APPROPRIATENESS OF DRUG PRESCRIPTIONS AMONG CHILDREN ON TREATMENT FOR TUBERCULOSIS AT KENYATTA NATIONAL HOSPITAL, NAIROBI - KENYA.

A dissertation in partial fulfillment for the award of the degree of Masters of Medicine (Paediatrics) in the department of Paediatrics and Child Health, College of Health sciences, University of Nairobi.

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July 2011.

DECLARATION AND SIGNATURE

This dissertation is my original work and has not been presented for the award of a degree in any other university.

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DEDICATION

I dedicate this dissertation to my wife Miriam and my children Janet and Griffin who stood by me even as I burnt the midnight oil to draft it, and at times was not available to them as much as I would have liked.

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LIST OF ABBREVIATIONS

BCG	Bacille Calmette-Guérin
CNR	Case Notification Rate
DOTS	Directly Observed Treatment Strategy
ETH	Ethambutol
HIV	Human Immuno-deficiency Virus
INH	Isoniazid
ISTC	International Standards for Tuberculosis Care
KNH	Kenyatta National Hospital
MDR-TB	Multi-drug resistant tuberculosis
PAS	Para-amino salicylic acid
PZA	Pyrazinamide
RIF	Rifampicin
SHO	Senior House Officer
TB	Tuberculosis
TBM	Tuberculous meningitis
TST	Tuberculin skin test
UON	University of Nairobi
WHO	World Health Organization

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ABSTRACT

Background: Tuberculosis is an ancient disease. It contributes significantly to the burden of disease in today's world. Globally, tuberculosis (TB) accounts for an estimated 9.4 million cases and 2 million deaths per year. Of the cases, one million occur in children. The disease can be cured in 6 months if the proper chemotherapeutic agents are provided. The management of tuberculosis in Kenya is guided by the National guidelines developed after consideration of internationally recognized recommendations. A continuous audit of the practice of the healthcare personnel involved in the management of the disease is paramount to maintaining provision of quality health care to the patients.

Objective: To determine the proportion of inappropriate prescriptions for the children on treatment for tuberculosis at Kenyatta National Hospital

Methodology: This was a hospital based cross sectional audit of the treatment records of children admitted in the general paediatric wards of Kenyatta National Hospital. Consecutive sampling was done till the sample size of 96 was achieved. The sample size of 96 was estimated using the Fischer's formula, assuming a precision of 0.10 and expected prevalence of inappropriateness of 50%. All patients aged 13 years and below whose parents/ guardians gave consent for participation in the study were recruited.

Results: Out of the 97 patients whose treatment records were analyzed, only 19 (19.6%) had the formulation of fixed dose anti-tuberculous drugs specified as either adult or paediatric. Similarly, when the dosage in mg/kg was calculated, only 19 (19.6 %) of the patients had correct dosage for all individual drugs in the fixed dose tablets prescribed. Thus 80.4% of the patients received inappropriate dosage. The inappropriateness of the dosing was not influenced by the age or the severity of the patient's disease. However, when the four general paediatric wards were compared, i.e., wards 3A, 3B, 3C and 3D; one ward, 3B was found to have performed significantly better than the others, p-value 0.038.

Conclusions: Majority, 80.4%, of the prescriptions done for the paediatric patients on treatment for tuberculosis at Kenyatta National Hospital general paediatric wards are inappropriate.

Recommendations: A study should be done to establish the factors that contribute to the large proportion of inappropriateness in the prescriptions for TB among the children at KNH. Once identified, efforts should be put in place to correct them, thus improving the care of children on treatment for TB at KNH.

1 BACKGROUND AND LIERATURE REVIEW

Tuberculosis (TB) is an ancient disease known to affect human beings. It is an infectious disease caused by a bacillus called *Mycobacterium tuberculosis,* an acid-fast rod shaped bacillus. Occasionally *Mycobacterium bovis*, transmitted through contaminated milk and *Mycobacterium africanum* also cause disease. In historical terms, tuberculosis was the greatest killer ever known to mankind. The 17th century English evangelist John Bunyan termed tuberculosis 'the Captain of all these Men of Death' [1] and, today, despite the availability of effective therapy, this epithet is still appropriate in many parts of the world, Kenya included.

At present one third of the world's population is infected with the tubercle bacilli, giving rise to 9 million new cases and about 2 million deaths from TB each year. Of the 9 million annual TB cases, about 1 million (11%) occur in children (under 15 years of age). Of these childhood cases, 75% occur annually in 22 high-burden countries that together account for 80% of the world's estimated incident cases. In low-burden countries, childhood TB constitutes approximately 5% of the TB caseload, compared with 20%-40% in high-burden countries [2, 3]. In countries worldwide, the reported percentage of all TB cases occurring varies from 3% to more than 25%. This gives an estimated global incidence of TB of 136 cases per 100,000 population per year, ranging from 39 per 100,000 per year in the WHO Region of the Americas to 343 per 100.000 per year in the WHO African Region.

Kenya is ranked 13th among the 22 high TB burden countries mentioned above [4]. The TB case notification rate (CNR) rose from 51 to 338 per 100,000 population between 1987 and 2007. As in the rest of Sub-Saharan Africa, the large increase of TB is attributed primarily to the Human Immunodeficiency Virus (HIV).

PATHOPHYSIOLOGY

Infection with *Mycobacterium tuberculosis* usually results from inhalation into the lungs of infected droplets produced by someone who has pulmonary TB and who is coughing. The source of infection of most children is an infectious adult in their close environment, usually the household. This exposure leads to the development of a primary complex which includes the Ghon focus with associated tuberculous lymphangitis. Pulmonary infection without progression to disease implies successful containment of the organism.

Immune response (delayed hypersensitivity and cellular immunity) to *Mycobacterium tuberculosis* develops about 4–6 weeks after the primary infection. In most cases, the immune response stops the multiplication of *M. tuberculosis* bacilli at this stage. Once the multiplication

is stopped successfully, a positive tuberculin skin test (TST) would be the only evidence of infection.

In some cases, the immune response is not strong enough to contain the infection and disease occurs. The patient at this stage manifests various clinical symptoms and/or additional radiological abnormalities apart from the primary complex.

Table 1. below outlines the risk of developing tuberculous disease by source of exposure and age [5]. Part 1 of the table shows the risk of progression from exposure to infection. Part 2 of the table shows the risk of the individual patient progressing from the stage of infection to manifestation of tuberculous disease.

The risk of progression to disease is increased when primary infection occurs at a young age and in the immune-compromised children. It is noted that among children less than 1 year of age, 50% of those exposed to the mycobacterium progress to develop disease; compared to less than 10% of children aged greater than 2 years.

Progression of disease occurs by:

(i) Extension of the primary focus with or without cavitation
(ii) Effects of pathological processes caused by the enlarging lymph nodes, or
(iii) Lymphatic and/or haematogenous spread.

