

**CHARACTERISTICS OF INFANTS EXPOSED TO MATERNAL TUBERCULOSIS
AND CHEMOPROPHYLAXIS USING THREE MONTHS OF ISONIAZID AND
RIFAMPICIN**

Khakhu Tshilidzi Mathivha, MBChB, FC Paed; Sithembiso Velaphi, MBChB, FC Paed, MMed

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DECLARATION

I Khakhu Tshilidzi Mathivha declare that this dissertation is my own work. It is being submitted for the degree of Master of Medicine in Paediatrics at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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.....18th day, of January..... 2016.

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ABSTRACT

Background: Though features of infants with congenital tuberculosis (TB) are known including being low-birth-weight (LBW), features of in-utero TB-exposed infants including non-infected are not well reported. Infants born to TB-infected women are at risk of contracting TB post-delivery, therefore chemoprophylaxis is recommended, and this includes use of isoniazid and rifampicin combination, but little is known about its effectiveness.

Objective: To determine features of in-utero TB-exposed infants and proportion with TB after chemoprophylaxis with isoniazid and rifampicin.

Methods: Retrospective review of records of TB-infected women and their infants, from 2007-2010. Clinical features of mothers and infants at time of delivery; and follow-up of infants after completion of isoniazid and rifampicin are described.

Results: Eighty-eight infants born to 86 women with a diagnosis of TB were studied. TB diagnosis was made peripartum in 24.4% of women, 23.3% had extra-pulmonary TB. Among those diagnosed antepartum 46.2% were on treatment for >2 months. Human immunodeficiency virus (HIV) was positive in 97.7%; with CD4 count <200 cells/mm³ in 74.6%. Eight mothers (9.3%) died before discharge. There were 56 (63.6%) LBW and 45 (51.2%) preterm infants. Culture for acid-fast-bacilli was positive in 4 (4.5%) infants. At 3-months follow-up, 17 (20.2%) defaulted, and among 67 who returned, 7 (10%) did not return for Mantoux test reading, 1/60 (1.7%) had positive Mantoux.

Conclusion: Majority of TB-exposed infants are born to mothers with TB/ HIV co-infection. A high proportion of TB-exposed infants are born preterm and LBW. The high attrition rate made it difficult to assess effectiveness of chemoprophylaxis with isoniazid and rifampicin.

Key words: Tuberculosis; Chemoprophylaxis; Rifampicin; Isoniazid

INTRODUCTION

Worldwide, tuberculosis (TB) has increased rapidly, particularly in human immunodeficiency virus (HIV) endemic and impoverished areas of Africa.¹ In South Africa (SA) the incidence of TB, is in excess of 300/100 000 people per year.² The age distribution of TB has changed from a peak median age of 50 to 30 years.³ This change in age distribution has resulted in a large number of women of child bearing age presenting with TB. Women of reproductive age have a higher rate of progression from TB infection to disease.^{4, 5} Both TB and HIV infection are major problems for women, and globally 17.7 -37.2 million adults with HIV are women.⁶ In communities where TB and HIV infection are endemic; women are at high risk of acquiring both infections. A study conducted in Durban, South Africa from 1996 to 1998, reported a dramatic increase in the case load of TB disease in pregnant women and 72% of these cases were attributable to HIV infection.⁷ Worldwide, TB is a leading infectious cause of death among women, killing more than a million women each year.⁸ HIV infection and TB disease during pregnancy are a deadly combination and individually they are also independent risk factors for maternal mortality.^{7, 9,10} There is a 3.2 fold odds of death reported in women with TB- HIV-coinfection compared with HIV-uninfected mothers with TB.¹⁰ A study from Zambia reported that TB accounted for 25% of all non- obstetric maternal deaths, and most of these were co-infected with HIV.¹¹

Women infected with TB during pregnancy are likely to infect their offspring resulting in perinatal tuberculosis. Perinatal tuberculosis is a descriptive term encompassing tuberculosis acquired in utero (congenital TB), intrapartum and postpartum during the neonatal period. In utero transmission occurs through haematogenous dissemination via the umbilical vein, or aspiration or ingestion of infected amniotic fluid. At time of labour and delivery (intrapartum) it is acquired through aspiration or ingestion of infected amniotic fluid or genital secretions during passage through the birth canal. Postpartum it is acquired through

inhalation of infected respiratory droplets or ingestion of infected milk.¹² The rate of mother to child transmission of TB has been reported to be 16%.¹³ The risk of developing disease in children after TB infection is high, reported to be 20 -50% in children infected before the first two years of life.^{14, 15} Among those who are infected (perinatal TB) clinical presentation is non-specific but is usually marked with multiple organ involvement.¹⁶ Clinical signs respiratory distress, hepatosplenomegaly, lymphadenopathy and failure to thrive.¹⁷ In addition to perinatal TB, infection during pregnancy in particular extra- pulmonary TB in sites other than lymph nodes, is associated with increased risk for delivering low birth weight infants with low Apgar scores.¹⁸

