.1.4 Confirmed pulmonary tuberculosis:

Mycobacterium tuberculosis was isolated on culture of sputum and in one case, TB was confirmed on a histological sample obtained post tubal ligation.

Mothers who did not fall into either of the above 2 categories, in whom no organism was isolated from sputum samples and who responded to antibiotic therapy were categorised as a group of women with suspected bacterial pneumonia.

2.10.2 Category of (TB) patients (WHO, 2001):

- 2.10.2.1 New cases: no previous antituberculosis treatment or having been treated for less than one month.
- 2.10.2.2 Relapse: Patient previously treated for TB who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) positive.
- 2.10.2.3 Failure: a patient who while on treatment is smear or culture positive at 5 months or later during the course of treatment.

2.10.3 Site of TB (Department of Health, SA, 2003):

- 2.10.3.1 Pulmonary TB: Disease involving lung parenchyma. If the case involves pulmonary and extra pulmonary site, it is classified as pulmonary TB.
- 2.10.3.2 Extra pulmonary TB: Results From the spread of mycobacteria to organs other than the lungs, commonly affecting the pleura, lymph nodes, spine, joints, genito urinary tract, central nervous system or abdomen. Disease of intra thoracic lymph nodes and TB pleural effusion are classified as EPTB.

2.10.4 TB outcomes (Department of Health, SA, 2003):

- 2.10.4.1 Defaulted: treatment interrupted for 2 consecutive months or more and remained bacteriologically positive.

2.10.5 Drug resistance (Department of Health, SA, 2003):

- 2.10.5.1 Single drug resistant tuberculosis: resistance to one drug
- 2.10.5.2 Multi-drug resistant tuberculosis: resistance to at least Rifampicin and Isoniazid
- 2.10.5.3 Global MDR TB “hotspots” have been identified using the proportion of TB cases that are MDR and refers to an area with greater than 3% primary or initial MDR TB as by well defined community based surveillance (personal communication, K Weyer)

2.10.6. Maternal outcomes (WHO, 1992):

2.10.6.1 Maternal mortality: Maternal deaths were defined as a death occurring during pregnancy, delivery and the postpartum period up to 42 days following birth. Maternal deaths were classified as direct and indirect obstetric deaths. Direct deaths are due to the obstetric complications of pregnancy, labour and the puerperium. In comparison, indirect deaths were defined as those resulting from previously existing disease or disease that developed during pregnancy which were not due to direct obstetric causes.

2.10.6.2 Maternal mortality rate: The number of maternal deaths over the number of deliveries expressed per 100 000 live births.

2.10.7 Neonatal outcomes (Williams Obstetrics, 1997; Anderson MS and Hay WW, Jr , 1999):

2.10.7.1 Stillbirths: death of a fetus after 28 weeks gestation with no signs of life at or after birth.

2.10.7.2 Early neonatal deaths: Neonatal death within the first seven days of life.

2.10.7.3 Perinatal deaths are a combination of 3.9.7.1 and 3.9.7.2.

2.10.7.4 Abortion: the termination of pregnancy by any means before the fetus is sufficiently developed to survive, before 20 weeks gestation or less than 500 grams in weight.

2.10.7.5 Premature birth: delivery prior to 37 completed weeks of gestation.

2.10.7.6 Intra uterine growth restriction (IUGR): rate of fetal growth that is less than normal for the population and for the growth potential of a specific infant. IUGR therefore produces infants who are small for gestational age.

2.10.7.7 Small for gestational age (SGA): infants with a birth weight that is more than two standard deviations below the mean or less than the 10th percentile of a population specific birth weight versus gestational age plot.

2.10.7.8 Large for gestational age (LGA): infants with a birth weight greater than the 90th percentile of a population specific birth weight versus gestational age plot.

2.10.7.9 Appropriate for gestational age (AGA): infants with a birth weight within the 10th and the 90th percentiles of a population specific birth weight versus gestational age plot.

2.10.7.10 Birth weight categories:

- i. Normal birth weight: greater than 2500 grams
- ii. Low birth weight: less than 2500 grams
- iii. Very low birth weight: less than 1500 grams
- iv. Extremely low birth weight: less than 1000 grams

2.10. 8 Treatment options for TB (Department of Health, SA, 2003):

- 2.10. 8. 1 First line drugs: Rifampicin, Isoniazid (INH), Pyrazinamide (Pza), Ethambutol (EMB) and Streptomycin (S), used to treatment of drug susceptible TB.
- 2.10. 8. 2 Second line drugs: Streptomycin, Ethionamide, para aminosalicylic acid, the aminoglycosides, cycloserine, flouroquinolones and Capreomycin, used to treat drug resistant TB.

2.10. 9 Laboratory methods:

2.10. 9. 1 Diagnosis of TB:

Diagnosis was based on detection of acid fast bacilli (AFB) on smear microscopy or culture of *Mycobacterium tuberculosis* from sputum samples. Gastric washing samples were transported in an equivalent volume of 1% sodium bicarbonate buffer solution to the laboratory.

Detection of AFB: Specimens were centrifuged at 3000g for 30 minutes. The sediment was then used for slide preparation and direct inoculation for mycobacterial culture. Standardised Ziehl Nielson staining technique was used to detect AFB. Lowenstein Jensen (LJ) media incubated at 35-37°C in 5-10 % CO₂ for up to 12 weeks were used for mycobacterial isolation. *M tuberculosis* is identified by growth rate, colony morphology and the niacin production test (Kleeberg *et al*, 1980).

Susceptibility of a strain: Judged by determining the proportion of bacilli resistant to the specific drug in comparison with growth on a specific control using international criteria (Department of Health, SA, 2003). The following drugs are injected into LJ media at these concentrations:

INH	0.2 and 1.0 ug/ ml LJ
SM	5.0 ug/ml LJ

RMP	30.0 ug/ml LJ
EMB	2.0 ug/ml LJ
ETH	20.0 ug/ml LJ

Resistance is defined as 1% or more growth for INH, SM, RMP and EMB and >10% for ETH .

2.10. 9. 2 Diagnosis of HIV:

Maternal and neonatal samples were taken and processed using the Roche Amplicor kits. T lymphocyte subset analysis was undertaken on fresh maternal and neonatal samples (EDTA anticoagulant) using the FACScan via flow cytometry (Becton Dickinson, USA). CD4 and CD8 counts were obtained using monoclonal antibodies.

CHAPTER 3 – RESULTS

The overall maternal and neonatal outcomes for King Edward VIII hospital (KEH) are initially presented and then the results are divided into 3 subheadings: in pregnancies complicated by pneumonia, in HIV-1 infected and uninfected pregnancies and in pregnancies with multi drug resistant tuberculosis. Each category discusses maternal and neonatal profiles and outcomes using various subheadings.

Overall maternal and neonatal outcomes for the study site:

In 2000, 7100 deliveries occurred at King Edward VIII Hospital (KEH) with 51 maternal deaths. The maternal mortality rate was 718 per 100 000 births. Sepsis, hypertensive disorders of pregnancy and tuberculosis were identified as the three leading causes of maternal mortality.

The corrected perinatal and neonatal death rate for 2000 at KEH was 49.6 and 13.7/ 1000 births respectively. A total number of 229 fresh stillbirths occurred with an overall number of 411 stillbirths (i.e. both macerated and fresh stillbirths).

The overall corrected caesarean section rate for KEH was 27.3 percent (uncorrected incidence rate of 44.1%).

3. 1 Pregnancies complicated by pneumonia at King Edward VIII Hospital

3.1.1 Maternal clinical profile

Demographics of study population (table 3, figure 2): Twenty nine pregnant women were diagnosed with pneumonia at KEH antenatal clinic and labour wards. The median age and parity was 28 years and 1 respectively. Twenty two mothers received antenatal care prior to the diagnosis of pneumonia and 7 were diagnosed with pneumonia at presentation to the labour ward. The median gestational age at first clinic visit was 21 weeks (range 12- 28 weeks). Pulmonary tuberculosis (PTB) was diagnosed prior to pregnancy in two women and the remainder were diagnosed with pneumonia at a median gestational age of 28 weeks.

Blood investigations: Syphilis testing was performed on 21 women and all tested negative. The median maternal haemoglobin, white cell count, platelet count and albumin at recruitment was 9.5g/ dL, 7.5×10^9 / L, 330×10^9 / L and 22g/ L respectively.

HIV status and clinical staging: Twenty seven women agreed to HIV-1 testing and 2 refused testing. Twenty women were (HIV) co infected and 7 were HIV-1 uninfected. According to the WHO clinical staging for HIV infection, 2 women were stage 2 disease, 6 were stage 3 and the remaining were stage 4.

Co-existing medical and obstetric conditions: Eleven of 29 women had co-existing medical conditions. Five had chronic medical illnesses such as hypertension and diabetes mellitus, 3 had anaemia and 3 had HIV related illnesses. HIV related illnesses were largely limited to a variety of skin related disorders including atypical psoriasis, disseminated scabies, eosinophilic folliculitis and Herpes zoster, HIV associated peripheral neuropathy and oral and oropharyngeal candidiasis. None of the women gave a history of illicit drug or tobacco use. One case required ventilatory support but suffered a cardiac arrest and demised prior to ventilation.

Fifteen women had obstetric co- morbidities outlined in table 5. There was difference in age, parity, booking status, HIV-1 co infection, complete blood counts, serum albumin levels in the presence of obstetric co morbidities.

3.1.2 Investigation and management of pneumonia:

Investigation for pneumonia was undertaken by the attending obstetrician on the basis of presenting symptoms and clinical signs.

Presenting complaints: A common presenting complaint was cough of more than 3 weeks duration (27.6%) with 61.5% of patients presenting with a combination of symptoms which included cough, fever, malaise/ fatigue, haemoptysis, loss of weight and chest pain.

Causative organisms: *Mycobacterium tuberculosis* (MTB) was the only causative organism isolated from sputum samples. There were no causative organisms identified in 15 cases. Of the 14 MTB samples 10 were smear positive (classified as probable TB) and 8 were culture positive (classified as confirmed TB). One case of drug resistant MTB with a resistance profile to R, I, P, E, Ethio and cycloserine was detected. This case is further discussed in section 3.3.

Treatment on admission to hospital: Intravenous or oral antibiotic treatment was initiated in all cases. The antibiotics prescribed included second generation cephalosporins, aminoglycosides, fluoroquinolones, penicillin and a combination of penicillin and β lactamase inhibitors. Twenty two women received anti TB treatment, one of whom was on second line anti TB drugs due to resistant strain of MTB. Nine women commenced empirical (TB) treatment based on clinical and radiographic

features suggestive of active TB. All nine received a course of antibiotics initially and were then switched to anti tuberculous treatment due to a failure of response and clinical and radiographic features suggestive of TB.

Of the 23 on anti TB treatment, 16 were HIV-1 co infected, five were uninfected and HIV status was unknown in the remaining two women.

Profile of women diagnosed with TB: Extra pulmonary TB accounted for 9 of the 14 MTB cases; all of which were pleural effusions. Three other cases involving extra pulmonary sites included PTB combined with a pericardial effusion, a case of miliary TB with confirmed fallopian tube involvement and the other involved the meninges and lung parenchyma. Ten women were HIV-1 co- infected, three were uninfected and the HIV-1 status was unknown in one. Six women had a past history of TB and five had a contact history with an infectious person.

Profile of mothers with suspected bacterial pneumonia (figure 2): Six mothers fulfilled the criteria for this category: no organism was isolated on sputum sample and all responded to a course of antibiotics.

As a result 4 categories of women developed: women with PTB (probable, confirmed and suspected TB) and women with suspected bacterial pneumonia.

Radiographic features at recruitment (table 4): Of the 29 available chest radiographs, 21 had a combination of left and right lobar involvement. In addition; cavitation was noted in 4 cases, destroyed lung fields in 2 cases and one case had a miliary pattern. The cavitatory picture was limited to TB women with 3 cases HIV-1 co- infected. Pleural effusions were detected in 10 cases with 7 women HIV-1 co- infected, 2 HIV-1 uninfected and one in whom HIV status was unknown.

Distribution of CD4 counts within the various subgroups: The median overall maternal CD4 and CD8 cell counts at baseline were 350 cells/ mm³ (range 13- 908) and 500 cells/ mm³ (118- 1558) respectively. The median CD4 count in the HIV-1 co- infected women with pneumonia was 186.5 cells/ mm³ (range 13- 908) and in comparison, the median in the HIV-1 uninfected women was 695 cells/ mm³ (range 118- 516). The median CD4 count in TB infection was 191 cells/ mm³ (range 37- 908) and in TB- HIV-1 co- infected women the median CD4 count was 174 cells/ mm³ (range 37- 908).

3.1.3 Loss to follow up

Depending on booking status and gestational age at which pneumonia was diagnosed, women were recruited during pregnancy and at presentation to the labour ward. Three women were lost to follow up

following recruitment during pregnancy as they were referred to their primary care facility for continued management and delivery. One woman absconded from hospital care. Therefore complete data sets are available for 25 women at the time of delivery.

3.1. 4 Impact of pneumonia on obstetric and maternal outcomes

In the group of 25 women, 16 delivered vaginally and six of nine caesarean sections were elective procedures. Emergency caesarean sections were performed for fetal distress and pre-eclampsia and the indications for elective procedures were previous caesarian sections, oligohydramnios, complete breech presentation, vulval warts, stage 3 cervical intra epithelial neoplasia and for fetal macrosomia.

Fourteen preterm deliveries occurred at median gestational age of 31 weeks (range 18- 37). Obstetric complications included premature labour (28%), eclampsia (8%), ante partum and post partum haemorrhage (8%) and oligohydramnios (4%).