Children who develop disease usually do so within 2 years following exposure and infection [5]. A small proportion of children with TB (generally older children) develop post-primary TB either due to reactivation of dormant bacilli acquired from a primary infection or by re-infection. Children can present with TB at any age, but the most common age is between 1 and 4 years [5].

TABLE 1: QUANTIFICATION OF THE RISK OF INFECTION AFTER TUBERCULOSIS (TB) EXPOSURE AND THE RISK OF PROGRESSION TO ACTIVE TB IN CHILDREN [5]

From TB exposure to infection, by exposure type	
Progression	Risk, %
Prolonged household exposure to an index case with sputum smear–positive TB	60–80
Prolonged household exposure to an index case with sputum smear–negative TB	30–40
From TB infection to active disease, by age group and disease type	
Progression	Risk %
Children aged < 1 year	
None	50
Pulmonary disease	30-40
Disseminated (miliary) disease or TBM	10–20
Children aged 1 to < 2 years	
None	75–80
Pulmonary disease	10–20
Disseminated (miliary) disease or TBM	2-5
Children aged 2 to < 5 years	
None	95
Pulmonary disease	5
Disseminated (miliary) disease or TBM	0.5
Children aged 5 to <10 years	
None	98
Pulmonary disease	2
Disseminated (miliary) disease or TBM	<0.5
Children aged > 10 years	
None	80–90
Pulmonary disease	10–20
Disseminated (miliary) disease or TBM	< 0.5

1.1 DIAGNOSIS OF TB IN CHILDREN

The gold standard for diagnosis of tuberculosis is the identification of *Mycobacterium tuberculosis* by microscopy and/or TB culture from sputum and various other body specimens. It is a major challenge and not always feasible in children but should be sought whenever possible. [6, 7]

The key elements to a successful diagnosis of pulmonary TB in children include careful history taking including history of TB contact and symptoms consistent with TB, clinical examination especially growth monitoring, smear microscopy, tuberculin skin testing, chest radiography and HIV testing [8,9].

Positive findings in sputum smear microscopy are noted for only 10%–15% of children with probable TB [8]. The yield from culture of 2–3 gastric aspirate samples obtained during fasting is ∼30%–40%. Nasopharyngeal aspiration provides a 30% yield [7].

One hypertonic saline–induced sputum collection provides the same yield provided by 3 gastric aspirate specimens [8].

Should it not be possible to isolate *Mycobacterium tuberculosis* from the specimens, a clinical diagnosis should be made. This is done by consideration of suggestive symptoms and signs, chest x-ray findings and tuberculin test as illustrated below.

i. Chronic symptoms suggestive of TB. These include [9, 10, 11] :-
- Chronic cough more than 3 weeks
- Unexplained fever lasting more than 2 weeks and
- Weight loss or failure to thrive.

ii. Physical signs highly suggestive of TB [9, 10, 11]. These include:-
- Gibbus, especially of recent onset (resulting from vertebral TB)
- Non-painful enlarged cervical lymphadenopathy with fistula formation

The following signs necessitate investigation for possible tuberculosis:-
- meningitis not responding to antibiotic treatment, with a sub-acute onset or raised intracranial pressure
- pleural effusion
- pericardial effusion
- distended abdomen with ascites

- non-painful enlarged lymph nodes without fistula formation
- non-painful enlarged joint
- signs of tuberculin hypersensitivity (e.g. phlyctenular conjunctivitis, erythema nodosum

iii. A positive tuberculin skin test- A TST should be regarded as positive as follows: [9, 10, 11]:-

- in high-risk children (includes HIV-infected children and severely malnourished children, i.e. those with clinical evidence of marasmus or kwashiorkor): >5 mm diameter of induration
- in all other children (whether they have received a bacille Calmette–Guérin (BCG) vaccination or not): >10 mm diameter of induration

A negative TST never rules out a diagnosis of TB in a child.

iv. Chest X-ray suggestive of TB [**9, 10, 11**]:-

- Persistent opacification in the lung
- Enlarged hilar or sub-carinal lymph glands.
- Miliary pattern of opacification in HIV-uninfected children is highly suggestive of TB.
- Persistent opacification which does not improve after a course of antibiotics.

In summary, the presence of three or more of the following in children should strongly suggest a diagnosis of TB.

i. Chronic symptoms suggestive of TB
ii. Physical signs highly suggestive of TB
iii. A positive mantoux skin test
iv. Chest radiograph suggestive of TB

Once a decision is made to initiate anti-TB therapy, the full course of treatment should be given.

1.2 PREVENTION

Prevention of TB includes interventions to reduce both transmission, and the risk of TB disease in infected persons. These interventions result in specific activities of National TB control programmes, including;

- **i.** Contact tracing: – This is useful especially to identify the young children who should be given chemoprophylaxis as mentioned below.
- **ii.** Detection of cases: - The aim is to provide treatment, cure the patient and minimize transmission to other persons.
- **iii.** Infection control: – This is especially so in the setting of the health care facility. The aim is to protect the health care workers and the community as a whole.
- **iv.** Preventive therapy: – Should be targeted to special groups like all children below five years of age who are in close contact with an infectious patient.
- **v.** BCG vaccination
- **vi.** Treatment of HIV-infected persons with ARV: - This reduces the chances of the HIV positive patient acquiring TB among other opportunistic infections.

There are other factors that strongly influence the risk of becoming exposed and infected (such as overcrowding) or developing active TB (such as poor nutrition, smoking, diabetes). These require an all inclusive approach of several sectors within the governance of a country.

Bacille Calmette-Guérin (BCG) vaccine was introduced in 1921 in Europe with hope of eliminating TB. Despite routine use of this vaccine in every country in the world except the Netherlands and the United States of America, TB has not been controlled by vaccination. BCG prevents the occurrence of severe forms of tuberculosis like tuberculous meningitis and miliary tuberculosis [12, 13].

Children less than 5 years of age who are close contacts of an infectious index patient and who, after careful evaluation, do not have active tuberculosis, should be treated for presumed latent tuberculosis infection with isoniazid, 10 mg/kg/day (up to a maximum of 300mg) for six months.

Each healthcare facility caring for patients who have, or are suspected of having, infectious tuberculosis should develop and implement an appropriate tuberculosis infection control plan. Infection control for tuberculosis consists of managerial activities at the facility level and a hierarchy of three categories of control measures including: administrative controls, environmental controls, and the use of respirators (special masks designed to protect the wearer).

1.3 TREATMENT

Earlier practices in TB treatment included prolonged bed rest, surgery, and nutritional supplements. The natural history of untreated TB before anti-tuberculosis medications were available was about 50% mortality, 50% recovery, with some chronic relapsing disease. The treatment of tuberculosis has however continued to experience a revolution over the decades since the discovery of the first chemotherapeutic agents. This has rendered the above practices irrelevant [17, 18].