Management of infants born to women with TB includes, excluding TB infection in the infants so that those who are infected are started on appropriate anti-TB treatment and prevention of TB transmission from the mother to those who are not infected. Investigation for TB includes chest X-ray especially in those who present with respiratory distress, full blood count, C-reactive protein, cerebrospinal fluid, tissue biopsy, and microscopy and culture of gastric aspirates or relevant specimen. The most effective way to prevent children from becoming infected with TB is to diagnose and treat pregnant mothers early during pregnancy. Where this is not achieved, TB chemoprophylaxis is recommended. The WHO and SA guidelines recommend monotherapy with isoniazid for six months be given to all children less than five years of age (including neonates) who are clinically well and, have been in contact with a person with TB.¹⁹ There are concerns about adherence with the use of six months duration of isoniazid as it has been reported that as low as 20-28% of patients adhere to this six months regimen.^{20, 21} Therefore a shorter duration could result in better adherence. A double-blind placebo controlled clinical trial in Hong Kong, in adults with a higher risk of developing tuberculosis, showed that taking rifampicin and isoniazid for three months was as effective as taking isoniazid only for six months.²² Ormerod et al also reported

that the 3 months chemoprophylaxis with rifampicin and isoniazid appears to be as effective as isoniazid monotherapy in reducing incidence of TB.²³ The Joint Tuberculosis Committee's guideline suggested that three months regimen may provide effective chemoprophylaxis for TB.²⁴ British Thoracic Society recommendations on chemoprophylaxis against TB include either a 6 month course of isoniazid or a three month course of combination of rifampicin and isoniazid.²⁵

In 2006 the Essential Drugs List (EDL) booklet of South Africa (SA) recommended three months of isoniazid and rifampicin for chemoprophylaxis against perinatal TB.²⁶ A three month course regimen has been suggested to be used where isoniazid resistance profiles are high and where compliance over a 6 month period is likely to be poor.⁹ Based on local experience of poor follow up of infants born to women with TB and on chemoprophylaxis with isoniazid for six months, the neonatal unit at Chris Hani Baragwanath Academic hospital changed its protocol on TB chemoprophylaxis from isoniazid for six months to isoniazid combined with rifampicin for three months. There are no studies that have specifically reported on experience with use of the three month regimen of isoniazid and rifampicin started during the neonatal period. In this study we sought to determine the proportion of infants born to women with TB who are diagnosed with TB soon after birth and those who are diagnosed with TB after three months of isoniazid and rifampicin. In addition we sought to determine maternal and infant characteristics of infants born to mothers with TB in an environment where HIV infection is prevalent. The study was conducted after getting approval from the Human Research Ethics Committee of the Witwatersrand.

STUDY POPULATION AND METHODS

Study Design: This was a retrospective, descriptive study of neonates referred or admitted for investigation for TB from October 2007 to September 2010.

Study Population and Setting: Women with a diagnosis of TB and their infants delivered and/ or admitted to the neonatal unit at Chris Hani Baragwanath Academic Hospital (CHBAH), Gauteng province in South Africa. During the study period the provincial HIV prevalence rate in pregnant women was 25-30%, and mothers who were HIV positive with CD4 count ≤ 200 cells/mm³ or had stage 3 or 4 AIDS were started on HAART, while those with CD4 count >200 cells/mm³ were started on antiretroviral drug/s to prevent mother to child transmission. As part of the neonatal unit protocol during the study period²⁷, all asymptomatic neonates who were born to mothers with TB were given BCG at birth. All neonates had gastric washings for TB microscopy (results available within 7 days) and culture (results available within six weeks) done and then put on three months isoniazid and rifampicin chemoprophylaxis while waiting for results, and continue for three months if results come back negative. Symptomatic infants had chest X-rays (CXR), full blood count (FBC), C-reactive protein (CRP) and gastric washings for TB microscopy and culture, and BCG given at time of discharge. On discharge all patients were given a follow-up date when they would have completed three months of chemoprophylaxis with. At follow up all infants had a Mantoux test administered and infants with positive test (induration size >10 mm) at this time were considered as infected and started on six months of anti-TB drugs. All infants were asked to come back again after another three months.

Data collection: Medical records of mothers with TB who had their infants either admitted or referred for work-up for TB were retrieved and reviewed for the following information: maternal age, parity, antenatal clinic attendance, time of TB diagnosis related to pregnancy or delivery, HIV results and CD4 counts, and maternal health at time of birth and/ or discharge.

of the infant. Information collected from infant records was birth weight, estimated gestational age, sex, and clinical presentation at birth. The following laboratory information was collected from infants: FBC and CRP among those who were admitted, gastric washing results, and polymerase chain reaction (PCR) for HIV at six weeks. Mantoux test results after three months of chemoprophylaxis were also collected. In order to assess defaulter rate, proportion of infants coming back for follow-up at three and six month was calculated. Data was entered into Microsoft Excel spreadsheets and then imported into STATISCA statistical software (Statsoft, USA) for analysis.

Ethical considerations: Retrieval of patients' records and data collection was only started after getting approval from the University of the Witwatersrand Human Research Ethics Committee.

Data analysis: Frequencies and percentages were used to report dichotomous or categorical variables, while medians with ranges and means with standard deviations were used to report non-parametric and parametric continuous variables respectively.

RESULTS

Eighty-eight neonates were born to 86 women with a diagnosis of TB and were admitted or referred for work-up for TB from October 2007 to September 2010. There were 2 sets of twins.

The median age of mothers diagnosed with TB was 29 years with ages ranging from 16 to 41 years and about three-quarters of mothers were less than 35 years old (Table 1). Most mothers (96.5%) attended antenatal care but gestation at first visit was not recorded.

Diagnosis of TB was made around the time of delivery in 21 (24.4%) mothers. Among the mothers who were diagnosed with TB antepartum, 30 (46.2%) were on treatment for a period of more than 2 months. Just over 50% of mothers delivered before term. At time of discharge of infants, eight mothers (9.3%) had died. Almost all mothers ($n = 84/86$; 97.7%) diagnosed with TB were HIV positive (Table 1). Extra pulmonary TB was noted in 20 (23.3%) of the mothers and site of infection included the placenta ($n=3$), bone marrow ($n=1$), Bartholin's abscess ($n=1$), renal abscess ($n=1$), abdominal lymphadenitis ($n=1$), pericarditis ($n=1$), TB spine ($n=2$), lymph node tuberculosis ($n=9$) and tuberculous meningitis ($n=1$). Among the HIV positive mothers with recorded CD4 count ($n = 71/84$), about 75% ($n = 53/71$) had CD4 counts below 200 cells/mm³. Only 54% of mothers with CD4 count <200 cells/mm³ were on HAART.