Seven maternal deaths occurred in this group with 6 of 7 HIV-1 co infected (refer table 6). The maternal mortality ratio was 99 per 100 000 births (number of maternal deaths as the numerator [n=7] and the number of deliveries at the hospital as the denominator [n=7100], expressed per 100 000). The case fatality rate was 25%. The median age was 27 years and median parity of 1. The median CD4 count was 137 cells/ mm³ (range 37- 209) with a median haemoglobin of 8.5g/ dL (range 6.4- 13.6). Excluding the mother who died pre delivery, the median day to death post delivery was 4.5 days (range 1-12). Contributing factors included end stage HIV disease and respiratory distress due to pulmonary embolus, PTB and atypical pneumonia.

3. 1. 6 Impact of pneumonia on perinatal and neonatal outcomes (table 7, 8)

Fetal distress occurred in three neonates. There were 19 live born neonates (one delivered at home), one intra uterine death and 5 stillbirths (table 9). The perinatal mortality rate calculated for 6 deaths of 25 deliveries was 240 per 1000 births. Permission for post mortem biopsy and examination was requested on all stillbirths but not pursued on a compassionate basis.

One newborn was delivered at home. Of the live births, 11 (57.9%) were appropriate for gestational age, 7 (36.8%) were small for gestational age (SGA) and 1 (5.3%) was large for gestational age (LGA). No overt features of teratogenicity were noted following exposure to anti tuberculosis drugs in utero.

The median birth weight was 2150 grams (range 450-4200) with median apgar scores at one and five minutes seven and above. Seven of the 18 live born were low birth weight (LBW, 39%) of which 4 were very low birth weight (VLBW, 57 %) and 1 was extremely low birth weight (ELBW, 14%).

The median neonatal haemoglobin at birth was 15g/dL (range 12.40- 19.40). CD4 and CD8 cell counts were performed on 10 of 18 neonates, with a median of 1231.5 cells/ mm³ (range 376- 2273) and 375.8 cells/ mm³ (range 143- 1745) respectively.

All the neonates were managed according to the principles of the neonatal unit. All neonates were investigated on the basis of maternal history and clinical features. Neonates, in particular those that were symptomatic and TB exposed, received a chest radiograph, relevant laboratory investigations and appropriate antibiotic treatment and supportive therapy.

Neonatal pneumonia was diagnosed in four with no causative organism identified (outlined in table 10). TB was not confirmed in any of the (TB) exposed live born neonates. Follow up of these neonates was not a component of the study; however all TB exposed neonates were followed up at the hospital's neonatal clinic. TB culture results were negative at subsequent outpatient visits at 4- 6 weeks and 12 weeks.

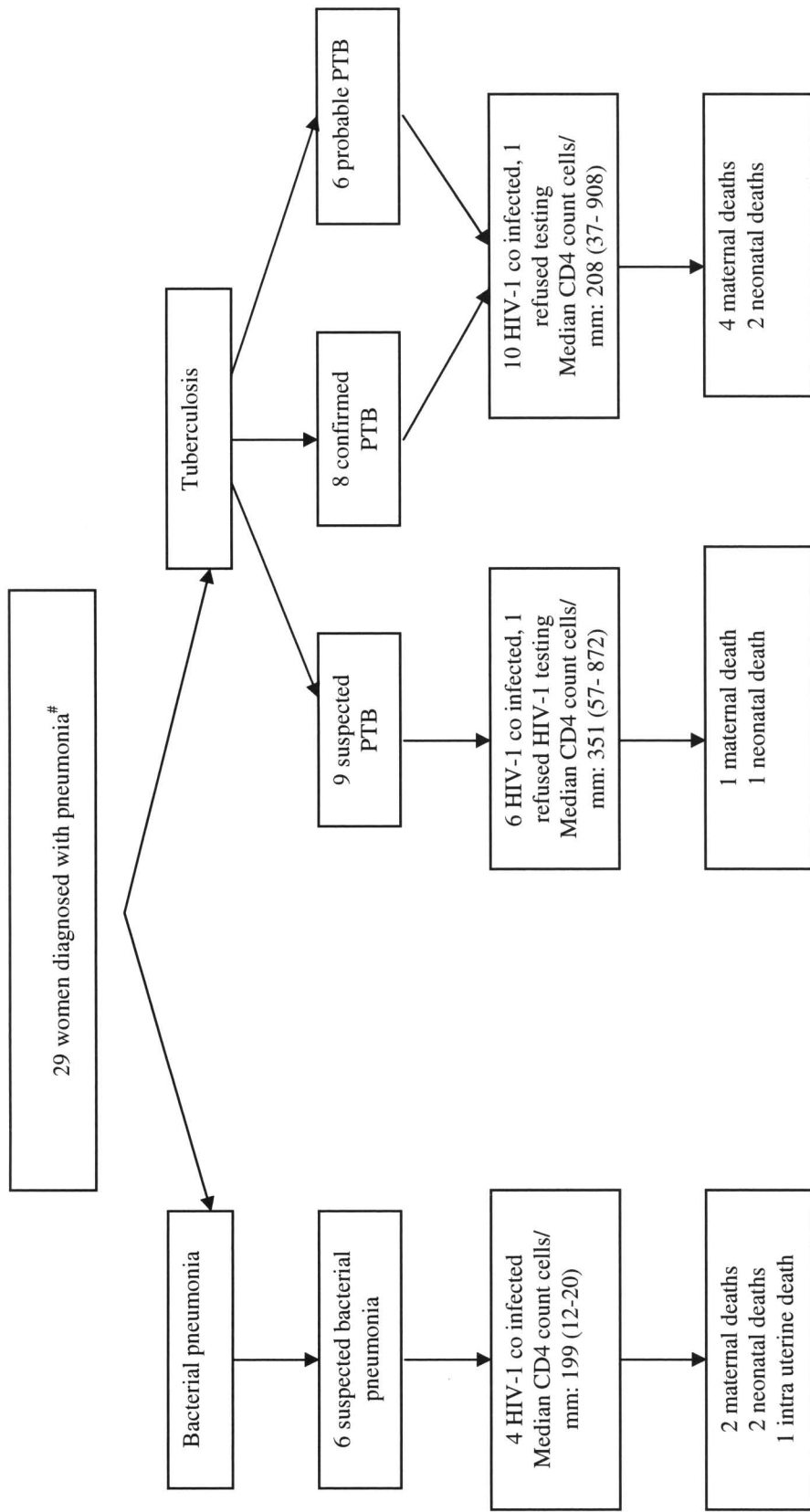


Figure 2: Diagram of patients with pneumonia in pregnancy

key: # = pre pregnancy diagnosis in 2; in 27 diagnosis of pneumonia for first time during pregnancy, 23 of which were suspected, probable or confirmed
 TB. = Tuberculosis
 PTB = pulmonary tuberculosis
 MTB = mycobacterium tuberculosis
 Range of CD4 counts in brackets

Table 3: Maternal descriptive statistics for the study and control arms

	Study arm	Control arm	p value
Median age in years (range)	28 (17-38)	26 (18- 40)	0.218
Median parity (range)	1 (0- 4)	1 (0-5)	0.044*
HIV status-			0.001*
Infected	20	43	
Uninfected	7	69	
Unknown	2	N/A	
Antenatal care received	22	85	0.997
Antenatal booking:			0.089
First trimester	2	1	
Second trimester	12	52	
Third trimester	8	32	
Median gestational age in weeks at first antenatal booking (range)	21 (12- 28)	23 (10- 34)	0.313
Medical conditions-			0.007*
Anaemia	3	15	
Chronic medical conditions	5	1	
HIV related conditions	3	0	
Obstetric co morbidities	14	17	<0.001*
Median Gestational age in weeks at diagnosis of pneumonia	28	N/A	N/A
Classification of TB:			
EPTB alone	10	N/A	N/A
EPTB and PTB	2	N/A	
Maternal deaths	7	0	<0.001*

Footnote: TB = tuberculosis
PTB = pulmonary tuberculosis
EPTB = extra pulmonary tuberculosis
* = statistically significant at the 0.05 level of significance

Table 4: Radiographic features in maternal pneumonia

	HIV infected n= 20	HIV uninfected n= 7	HIV status unknown n= 2
RML involvement	1	0	0
LUL involvement	1	0	0
LLL involvement	2	1	0
Combination of above	7	3	0
Lobar distribution indeterminate	4	2	1
Destroyed lung fields	1	1	0
Cavitation	3	0	1
Miliary picture	1	0	0
Pleural effusion	7	2	1

Footnote: HIV= human immunodeficiency virus
RML= right middle lobe
LUL= left upper lobe
LLL= left lower lobe

Table 5: Co- existing obstetric conditions

	Study arm n=29	Control arm n= 112
None identified	15	95
Pre eclampsia/ eclampsia	2	0
Antepartum haemorrhage	1	1
Pre term labour	5	0
Per vaginal discharge	1	4
Multiple pregnancies	1	0
Vulval warts	2	2
Gestational hypertension	0	8
Bad obstetric history	0	1
Fetal abnormalities detected on ultrasound	1	0
Intra uterine growth restriction	1	1

Table 6: Profile of maternal mortalities

Case	Age (years)	Parity	HIV status (WHO clinical stage)	ANC	CD4 count (cells/ mm ³)	Hb (g/Dl)	Medical and obstetric conditioning	Day of death post delivery	Neonatal outcome
1.	20	1	Uninfected	No	Not done	13.6	DVT, pleural effusion, no confirmation of PTB	28 wks gestation (prior to delivery)	IUD
2.	29	0	Infected (WHO stage 4)	Yes	108	7.9	PTB (pleural effusion) with fibrocavitary changes, pericardial effusion, oligohydrannios	4 days	1100 g liveborn NVD at 31/ 52
3.	23	1	Infected (WHO stage 4)	No	126	9.1	Disseminated KS, atypical bronchopneumonia (MTB smear positive), anaemia, recurrent cellulitis, UTI	5 days	1100g FSB NVD at 26/ 52
4.	27	2	Infected (WHO stage 3)	Yes	209	8.5	Lobar pneumonia with lamellar effusion (PTB on treatment)	1 day	1050g FSB NVD at 26/ 52
5.	26	0	Infected (WHO stage 4)	Yes	148	11.5	Pre eclampsia, pleural effusion with lobar pneumonia (empirical TB treatment)	7 days	800g MSB NVD at 28/52
6.	27	2	Infected (WHO stage 3)	No	207	6.4	HIV related medical conditions, PTB, pre term labour	4 days	1650g liveborn NVD at 30/52
7.	32	1	Infected (WHO stage 3)	Yes	37	6.4	PVD, MSL, pleural effusion	12 days	2500g liveborn NVD at 40/52

Key: UTI= urinary tract infection

PTB= pulmonary tuberculosis

MSL= meconium stained liquor

PVD= per vaginal discharge

NVD= normal vaginal delivery

FSB/ MSB= fresh/ macerated stillbirth

Table 7: Neonatal descriptive statistics for the study and control arms

	Study arm	Control arm	p value
Gestational age:			<0.001*
term	3	99	
pre term	14	3	
post term	8	10	
Birth weight #:			<0.001*
≥2500 grams	11	110	
1500- 2490 grams	4	2	
<1500 grams	9	0	
Outcome:			<0.001*
AGA	11	104	
SGA	7	1	
LGA	1	7	
SB	5	0	
IUD	1	0	
Clinical condition:			<0.001*
Well	12	101	
Ill	6	11	
Dead	6	0	
Neonatal pneumonia:			<0.001*
Yes	4	0	
No	9	0	
Not known §	12	112	

Key:

= one intra uterine death in the study arm, unweighed.

§ = these neonates were not routinely investigated for pneumonia as there were no clinical indications in the neonate or a maternal history to prompt such investigation.

* = statistically significant at the 0.05 level of significance

AGA= appropriate for gestational age

SGA= small for gestational age

LGA= large for gestational age

SB= stillbirth

IUD= intra uterine death

Table 8: Clinical features of neonates in the study and control arms

	Maternal HIV-1 infection and pneumonia (n= 20)	Maternal pneumonia, HIV-1 uninfected (n= 5)	Maternal HIV-1 infection, no maternal pneumonia (n= 43)	Maternal HIV-1 uninfected, no maternal pneumonia (n= 69)
Mean gestational age at birth in weeks (range)	40 (28- 40)	40 (30- 40)	39 (36- 41)	39 (39- 41)
Mean birth weight in grams (range)	2583 (450- 4200)	3050 (1100- 3250)	3131 (2300- 3850)	3440 (2700- 4410)
Stillbirths	4	1	0	0
Neonatal pneumonia	4	0	0	0
Low birth weight (%)	8 (42%)	2 (50%)	0 (0%)	0 (0%)
Premature (%)	10 (50%)	2 (40%)	1 (2%)	1 (1%)

Table 9: Neonatal deaths associated with maternal pneumonia

Case	Neonatal characteristics	Maternal age (in years)	Maternal parity and booking status	Maternal HIV status, CD4 count in cells/mm ³	Maternal medical Conditions	Obstetric conditions	Maternal outcome
1.	450g FSB NVD at 20/52	Not available	1, booked at 18 weeks	Infected, 199	HIV related medical conditions, PTB	TOP	Alive
2.	IUD at 28 wks gestation	20	2, unbooked	Uninfected	DVT	Nil	Demised
3.	800g MSB NVD at 28/52	26	0, booked at 14 weeks	Infected, 148	Pleural effusion	Pre eclampsia	Demised
4.	1100g FSB NVD at 26/ 52	23	2, unbooked	Infected, 126	Disseminated KS, anaemia, recurrent cellulitis, UTI	Nil	Demised
5.	1100g MSB NVD at 38 wks	38	4, booked at 26 weeks	Uninfected	Miliary TB	IUGR	Alive
6.	1050g FSB NVD at 26/ 52	27	3, unbooked	Infected, 209	PTB	Nil	Demised

Key: UTI= urinary tract infection

NVD= normal vaginal delivery

UTI= urinary tract infection

IUGR= intra uterine growth restriction

KS= kaposi's sarcoma

FSB/ MSB= fresh/ macerated stillbirth

TOP= termination of pregnancy

Table 10: Characteristics of neonates with neonatal pneumonia

Case	Gestational age and mode of delivery	Weight (in grams)	Apgars at 1 and 5 minutes	CD4 count	Radiographic features	Maternal features	Obstetric complications
1.	Term AGA female, NVD	2500	8, 10	Not done	Right perihilar infiltrate	MDR TB (smear and culture positive), anaemia, HIV infected	MSL grade 3
2.	34wk SGA female, C/S	1400	8, 10	1004.1	Left upper lobe infiltrates	Pleural effusion (empirical anti TB treatment), anaemia, HIV infected	Fetal distress and PROM
3.	Term AGA female, C/S	2950	8, 10	1432	Right lobe pneumonia	MTB (sputum culture positive post delivery), anaemia, HIV infected	Antepartum haemorrhage and cervical intra epithelial neoplasia grade 3
4.	30wk SGA female, NVD	1100	8, 10	739	Congenital pneumonia	MTB (smear and culture positive), anaemia, HIV infected	Nil

- MTB not isolated in the above neonates, none required ventilation.