The introduction of streptomycin in 1944 marked the beginning of effective treatment of TB [19, 20]. Para-amino-salicylic acid (PAS) was then introduced soon after. In 1949, it was discovered that PAS prevented the emergence of drug resistance if given in combination with streptomycin [21]. In 1952, isoniazid (INH) was introduced and proved to be a powerful chemotherapeutic agent against TB [22]. It is highly effective, of relatively low toxicity, and inexpensive. The efficacy was even more when combined with PAS to achieve a 90% cure rate. However, the duration of treatment was too long- 18 to 24 months- which was not acceptable to patients and could be intolerable because of the side effects of PAS. Ethambutol, which is better tolerated, replaced PAS in the 1960's. The duration of treatment though remained 12 to 18 months.

A major break-through occurred in the 1970s, with the introduction of rifampicin [23, 24]. All current studies indicate that a rifampicin-containing regimen is the backbone of anti-tuberculosis chemotherapy and is highly effective in treating tuberculosis caused by drug-susceptible *Mycobacterium tuberculosis*. It is also clear from these studies that the minimum duration of treatment for smear- and/or culture positive tuberculosis is six months. For the six-month treatment duration to be maximally effective the regimen must include pyrazinamide during the initial two-month phase and rifampicin must be included throughout the full six months. The efficacy of combined drug therapy has been demonstrated especially in terms of cure rates, prevention of emergence of drug-resistant organisms and reduction in the duration of therapy. Currently, the disease can be cured within 6 months or less of therapy if the proper drugs are used [25, 26].

PRINCIPLES OF TREATMENT

The aims of treatment are to cure the patient, prevent death from active disease or its late effects, prevent the emergence and spread of drug-resistant organisms, minimize relapse and protect the community from continued transmission of infection. Host factors, such as type of disease and patients' immune responses, are of minor importance. The bacilli are killed by the drugs, not by the patient.

STRATEGIES OF TREATMENT

Various strategies have been put in place by different organizations towards the management and possible eradication of TB. The Stop TB Strategy particularly, which builds on the DOTS strategy developed by the World Health Organization (WHO) and the International Union Against TB and Lung Disease, has a critical role in reducing the worldwide burden of disease and thus in protecting children from infection and disease [27]. The WHO recommends that the management of children with TB should be in line with the Stop TB Strategy, taking into consideration the particular epidemiology and clinical presentation of TB in children [27].

The DOTS strategy is based on five key elements:

- **i.** Sustained political commitment to increase human and financial resources and make TB control a nationwide priority integral to the national health system
- **ii.** Access to quality-assured sputum smear microscopy for case detection among persons presenting with, or found through screening to have, symptoms of TB (most importantly, prolonged cough)
- **iii.** Standardized short-course chemotherapy for all cases of TB under proper case management conditions, including direct observation of treatment
- **iv.** An uninterrupted supply of quality-assured drugs
- **v.** A recording and reporting system enabling outcome assessment of all patients and assessment of overall programme performance

The vision of Stop TB Strategy is to have a world free of TB. The Goal is to dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals (MDGs) and the Stop TB Partnership targets [27].

Four key objectives have been identified as the means to achieving this vision. The first is to achieve universal access to high-quality diagnosis and patient-centered treatment. The second is to reduce the human suffering and socioeconomic burden associated with TB. The third is to protect poor and vulnerable populations from TB, TB/human immunodeficiency virus (HIV) and multidrug-resistant TB (MDR-TB) and the fourth is to support development of new tools and enable their timely and effective use [27].

With global implementation of these objectives, it is expected that by 2015 the increase in TB will have been halted. Targets linked to the MDGs and endorsed by the Stop TB Partnership include that by the year 2005; it should be possible to detect at least 70% of new sputum

smear-positive TB cases and cure at least 85% of these cases, and by 2015, reduce the prevalence of and deaths due to TB by 50% relative to 1990. Ultimately, the aim is to eliminate TB as a public health problem (<1 case per million population) by 2050 [27].

Components of the strategy and implementation approaches include to Pursue high-quality DOTS expansion and enhancement, address TB/HIV, MDR-TB and other challenges, contribute to health system strengthening Engage all care providers Empower people with TB, and communities Enable and promote research [27].

INTERNATIONAL STANDARDS FOR TUBERCULOSIS CARE

Development of the International Standards for Tuberculosis Control (*ISTC*) was funded by the United States Agency for International Development (USAID) via the Tuberculosis Coalition for Technical Assistance (TBCTA) and was guided by a steering committee of 27 members from 14 countries, representing relevant perspectives and areas of expertise. The first edition was released in the year 2006 [28]. This has since been revised and a second edition published in 2009 [16]. The WHO Guidelines Review Committee examined the final draft and offered comments which were also addressed. The purpose of the International Standards for Tuberculosis Care is to describe a widely accepted level of care that all practitioners, public and private, should seek to achieve in managing patients who have, or are suspected of having tuberculosis. The standards are intended to facilitate the effective engagement of all care providers in delivering high quality care for patients of all ages [16].

Prompt, accurate diagnosis and effective treatment are not only essential for good patient care; they are the key elements in the public health response to tuberculosis and are the cornerstone of tuberculosis control [16]. Thus, all providers who undertake evaluation and treatment of patients with tuberculosis must recognize that, not only are they delivering care to an individual, they are assuming an important public health function that entails a high level of responsibility to the community, as well as to the individual patient [16].

The standards in the ISTC are intended to be complementary to local and national tuberculosis control policies that are consistent with World Health Organization recommendations. They are not intended to replace local guidelines and were written to accommodate local differences in practice.

Between June 2006 and July 2007, four ISTC planning and implementation meetings were convened in Kenya. The initial meeting was intended to introduce key stakeholders representing select medical associations and all three medical colleges in the country to the

ISTC and to discuss ways the ISTC could be used to improve tuberculosis care in Kenya. In two subsequent meetings, the group of stakeholders was enlarged and plans for a larger "ISTC Endorsement Meeting" were developed. The meeting included key stakeholders representing various organizations and institutions, including Kenyatta National Hospital, Kenya Paediatric Association and the University of Nairobi. At the conclusion of the meeting, the attendees signed a statement on behalf of their organizations and institutions that reads as follows:

"On Tuesday, 3rd July 2007, we the undersigned, having attended a sensitization workshop in which the International Standards for Tuberculosis Care (ISTC) were presented and extensively discussed; in recognition of the strategic role that the ISTC can play in the care and prevention of tuberculosis in Kenya, do hereby endorse the ISTC for implementation in Kenya [16]*."*