The median birth weight was 2198 grams, with 63.6% of them being of LBW and 43.2% were small for gestational age (SGA) (Table 2). Majority of the babies (59.1%) were assessed to be well at birth. Among those who were assessed to be ill, signs and symptoms were assessed to be non-specific. The diagnoses were respiratory distress syndrome (38%), congenital pneumonia (30.6%), and perinatal asphyxia (30.6%). Most of the sick infants had normal FBC and CRP.

Table 1. Maternal age, parity, antenatal care, time at diagnosis of tuberculosis and maternal outcome at time of infant discharge (n = 86).

Maternal characteristics	Number (%)
Maternal age (n=86)	29 (24.5 -35)*
- <20 years	7 (8.1)
- 20 – 35 years	58 (67.4)
- >35 years	16 (18.6)
- Not recorded	5 (5.8)
Received antenatal care (n=86)	
- Yes	83 (96.5)
- No	3 (3.5)
Time at which TB was diagnosed (n=86)	
- Antepartum	65 (75.6)
On treatment for ≤ 2 months at time of delivery	- 35 (53.8)
On treatment for > 2 months at time of delivery	- 30 (46.2)
- Peri-/postpartum (Not on treatment)	21 (24.4)
Site of TB infection (n=86)	
- Pulmonary	66 (76.7)
- Extra-pulmonary	20 (23.3)
Maternal outcomes on discharge of infant(n=86)	
- Alive	78 (90.7)
- Died	8 (9.3)
HIV status, (n=86)	
- Negative	2(2.3)
- Positive	84(97.7)
Antiretroviral drugs, (n=84)	
- No	27 (32.1)
- Yes	57 (67.9)
○ PMTCT	16 (28)
○ HAART	41 (72)
Median CD4 count (n=84)	121 (41 -230.5)*
- <200/mm ³	55 (65.5)
- 200 -350/mm ³	9 (10.7)
- >350/mm ³	9 (10.7)
- Not recorded	11 (13.1)
Mothers with CD4 counts < 200/mm ³ (n=55)	
- HAART	31 (56.4)
- PMTCT	8 (14.5)
- No HAART nor PMTCT	16 (29.)

TB – tuberculosis, HIV – human immunodeficiency virus, PMTCT – prevention and mother to child transmission, HAART- highly active antiretroviral therapy

* _ Numbers represent median (25th- 75th centiles)

Table 2. Features of neonates born to mothers with tuberculosis (TB) (n=88).

Characteristics	Number (%)
Gender	
- Male	41 (46.6)
- Female	47 (53.4)
Median birth weight (grams)	2198.5 (1710 – 2680)*
- <1500 grams	12 (13.6)
- <2500 grams	44 (50)
- ≥2500 grams	27 (30.7)
Not recorded	5 (5.7)
Gestational age (weeks)	37 (33.5-37)*
- ≤ 37 weeks	43(48.9)
- >37 weeks	45(51.1)
Growth:	
- SGA	38 (43.2)
- AGA	50 (56.8)
Sex	
-Male	41 (46.6)
-Female	47 (53.4)
Condition of infant at birth	
- Well	52 (59.1)
- Sick	36 (40.9)
Diagnosis on admission of the sick infants	
- Respiratory distress syndrome	14 (38.8)
- Congenital pneumonia	11 (30.6)
- Perinatal asphyxia	11 (30.6)
White cell count($\times 10^9/L$) on sick infants	8 (5.9 -11.4)*
- <5	5
- 5-25	27
- >25	0
- -Not recorded	4
Platelet count ($\times 10^9/L$)	267 (187.5 -373.5)*
- <100	4
- 100-150	1
- >150	27
- Not recorded	4
C-reactive protein (mg/l)	3.3 (1.05 -11.4)*
- <10	23
- ≥10	6
- Not recorded	7

SGA- small for gestational age, AGA- Appropriate gestational age, IQR-interquartile ranges.

*_ Numbers are median (25th -75th centiles)

Tuberculosis related management

All infants were given BCG at birth except those who were assessed to be sick at birth (n=36, 40.9%). All patients had CXR done soon after birth, except for 4, and 20 (30.5%) of those who had CXR, had abnormal findings consistent with respiratory distress syndrome or congenital pneumonia at the time of admission at birth. Culture results for acid fast bacilli (AFBs) from gastric washings were available within six weeks of life, and were positive in 4 (4.6%) of the 86 infants who had gastric aspirates done, and 2 were discharged before aspirates could be done. Those with positive gastric washings for AFBs were changed from chemoprophylaxis to full TB treatment with three drugs, and those who were negative for AFBs continued with chemoprophylaxis using isoniazid and rifampicin for a period of three months.