- Key:

- AGA= appropriate for gestational age
- SGA= small for gestational age
- MTB= mycobacterium tuberculosis
- MSL= meconium stained liquor
- PROM= premature rupture of membranes

3.2 Profile of HIV-1- infected and -uninfected pregnancies at King Edward VIII Hospital (control arm)

3.2.1 Selection of controls

A control arm of 116 women was selected from the antenatal population attending the antenatal clinic and labour wards. This group of women had consented to HIV-1 testing and delivered at the study site. Four women were subsequently excluded from the group as they were found to have pneumonia and PTB following consultation of their medical records. As a result, the control arm consists of 112 women.

3.2.2 Maternal profiles

The maternal demographic data and co existing medical conditions are outlined in table 3. The obstetric co morbidities are captured in table 5. Twenty seven women did not seek antenatal care. The median gestational age at first antenatal visit in the booked population was 22 weeks (range 10-34).

Forty three women (38%) were HIV-1 infected and 69 (62%) were HIV-1 uninfected. Clinically 40 of 43 HIV-1 infected mothers were WHO stage 1 and the remainder was WHO stage 2. CD4 and CD8 assays were only performed on HIV-1 infected women. Syphilis serology was available for 91 mothers with 4 reactive results. The median hemoglobin was 11.5g/dl (range 7.3- 14.9).

3.2.3 Obstetric complications and maternal outcomes

The three common complications that arose during labour were meconium stained liquor (MSL) and resultant fetal distress (59%), slow progress in labour (12.5%) and pre labour rupture of membranes (12.5%). Ninety nine term (88%), 10 post term (9%) and 3 pre term deliveries (3%) occurred between 24- 37 weeks. The overall median gestational age at delivery was 39 weeks (range 36- 42). Eighty two women delivered vaginally and 30 caesarean sections were performed. The indication for the 2 elective procedures was for a breech presentation and a poor obstetric history. The remaining 28 caesarean sections were emergency procedures and were as a result of the complications outlined above. There were no maternal deaths during labour and in the puerperium in this group of women.

3.2.4 Neonatal outcomes (table 7, 8)

All of the 112 neonates were liveborn with a median birth weight of 3200 grams (range 2050-4950). One baby was growth restricted (IUGR, SGA) and seven were LGA and the rest were AGA.

Eleven neonates experienced problems at birth: respiratory distress as a result of exposure to MSL grade 3 (n=6, 55%), neonatal jaundice (n=1, 9%), birth asphyxia resulting in extensive seizures (n=1, 9%), congenital syphilis (n=1, 9%), conjunctivitis (n=1, 9%) and dysmorphism (n=1, 9%). There were no intra uterine, perinatal or neonatal deaths. CD4 counts and haemoglobin were not performed routinely on neonates at birth and further blood investigations were based on clinical findings.

3.3 Multi drug resistant tuberculosis (MDR TB) in pregnancy

The one case of MDR TB noted in our series of women with pneumonia is outlined in detail below. (The 4 other cases of MDR TB in pregnancy has been described in section 1.5 and in the tables 11, 12 and 13. Case 5 is the case recruited in 2000).

3.3.1 Maternal profile and outcome (refer table 11)

The patient had received prior anti TB treatment and multi drug resistant tuberculosis was diagnosed 7 months prior to gestation. The sensitivity profile on sputum samples showed resistance to 4 drugs (including an injectable) and second line treatment was initiated based on these results. She was also HIV-1 co infected and clinically WHO stage 3.

The patient sought antenatal care at a gestational age of 24 weeks. Blood investigations showed a normochromic normocytic anaemia and syphilis serology was negative. At the time of diagnosis of pregnancy, she remained *Mycobacterium tuberculosis* sputum and culture positive. The patient was hospitalised at King George V hospital until delivery. There were no side effects from second line treatment noted during hospitalization. However, long term complications cannot be commented on.

The mother remained culture positive at the time of delivery. The labour was complicated by foetal distress and resultant meconium staining of the liquor. A normal vaginal delivery occurred.

3.3.2 Neonatal profile and outcome (table 13)

Overt teratogenicity was not observed in the neonate despite exposure to potentially teratogenic drugs. The neonate (case 5) however showed right perihilar infiltrates on chest radiograph and was diagnosed with congenital pneumonia. *M tuberculosis* was not cultured from their gastric aspirates, cerebrospinal fluid or (maternal) endometrial scraping. The decision was made to initiate anti TB treatment on the basis of maternal history and clinical signs in the neonate. HIV-1 status was indeterminate at the time of last contact. The baby was discharged into the care of a relative but was subsequently lost to follow up.

All attempts at contact tracing of this mother baby pair was unsuccessful.

Table 11: Maternal characteristics associated with MDR TB and HIV-1 in pregnancy

	Age (in years) at diagnosis of MDR TB	HIV-1 status	Resistance profile of MTB	Drugs used at initiation	Chest radiograph features on admission	Maternal outcome
1	42	+	R,I,S	R,I,P,E,S,Eth,Cyc,INA T	Destroyed Lt* lung with calcification on Rt❖	Alive up to 9 mths ffup^
2	28	-	R,I,S,E	R,I,P,E,Eth,Kana, Oflox	Consolidation on Lt lower zone, patchy infiltrates through out bilaterally with fibro-cavitary disease, large Rt upper lobe bulla	Alive up to 24 mths ffup
3	32	+	R,I,S,E,Eth, Thia	R,I,P,E,Pyr	Extensive patchy consolidation with cavitation in Rt and Lt upper lobe	Discharged to MDR TB clinic
4	26	-	R,I,S	E,P,Cipro,Kana	Infiltrates in Lt upper, middle and lower lobes and Rt lower zone	Alive up to 18 mths ffup
5	26	+	R,I,S,E	Kana,Oflox,Cyc,Eth,P	Miliary TB	Lost to follow up following delivery

* R=rifampicin, I=isoniazid, P=pyrazinamide, E=ethambutol, Eth=ethionamide, S=streptomycin, Thia=thiacetazone, Cyc=cycloserine, Kana=kanamycin,

Oflox=ofloxacin, Pyr=pyridoxine, Cipro=ciprofloxacin, INAT= isonozid and thiacetazone

*mths= months

* Lt= left

^ ffup= follow-up

❖ Rt= right

Footnote: of the 5 cases of MDR TB, only one was diagnosed at 14 weeks of gestation and the remainder were diagnosed prior to pregnancy.

Table 12: Complications associated with MDR TB in pregnancy

Maternal complications:		Interventions:
<i>a) Therapy related</i>	Sensorineural loss (2), drug induced hepatitis (1)	
<i>b) Extensive TB disease</i>	Destroyed lung and haemoptysis (1)	Pneumonectomy and bronchial artery embolisation (1)
<i>c) Pregnancy</i>	Preterm labour (1)	
Neonatal complications:		
<i>a) Teratogenic effects</i>	Nil	

Table 13: Neonatal outcomes associated with maternal MDR TB and HIV-1 infection

Baby	Gestational age in weeks (neonatal complication)	Birth weight in grams	Mode of delivery	Apgars at 1 and 5 minutes	SGA
1	38 (IUGR)	2800	NVD	9, 10	Yes
2	34 (Prematurity)	1800	NVD	8, 10	No
3	20 (Aborted)	n/a #	NVD	n/a	n/a
4	38	3200	NVD	8, 10	No
5	38 (IUGR)	2500	NVD	unknown	No

n/a = not applicable

SGA = small for gestational age

NVD = normal vaginal delivery

IUGR = intra uterine growth retardation

3.4 Comparative data between the women with pneumonia (study) and control arms

3.4.1 Antenatal attendance:

A total of 141 women (29 from the study arm and 112 from the control arm) are included in this analysis. One hundred and four women sought antenatal care with 61 (56.4%) attending the antenatal clinic during the second trimester and 37 (34.2%) in the third trimester. Thirty three women (unbooked) did not receive antenatal care. Six of the unbooked mothers were diagnosed with pneumonia at presentation to the labour ward. Antenatal care did not impact statistically on maternal outcome in the presence of antenatal pneumonia ($p=0.169$).

The diagnosis of pneumonia occurred mainly in the second trimester, however in the presence of pneumonia, this variable did not impact on maternal outcome ($p=0.244$).

3.4.2 Obstetric complications:

The difference in the incidence rate of obstetric complications between the group of women with pneumonia and those without pneumonia reached statistical significance ($p = 0.001$) with complications more frequent in women without pneumonia (64% vs 28.8%).

3.4.3 Medical co morbidities (table 3):

Thirty six women (26.3%) had medical conditions with 12 (of 36 [33.3%]) co infected with pneumonia. Seventy four women (54%) were anaemic with 21 (28.4%) of these women co infected with pneumonia while 7.9% of those with normal haemoglobin levels had pneumonia ($p=0.002$). Thus there was a significant association between anaemia and the development of pneumonia.

3.4.4 The relationship of pneumonia and obstetric outcome and multiple variables:

Pneumonia was significantly associated with obstetric outcome ($p=0.002$) overall, in the presence of HIV-1 infection ($p<0.001$, in the presence of antenatal care ($p=0.009$), second trimester booking ($p=0.003$) and in the presence of anaemia ($p=0.002$). There was no association between pneumonia and obstetric outcome either in the presence or absence of associated medical or obstetric conditions.

The presence of pneumonia and pneumonia in the presence of HIV-1 infection impacted statistically on obstetric outcome ($p= 0.001$ and $p=0.000$).

3.4.5 Impact of maternal HIV-1 infection:

The presence of HIV-1 infection in women with antenatal pneumonia did not impact on obstetric outcome ($p= 0.911$), maternal outcome ($p= 0.29$), neonatal birth weight ($p= 0.47$) or neonatal deaths ($p=0.270$).

3.4.6 Maternal outcomes:

Of one hundred and thirty seven women who delivered at the study site, 130 were alive post delivery and 7 died during gestation, delivery or post partum. Three of the women who died did not receive any antenatal care prior to diagnosis of pneumonia.

The presence of pneumonia was significantly associated with maternal mortality ($p \leq 0.001$) as was the presence of pneumonia in HIV-1 infected women ($p \leq 0.001$). Within the maternal deaths, the association with HIV status, the CD4 count, the receipt of antenatal care did not reach statistical significance.

The maternal outcome in women with PTB did not differ from those with suspected bacterial pneumonia ($p=0.943$) and the presence of HIV-1 co infection in women with PTB also did not impact on maternal outcome ($p=0.409$).

3.4.7 Neonatal profiles and outcomes:

Of 137 deliveries, 16 (11.3%) pre term deliveries occurred. The impact of maternal pneumonia, maternal HIV-1 infection and co infection on the gestational age at delivery, reached statistical significance ($p \leq 0.001$, $p= 0.005$ and $p \leq 0.001$ respectively).

One hundred and twelve neonates were well at birth. Seventeen neonates were ill at birth of which 6 were exposed to maternal pneumonia. Six neonatal deaths occurred in the study arm.

3.4.8 Birth weight:

All LBW neonates were exposed to maternal pneumonia ($p \leq 0.001$). Maternal HIV infection and the presence of medical and obstetric conditions were significantly associated with LBW ($p = 0.047$, ≤ 0.001 and 0.001 respectively). Statistically the presence of maternal TB and anaemia did not impact on birth weight.

The median CD4 counts in HIV infected mothers in neonates with birth weights above and equal to 1500 grams was 367 cells/ mm^3 (range 37- 908). In comparison, the median CD4 counts in HIV

infected mothers in neonates with birth weights below 1500 grams was 109 cells/ mm³ (range 13-199), $p < 0.001$.

3.4.9 Neonatal outcomes:

One hundred and twelve neonates were well at birth, 90% of the non pneumonia exposed neonates were well compared with 50% of the pneumonia exposed neonates. All six neonatal deaths occurred in those exposed to maternal pneumonia and 17 neonates were ill at birth, 6 were exposed to maternal pneumonia. There was a highly significant association between exposure to pneumonia and poor neonatal outcome ($p < 0.001$).