The focus of ISTC activities in Kenya is to use the document as a vehicle to unify approaches to diagnosis and treatment of tuberculosis in the private and public sectors and to improve collaboration between the two sectors

STANDARD TREATMENT GUIDELINES

The basic principles of treatment and recommended standard anti-TB regimens for children are similar to those for adults. Treatment for most forms of pulmonary and extra-pulmonary TB consists of a 6-month short-course chemotherapy regimen with 4 drugs (Isoniazid [INH], Rifampicin[RMP], Ethambutol[EMB], and Pyrazinamide [PZA]) in the initial intensive phase, followed by 2 drugs (INH and RMP) in the continuation phase [29]. For uncomplicated pulmonary disease (primary complex) and single-site lymph node disease, EMB may be omitted from the intensive phase. Doses for children are usually extrapolated from adult pharmacokinetic studies, and recent data point to the inadequacy of currently recommended doses of RMP, INH, and EMB. Children eliminate INH faster and require a higher body weight dose (mg/kg) to achieve serum concentrations comparable to those in adults; hence the recommendation by the World Health Organisation for 10 mg/kg rather than 5 mg/kg as shown below [29, 30].

Table 2 shows that there are significant discrepancies between the WHO and Kenyan guidelines on the treatment of tuberculosis in children. Programme officers at the Kenyan Ministry of Public health and Sanitation did not seem to be aware of the latest WHO recommendations. Thus, for instance, the dose of isoniazid as per the Kenyan guidelines is half that recommended by the WHO [29].

TABLE 2: PAEDIATRIC DOSAGE RECOMMENDATIONS AS PER WHO (SEPT 2009) AND KENYAN MINISTRY OF PUBLIC HEALTH AND SANITATION TB GUIDELINES (JUNE 2009) [29, 31]

Drug	Daily recommended dosage in mg/kg		Maximum daily dose	
	WHO, Sept 2009	Kenya, June 2009	WHO, Sept 2009	Kenya, June 2009
Isoniazid	10 (10 –15),	5 (4-6)	300 mg	300 mg
Rifampicin	15 (10–20)	10 (8-12)	600 mg	600 mg
Pyrazinamide	35 (30–40),	25 (20-30)	2,000 mg	-
Ethambutol	20 (15–25),	20 (15-25)	1,000 mg	Not to exceed 25 mg/kg
Streptomycin		15(12-18)		-

Table 3 shows the WHO recommendations regarding the use of fixed dose tablets in the management of tuberculosis in children [29]. There have been no child-friendly formulations of anti-TB drugs available in the market. Recently, there was the introduction of dispersible tablets for use by children. These however come in different strengths compared to the adult tablets hence the need for clear guidelines on their prescription.

TABLE 3: TABLET DOSAGE GUIDE FOR CHILDREN [29, 31]

Drug Dosages		Pre-Treatment Weight				
Drug	Formulation	< 10 kg	10-14 kg	15-19 kg	20-24 kg	25-29 kg
Fixed Dose Combination (No. Of Tablets Per Dose Per Day – Paediatric Dispersible Tablets)						
RIF60/INH30/PZA150	3-FDC tab- RHZ	1	2	3	4	5
RIF60/INH30	2-FDC tab - RH	1	2	3	4	5
Fixed Dose Combination (No. Of Tablets Per Dose Per Day – Adult Tablets)						
RIF 150/ INH 75/ PZA 400	3- FDC TAB – RHZ	¼	½	1	1 ½	2
RIF 150/ INH 75	2 FDC TAB -RH	¼	½	1	1 ½	2

CHALLENGES IN CURRENT MANAGEMENT OF TUBERCULOSIS

Despite remarkable success in reducing the duration of treatment and achieving higher rates of cure, several factors in the last few years have changed the epidemiology of the disease, undermining the progress made [32- 34]. These include:

(i) HIV/AIDS: – HIV infection increases the rate at which *M.tuberculosis* infections are acquired and increases the likelihood that people who are already infected will develop active TB disease. In southern and eastern African countries, HIV has caused a 4-5 fold increase in TB cases over a period of 10 years.

(ii) The emergence of and rapid increase in the magnitude of drug-resistant disease: - Drug-resistant TB is much more difficult and costly to treat than fully drug susceptible TB. An estimated 450,000 cases of multi-drug resistant tuberculosis (MDR-TB) occur each year among new and previously treated TB cases, and extensively drug-resistant TB (XDR-TB) has been reported from many countries. Drug resistance occurs where cure rates are low. Thus the emphasis on;

- Achieving high cure rates and optimizing the quality of and access to anti-TB drugs.
- Increasing case detection rates
- Ensuring good treatment outcomes for patients with MDR or XDR-TB
- Ensuring that TB patients are tested for HIV and that people with HIV are examined for TB.

MDR-TB is defined as tuberculosis with resistance to, at least, isoniazid and rifampicin.

XDR-TB is tuberculosis with resistance to, at least, isoniazid and rifampicin and to any of the fluoroquinolones and to one of the following injectable drugs: amikacin, capreomycin, kanamycin.

(iii) Deteriorating social conditions, such as homelessness, poverty, drug abuse and immigration from countries with high prevalence of drug-resistant disease.

Events of the past few years have shown that expectations of TB elimination, as entertained there earlier, were too optimistic. Tuberculosis is far from eliminated, even in the developed countries, and remains a major world's health problem in the 21st century as it was in the last century [33, 35].

A thorough understanding of the appropriate use of chemotherapeutic agents, including newer ones, and application of other modalities is essential in curing the disease in individual patients and in the eventual control of tuberculosis in the population.

PREVIOUS STUDIES

Various studies have been done to evaluate the knowledge of doctors on correct practice in treatment of tuberculosis. Table 4 shows a summary of some of the studies. It is noted that majority of the private practitioners were not able to prescribe anti-TB drugs correctly as per the guidelines of the particular country where the various studies were carried out. These were studies carried out among doctors prescribing anti-TB for both adults and children. Prescription of drugs for children is generally more challenging than for adults. There were no studies found to have been carried out to specifically assess the appropriateness of prescriptions for children on anti-TB medication.

TABLE 4: STUDIES DONE TO ASSESS DOCTOR'S KNOWLEDGE ON THE PRESCRIPTION OF ANTI-TB DRUGS.

Author	Country	Year published	Sample size	Correct regimen
Ayaya SO [36]	Eldoret, Kenya	2003	70 – (private practitioners)	11%
Suleiman [37]	Somalia	2003	53 doctors	7.5%
Vandan N [38]	India	2008	141 doctors	66.7%
Vandan N [39]	India	2009	141(79 public, 62 private)	84% pub, 66% private

STUDY JUSTIFICATION

1. Tuberculosis is endemic in Kenya and remains a major cause of morbidity and mortality among children.

2. Correct drug dosing is vital towards achieving cure of TB and for the avoidance of emergence of drug resistant forms of TB. Lower than adequate dosages carry the risk of sub-inhibitory drug concentrations, which is one of the mechanisms responsible for the development of drug resistance. Higher than adequate dosages are associated with an increased risk of drug toxicity.