Table 3. Management of infants born to mothers with tuberculosis (n=88)

Management	Number (%)
BCG given at birth	
- No	36 (40.1)
- Yes	52 (59.1)
CXR done with initial work-up	
- No	4 (4.5)
- Yes	84 (95.5)
o Findings not recorded	2 (2.3)
o Findings normal	57 (69.5)
o Findings abnormal	25 (30.5)
Gastric aspirates for AFB	
Negative	82 (93.2)
- Positive	4 (4.5)
- Not done	2 (2.3)
TB chemoprophylaxis with isoniazid and rifampicin	
- Yes	84 (95.5)
- No (put on treatment)	4 (4.5)

Follow up at completion of chemoprophylaxis

At three months follow up, 17 (20.2%) of the 84 patients who were not infected and on TB chemoprophylaxis did not come back for follow (defaulted). Among the ones who came back for follow up, 59/67 (88.1%) had a negative Mantoux test, 1 (1.5%) had a positive test and 7 (10.4%) did not come back for reading of Mantoux test (Table 4). Among the 84 HIV exposed infants, HIV PCR test was done at 6 weeks of age in 69 infants, of whom 5 (7.2%) had a positive HIV PCR result. Infants with a positive HIV PCR (n=5) had birth weights <1800 grams except for one who weighed 2700g (Table 5). Of these five infants, one had positive gastric washings for AFBs at birth. Regarding maternal use of ARV's in the mothers of the above infants, four mothers received HAART, one received no ARV treatment neither HAART nor for PMTCT. All five of their mothers had CD4 count ranging 25 to 200 cells/mm³.

Table 4. Follow up at 3 and 6 months, Mantoux test and HIV-PCR results at 6 weeks in infants born to mothers with TB

Factors	Number (%)
Follow up at 3 months among those on chemoprophylaxis (n=84) - Number who attended follow-up - Number who defaulted	67 (79.8) 17 (20.2)
Follow up at 6 months among those on chemoprophylaxis (n=84) - Numbers who attended follow-up - Numbers who defaulted	56 (66.7) 28 (33.3)
Mantoux test result after completion of 3 months of chemoprophylaxis(n= 67) - Negative - Positive - Done but did not return for reading	59 (88.1) 1 (1.5) 7 (10.4)
HIV PCR done at 6 weeks and/ or followed up at 3months (n=69) - Negative - Positive	64 (92.8) 5 (7.2)

Table 5. Infant features, maternal CD4 counts and use of antiretroviral drugs, in infants with positive HIV-1 PCR result (n=5)

Characteristics	Numbers (%)
Infant	
Median Birth weight, in grams	1695 (1455-2213)*
Number positive for AFBs	1 (20%)
Number negative for AFBs	4 (80%)
Maternal ARV use and CD4 counts	
- HAART	4 (80%)
- No ARV's	1 (20%)
Median maternal CD4 count /mm ³ (IQR)	115.5 (19-223.5)*

*Numbers in parenthesis are 25th and 75th centiles

DISCUSSION

Infants born to mothers with TB are at risk of being affected in-utero through disturbances in placental function and might develop the disease unless mothers are treated during pregnancy or infants are given chemoprophylaxis post-delivery. Thus in this study we describe the features of neonates born to mothers with TB, proportion of infants who are infected in-utero and of those who develop infection despite three months of isoniazid and rifampicin and attrition rate at three and six months. The findings in this study were that majority of mothers with TB were in the age range of 20 to 53 years. Though about three quarters of mothers were diagnosed antenatal, only 46% were on treatment for two months. Common site of infections was pulmonary with only 23% having extra-pulmonary TB. Most mothers (97.7%) were HIV positive, with 65% of those with known CD4 counts having a CD4 count $< 200/\text{mm}^3$. About 10% of mothers diagnosed with TB died before discharge. More than three quarters (78.4%) of infants were low birth weight, 48.9% were preterm and 43% were SGA. Only 4.5% of infants diagnosed with TB and had positive gastric aspirates culture for acid fast bacilli, and none of them had hepatosplenomegaly. At three months follow-up; 20% defaulted and only one infant had a positive Mantoux after completing chemoprophylaxis.

Majority of mothers attended antenatal care yet still a quarter of them were only diagnosed with TB around the time of delivery. This suggests either mothers started attending antenatal care late during pregnancy therefore delivered before TB could be screened and diagnosed or that there is inadequate screening of TB during pregnancy. This high number of mothers being diagnosed with TB during labour or around time of delivery is similar to that reported by Pillay et al, who reported that 20% of mother with TB were diagnosed post-delivery¹³ but lower than that reported by Bekker et al who reported that 45% of mothers with TB were diagnosed intra/post-partum.²⁸ The incidence of women with extra-pulmonary TB in this

study was 23.3%, which was similar to that reported by Jana et al who reported that extra-pulmonary TB occurred in 24% of pregnant women who have TB but not HIV-infected.¹⁸ This difference is most likely due to the fact that this study had a high incidence of HIV infection in mothers with TB. Studies that have reported on extra-pulmonary TB in TB-infected mothers with HIV co-infection reported similar or higher incidence to this study, Bekker, et al²⁸ reported an incidence of 24%, while Pillay, et al reported an incidence of 38%.¹³ This study highlights the importance of the recommendation that symptomatic screening for TB; should be considered for incorporation into routine antenatal care.²⁹

A high number of mothers with TB infection were co-infected with HIV. This is much higher than that previously reported in other regions in South Africa where the proportion of mothers with TB/HIV co-infection, was reported to be 60-79%.^{13,28} There was a high mortality rate at 9.3% amongst these mothers and this is most likely due to this combination of infections. Mortality rate in mothers with TB only has been reported to be 0- 6.6%^{10, 11, 30, 31}; much lower than that reported for mothers with co-infections with TB and HIV at 12-14%.^{10, 11} The high mortality rate in this study is most likely due to the fact that these mothers had advanced HIV disease as their median CD4 count was 94 mm³ and 75% of mothers had CD4 counts less than 200 cells/mm³. The effect of this combination is also seen on perinatal outcomes where just over 50% of mothers delivered preterm and 64% of infants; had LBW. Tuberculosis on its own is associated with prematurity^{3, 32} and LBW^{3, 33} as it is for HIV infection^{34, 35}; thus it explains this very high incidence of prematurity and LBW in this study where almost all mothers had a combination of these infections.