The impact of maternal pneumonia on neonatal outcome and birth weight reached statistical significance (p value = 0.000). In addition, the presence of neonatal pneumonia was significantly associated with maternal pneumonia (p value ≤ 0.001). Further, maternal pneumonia and HIV infection in the presence of maternal pneumonia was significantly associated with neonatal death (p value ≤ 0.001 and =0.002 respectively).

3.4.10 Neonatal deaths:

The association between neonatal deaths and anaemia or lack of antenatal care did not reach statistical significance. However neonatal deaths were significantly associated with pneumonia diagnosed in the second trimester ($p = 0.025$), the presence of (maternal) medical conditions ($p = 0.002$), (maternal) pneumonia ($p \leq 0.001$), HIV-1 infection in presence of pneumonia ($p \leq 0.001$) and the absence of obstetric complications (p value = 0.003).

CHAPTER 4 – DISCUSSION

Pneumonia in pregnancy: Factors associated with its development and the impact on maternal and neonatal outcomes

The incidence of pneumonia in pregnancy does not differ from that in the non pregnant state yet it carries significant morbidity and mortality. It is ranked as the third leading cause of maternal mortality in the United States (Kaunitz *et al*, 1985) and the leading cause of non obstetric related deaths in South Africa (Department of Health, SA, 2006). Risk factors identified in the development of pneumonia in pregnancy include asthma, anaemia, chronic medical disease, drug and tobacco use, HIV co- infection and the pregnant state itself with its associated anatomical, physiological and immunological changes (Munn *et al*, 1999; Sridama *et al*, 1982; Baley and Schacter, 1985; Berkowitz and LaSala, 1990; Fishburne, 1979; Elkus and Popovich, 1992). The presence of pneumonia can result in premature labour and delivery, low birth weight neonates, transmission of pathogens from mother to neonate and contributes negatively to maternal, perinatal and neonatal mortality rates (Benedetti *et al*, 1982; Madinger *et al*, 1989; Yost *et al*, 2000; Richey *et al*, 1994; Goodrum, 1997).

Risk factors for the development of pneumonia identified in our study population were chronic medical conditions specifically hypertension and diabetes, anaemia and HIV-1 infection. Other reported factors that influence outcomes in pregnancies complicated by pneumonia included age, parity, extent of lung involvement and gestational age at the time of diagnosis. Although younger women and primigravidae within the study arm were more commonly affected, neither variable reached statistical significance. This is probably a reflection of the TB and HIV-1 epidemics in females in the reproductive age group in KwaZulu- Natal (Wilkinson and Davies, 1997b; Department of Health, SA, 2005; Pillay *et al*, 2001).

The proportion of mothers in the study arm with HIV-1 co- infection was more at risk of developing pneumonia than the (HIV) uninfected mothers. In addition, the prevalence of risk factors did not differ between HIV-1- infected and uninfected mothers. It was perhaps the pregnant state itself that was the common risk factor.

The role of the attending obstetrician or nurse should not be underestimated as they are the first point of contact for pregnant women seeking antenatal care. The presenting symptoms of pneumonia and TB vary from asymptomatic to non specific complaints which mimic the physiologic changes and symptoms of pregnancy (Good *et al*, 1981; Kothari *et al*, 2006). Health care givers need to be

made aware of the need for referral of pregnant women presenting with respiratory symptoms or a non resolving upper respiratory tract infection. Close to one third of women in our study presented with a chronic cough and approximately two thirds with a combination of respiratory symptoms which alerted the health care provider to exclude pneumonia and a chest radiograph with abdominal shielding and sputum microscopy was performed, as has been described in previous studies (Pillay *et al*, 2001; Good *et al*, 1981).

Antenatal care directly impacts on maternal and neonatal outcomes and in Africa, most women “book” late in pregnancy. It is common practice for antenatal attendees in KwaZulu-Natal to “book” at a median gestational age of 28 weeks (Pillay *et al*, 2001) and 10% have no antenatal care (Matambo *et al*, 1999). In our study, 91% of women “booked” in the second and third trimester of pregnancy. Twenty two of the women with pneumonia sought antenatal care at a median gestational age at first antenatal attendance late in the second trimester. Pneumonia was diagnosed at a median gestational age in the third trimester. Mothers in the control arm might have “booked” later or not sought antenatal care as they were less ill than mothers with pneumonia and were clinically WHO stage 1 if HIV-1 infected. The difference in median gestational age at first antenatal visit did not reach statistical significance between the 4 groups of women within the study and control arms (i.e.: with HIV-1 and pneumonia, HIV-1 uninfected with pneumonia, HIV-1 infected and HIV-1 uninfected).

Reasons for delayed or lack of attendance are unclear. The seeking of professional care late in the second and early third trimester not only delays thorough investigation and management but also impacts on the spread of the disease to other body organs and transmission to the neonate. This was significant in our study as the only causative organism that was isolated (in the mothers) was *Mycobacterium tuberculosis* (MTB).

In 40- 61% of cases of community acquired pneumonia, a causative organism is not identified (Madinger *et al*, 1989) and there could be a number of explanations for the detection of MTB alone in our study. Firstly, it could be a reflection of the TB epidemic in KwaZulu-Natal in females in the reproductive age group which increased from 28% to 37% between 1991 and 1995 (Wilkinson and Davies, 1997b). Secondly, the antenatal prevalence of HIV-1 infection in South Africa is highest in KwaZulu-Natal (Department of Health, SA, 2005) and PTB is the commonest pulmonary presentation of HIV/ AIDS in under- resourced countries (Anonymous, 1996a). Thirdly, TB in

pregnancy increased from 0.1% in 1996 to 0.6% in 1998 in the study setting, with 71.7% of TB attributable to HIV-1 co infection (Pillay *et al*, 2001).

Treatment was initiated with second generation cephalosporins, aminoglycosides, fluoroquinolones, penicillin and a combination of penicillin and β lactamase inhibitors in the group following the diagnosis of suspected community acquired pneumonia. There are no antimicrobial agents licensed for use in pregnancy and their use is directed by the benefits to the mother and fetus weighed against the risks of adverse events. The choice of antibiotics depends on their safe use in pregnancy and the antibiotics prescribed in our study with the exclusion of aminoglycosides, are considered non-teratogenic and effective against possible causative organisms. Aminoglycosides are only used if there is a strong clinical indication as toxicity to the fetal auditory nerve has been reported (Holdiness, 1987b).

Twenty two patients commenced anti TB treatment on the basis of clinical, radiographic, sputum and histology results. The safety of first line anti TB therapy has been established (appendix E. 3) and the benefit of drug treatment compared to miliary spread of disease in the mother and transmission to the fetus and community outweighs potential teratogenicity.

Specifically with regards to TB, the failure to treat, initiation of treatment in late pregnancy, the presence of advanced pulmonary lesions and incompletely treated TB is associated with a two fold increase in adverse perinatal outcomes, a four fold increase in obstetric morbidity and a nine fold increase in preterm labour (Pillay *et al*, 2001; Jana *et al*, 1994; Figueroa- Damian and Arredondo-Garcia, 1998). Despite our study population being too small to comment on the impact in the antenatal community, pneumonia in pregnancy was significantly associated with maternal and neonatal deaths.

Furthermore, delays in the diagnosis of and initiation of treatment for TB and multi- drug resistant TB (MDR TB) impacts on maternal and fetal outcomes. One of the factors affecting early diagnosis and treatment is the delay in obtaining susceptibility results. Despite newer laboratory methods being available, in the developing world the Lowenstein Jenson medium remains the gold standard for diagnosis. Current practice locally is to use direct and indirect susceptibilities, with direct being set up from acid fast bacilli (AFB) smear positive specimens and indirect from MTB culture including confirmation of direct susceptibilities. Drugs tested in direct susceptibility include INH 1 mg/ l, RIF 1mg/ l and EMB 7.5mg/l. In addition, Kanamycin 5mg/ l, Ofloxacin 2mg/ l, ETH 5mg/l and Cycloserine 30mg/l are tested for in indirect susceptibility testing (verbal communication

Medical Microbiology Department, University of KwaZulu-Natal). Delays in the availability of results range from 3- 12 weeks which impact on patient care in a number of ways which include firstly, an inability to trace patients following discharge from a health care facility to local centres with subsequent loss to follow up at both centres and secondly, a delay in the implementation of treatment.

Pneumonia is classified as an indirect cause of maternal death. The contribution of pneumonia to maternal mortality has not been previously described in the KEH population. The maternal mortality ratio (MMR) in pregnancies complicated by pneumonia was 99 per 100 000 births which contributed to the overall MMR of 718 (with a denominator of 7100) for the hospital. It should be noted that the MMR in the study group is on a selected group of young women, whereas the maternal mortality ratio for the hospital is based on women with varying age group and disease profiles.

Maternal mortality rates associated with pneumonia were high prior to the introduction of antibiotics but have fallen with the use of effective antibiotics to 12.5%. The standard of care at the study setting was to provide a course of antibiotics on the diagnosis of pneumonia and monitor response to treatment. The high MMR could be related to advanced HIV-1 infection, the presence of co- morbid disease, late ANC attendance, diagnosis late in pregnancy, short duration of antibiotic/ TB treatment and the extent of pulmonary disease.

Despite the prevalence of the TB and HIV epidemics in women in the reproductive age group, the documentation of the contribution of co- infection to MMRs has been limited to Zambia, India and Mexico with MMRs of 6.3% to 25% reported (Ahmed *et al*, 1999; Juneja *et al*, 1994; Figueroa-Damian and Arredondo- Garcia, 1998). Locally TB emerged as the third leading cause of maternal deaths in TB- HIV-1 co infection (Khan *et al*, 2001) accounting for 14 of 101 maternal deaths. In the study arm, probable or suspected TB was present in 71% of deaths and HIV-1 co infection in 86% of deaths, again highlighting the contribution of the twin epidemics.

Other studies have found the presence of pneumonia to have a negative impact on maternal mortality (Findland and Dublin, 1939, Ramsdell, 1905). These reports are from affluent societies and do not indicate whether HIV-1 and TB were contributory factors. In addition, the impact of HIV-1 related pulmonary complications on pregnancy and vice versa has been poorly documented, despite pulmonary disease being the commonest manifestation of AIDS defining illnesses (Anonymous, 1996a) and that most of the data is drawn from the non pregnant population.

The South African HIV antenatal sero-prevalence rates are currently amongst the highest in the world at 27.9% with a prevalence of 37.5% in KwaZulu-Natal (Department of Health, SA, 2005). At the time of the study, an increase from 26% in 1997 to 28% in 1999 was documented locally (unpublished data, Department of Virology). Overall for both study and control arms the prevalence of HIV-1 infection was 45%. Within our study population, 74 % were HIV-1 co-infected, 90% had advanced HIV infection (WHO stage 3 and 4 disease) and 44 % had a CD4 count less than 200 cells/ mm³. Within the control arm, 38% were HIV-1 infected, 93% were WHO clinical stage 1 with a median CD4 count of 367 cells/ mm³. These differences in HIV status and extent of disease highlight the advanced degree of illness in the study arm and are contributory factors to the MMR and perinatal mortality rate (PMR).

Within the study arm, women with TB- HIV-1 co infection had lower CD4 counts than HIV- 1 women with pneumonia. The impact of TB HIV-1 co infection on the CD4 count in pregnancy has been previously documented in the study setting with a mean CD4 count of 348 cells/ mm³ reported (Pillay *et al*, 2004b). Limited literature is available on the range of CD4 counts in HIV-1 infected and uninfected pregnant women. Data from a breast feeding population in Dar es Salaam showed CD4 counts less than 200 cells/ mm³ in 14.5% of the women and in the PACTG 185 trial, all women had CD4 counts less than 500 cells/ mm³ and 22% had CD4 counts less than 200 cells/ mm³ (Kilewo *et al*, 2005; Stiehm *et al*, 1999).

There are few reports of HIV-1 related morbidity in pregnancy (Semprini *et al*, 1995; Burns *et al*, 1999; Wawer *et al*, 1999; Verhoeff *et al*, 1999; Michielsen and Van Damme, 1999; De La Cruz Moron *et al*, 1999; Dao *et al*, 1997; Saade, 1997). Maternal HIV-1 infection is associated with lower birth weight, prematurity (Temmerman *et al*, 1994) and a higher risk of infant death (Brocklehurst and French, 1998), especially in advanced HIV-1 infection in resource constrained settings. This was evident in neonates of the study arm. In comparison neonates born to HIV-1 infected mothers were liveborn, delivered at term and were not low birth weight. The combined impact of TB HIV-1 co- infection on neonatal outcome has been poorly documented. In a South African study, neonates exposed to TB HIV-1 co- infection were two times more likely to be premature, 46% were low birth weight and 49% were growth restricted (Pillay *et al*, 2004b). In addition, the neonates were of lower birth weight compared to the general birth weight (of neonates) at the hospital. The combination of pneumonia and HIV in pregnancy resulted in comparable results with 42% premature, 33% SGA and 39% LBW. The impact of HIV co- infection on pre term labour, maternal

morbidity and outcome ($p \leq 0.001$), birth weight ($p \leq 0.001$) and neonatal deaths was statistically significant ($p \leq 0.001$).

The impact of HIV infection on maternal mortality has been poorly documented. At the time of the study, the confidential enquiry into maternal deaths by the Department of Health in South Africa (2000b) found 12.7% of deaths to be attributable to HIV/ AIDS and 2.4% of HIV-1 infected women in Malawi died (Bicego *et al*, 2002). The most recent Saving Mothers Report indicates that 20.1% of all deaths were related to AIDS (Department of Health, SA, 2006). There were no maternal deaths in the HIV-1 infected women and in the co infected women, the mean age, CD4 count and Hb in the maternal deaths was lower than previously reported (Khan *et al*, 2001).