3. There were anecdotal observations of errors in dosing of anti-tuberculous drugs made during routine ward rounds in the paediatric wards at KNH.

4. The magnitude of the errors mentioned above was not known. The study was done to establish the practice in Kenyatta National Hospital as pertains to the dosing of anti-TB drugs in children.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To determine the proportion of inappropriate prescriptions for the children on treatment for tuberculosis at Kenyatta National Hospital.

2.2 SECONDARY OBJECTIVES

1. To describe the demographic and clinical characteristics of children treated for tuberculosis at Kenyatta National Hospital.

2. To describe the determinants of inappropriate dosing of TB medication among children on treatment for tuberculosis at Kenyatta National Hospital.

3 MATERIALS AND METHODS

3.1 STUDY DESIGN

This was a hospital based cross sectional audit of the treatment of tuberculosis among children at Kenyatta National Hospital, Kenya.

3.2 STUDY SITES

Kenyatta National Hospital (KNH) is the National Referral and Teaching Hospital in Kenya, serving as the referral hospital for the whole country and also for the region of East and Central Africa. It is the pinnacle of health care provision in Kenya. It also serves as the Teaching Hospital for the School of Medicine, University of Nairobi and the Kenya Medical Training College, Nairobi. The hospital further provides attachment opportunities for students on training in all disciplines of health care provision from various colleges within the country.

The medical management of the children at KNH is primarily carried out by:

- **i.** Consultant paediatricians. These are either employees of KNH or members of faculty of the Department of Paediatrics and Child Health, University of Nairobi. Their main role is supervision of the team of doctors working in the wards, which comprises mainly of Senior House Officers, medical officer interns, and clinical officers.
- **ii.** Paediatric Senior House Officers (SHOs). These, who are the Resident Doctors in the Department of Paediatrics and Child health - University of Nairobi, attend to the very sick patients in the Paediatric Emergency and Filter Unit (PEU) and conduct daily reviews of all the patients in the general paediatric wards. They also review paediatric patients in other units, especially surgical and intensive care units, as may be necessary.
- **iii.** Medical and clinical officers who are undertaking their internship programme in the hospital. These are directly under the supervision of the Paediatric Senior House Officers (SHOs) and the consultant paediatricians.
- **iv.** Registered Clinical Officers with higher diploma training in Paediatrics and Child Health. These officers attend to the bulk of the patients seen in the PEU.

The study was carried out at the General Paediatric Wards. These are the wards which deal with all non-surgical paediatric cases which require management on an in-patient basis. There are four wards, 3A, 3B, 3C, and 3D, all located on the third floor of the hospital, and

similar in organizational and management structure. The patients in the wards are managed primarily by the paediatric SHOs, under the supervision of the consultant paediatricians. The intern medical and clinical officers also play a crucial role in the management of the patients in the wards, all done under supervision of the senior doctors mentioned above.

Those patients admitted to the paediatric wards with signs and symptoms suggestive of tuberculosis are investigated while in the ward and, once the diagnosis is confirmed, the treatment is initiated. However, as soon as they are stable enough, they are discharged for follow up in the TB centers near their areas of residence. Also, there are patients who are already on treatment for TB initiated in other health facilities and who present to KNH with complications of the TB, or with other illnesses requiring management on an in-patient basis. The treatment regimen is re-evaluated and continued in the wards as appropriate.

3.3 STUDY POPULATION

We examined the records of all children aged less than 13 years, with a diagnosis of Tuberculosis and on anti-TB therapy at the time of recruitment, either in the intensive or the continuation phase. As per the existing criteria of admission into the pediatric wards of KNH, 13 years is the upper limit in age for all patients. This explains the cut off in age in our study population.

3.4 INCLUSION CRITERIA

The study population included all patients, aged 13 years and below, on first line treatment for tuberculosis in the General Paediatric Wards of Kenyatta National Hospital. Consent was sought from the parent/guardian to access patients' information and recruit the child to the study.

3.5 EXCLUSION CRITERIA

Any patients, whose records were not available for scrutiny or whose parents declined consent for recruitment into the study, were excluded.

3.6 SAMPLE SIZE

The Fischer's formula, used to estimate sample size in prevalence studies, was used to estimate number of patients to be recruited in this study as follows:

$$n = \frac{Z^2 P (1-P)}{d^2}$$

Where;

n = sample size,

Z = Z statistic for a level of confidence – 1.96 for a 95% Confidence.

P = expected prevalence or proportion – 50%

d = precision – 0.10

Thus n= 96 patients.

Consecutive sampling was done for all patients who met the criteria above until the sample size was achieved.

The patient's demographic, clinical and treatment data was obtained from the parent/caretaker of the child in the ward. This was then correlated with the data in the patient's records. Body weight was retaken for all patients at the time of recruitment.

4 DATA ANALYSIS

Data was collected in questionnaires, cleaned and entered using SPSS version 17.0. Measures of central distribution – means and medians were used to describe the study population in terms of demographic and clinical characteristics that included age, sex, type of disease – pulmonary versus extra-pulmonary.

Using simple proportions the appropriateness of prescriptions done for the treatment of tuberculosis among children with respect to (i) Correct dosage, (ii) Specified fixed dose combination tablet.

Association was sought between the appropriateness of the prescription and the clinical/demographic data of the patients recruited. A comparison of the four wards in terms of appropriateness of therapy was done.

5 ETHICAL CONSIDERATIONS

1. Approval was sought and obtained from the Kenyatta National Hospital Ethical and Research Committee and the department of Paediatrics and Child Health, University of Nairobi.
2. Informed consent was obtained from parents or guardians accompanying the child.
3. Confidentiality was maintained by use of coded anonymised questionnaires and observing patient-clinician confidentiality.
4. Where feasible feedback was given to the clinical team to facilitate adjustment of treatment as may be necessary.
5. The results of this study will be availed to KNH and the UON with appropriate recommendations for consideration.

6 RESULTS

6.1 DEMOGRAPHIC CHARACTERISTICS;

A total of 97 children were identified. Their demographic data is as shown in table 5a below. The median age of patients at initiation of treatment was 2 years (IQR of 1 year to 6 years). The most affected age group was the infants, who contributed 41% of the patients recruited. Male patients were slightly more, forming 52.6% of the study group.