The vertical transmission rate of TB of 4.5% in this study was low compared to that of 16% previously reported in neonates born to similar settings.^{28, 36} This difference, could be due to

the fact that in this study about 76% of mothers were on anti-TB treatment and 46% of them were on treatment for more than 2 months. The diagnosis of TB in the newborn is challenging as yield for AFB culture even in those who are infected is not 100%, therefore it is possible to miss the diagnosis especially in those who are asymptomatic. Clinical suspicion is important as early symptoms are often non-specific and may be indistinguishable from those of other congenital infections.^{3, 37} The introduction of chemoprophylaxis with rifampicin and isoniazid in 1981 reduced paediatric notifications from 33.5% to 3.9% of total notifications, a reduction of 88% and this was sustained throughout the years^{23,24}, similar to 6 months of isoniazid with reported reduction of 69-93%.³⁸ Thus both isoniazid for 6 months and isoniazid and rifampicin for 3 months appear to be effective in preventing infection to TB disease in children. A number of studies have recommended 3 months of isoniazid and rifampicin over 6 months of isoniazid because of reported better effect³⁹ and risk of poor adherence with long periods of chemoprophylaxis.^{20, 21} But there is a concern with the use of rifampicin as part of TB chemoprophylaxis, the risk of development of resistance might be increased; and that in neonates who are nevirapine for PMTCT, it might affect nevirapine metabolism and therefore its effectiveness. In this study, only one patient developed TB after the 3 month course of rifampicin and isoniazid; and the AFBs were sensitive to rifampicin. The HIV transmission rate was 7.2% and was not different from the average transmission rate during the study period, which was reported to be 9.7%, 6.4% and 4.4% in 2008, 2009 and 2010 respectively.³⁹

In this study isoniazid and rifampicin chemoprophylaxis appears to be effective in reducing the number of infants who developed TB disease as only 1 patient out of 60 (1.5%) developed the infection. Though this number supports the effectiveness of isoniazid and rifampicin, the concern is that a high number of infants did not come back for follow up and is possible that some of them were infected. If one accepts the worse scenario that about 30%

of infants (n=17+7) who did not come back for follow up or for reading of Mantoux test had pulmonary TB, the effectiveness of isoniazid and rifampicin will still be high at 89%. The major concern in this study is that 20% and 33% of mothers defaulted by 3 and 6 months respectively supporting the concern of giving prophylaxis for 6 months, as the longer the duration of follow up the higher the attrition rate. Limitations of this study are that it was a retrospective study and therefore not all information could be retrieved due to inadequate and sometimes incomplete documentation of notes in the maternal files and neonatal files of the babies screened for TB.

In conclusion a high proportion of mothers with TB are co-infected with HIV, and a high proportion of their infants are low birth weight and small for gestational age. Role of chemoprophylaxis with isoniazid and rifampicin for three months in neonates could not be determined in this study because of high attrition rate. Therefore we recommend that further studies looking at effectiveness of this 3 month regimen must ensure complete follow up of all infants started on chemoprophylaxis.

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APPENDIX A: LETTER FROM CO-AUTHOR



*Chris Hani Baragwanath Hospital
Department of Paediatrics
P. O. Berisham, 2013
Johannesburg, South Africa
Tel: (011) 933-8416-8400
Fax: (011) 938-9074*



30 November 2015

**The Chairperson
Postgraduate Committee
Faculty of Health Sciences
University of the Witwatersrand
Parktown
Johannesburg**

Dear Madam/ Sir

Re: Submission of MMed Report through Publication Submissible Format

This is to confirm that Dr. Khakhu Tshilidzi Mathivha was the main person involved with conception, design, analysis and interpretation of data. She developed the protocol, collected and analyzed the data, wrote the results and discussion on her own. She drafted and revised the content of the paper, and was involved in the final approval of the version to be submitted for consideration for publication. I was her supervisor who guided her on how to develop the protocol, collect and analyze data, and with the writing up of the report/ manuscript. I was involved in the final approval of the version to be submitted to the University for Dr. Mathivha's MMed and to the journal, Paediatric and International Child Health for consideration for publication.

Yours sincerely

Sithembiso Velaphi (Supervisor)

APPENDIX B: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Khakhu T Mathiva

CLEARANCE CERTIFICATE

M10M101145

PROJECT

Characteristics and Outcomes of Infants Given
Three Months of Rifampicin and Isoniazid
Chemoprophylaxis against Tuberculosis

INVESTIGATORS

Dr Khakhu T Mathiva

DEPARTMENT

Department of Paediatrics

DATE CONSIDERED

26/11/2010

DECISION OF THE COMMITTEE*

Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE

26/11/2010

CHAIRPERSON


(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Dr RM Maphahlele

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10004, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress report.

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX C: PROTOCOL

CHARACTERISTICS OF INFANTS EXPOSED TO MATERNAL TUBERCULOSIS AND CHEMOPROPHYLAXIS USING THREE MONTHS OF ISONIAZID AND RIFAMPICIN.

BACKGROUND.