The lack of anti retroviral therapy (ART) could also be a contributing factor to maternal morbidity and mortality, thereby impacting on perinatal and neonatal outcomes. The benefit of ART is unquestionable. The prevention of mother to child transmission (PMTCT) programs have shown a decrease in the transmission rate (Centres for Disease Control and prevention, 1998) by 50% and the local PMTCT program reported a vertical transmission rate of 20.6% at 6 weeks (Rollins *et al*, 2005). Adult mortality is reduced to between 20 and 62% (Correll *et al*, 1998; Detels *et al*, 1998) post highly active ART. One in 5 women with TB HIV-1 co infections transmit HIV-1 to their babies in utero (Pillay *et al*, 2004b) therefore the reduction of vertical transmission either with PMTCT or long term ART is imperative. It would be interesting to monitor the impact of the government anti retroviral roll out program which commenced in South Africa in April 2004. The scaling up of the anti retroviral program should be directed at women in the reproductive age group for three reasons: firstly, they have the highest HIV sero prevalence; secondly, antenatal clinics provide an entry point for the provision of counseling and testing for HIV-1 infection and a point of ART provision and thirdly, ART would improve the maternal clinical and immunological status thereby impacting on maternal, perinatal and neonatal morbidity and mortality.

It is important at this stage to acknowledge that the MMR might be underestimated as maternal deaths could have occurred “ at home” (home deaths) or in the puerperium, in the internal medicine or general surgery wards and the lack of follow up prevents a true reflection of the overall MMR. On the other hand, the MMR particularly in co-infected mothers might be higher than the overall MMR as mothers with dual infection are clinically ill and have been referred from an outlying clinic or hospital for further management, had medical and obstetric co- morbidities and had advanced HIV-1 infection with low CD4 counts. The attributable fraction of HIV-1 and pneumonia could not be calculated due to small numbers.

HIV-1 infection has altered the presentation of pulmonary disease on chest radiograph. Radiographic features of TB in early HIV-1 infection resemble that of an immunocompetent person. Features are atypical in advanced HIV-1 disease with a lower lobe, non-cavitary picture associated with intra thoracic (hilar and/ or mediastinal) lymphadenopathy. Interestingly, 75% of women in our study arm who had cavities on chest radiograph, were TB-HIV-1 co infected with a median CD4 cell count of 290.5 cells/ mm³ (range 109- 908). In addition 64% of women had unilateral pleural effusions. Three women had involvement of extra pulmonary sites including the pericardium, fallopian tube and meninges. Other reported EP sites include bone, lymph nodes, genital tract, placenta, renal system, abdomen, peritoneum and spine (Kothari *et al*, 2006; Pillay *et al*, 2004a, Jana *et al*, 1999; Lee *et al*, 2005).

Pleural effusions have been described in HIV-1 infected populations with a variety of aetiologies, with the contribution of MTB ranging from 22.5- 86% (How *et al*, 2006; Batungwanayo *et al*, 1993). This is comparable to the incidence of 68% in the study population.

In summary, all efforts to improve maternal outcomes need to be explored especially in resource constrained settings. The increasing rate of the TB and HIV-1 pandemics does beg the question whether all HIV-1 infected pregnant women should have a screening chest radiograph with “shielding” of the maternal abdomen at the first antenatal visit. Almost two thirds of the mothers had a chronic cough and other predictive indices such as anaemia which alerted caregivers to screen for pneumonia. However in a setting of high HIV prevalence combined with a possible lack of symptoms, it might be cost effective to use a screening questionnaire to identify women at risk of pneumonia and to strongly consider a chest radiograph in HIV infected women in pregnancy.

Neonatal outcomes:

All neonates in the control arm were liveborn and 18 livebirths occurred in the study arm. Five stillbirths and one intra uterine death occurred in the study arm. The only common exposure in the deaths was maternal pneumonia which has been previously reported by Bennedetti *et al* (1982) and Madinger *et al* (1989) as a contributory factor to perinatal deaths. No women in our study gave permission for neonatal autopsies and therefore this was not pursued on a compassionate basis. Other causes of antepartum stillbirth include congenital infection, foetal abnormality and medical conditions and their complications. In the majority of antepartum stillbirths, no direct obstetric causes have been reported to be identified and therefore remain unexplained (Pasupathy and Smith,

2005). Maternal characteristics that are the most prevalent independent risk factors are smoking, advanced age, obesity and nulliparity (Smith, 2006).

The perinatal mortality rate (PMR) was 4.8 fold higher in pregnancies complicated by pneumonia irrespective of HIV-1 status compared to the overall PMR's of the hospital and province. It was 280 fold higher than pregnancies complicated by HIV-1 infection alone in the control arm and 2.8 fold higher than in neonates exposed to TB HIV-1 co- infection studied at the same centre (Pillay *et al*, 2004b). In India, the presence of antenatal TB resulted in a 6 fold increase in perinatal deaths (Jana *et al*, 1994) whereas in London (UK), no impact on the PMR was noted (Kothari *et al*, 2006). Despite the contributions of the low median CD 4 count, HIV-1 co- infection and the general ill health of the study group compared to the general antenatal population, the PMR for the pneumonia exposed neonates highlights the increased risk of perinatal and neonatal deaths in this group.

Perinatal morbidity specifically relating to low birth weight and prematurity was also addressed in our study. Low birth weight neonates were 0.8 fold higher in those exposed to maternal pneumonia and HIV-1 infection compared to those exposed to pneumonia alone. In the study arm, the median birth weight was 2.15 kg; 68% (13 of 19 live births) were low birth weight and a third of the live births were SGA. In comparison, neonates of the control arm were of a higher median birth weight at 3.2 kg. Within this control arm, HIV-1 unexposed neonates had a median weight higher than HIV-1 exposed neonates (3.44kg compared to 3.13kg respectively). Factors that influenced neonatal birth weight included maternal pneumonia, maternal HIV-1 infection and the presence of medical and obstetric conditions. This finding supports previous studies that have documented the negative impact of antenatal pneumonia (Figueroa- Damian and Arredondo- Garcia, 1998; Leroy *et al*, 1995) and maternal HIV-1 infection in under resourced countries (Temmerman *et al*, 1994) on neonatal birth weight. In addition, the perinatal outcome was poorer with advanced HIV-1 infection and low CD4 counts (Brocklehurst and French, 1998). Previous studies at KEH showed 66% of neonates exposed to maternal TB HIV-1 co infection to be LBW (Pillay *et al*, 2004b) while a study done in India reported that 34.2% of neonates exposed to TB alone were LBW (Jana *et al*, 1994).

It has been documented that pneumonia (Benedetti *et al*, 1982; Madinger *et al*, 1989) and maternal TB specifically results in premature labour and delivery (Figueroa- Damian and Arredondo- Garcia, 1998; Ratner *et al*, 1951). The number of premature deliveries was disparate between the study and control arms in our study. The likelihood of prematurity was 18.7 times higher in the study arm compared to the control arm, highlighting the risk for preterm deliveries in mothers with pneumonia which has been previously reported by Benedetti *et al* (1982) and Madinger *et al* (1989).

The detection of 4 cases of congenital pneumonia was limited to neonates in the study arm. Common maternal features linked with this included anaemia, PTB and HIV-1 co infection. Investigation of the neonates was prompted by the maternal medical history and the presence of physical signs. No causative organisms were identified. The most likely causative organism of pneumonia within the neonatal period in term deliveries is group B streptococcus (Sherman *et al*, 1980, Hoffman *et al*, 2003). Neonates were managed according to the clinical management protocols of the neonatal unit and monitored at the neonatal outpatient clinic following discharge from the hospital.

Factors relating to the management of neonates exposed to MTB during gestation include the provision of prophylactic anti tuberculosis treatment (appendix D.5) and the administration of BCG. The protective efficacy of the BCG vaccine in the prevention of pulmonary TB in adults and adolescents is controversial (Anonymous, 1972; Anonymous, 1980). However a recent meta analysis of published literature showed a 64% protective efficacy against miliary TB and TB meningitis in clinical trials in children, 75% efficacy in case control studies and 71% protective efficacy against death (Colditz *et al*, 1994; Rodrigues *et al*, 1993). Therefore, in areas with endemic TB where contact with an untreated, infectious person is high, the BCG vaccine is advocated in infants by the WHO as part of the Extended Program for Immunization for Infants (von Reyn *et al*, 1987). In countries with a high prevalence of TB, it should be administered soon after birth (WHO, 2004).

In summary, pneumonia has a significant adverse perinatal outcome which is more pronounced with extensive pulmonary involvement. The delay in diagnosis and provision of treatment for TB; the late or lack of antenatal attendance and co morbid medical conditions further negatively impact on perinatal outcomes. The impact of pneumonia on obstetric outcome was significant in the presence of HIV-1 infection.

Multi drug resistant tuberculosis in pregnancy

Previous reports of MDR TB in pregnancy have been limited to 12 cases (Nitta *et al*, 1999; Shin *et al*, 2003; Lessnau and Qarah, 2003; Gach *et al*, 1999) with no reports of HIV-1 co-infection (Table 11). Although it was not our primary intention to study MDR TB and HIV co infections, this report includes the impact of these dual infections in pregnancy. Prematurity, IUGR, maternal drug use and disease related complications were observed, indicating that the dual infection carried with it significant perinatal and maternal morbidity. Perinatal transmission of MDR TB from mother to

child was not established despite clinical signs in two cases.

Multiple management dilemmas were faced by health care workers attending to these mothers. An approach to the management of the MDR TB infected pregnant woman is outlined in appendix K. Firstly, treatment of the pregnant woman co-infected with MDR TB and HIV-1 with potentially teratogenic drugs had to be weighed against whether pregnancy should continue or termination of pregnancy offered. Prior to the introduction of successful chemotherapeutic agents, mothers diagnosed with TB during pregnancy were advised to terminate their pregnancies (Bjerkedal *et al*, 1975). Maternal outcome improved with the advent of first line drugs that were safe to use in pregnancy (Miller and Miller, 1996; Schaefer *et al*, 1975). However, treatment of MDR TB with these drugs is inadequate and the potential teratogenic and side effect profile of second line agents used in MDR TB regimens have complicated the choice of treatment during pregnancy (Shin *et al*, 2003; Holdiness, 1987b). In the few reported cases, one mother chose to terminate her pregnancy for social reasons and not for the further management of the infection (Nitta *et al*, 1999) and one experienced pre term labour (Lessnau and Qarah, 2003). Of twelve MDR TB complicated pregnancies previously reported, nine mothers delivered at term with no congenital or neonatal abnormalities noted at birth (Nitta *et al*, 1999; Shin *et al*, 2003).

Secondly, reports on the teratogenic effects of second line drugs are limited. Streptomycin has been reported to affect hearing and/ or balance in one in six neonates (Holdiness, 1987b). Despite the lack of data for other aminoglycosides, potential ototoxicity is considered possible if used during pregnancy. Although there is no data available the use of Capreomycin in pregnancy it is considered to have a similar profile as the aminoglycosides. The use of fluoroquinolones during pregnancy for five to 10 days carries no reported adverse effects but their long term use may impair childhood growth and produce injury to growing cartilage (Medical Research Council, 1999; Loebstein *et al*, 1998). Ethionamide is not advised in pregnancy as it is teratogenic in animals (Medical Research Council, 1999). Therefore with the exception of ethionamide and long term fluoroquinolone use the potential teratogenicity with the more common second line antimycobacterial agents may not be sufficient grounds for termination of pregnancy.

Thirdly, withholding MDR TB treatment during pregnancy is based on the patient's decision following counseling, clinical condition, evaluation and stage of pregnancy (Nitta *et al*, 1999; Shin *et al*, 2003). However, the risk of dissemination and progression of disease in the mother and transmission to the fetus far outweighs the potential teratogenic risk (de March, 1975; Pillay *et al*, 2001), and in the face of HIV-1 co-infection is less likely to be an option favored by health care

workers today.

Fourthly, how should one manage a neonate exposed to HIV-1 and MDR TB? The neonate and infant must be investigated (appendix L), and if MDR TB is confirmed on susceptibility testing of cultures, treatment commenced according to drug susceptibility. However, the course of action where a diagnosis of TB cannot be established and symptoms of HIV-1 or TB disease emerge in the dually exposed infant remains contentious. In the non-MDR TB equivalent scenario in endemic areas, full investigation and confirmation of TB disease is followed by a full course of (first line) drug therapy (Pillay *et al*, 2004). With exposure to MDR TB, a further dilemma is posed; if the mother has MDR TB, is the maternal MDR strain always transmitted to the infected infant? There is some evidence that not all adults exposed to MDR TB will necessarily acquire the organism with the same MDR profile (Samper *et al*, 1999) whereas children are more likely to contract drug resistant TB rather than drug susceptible strains (Schaaf *et al*, 2000). Therefore the dilemma posed is whether to offer (neonatal) anti TB drugs based on the maternal profile of multidrug resistance or conventional therapy. In our series, prophylaxis with R, I and PZA was offered to all neonates at birth. In contrast routine prophylaxis was not offered in other studies (Nitta *et al*, 1999; Shin *et al*, 2003; Lessnau and Qarah, 2003). Since our original observations routine prophylaxis for MDR TB exposed neonates in our region now include PZA, ETH and a quinolone as prophylaxis (personal communication with Dr S Bamber, King George V hospital).

Fifthly, the issue of BCG administration to neonates exposed to mothers with MDR TB has been previously addressed with regards to TB exposed neonates.