TABLE 5A: DEMOGRAPHIC CHARACTERISTICS

Variable	Frequency (%)
Age, median (IQR)	2.0 (1.0-6.0)
Age group	
1-12 months	41 (42.3)
1-5 years	24 (24.7)
>5 years	32 (33.0)
Sex	
Male	51 (52.6)
Female	46 (47.4)

6.2 CLINICAL CHARACTERISTICS

Weight was retaken in all the patients at the time of the study. This is shown in table 5b below. In management of tuberculosis, the calculation of dosage is based on the age and weight of the patient. Other parameters of nutritional assessment, including height, were not taken in this study as the emphasis was on calculation of dosage as per the established guidelines. It was found that the weight taken at the time of the study was significantly higher than that taken at start of treatment (P=0.004).

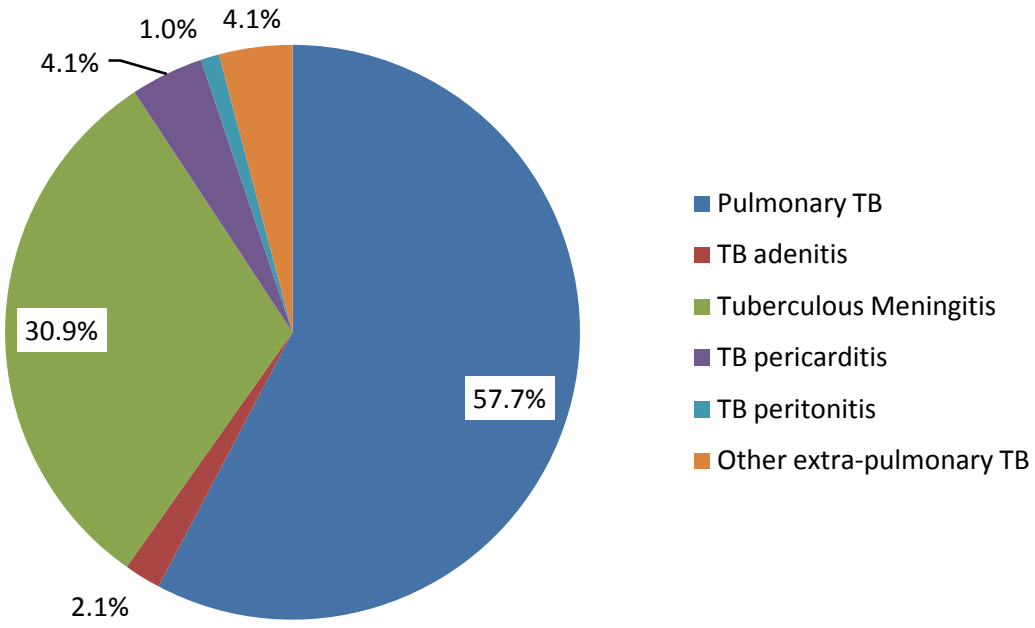
TABLE 5B: CLINICAL CHARACTERISTICS

Variable	Frequency (%)	P value
Weight at treatment, median (IQR)	9.2 (5.6-18.0)	0.004
Current weight, median (IQR)	9.5 (6.0-20.0)	

6.3 DIAGNOSIS;

The diagnosis of the patients recruited was taken as per the medical records. The criterion for diagnosis was not interrogated in this study. Results revealed that majority of the patients had pulmonary tuberculosis, contributing 57.7% of those recruited. Of note is the significant (30.9%) proportion of patients with a diagnosis of Tuberculous Meningitis (TBM).

Figure 1: Diagnosis As Per The Treatment Records



6.4 PRESCRIPTIONS;

An audit of all the prescriptions was done. This is as shown in table 6 below. Only 19 out of the 97 patients had the formulation of fixed dose anti-tuberculosis drugs specified as either adult or paediatric. Similarly, although all patients recruited were on Isoniazid among the other drugs, only 16 (16.5%) were on vitamin B6 supplementation.

TABLE 6: SPECIFICS OF PRESCRIPTIONS FOR THE CHILDREN ON TREATMENT FOR TUBERCULOSIS AT KENYATTA NATIONAL HOSPITAL

Variable	Frequency (%)
Formulation Prescribed	
Adult tablet	8 (8.3)
Paediatric tablet	11 (11.3)
Not indicated	78 (80.4)
Vitamin B6 supplementation prescribed?	
Yes	16 (16.5)
No	81 (83.5)

The dosages for the individual drugs as per the fixed dose tablets prescribed were calculated for all the patients. Taking into consideration the fact that the formulations were not specified in a majority of the prescriptions as shown above, we sought to establish from the parents/caretakers in the wards, the particular formulation been administered to their child. This was done by way of demonstration of the two available formulations and asking them to choose one. Where this was not possible, we relied on the information by the nurses in the wards. We established that the paediatric formulation is what is routinely available in the wards. Thus, for all prescriptions done without specification of the formulation, the nurses would administer the paediatric dispersible tablets. The calculations below were done after the consideration of all these factors.

The appropriateness of the dosages was checked as per the Kenyan guidelines and also as per the WHO recommendations as shown in table 7a and 7b below.

TABLE 7A: INDIVIDUAL DRUG DOSAGE CALCULATIONS BASED ON THE WEIGHT IN THE TREATMENT RECORDS

Drug	Dosage As per Kenyan Guidelines, June 2009			**Total**	Dosage As per the WHO Recommendations , Sept 2009		
	Appropriate	Under-dose	Over-dose		Appropriate	Under-dose	Over-dose
Rifampicin	42 (43.8)	15 (15.6)	39 (40.6)	**96**	56 (58.3)	30 (31.3)	10 (10.4)
Isoniazid	27 (28.1)	27 (28.1)	42 (43.8)	**96**	11 (11.5)	82 (85.4)	3 (3.1)
Pyrazinamide	43 (45.3)	15 (15.8)	37 (38.9)	**95**	21 (22.1)	58 (61.1)	16 (16.8)
Streptomycin	1 (11.1)	2 (22.2)	6 (66.7)	**9**	-	-	-
Ethambutol	5 (83.3)	-	1 (16.7)	**6**	5 (83.3)	-	1 (16.7)

The table above shows that, of the three drugs commonly prescribed for the patients recruited, pyrazinamide was the best in terms of dosing as per the Kenyan guidelines, albeit with only 43 (45.3%) patients receiving appropriate dose. This was followed by rifampicin and isoniazid with correct dosage recorded in 42(43.8%) and 27 (28.1%) patients respectively. On individual basis, all the three key antimicrobials were incorrectly prescribed in approximately 60% of the patients for rifampicin and pyrazinamide and 73% for isoniazid.

When compared with the WHO recommendations, rifampicin performed best with 56 (58.3%) patients having correct prescriptions. The dose of Ethambutol, when prescribed, was incorrect in only 16.7% of the patients.

Table 7b below shows a trend similar to that seen and described in table 7a above. The degree of under-dosing was however higher for all the individual drugs. This is to be expected because the difference in the weights taken at the time of study as compared to the weights in the records, as discussed above.