South Africa has a high incidence of tuberculosis (TB), with the incidence in excess of 300/100 000 population.^{1, 2} The distribution of tuberculosis has changed from a peak in people over the age of fifty years to a median age of 30 years.³ This change in age distribution makes women of child bearing age to be at risk of contracting TB.^{4, 5}

Tuberculosis has emerged as the third leading cause of disease associated with maternal mortality after sepsis and hypertensive disorders of pregnancy⁶. This is also the peak age during which women are infected with human immunodeficiency virus (HIV).^{7, 8} In developing countries there is a considerable overlap in age periods during which TB and HIV are most prevalent. The increase in incidence of TB infection has been associated with an increase in HIV co-infection. Consequently TB is the commonest HIV related illness and cause of mortality in young women in impoverished regions of Africa where TB is endemic.⁹ TB and HIV are independent risk factors for maternal mortality¹⁰ and adverse perinatal outcomes.¹¹ TB infection during pregnancy in particular extra-pulmonary TB is associated with increased risk for preterm births, intrauterine growth retardation, maternal mortality and perinatal infant mortality when compared to healthy pregnant women.^{6, 12, 13}

Infants born to mothers with TB are at risk of being infected. Though TB acquired during the perinatal period is uncommon, it has a high mortality rate.^{4, 7, 14} The risk of developing disease after infection is high, at 20 -50% in children infected before the first two years of life.¹³ Maternal TB poses a serious risk to both fetus and newborn infants because congenital TB carries a high mortality.¹⁵ Perinatal TB is a descriptive term encompassing TB acquired in utero, intrapartum and postpartum. In utero TB is acquired through haematogenous dissemination via the umbilical vein, and aspiration or ingestion of amniotic fluid infected with tuberculous bacilli. At time of labour and delivery (intrapartum) TB is acquired through aspiration or ingestion of

amniotic fluid or cervico-vaginal secretions and postpartum the infant is infected through breastfeeding or inhalation of infected respiratory droplets from an infectious contact.

The most effective way to prevent children from becoming infected with *Mycobacterium tuberculosis* is to diagnose and treat adult TB patients as early as possible.^{16, 17} TB disease can be prevented by providing appropriate therapy to young and vulnerable children.¹⁷ There are two regimens that are used for chemoprophylaxis in infants, one using isoniazid monotherapy for at least six months and the other using and rifampicin for three months.^{17, 18} Isoniazid monotherapy has been formally validated in clinical trials and, has been used to effectively prevent TB in HIV infected children, but did not improve tuberculosis-disease-free survival among HIV-infected children or tuberculosis-infection-free survival among HIV-infected children immunized with BCG (Bacille Calmette Guerin) vaccine.¹⁹

This will include the newborn babies born to mothers with TB. Limited data exist on adherence to anti-TB treatment and chemoprophylaxis in children in high burden settings.¹⁶ The draft South African National Tuberculosis Control Programme endorses the use of isoniazid monotherapy regimen.²⁰ Both regimens (isoniazid monotherapy, isoniazid and rifampicin chemotherapy) have been found to be equivalent in terms of efficacy, proportion of side effects and mortality in adult trials.²¹ Adherence to three months chemoprophylaxis regimen of isoniazid and rifampicin was found to be significantly better than adherence to six months chemoprophylaxis of isoniazid only in a retrospective study conducted in Cape Town from 1996 to 2003.¹⁶ The recommendation was that shorter periods of chemoprophylaxis such as isoniazid and rifampicin combination should be considered to improve adherence but further studies are required. Preventive treatment of three months isoniazid and rifampicin has been found to be well tolerated in children with minimal side effects (particularly hepatitis).²² The Essential Drugs List for South Africa in 2006 recommended three months of isoniazid and rifampicin at a dosage of 5mg/kg/day and 10mg/kg/day respectively for chemoprophylaxis of congenital (perinatal) TB.²³ Childhood TB guidelines of the South African Society for Paediatric Infectious Diseases (SASPID) 2009, recommended INH at a dose of 8-12mg/kg/day for six months.¹⁷ At Chris Hani Baragwanath Academic Hospital (CHBAH), about 30% of women attending antenatal clinic are HIV infected and have co-infection with TB.²⁴ In this hospital the characteristics of women with TB and their infants have not been reported. We had been using three months of isoniazid and rifampicin for TB chemoprophylaxis since 2007 to 2010 because of the reported benefit of adherence compared to six months of isoniazid. In this study I would like to characterize the infants who are born

to mothers with TB at CHBAH and assess the effect of three months chemoprophylaxis in preventing TB.

Aim of the study

To determine the characteristics and outcomes of infants exposed to TB and given three months chemoprophylaxis with isoniazid and rifampicin at Chris Hani Baragwanath Academic Hospital.

Objectives.

1. To determine the maternal demographics and maternal HIV status.
2. To determine the clinical presentation and management of maternal TB.
3. To determine the prevalence of congenital TB in infants that were TB exposed.
4. To determine the demographics, clinical presentation and laboratory findings of infants born to mothers with proven TB.
5. To determine the outcomes to hospital discharge of infants born to mothers with TB.
6. To determine the number of infants who are infected with TB despite three months of chemoprophylaxis.

Methods.

Study design

The study will be a retrospective review of maternal and infant hospital records. The period for which records will be reviewed will be October 2007 to October 2010.

Study participants

1. The participants (maternal) hospital records referred to the Obstetric division and were known to be having proven TB will be reviewed.
2. The participants (infant) hospital records referred to the neonatal division at birth and were known to be born to mothers with proven TB will also be reviewed.

Inclusion criteria

1. All infants including sick and well irrespective of gestational age, who are born at Chris Hani Baragwanath Academic Hospital and Soweto clinics who are TB exposed.
2. All mothers who are proven to have TB in the first week post-delivery.
3. All mothers with proven TB antenatally.

Exclusion criteria

All mothers and infant pairs, sick and well who were proven to have TB beyond one month post delivery

Terminology

TB infection in the infant : An individual; for the purpose of this study, an infant who has a positive Mycobacterium tuberculosis culture in blood, cerebrospinal fluid, gastric washings, tracheal aspirates, tissue biopsy and/or positive PPD (> 10mm).

TB infection in the mother: Based on history from the obstetricians and the mother. This is usually based on positive culture results for Mycobacterium tuberculosis from sputum or other biological specimens/tissues.