In summary, successful TB control programs with early detection and completion of treatment is the key to the control of MDR TB. In TB endemic areas, a high index of suspicion must be maintained to appropriately investigate and monitor a pregnant woman. Lack of response to (current) TB treatment and a past history of incomplete TB treatment should be triggers for further investigation for MDR TB.

Limitations of the study:

1. Limited numbers:

The study was conducted over a 10 month period and patients were recruited according to certain criteria resulting in small numbers. This limits the manner in which the data can be analysed.

2. Selection bias:

Investigation of the mother for pneumonia depends on the index of suspicion of the attending obstetrician. It is thus possible that some cases were either undiagnosed or diagnosed late in pregnancy. Therefore with the vague presentation and delay in diagnosis, as described in chapter 1.2 only “the sick mothers” would have been investigated and thereafter included in our study. Another factor that impacts on the prevalence of pneumonia amongst antenatal attendees is that patients were recruited from a tertiary centre which is a referral centre for further investigation and treatment of complicated pregnancies from outlying clinics.

3. HIV-1 transmission:

With the study design and the financial constraints, the transmission and impact of HIV-1 infection from mother to child could not be commented on.

4. Transmission of TB:

It is not within the scope of the study to comment on the development of TB in the early infant period in those neonates exposed during gestation. We are therefore unable to comment on the transmission of TB from mother to child during gestation and not as a result of post delivery exposure.

5. Follow up of mother baby pairs:

Similarly, long term follow up of these pairs could not be conducted which impacted on the ability to comment on the transmission of pneumonia, TB and MDR TB from mother to infant.

6. Loss to follow up:

With mothers referred from outlying clinics, contact was limited to the time they were admitted to hospital and upon discharge to their local health care facilities, most mothers were lost to follow up despite attempts to trace them.

7. Screening for pneumonia:

The control group was not actively screened for pneumonia as they were all asymptomatic. Again, investigation was dependent on symptoms and clinical suspicion. Also, screening for pneumonia and TB is not routine in pregnancy and a significant number of patients may remain undiagnosed.

Future research:

1. A long term research study with a one year follow up post delivery to assess the impact and transmission of HIV-1 infection and pneumonia on maternal and infant morbidity and mortality.
2. The feasibility of screening pregnant women with a symptom questionnaire for pneumonia as the basis of investigation for pneumonia.
3. Training of staff at primary health care facilities to identify potential cases of pneumonia and refer timeously for further investigation and treatment at secondary or tertiary centres.

Conclusion paragraph:

Despite the sample size of the study population, the impact of antenatal pneumonia on maternal and neonatal morbidity and mortality is significant. Pneumonia in pregnancy resulted in 7 maternal deaths and 5 perinatal deaths. In addition, 4 cases of congenital pneumonia were diagnosed. The isolated finding of *MTB* as a causative organism is possibly reflective of the TB and HIV epidemics in Kwa Zulu Natal in women of child bearing age. The impact of these twin epidemics on the antenatal population has been well documented at the site in previous studies. This is however the first report on MDR TB and HIV co infection in pregnancy. Efforts to improve detection of pneumonia particularly in HIV infected pregnant women needs to be strengthened. Antenatal clinics provide an opportunity to administer risk questionnaires and staff can be trained to refer women for further investigation on the basis of symptoms.

APPENDICES

Appendix A: WHO disease staging system for HIV infection and disease (Conway and Bartlett, 2004)

The system is based on four groups of clinical conditions that are considered to have prognostic significance and therefore constitute stages, plus an assessment of physical activity performance expressed as a four-point score. Patients are classified according to the highest stage recorded for either clinical condition or physical activity.

<p>Clinical stage I Performance scale: 1: asymptomatic, normal activity</p>	<ol style="list-style-type: none"> 1. Asymptomatic 2. Generalized lymphadenopathy
<p>Clinical stage III And/or performance scale 3: bedridden < 50% of the day during last month</p>	<ol style="list-style-type: none"> 1. Weight loss, < 10% of body weight 2. Minor mucocutaneous manifestations (seborrheic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular cheilitis) 3. Herpes zoster within the last five years 4. Recurrent upper respiratory tract infections (i.e. bacterial sinusitis)
<p>Clinical stage III And/or performance scale 3: bedridden < 50% of the day during last month</p>	<ol style="list-style-type: none"> 1. Weight loss, > 10% of body weight 2. Unexplained chronic diarrhoea > 1 month 3. Unexplained prolonged fever (intermittent or constant), > 1 month 4. Oral candidiasis (thrush) 5. Oral hairy leucoplakia 6. Pulmonary tuberculosis in the last year 7. Severe bacterial infections (i.e. pneumonia, pyomyositis)

<p>Clinical Stage IV And/or performance scale 4: bedridden > 50% of the day during last month</p>	<ol style="list-style-type: none"> 1. HIV wasting syndrome 2. Pneumocystis carinii pneumonia 3. Toxoplasmosis of the brain 4. Cryptosporidiosis with diarrhoea > 1 month 5. Cryptococcosis, extrapulmonary 6. Cytomegalovirus disease of an organ other than liver, spleen or lymph node (ex: retinitis) 7. Herpes simplex virus infection, mucocutaneous (>1month) or visceral 8. Progressive multifocal leucoencephalopathy 9. Any disseminated endemic mycosis 10. Candidiasis of esophagus, trachea, bronchi 11. Atypical mycobacteriosis, disseminated or lungs 12. Non-typhoid Salmonella septicemia 13. Extrapulmonary tuberculosis 14. Lymphoma 15. Kaposi's sarcoma 16. HIV encephalopathy
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Appendix B: The CDC classification scheme for HIV disease (Classification and Staging of HIV Infection, HIV InSite Knowledge Base Chapter June 1998. Dennis H. Osmond, PhD, University of California San Francisco [online])

This system combines three CD4 + T lymphocyte categories with three symptom categories, as listed below.

- CD4 categories are:
- Category 1: > 500 cells/mm³ (or CD4% > 28%)
 - Category 2: 200-499 cells/mm³ (or CD4% 14% - 28%)
 - Category 3: < 200 cells/mm³ (or CD4% < 14%)

Symptom categories:

Patient qualifies as Category A if conditions in B and C have not occurred. Similarly, Category B conditions take precedence over those in Category A. For example, someone previously treated for oral or persistent vaginal candidiasis (and who has not developed a Category C disease) but who is now asymptomatic should be classified in Category B. Category C includes the clinical conditions listed in the 1993 AIDS surveillance case definition. For classification purposes, once a Category C condition has occurred, the person will remain in Category C.

- *Category A* occurs in an adolescent or adult (> 13 years) with documented HIV infection. Conditions listed in Categories B and C must not have occurred.

Asymptomatic HIV infection

Persistent generalized lymphadenopathy

- *Category B* consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical Category C and that meet at least one of the following criteria: (a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or (b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. Examples of conditions in clinical category B include but are not limited to:

Bacillary angiomatosis

Candidiasis, oropharyngeal (thrush)

Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy

Cervical dysplasia (moderate or severe)/cervical carcinoma in situ

Constitutional symptoms, such as fever (38.5 degrees centigrade) or diarrhea lasting greater than 1 month

Hairy leukoplakia, oral

Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome

Idiopathic thrombocytopenic purpura

Listeriosis

Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess

Peripheral neuropathy

Appendix C: Symptoms and signs of pneumonia:

Investigation of pneumonia in pregnancy is based on a combination of the following (Powrie, 2001; Good *et al*, 1981):

1. Cough for more than 3 weeks (73%),
2. Fever (30%),
3. Loss of weight (41%),
4. Malaise and fatigue (30%)
5. Haemoptysis (19%)
6. Tacchypnoea (respiratory rate > 24/min),
7. Tachycardia (heart rate >100/min), and
8. +/- crackles on pulmonary auscultation.

Appendix D: Radiographic features in maternal pneumonia/ TB

Chest radiography (CXR) is the only diagnostic tool available but is only diagnostic in 39% of cases of pneumonia and TB (Woodhead *et al*, 1987).

In HIV infected and uninfected adults (Good *et al*, 1981; Johnson *et al*, 1998): Upper lobe involvement is minimal (7%) in both HIV infected and uninfected patients in areas with a high TB prevalence. Cavitory or fibrocavitory disease is found in two thirds of patients with predominantly upper lobe disease (85%).

CXR in HIV infected patients with TB (Salomon *et al*, 1995; Mannheimer *et al*, 1997; Fischl *et al*, 1992, Farber and Barber, 1996): In the latter stages of HIV infection, the CXR is characterized by adenopathy with middle and lower lobe involvement. Drug resistant TB is characterised by the presence of interstitial infiltrates, hilar or mediastinal lymph nodes and cavitation.

Appendix E: Pharmacology

Appendix E.1: WHO TB short course chemotherapy for adults (Brost and Newman, 1997; Snider *et al*, 1980; Llewelyn *et al*, 2000; Anderson MS and Hay WW, Jr, 1999):

A 6 month treatment course is prescribed. The initial 2 month intensive phase involves a combination of Rifampicin (R), Isoniazid (H), Pyrazinamide (Z) and Ethambutol (E) or Streptomycin (S). It is followed by a 4 month continuation phase of R and H. Drugs and dosages are outlined in table below.

DRUGS	DOSAGE	MODE OF ACTION	SIDE EFFECTS	DRUG INTERACTIONS
R	8- 12 (10) mg / kg (maximum 300mg) orally	Bactericidal	Nausea/ emesis Fever Hepatitis Orange discoloration of body secretions	Induces cytochrome P450 which reduces serum half life for drugs
H★	4- 6 (5) mg/ kg (maximum 600mg) orally	Bactericidal	Cutaneous hypersensitivity Hepatitis Peripheral neuropathy	Potentiates anti convulsant medication
Z	20- 30 (25) mg/ kg	Bactericidal in acid environment		
E, or	15- 20 (15) mg/ kg	Bacteriostatic	Retrobulbar neuritis (visual blurring, scotoma, red- green colour blindness)	
S	12- 18 (15) mg/ kg	Bactericidal in alkaline environment	Vertigo Hearing loss (less common)	

★ All patients on H treatment should receive pyridoxine hydrochloride (Vit B6) 50mg orally with each dose of H to decrease peripheral neuritis and CNS side effects.

Appendix E.2: The use of fixed dose combination drugs in the treatment of TB in South Africa (Department of Health, SA, 2000a)

Fixed dose combination drugs are more popular as dose can be altered more easily with weight changes and the number of tablets taken is reduced due to combination of drugs. Below are the recommendations for the different weight bands in new and retreatment cases in South Africa.

Regimen 1 (New cases, age above 8 years and adults)

New smear-positive patients, new smear-negative patients and extra-pulmonary TB.

Pretreatment body weight	Two months initial phase given FIVE times a week	Four months continuation phase			
		When given FIVE times a week		When given THREE times a week	
		RHZE (150,75,400,275)	RH (150,75)	RH (300,150)	*RH (150,150)
30-37 Kg	2 tabs	2 tabs		2 tabs	
38-54 Kg	3 tabs	3 tabs		3 tabs	
55-70 Kg	4 tabs		2 tabs		3 tabs
>71 Kg	5 tabs		2 tabs		3 tabs

Regimen 2 (Retreatment cases)

Previously treated TB patients after cure, after completion, interruption and failure

Pretreatment body weight	Two months initial phase treatment given FIVE times a week		3 rd month initial phase	Five months continuation phase When given FIVE times a week			
	RHZE (150,75,400,275)	Streptomycin * (g)		RHZE (150,75,400,275)	RH (150,75)	E (400)	RH (300,150)
30-37 Kg	2 tabs	0.5	2 tabs	2 tabs	2 tabs		
38-54 Kg	3 tabs	0.75	3 tabs	3 tabs	2 tabs		
55-70 Kg	4 tabs	1.0	4 tabs			2 tabs	3 tabs
>71 Kg	5 tabs	1.0	5 tabs			2 tabs	3 tabs

Pretreatment body weight	Two months initial phase treatment given FIVE times a week		3 rd month initial phase	Five months continuation phase When given THREE times a week			
	RHZE (150,75,400,275)	Streptomycin * (g)		RHZE (150,75,400,275)	RH ** (150,150)	E (400)	RH (300,150)
30-37 Kg	2 tabs	0.5	2 tabs	2 tabs	2 tabs		
38-54 Kg	3 tabs	0.75	3 tabs	3 tabs	3 tabs		
55-70 Kg	4 tabs	1.0	4 tabs			3 tabs	4 tabs
>71 Kg	5 tabs	1.0	5 tabs			3 tabs	4 tabs

* Streptomycin should **NOT** be given during pregnancy and to those over 65 years.

** RH (150,150) should only be used when treatment is given **THREE** times weekly in the continuation phase only.

R-Rifampicin, H-Isoniazid, Z-Pyrazinamide, E-Ethambutol

Appendix E.3: First line anti TB drugs- Pregnancy and breastfeeding data (Brost and Newman, 1997; Snider *et al*, 1980; Llewelyn *et al*, 2000; Anderson MS and Hay WW, Jr 1999; Department of Health, SA, 2000a; Steen and Stainton- Ellis, 1977; American Academy of Pediatrics 1992; Holdiness, 1984)

DRUG	PREGNANCY DATA	BREASTFEEDING
R*	Limited data suggests adverse fetal effects not unusually high, 4.4% malformation rate versus 1.8% in other studies	Compatible with breastfeeding
H*	High lipid solubility, and easily into fetal circulation Safe to use in pregnancy Risk is outweighed by benefit but hepatotoxicity in pregnancy not for routine prophylactic use	
Z	Human data extremely limited Use in pregnancy reserved for MDR TB and HIV infected patients where potential risk is outweighed by benefits as risk of teratogenicity has not been determined.	Excretion into breast milk minimal but long half life of 9 hours and longer duration of action in newborn results in accumulation
E*, or	Limited data 2.2% incidence of fetal abnormalities with no specific pattern of anomalies. Lack of long term ocular examination data on these exposed neonates	Compatible with breastfeeding
S	Reported to cause fetal ototoxicity Use in pregnancy strongly discouraged unless specifically necessary for MDR TB treatment	Compatible with breast feeding

* crosses the placenta and reaches fetal levels of 10- 15% of maternal levels but no teratogenic effects have been noted with these drugs.