TABLE 7B: INDIVIDUAL DRUG DOSAGE CALCULATIONS BASED ON THE WEIGHTS TAKEN AT THE TIME OF THE STUDY

Drug	Dosage As per Kenyan Guidelines, June 2009			**Total**	Dosage As per the WHO Recommendations , Sept 2009		
	Appropriate	Under-dose	Over-dose		Appropriate	Under-dose	Over-dose
Rifampicin	40 (41.2)	20 (20.6)	37 (38.1)	**97**	50 (51.5)	39 (40.2)	8 (8.2)
Isoniazid	22 (22.7)	36 (37.1)	39 (40.2)	**97**	10 (10.3)	86 (88.7)	1 (1.0)
Pyrazinamide	41 (43.2)	20 (21.1)	34 (35.8)	**95**	23 (23.7)	57 (58.8)	15 (15.5)
Streptomycin	3 (30)	2 (20)	5 (50)	**10**	-	-	-
Ethambutol	5 (83.3)	-	1 (16.7)	**6**	5 (83.3)	-	1 (16.7)

Analysis was done to establish if there was any association between the appropriate dosages of one drug as compared to another. The main aim was to see if the fixed dose formulations used were possibly to blame for the incorrectness of the calculated doses. Table 8 below shows that if the dose of rifampicin was appropriate, there was a high chance that the doses of INH and PZA were appropriate too, p value <0.001.

TABLE 8. ASSOCIATION BETWEEN THE DOSE OF RIFAMPICIN WITH THE DOSE OF ISONIAZID AND PYRAZINAMIDE (KENYAN GUIDELINES JUNE 2009)

Drug	**RIFAMPICIN**		**p – value**
	Appropriate	**Inappropriate**	
INH			
Appropriate	27 (64.3%)	0 (0.0%)	<0.001
Inappropriate	15 (35.7%)	54 (100.0%)	
PZA			
Appropriate	40 (95.2%)	3 (5.7%)	<0.001
Inappropriate	2 (4.8%)	50 (94.3%)	

The ideal prescription is where a patient receives all individual drugs in their correct dosages as recommended. Table 9 was generated after analysis was done to establish the proportion of patients with this degree of appropriateness. It is evident that only 21 (21.6%) of the 97 patients received the correct dose of all the individual anti-tuberculosis drugs, leaving 75 (77.3%) with incorrect prescriptions. The number of patients with incorrect dosage rose to 78 (80.4%) when the dosage was recalculated using the weight taken at the time of the study.

None of the patients had the correct dosage for all the individual drugs when comparison was done as per the WHO recommendations.

TABLE 9: OVERALL APPROPRIATENESS OF DOSAGE OF ANTI-TB DRUGS

Variable	**Appropriateness As per Kenyan Guidelines June 2009.** **Frequency (%)**
Doses as per treatment records	
Appropriate	21 (21.6)
Inappropriate	75 (77.3)
Not indicated	1 (1.0)
Doses at the time of study	
Appropriate	19 (19.6)
Inappropriate	78 (80.4)

6.5 DETERMINANTS OF APPROPRIATENESS

The appropriateness of the dosages was then tested to establish if there was any association with various variables as shown below. This was done for calculated doses as per the weight recorded at the initiation of therapy, table 10a, and also as per the weight taken at the time of the study, table 10b. The guidelines as per the Kenyan Ministry of Public Health and Sanitation were taken as the gold standard for purposes of these comparisons.

Table 10a below shows that the various parameters had no statistically significant influence on the appropriateness or otherwise of the dosage of anti-tuberculous drugs.

TABLE 10A: COMPARISON TABLE TO ESTABLISH DETERMINANTS OF DOSE APPROPRIATENESS AS PER TREATMENT RECORDS

Variable	Appropriate doses		P value
	Yes	No	
Age group			
1-12 months	11 (52.4%)	30 (40.0%)	0.581
1-5 years	4 (19.0%)	20 (26.7%)	
>5 years	6 (28.6%)	25 (33.3%)	
Sex			
Male	14 (66.7%)	36 (48.0%)	0.130
Female	7 (33.3%)	39 (52.0%)	
Ward			
3A	5 (23.8%)	17 (22.7%)	0.881
3B	3 (14.3%)	10 (13.3%)	
3C	7 (33.3%)	20 (26.7%)	
3D	6 (28.6%)	28 (37.3%)	
Diagnosis			
Pulmonary TB	10 (47.6%)	46 (61.3%)	0.516
TB meningitis	8 (38.1%)	21 (28.0%)	
Others	3 (14.3%)	8 (10.7%)	

Table 10b below shows that the patients in ward 3B were significantly more likely to get correct dosage of anti-tuberculous drugs, p value 0.038. Of all the incorrect prescriptions among the patients studied, only 7 (9%) originated from ward 3B as compared to ward 3D which contributed 32 (41.0%) of the incorrect prescriptions. The difference in number of the patients from each ward when re-analyzed did not change the performance.

TABLE 10B: COMPARISON TABLE TO ESTABLISH DETERMINANTS OF DOSE APPROPRIATENESS BASED ON THE BODY WEIGHTS AT THE TIME OF STUDY;

Variable	Appropriate doses		P value
	Yes	No	
Age group			
1-12 months	8 (42.1%)	33 (42.3%)	1.000
1-5 years	5 (26.3%)	19 (24.4%)	
>5 years	6 (31.6%)	26 (33.3%)	
Sex			
Male	9 (47.4%)	42 (53.8%	0.612
Female	10 (52.6%)	36 (46.2%)	
Ward			
3A	4 (21.1%)	18 (23.1%)	0.038
3B	6 (31.6%)	7 (9.0%)	
3C	6 (31.6%)	21 (26.9%)	
3D	3 (15.8%)	32 (41.0%)	
Diagnosis			
Pulmonary TB	8 (42.1%)	48 (61.5%)	0.192
TB Meningitis	9 (47.4%)	21 (26.9%)	
Others	2 (10.5%)	9 (11.5%)	

6.6 DISCUSSION

The treatment records of 97 patients were studied and analyzed as indicated above. There was one multi-centre study by Diop et al [40] done previously and with objectives similar to this study. This is discussed below. There are a number of other studies which have looked at the knowledge, altitude and practices of health care workers about the treatment of tuberculosis in children as shall be discussed below [36, 37].

There were no drop outs reported, mainly because this was a cross sectional study which did not require follow-up.

The main findings were as follows;

6.6.1 DOSAGE GUIDELINES

From the literature review, it was evident that the Kenyan Guidelines were not consistent with the recommendations by the WHO made almost two years before this study was carried out (table 2). There is enough evidence to support the fact that higher doses for both Isoniazid and Rifampicin are needed to achieve the recommended plasma peak levels of the individual drug. The study by Mclleron et al [30] illustrates the fact that the dose of isoniazid of 4-6 mg/kg recommended by the Kenyan guidelines is way below the ideal.