TB exposed: An infant who is born to a mother infected with TB infection..

Well infant/newborn: A newborn baby who is sent to the postnatal wards with the mother and never been admitted during the neonatal period.

Sick infant/newborn: A newborn (preterm and term in all weight categories who requires admission to the neonatal wards after birth or within the first month of life.

Data collection

Maternal: The demographic characteristics, HIV status, CD4 counts, clinical diagnosis of TB at time of delivery, when the TB was diagnosed, duration of treatment, type of TB (pulmonary or extra-pulmonary, multidrug/ extremely drug resistant) and hospital outcome of the mother where available will be recorded, using a data capturing sheet (Appendix A).

Infant: The following data will be collected: Demographic characteristics, clinical presentation (sick or well infant), laboratory findings on those sick infants admitted to the division of Neonatology. Duration of stay in hospital after delivery or admission of the infant, results of Gastric washings taken prior to commencing chemoprophylaxis if any, HIV-PCR at six weeks (in the HIV-exposed infants), chest X-ray findings on admission/ before initiation and at completion of chemoprophylaxis if done, the number with abnormal chest X-ray findings and the number with a positive Mantoux, if it was done. Data will be captured in a data capturing sheet (Appendix B).

Data Analysis

Data will be entered into Microsoft Excel spreadsheets and will then be imported into Statistica for statistical analysis. Means, standard deviation, medians, 25th and 75th percentiles, and ranges will be used to describe the data. Where comparisons are made

Student t-test will be used to compare continuous variables if they have normal distribution but if not, Mann- Whitney U-test will be used. I will use Chi- Square for categorical variables.

Ethical considerations.

Permission to perform the study has been granted by the University of The Witwatersrand Human Research Ethics Committee (HREC) and Chris Hani Baragwanath Academic Hospital Research Review Committee (see copies of ethics approval attached).

Timeline for the study

1. Participant's hospital records review : 1st December 2011 to 28 February 2012 (three months).
2. Data analysis: 1st March to 30 April 2012 (two months).
3. Writing up the study: 1st May 2012 to 31st July 2012 (three months).

Financial costs.

1. Participants: no financial costs to participants.
2. Hospital/Institution: no financial costs to the hospital
3. Other: financial costs towards stationery to be used and this will be self

References.

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File formats

The preferred file format is Word (.doc) or rich text format (.rtf), but Word-compatible word processor files (e.g. .wpd) will also usually be acceptable. Please do not upload PDF files as we require source files so that the article can be typeset for publication. Failure to comply may delay publication. Permitted file formats for figures are TIFF (.tif), JPEG (.jpg) and EPS (.eps). Separate high-resolution files of each figure will be required – please see the figure section of the presentation guidelines for more detail.

Language & language editing

Submissions are vetted for quality of written language and may be rejected on these grounds. Maney recommends that any non-native English-speaking author who is not confident of his or her English language skills should ask a native English-speaker or professional language editing service to review their manuscript before submission. This is not mandatory but will help ensure that the Editors and reviewers fully understand the academic content of the article.

Use of an editing service does not guarantee publication. A decision will be made following the usual peer-review process.

For information about the language editing service and discounts for Maney authors, please visit Maney's language editing page.

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Spelling

US and UK spelling are both permitted as long as the spelling is consistent throughout the article. Please ensure that '-ize' spelling is used (e.g. organize, prioritize, mobilization). Consistency in spacing, punctuation, and spelling is essential.

References

References should be presented in the Vancouver style. References should be numbered consecutively in the order in which they are first mentioned in the text. References should be entered consecutively as Arabic numerals in superscript form outside the punctuation mark e.g. ⁶. When citing more than one source at a time, list each reference number separately with a comma or dash (without spaces) between each reference e.g. ^{2,5,9,13}. The references should be listed in numerical order in single spacing at the end of the paper. The list should be arranged in the order of citation in the text of the publication, not in alphabetical order. Manuscripts with references that are incorrectly formatted will be returned to the author. Please format references as follows.

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Please provide the names and initials of all authors (if there are more than six, only the first six should be given followed by *et al*). Endnote should not be used. The authors' names are followed by the full title of the article, the abbreviated title of the Journal (the titles of journals should be abbreviated as they appear in the MEDLINE Journals Database), the year of publication, the volume number, and the first and last page numbers.

Capitalise only the first word of an article title, except for proper nouns or acronyms.

Volume and page numbers should be given but not labelled. To indicate a page range use 123-9, 126-34 or 111-222. If you refer to only one page, use only 111.

Duggan MB. Prevention of childhood malnutrition: immensity of the challenge and variety of strategies. *Paediatr Int Child Health*. 2014;34:271–8.

E-Journals

Evans C, Dunstan HR, Rothkirch T, Roberts TK, Reichelt KL, Cosford R et al. Altered amino acid excretion in children with autism. *Nutr Neurosci* [Internet]. 2008 [cited 12 Aug 2009]; 11:259–64. Available from <http://www.maneyonline.com/loi/nns>.

Books

Starke JR, Munoz F. Tuberculosis. In: Behrman RE, Kliegman RM, Jenson HB, eds. *Nelson Textbook of Pediatrics*, 16th edn. Philadelphia, PA: WB Saunders, 2000; p. 212.

Books with an organisation as author

Department of Health. *Our health, our care, our say. A new direction for Community Services*. London: Stationary Office; 2006.

Internet documents

Department of Health [Internet]. The NHS in England: the operating framework for 2008/9. 2007 Dec 13 [cited 2008 Nov 1]. Available from: http://webarchive.nationalarchives.gov.uk/+/www.dh.gov.uk/en/publicationsandstatistics/publications/publications/policyandguidance/dh_081094.