Appendix E.4: Treatment schedules, doses and side effects of second line agents used in the treatment of multi drug resistant TB (Bastian and Colebunders, 1999; Pillay *et al*, 2004a; Nemir and O'Hare, 1985)

CLASS OF DRUG	TYPE OF ACTIVITY	EXAMPLES	DOSE	SIDE EFFECTS	PARAMETERS TO MONITOR
1. Aminoglycosides	Class is moderately bactericidal	Streptomycin	15mg/ kg	Tinnitus, high frequency hearing loss, ataxia, vertigo, renal impairment	Audiometry, blood urea, nitrogen and creatinine
		Kanamycin	15mg/ kg	As for Streptomycin	
		Amikacin	15mg/ kg	As for Streptomycin	
		Capreomycin*	15 mg/ kg	As for Streptomycin	
2. Thioamides	Class is moderately bactericidal	Ethionamide	5- 10 mg/ kg	Gastro intestinal side effects, hepatitis, hypersensitivity	Monthly hepatic enzymes
		Prothionamide*		As for Ethionamide	
3. Fluoroquinolones	Class is weakly bactericidal	Ofloxacin	7.5- 15 mg/ kg	Abdominal distress, headaches, tremulousness	
		Ciprofloxacin	7.5- 15 mg/ kg	As for Ofloxacin	
4. Ethambutol	Bacteriostatic		15- 20 mg/ kg	Retrolubar neuritis, visual blurring, scotoma, red-green colour blindness	
5. Cycloserine	Bacteriostatic		5- 10 mg/ kg	Psychosis (particularly depression and suicide), dizziness, slurred speech, convulsions, headache	Assess mental status regularly
6. Para aminosalicylic acid *	Bacteriostatic		10 mg once daily	Gastro intestinal side effects, hepatitis, hypersensitivity (fever and rash)	

* not available in South Africa

Appendix E.5: Treatment of TB in the newborn (Pillay *et al*, 2004a):

i. Decision to treat based on the following:

- Duration of treatment of mother i.e.: gestational age at which TB treatment was commenced
- Clinical condition of the neonate
- Results of (neonatal) investigations

Prophylaxis to the neonate is provided if the mother is considered infectious either if she is non adherent to TB treatment, received treatment for less than three months of her pregnancy or if she remains acid fast bacillus (AFB) sputum positive at the time of delivery.

ii. Dosage and Duration of treatment of Neonatal Tuberculosis:

In the treatment of PTB, a combination of Rifampicin 10mg/ kg, Isoniazid 10mg/ kg and Pyrazinamide 30mg/ kg is commenced for two months followed by a maintenance phase of 4 months with R and H.

The duration and dosage for prophylaxis differs: Rifampicin and INH is offered for 3 months at 10mg/ kg (for both).

Upon completion of both treatment and prophylaxis, the infant is re- examined and investigated to confirm cure and/ or absence of disease.

Appendix F: Signs and symptoms of congenital tuberculosis (Nemir and O'Hare, 1985)

1. Respiratory distress syndrome (77%)
2. Fever (62%)
3. Epatosplenomegaly (62%)
4. Poor feeding (46%)
5. Lethargy and irritability (42%)
6. Lymphadenopathy (35%)
7. Abdominal distention (27%)
8. Failure to thrive (19%)
9. Ear discharge (15%)
10. Skin lesions (12%)

Appendix G: Cantwells diagnostic criteria for congenital tuberculosis (Cantwell *et al*, 1994)

Tuberculous lesions with one of the following:

1. Lesions in the first week of life, or
2. A primary hepatic complex or caseating granuloma, or
3. Documented primary infection of the placenta or endometrium, or
4. Exclusion of infection by a caretaker in the postnatal period.

Appendix H: WHO/ IUATLD surveillance for drug resistant TB globally

Multidrug resistant tuberculosis (MDR TB) is an emerging epidemic with pockets of infection identified globally. These “hotspots” are primarily in countries of the former Soviet Union, India and China (WHO, 2000) with an estimated 70% of cases confined to 10 countries (Espinal *et al*, 2001b). Factors influencing the incidence of MDR TB include inappropriate management of patients with TB disease, inadequate implementation of the World Health Organization Directly Observed Therapy strategy and non- compliance with treatment regimens (Iseman et al, 1993; Mwinga, 2001; Espinal *et al*, 2001a).

The graph below shows the prevalence of MDR TB in the identified “hotspots” and the map provides an overview of global MDR TB prevalence (WHO, 2000).

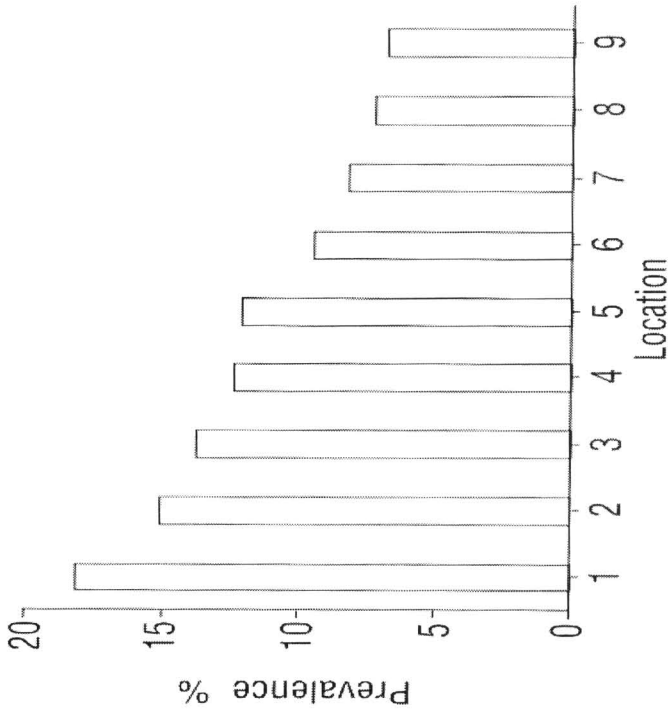


Fig. 4. - Locations with the highest prevalence of combined multidrug-resistant tuberculosis (among both new and previously treated cases). 1: Estonia; 2: Henan province, China; 3: Tomsk Oblast, Russian Federation; 4: Ivanovo Oblast, Russian Federation; 5: Latvia; 6: Zhejiang province, China; 7: Israel; 8: Tamil Nadu state, India; 9: Iran.

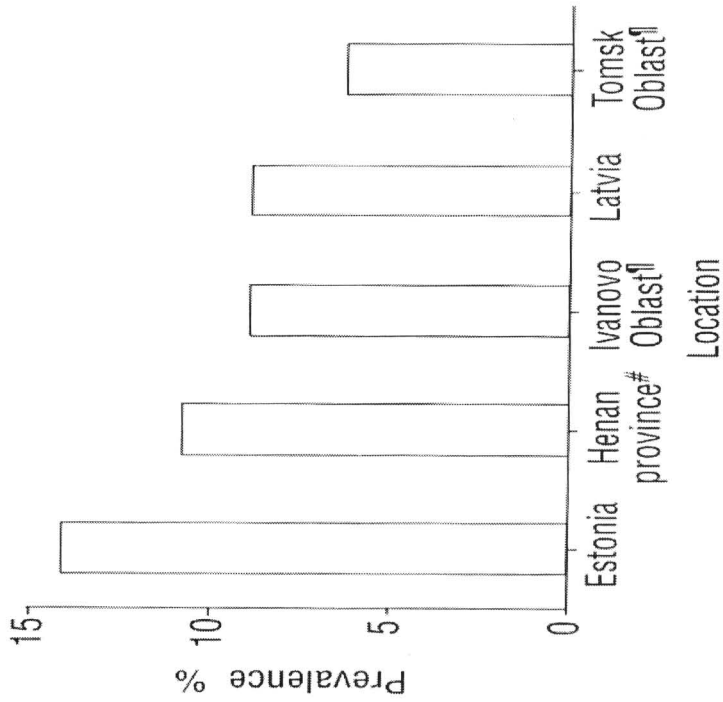
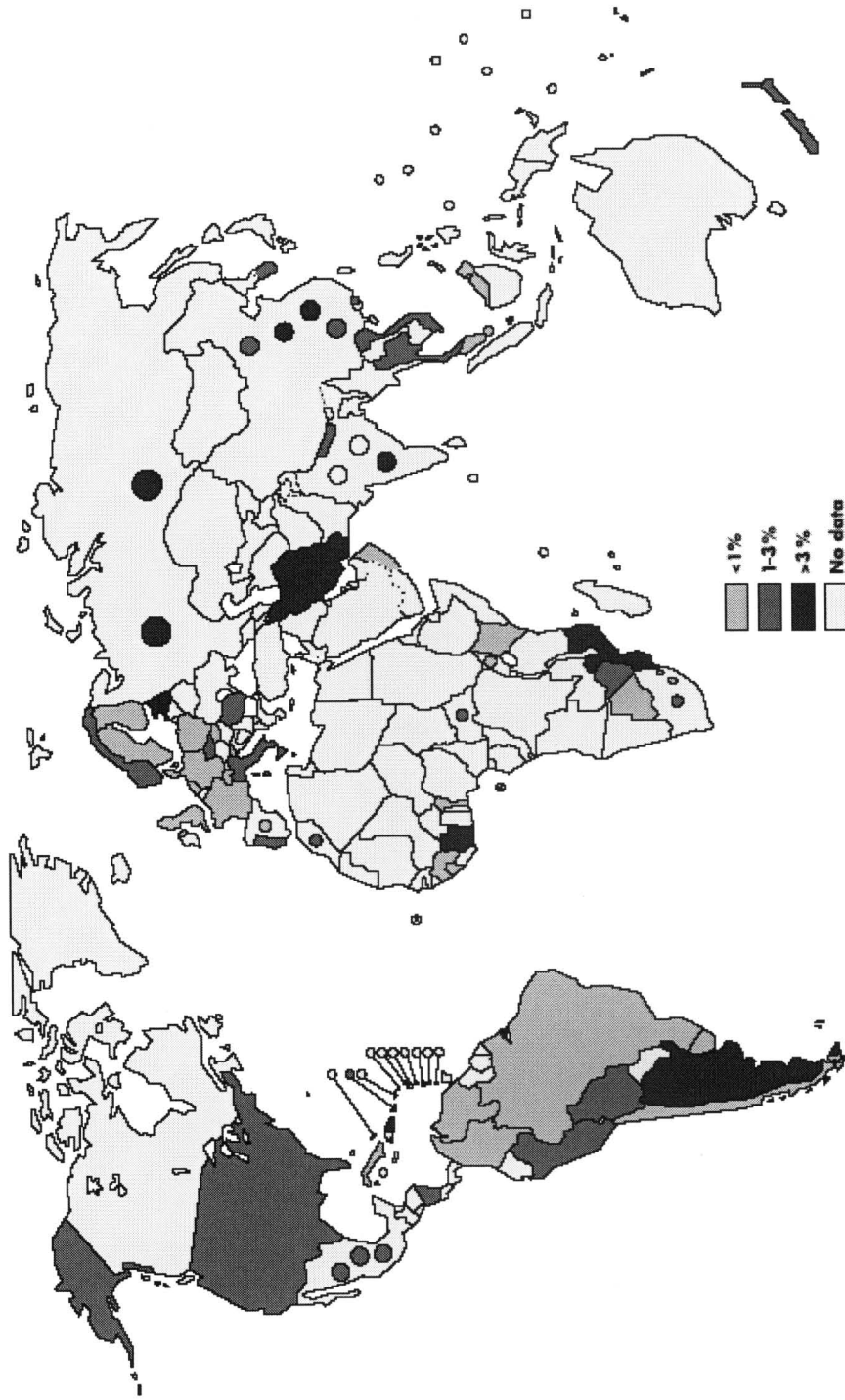


Fig. 3. - Locations with the highest prevalence of multidrug-resistant tuberculosis among new tuberculosis cases ("hot spots"). #: China; #: Russian Federation.

Map 3. Prevalence of MDR-TB among new TB cases in countries and regions surveyed, 1994-1999



The designations employed and the presentation of material on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines represent approximate boundaries for which there may not yet be full agreement.

Appendix I: Directly observed therapy

Directly observed therapy (DOT) is defined as the process in which a trained and supervised person observes the patient swallowing TB medication. It is a strategy implemented by the World Health Organization to help curb the growing TB epidemic. It includes a 5 point plan outlined below (Raviglione and Pio, 2002; Sterling *et al*, 2003).

1. Identification of patients with respiratory symptoms and establishing the diagnosis using microbiological methods,
2. The use of standardised short course chemotherapy regimens of six to eight months for all smear positive cases. Good case management includes directly observed therapy during the intensive phase for all new sputum smear positive cases, the continuation phase of rifampicin containing regimes and the whole retreatment programme,
3. Governmental commitment to ensuring resources for TB control programmes,
4. Regular and uninterrupted supply of antituberculosis medication and
5. A standardized recording and reporting system that will generate data for monitoring and assessing success of the control programme.