Legal material

Local Government and Public Involvement in Health Act of 2007, Pub. L. No. 107-9, Stat.11 (30 Oct, 1997).

Abbreviations

Acronyms, such as titles of organisations etc. should be written out first in full, followed by the initials in brackets, and thereafter the initials only should be used.

Units of measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram or litre) or their decimal multiples.

Temperatures should be in degrees Celsius.

Scientific measurements should be given in SI units, except for blood pressure, which should be expressed in mm Hg.

Raw numbers should be given alongside percentages, and as supporting data for P values.

For P values use the upper case roman P ($P < 0.05$).

Proprietary names & identification of product manufacturers

Proprietary names of drugs and instruments should be indicated by the use of capital letters. Any medications, materials and devices must be identified by full non-proprietary names as well as brand name and the manufacturer's name, city, state and country should be included in parentheses in the text, not in a footnote.

When using a word which is, or is asserted to be, a proprietary term or trade mark authors must use the symbol ® or ™.

For technical and scientific terms, spell the name in full at first appearance. Acronyms or abbreviations should be introduced in parentheses following the first appearance of the full term.

Manuscript files

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Tables

Each table should be presented with double spacing on a separate page. Do not use internal horizontal or vertical lines. Care should be taken to ensure that all units are included. Identify statistical measures of variations, such as standard deviation and standard error of the mean. Give each column a short or an abbreviated heading. A short descriptive title should appear above each table and any footnotes, suitably identified, should appear below.

Tables should be numbered consecutively using Arabic numerals in the order of their first citation in the text. Within the text tables should be referred to by number (e.g. Table 1), and preferred position and groupings in the text should be clearly indicated.

Figures

Figures should be numbered consecutively using Arabic numerals in the order of their first citation in the text.

These should be submitted in separate files. Sub-figures should be appropriately lettered in capitals (e.g. A, B); the size of letters should be appropriate to that of the illustration. Each illustration must have a caption and source. Captions should be typed, double-spaced, on separate sheets from the main text. Within the text, figures should be referred to by number (e.g. Figure 1), and preferred position and groupings in the text should be clearly indicated.

Figures should be either professionally drawn and photographed or submitted as photographic-quality digital prints. The author will be required to provide all images in CMYK format as TIFF or EPS files at high resolution suitable for printing.

As a guideline, images should be submitted at the following minimum input scanning resolutions:

full colour images	half tones	slides or transparencies	simple line illustrations	fine line illustrations
300 dpi	350-400 dpi	600 dpi	800 dpi	1200 dpi

Please note that the final reproduction quality is dependent on the quality of the original illustration. Prior to submission, we would advise authors to print out, at roughly the size required for publication, all images supplied electronically so the hard copy image can be assessed for contrast etc.—what might be clear and legible on a full computer screen will not be the same printed out at journal text/column width or less.

If relevant, the magnification and staining techniques of X-ray films, scans and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, should be stated. To highlight the detail to be illustrated, X-ray film should be submitted with an overlay indicating the area of importance.

Manipulation of images to enhance, obscure or remove individual features is not permitted. Adjustment of brightness, contrast or colour balance may be applied to the entire image, as long as the result does not mislead the viewer. Significant digital manipulation of images must be acknowledged in the figure caption.

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To use any illustrative matter in the journal, the author must obtain written evidence of permission from the copyright owner to reproduce the images (in all formats, in perpetuity and in all geographical regions worldwide), and will be liable for any fee charged by the owner of the image. The caption should include the relevant permission of the copyright holder to reproduce the image. See the submission policy section for more detail about obtaining permission.

Illustration checklist:

- Files are provided in TIFF or EPS format.
- Artwork is of sufficient resolution for its style.
- All images are the size intended for publication and all unnecessary elements have been removed.
- All fonts used for any text are embedded and use standard fonts (Arial/Times New Roman). Ensure font size is consistent.

- Any lines are a minimum of 0.3pt.
- Images do not contain any layers or transparent objects.
- Files are named according to convention.
- Artwork is provided in files separate to the main text.
- Captions and figure titles are provided in separate file.
- All rights/permissions have been secured.

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Authors submitting manuscripts containing statistical analysis should consider the guidelines set out at the Equator Network.

Supplementary material

Supplementary material gives authors the opportunity to enhance their work by including material that cannot be included in an article for reasons of space, is of very specific interest, or is not compatible with the standard journal format (e.g. audio or video files, animations, software, models, or large datasets). Supplementary material is intended to support arguments advanced in the article; it should not refer to other work nor contain discussion or conclusions that go beyond the content of the article. The inclusion of supplementary material is at the discretion of the Editor whose decision is final.

Supplementary material will be published online and linked to and from the article. It is considered to form an integral part of the article and will be peer reviewed and subject to the same ethical standards, warranties and conditions of submission. Authors will be required to sign a copyright transfer form and provide the same warranties in respect of supplementary material as for the article itself.

To assure continuity of access and effective archiving, supplementary files will be published online with the journal content, unless the data appear in an open-access database such as GEO or CIF or a widely recognised subject-based repository. It is not acceptable to link to files held on personal or other websites.

Whenever possible, include supplementary material on initial submission of the article since peer review at a later stage may cause delays. Supplementary material will be hyperlinked from the main article. In preparing an article:

- Ensure each supplementary file is referred to at the appropriate point in the manuscript using the correct style for the journal: (Supplementary Material 1), (Supplementary Material 2), etc.
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Distinguish supplementary tables, figures and references using the numbering system S1, S2, S3 etc.

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Instructions for authors

Journal information

Paediatrics and International Child Health

Aims & scope

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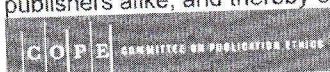
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