The DOTS PLUS (Sterling *et al*, 2003) strategy was developed in response to the emergence of MDR TB and in addition to the above includes 2 other principles:-

- a. Combination of at least three second line antituberculosis drugs to which the isolate is susceptible, is administered for 18-24 months under direct observation.
- b. Treatment is either individualized according to susceptibility results or administered using a standard regimen in patients who failed supervised treatment.

Appendix J: New laboratory methods for the diagnosis of MDR TB

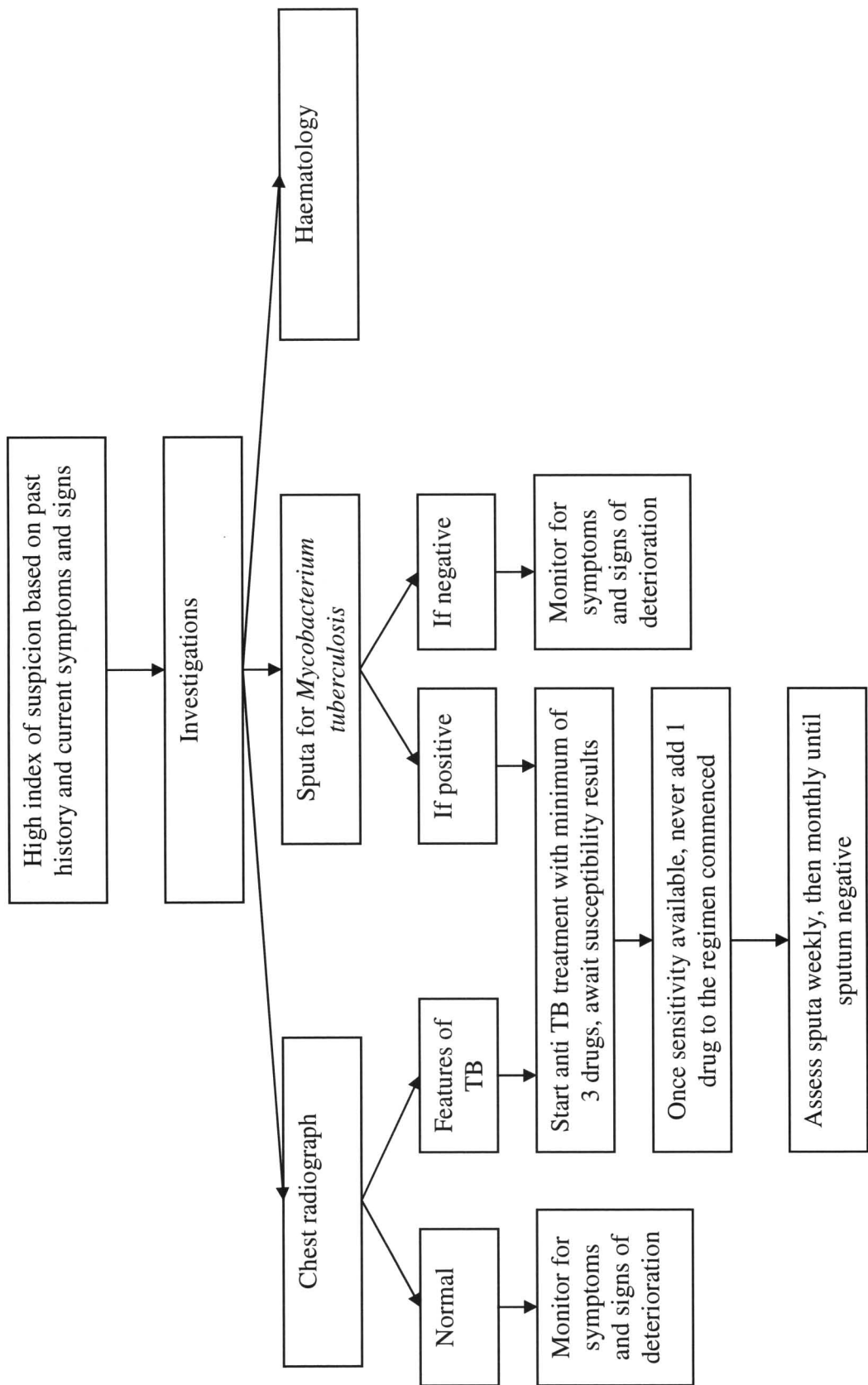
One of the key principles in the implementation of a successful DOTS control programme is early diagnosis and treatment of patients with active disease thereby decreasing the pool of infectious people. The significant delay in conventional susceptibility tests (between 3-4 weeks) results in increased morbidity and prolonged transmission of TB and MDR TB. Rapid diagnostic tests are available but their cost and operational difficulty provide a barrier in their implementation in developing countries.

A variety of tests are available with newer diagnostics still requiring adequate clinical trials validating their sensitivity, specificity, reliability and operator friendliness. The following are available:

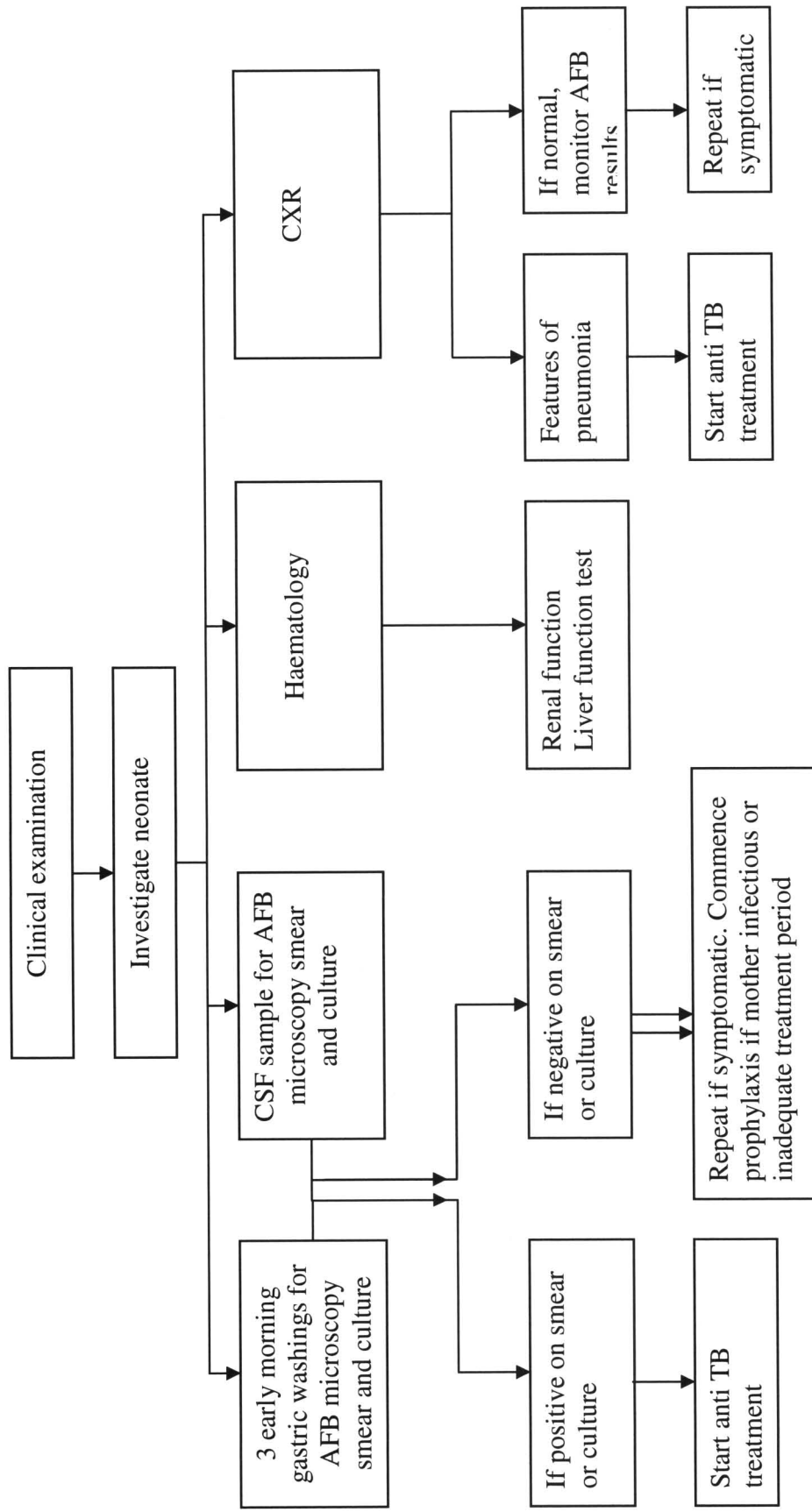
1. *Conventional smear microscopy and culture on solid medium:* The Lowenstein- Jensen proportion method is the most widely used method worldwide to detect drug susceptibility to *M tuberculosis*. The limited sensitivity, specificity and delayed results however make this option inadequate. One method to improve recovery at the bench top is to centrifuge sample at 4000g for 15 minutes (Perkins, 2000).
2. *Serology:* Available commercialized tests use well described immunodominant antigens to detect IgG or other immunoglobulin classes in dipstick or ELISA format. However, clinical data on the performance of this test is poor and detection in HIV uninfected patients is between one-third to three-quarters in smear positive patients and a smaller proportion of smear negative patients. In HIV infected patients with active TB disease, detection occurs in less than a third of patients (Perkins, 2000).
3. *Radiometric liquid culture systems:* Automated, culture based susceptibility tests with the Bactec 460 radiometric method is widely used. It is useful in industrialized countries but the expensive apparatus, difficulties involved in usage of radioactive materials and cost of materials are a disadvantage for developing countries despite rapid turnover for results (5 to 7 days) (Perkins, 2000).
4. *Molecular detection of Rifampin resistance:* Molecular designs have been developed to detect mutations encoding resistance to anti tuberculosis drugs which are highly efficient for RIF- r and INH- R mutations. One of the diagnostics available, the line probe assay, uses simple amplification and reverse hybridization and is mainly used on culture isolates (Perkins, 2000).

5. *Nucleic acid amplification*: Most studies have found this to be more sensitive than smear but less sensitive than culture (Pfyffer, 1999; Roth *et al*, 1997).
6. *Phage systems*: Two research based mycobacteriophage systems have been developed; one using a replication system that detects live mycobacteria in clinical samples and the other using liquid cultures using phages that infect and replicate in mycobacterial cells as indicators. Clinical trials need to be conducted to determine their sensitivity, reproducibility and the costs involved (Perkins, 2000).
7. *FAST Plaque TB- RIFTM* test has an overall accuracy of 98% within 48 hours (Albert *et al*, 2001; Foulds and O'Brien, 1998). This manual test compares the number of plaques in a Rifampicin- free control to the number of plaques produced from a sample incubated in the presence of Rifampicin. The sensitivity, specificity and overall accuracy of the *FAST Plaque TB- RIFTM* test compared to 7H11 and Bactec were 100%, 97%, 98% and LJ media 100%, 94% and 97% respectively (Albert *et al*, 2001).

Appendix K: Algorithm for the investigation and management of the pregnant woman with suspected multi drug resistant tuberculosis



Appendix L: Algorithm for the management of the neonate exposed to suspected or confirmed MDR TB in the mother



KEY: CSF= cerebrospinal fluid

AFB= acid fast bacilli

Appendix M: Informed consent administered to all participants at entry into the study

Human subjects consent form

Thank you for sharing some of your time with me. We are conducting a study on pneumonia in pregnancy and would like to explain it to you. In this study mothers who are both HIV-1- infected and –uninfected will be included. I understand that you have been counseled about the HIV-1 virus and the results of your test. Do you understand the implications it has on your health and future behaviour? Are there any questions you have that you need answered?

To explain this study, pneumonia is a term used to describe infection in the lungs. Over the last three years we have found that pregnant mothers are developing pneumonias more frequently than before. If you have pneumonia it has a direct impact on your baby and therefore the rest of your family. It is known that babies born to mums with pneumonia tend to be born earlier and are smaller. If we are able to diagnose the infection early, we can treat earlier and that would be better for both you and your baby.

All mothers who attend this antenatal clinic, deliver here and are diagnosed with pneumonia will be studied. We wish to determine the cause of your illness so that the correct treatment can be given. To determine the cause I will take sputum samples, nasopharyngeal swabs and a CXR even if you are asymptomatic. In addition, I will take bloods on 3 occasions: at entry, at delivery and at one follow up visit. This will not cause you any harm or have any negative effect on your baby.

When your baby is born, s/he will be examined and a CXR and bloods will be taken. Other necessary tests will be done if s/he is ill. S/ he will be followed up at our neonatal clinic.

It is important to understand that the decision to be part of this study is yours to make- if you do not agree, it will not affect the level of your care and you will continue to be followed up at our clinic. Even if you decide to discontinue after initial consent, that also will not affect your care.

Thank you for your time once again.

A) Informed consent for inclusion in a Clinical Trial

1. I, (name)

hereby consent to the following procedure and/ or treatment being conducted on the person named below or myself.

2. I acknowledge that I have been informed by:

(name)

concerning the possible advantages and possible adverse effects which may result from the above mentioned procedure and/ or treatment.

3. I, (name)

hereby acknowledge that I understand the information provided for this trial.

4. I agree that the above procedure and/ or treatment will be carried out and/ or supervised by

(name)

5. I acknowledge that I understand the contents of this form and as the *subject, parent, guardian, other (specify) freely consent to the above procedure and/ or treatment being conducted on:

(name)

6. I am aware that I can withdraw my consent at any time without prejudice to further care.

Signature:

Date:

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