Mclleron H. et al [30] studied isoniazid concentrations in 56 hospitalized children (median age, 3.22 years; IQR 1.58–5.38 years) who received isoniazid daily (median dosage, 5.01 mg/kg/day; range, 2.94–15.58 mg/kg/day) as part of anti-tuberculosis treatment. This was done at the Brooklyn Hospital for Chest Diseases in Cape Town, South Africa. They found that the median peak concentrations of isoniazid in children prescribed a dose of 4–6 mg/kg were 58% lower than those in children prescribed a dose of 8–10 mg/kg (2.39 mg/L [IQR, 1.59–3.40] vs. 5.71 mg/L [IQR, 4.74– 7.62]). Peak concentrations were <3 mg/L in 70% of children prescribed a dose of 4–6 mg/kg. In contrast, children prescribed a dose of 8–12 mg/kg achieved peak concentrations approximating those in adults treated with 300 mg of isoniazid daily.

The conclusions were that younger children require higher doses of isoniazid per kilogram of body weight to achieve isoniazid concentrations similar to those in adults. A daily isoniazid dose of 8–12 mg/kg should thus be recommended in order to achieve and maintain peak plasma concentration for INH above the lower limit of 3 mg/L.

A study done in Western Cape Province of South Africa by H S Schaaf et al [41] showed similar results as above. They studied 64 children with a median age of 3.8 years (lower quartile 1.8 years, upper quartile 7.8 years), majority of who had a diagnosis of primary respiratory tuberculosis. Four blood specimens of 1–1.5 ml each, taken at 2, 3, 4, and 5 hours post-dose of isoniazid were used to determine the serum concentrations of INH. The results led to the conclusion that children less than 5 years of age should receive an INH dose of at least 10 mg/kg.

These studies formed the basis for the current recommendation by the WHO of the dosing of INH in children at 10-15 mg/kg [30]. It would be prudent for the relevant division in the Kenyan Ministry of Public Health and Sanitation to look at the WHO recommendations and expedite the process of adopting them as local guidelines.

6.6.2 DEMOGRAPHICS

From the demographic data of the patients recruited into this study, it was found that infants formed a large proportion, 42.3%, as compared to the other age groups. Although this study was not aimed at establishing the susceptibility of patients to TB disease per se, it would appear that younger children are more likely to develop TB disease. This is as demonstrated by Marais et al [5] and is also shown in table 1 above.

6.6.3 DIAGNOSIS

Pulmonary tuberculosis contributed to majority, 57.7% of the diagnosis among the patients recruited into the study. This is as expected, though the percentage is less than reported in the general population of children with tuberculous disease. In South Africa, 70% of children with TB have intra-thoracic disease [42]**.** The reason for this difference is possibly the fact that the current study was done in an in-patient setting of a tertiary hospital hence a bias towards the severe forms of the disease. This also explains the high number of patients with a diagnosis of TB meningitis, representing 30.9% of the 97 patients recruited. An audit of the diagnostic criteria used could however be useful in establishing whether these cases were suspected or actual cases of TBM.

6.6.4 WEIGHT

During the calculation of anti-tuberculous drugs, and largely true for all drugs in paediatrics, establishing the correct weight of the patient is paramount. It thus has to be taken accurately and dosages adjusted accordingly as the weight changes. From the study, it was evident that there was a significant weight difference, p-value <0.004, between the weight in the treatment records and the weight taken at the time of the study, as shown in table 5b. The children were heavier at the time the study was done. When the dosing of the anti-TB drugs was calculated, this resulted in a lower degree of appropriateness, 19.6 % as compared to 21.6% as shown in table 10a. This difference was however not statistically significant.

The weight difference can best be explained by the expected weight gain among the children once the TB treatment has been initiated.

The WHO recommends that all children being treated for tuberculosis should be weighed at least once every month to allow for adjustment of dosage administered as necessary [43].

6.6.5 DOSAGE

The overall dosing of anti-TB drugs was found to be appropriate in only 19.6% of the patients. This reveals that majority, 4 out of 5, of the paediatric patients on treatment for tuberculosis at KNH received inappropriate dosage of anti-TB drugs. The reason for this poor performance in dosing was not clear. The current study was not designed to look for factors contributing to the inappropriateness of the prescriptions.

There was no study found to have been done previously calculating the actual dosage, specifically in children, as done in our study. The study conducted by Diop et al [40] in 1996 and discussed below looked at the accuracy of dosages both in adults and in children, with the children being 8% of the 5575 patients in studied in Kenya. However, a number of other studies have looked at the knowledge altitude and practice of doctors involved in the management of tuberculosis.

Diop, H et al [40] conducted a multicentre study in Kenya, Nepal and Senegal to check on the Dosages of anti-tuberculous medications in the national tuberculosis programs of each of the three countries. The methodology involved collection of patient treatment cards in a representative sample of treatment centers in Kenya, Nepal, and Senegal. They then proceeded to calculate drug dosages in milligram per kilogram body weight of isoniazid, rifampicin, and pyrazinamide and did a comparison with international recommendations for dosage of these medications. The final analysis involved 5575 treatment cards in Kenya, 612 in Nepal, and 2453 in Senegal. Children aged less than 15 years of age accounted for 8% of patients in Kenya, 1% in

Nepal, and 2% in Senegal. It was found that of those patients whose records were analyzed, 6.2%, 0.4%, and 1.0% in Kenya, Nepal, and Senegal, respectively, were not prescribed a nationally recommended treatment regimen (only two drugs or, rarely, mono-therapy were recorded). Thus, comparatively Kenya's performance was not as good as in the other two countries.

This study reported more of an overdose problem. The rate of under-dosing in their study was minimal at 4.8%, 5.8% and 1.5% reported for rifampicin, isoniazid and pyrazinamide respectively. In the current study, the error was both ways as shall be discussed below.

In the current study, isoniazid dosing was accurate in 22.7% of the treatment records analyzed. Among the Kenyan participants in the study by Diop et al, it was found that INH was given in correct dosage in 33.7% of the patients. In Nepal and Senegal a correct dosage was given to less than 15% of patients. The current study reported the dose of rifampicin as correct in 41.2% of the patients. This is low compared to the 76.5% reported by Diop et al who found that Rifampicin was the medication found to be most frequently within the therapeutically recommended range. Pyrazinamide was correct in numbers similar to those of rifampicin in our study. Diop et al however, reported a high proportion of over-dosing at 73.6%.

The numbers of patients on Ethambutol in the current study was small and thus no comparisons can be made.

Ayaya [36] et al, in a study done at Eldoret Kenya, interviewed 53 doctors in private practice. This was a cross-sectional descriptive qualitative study aimed at determining the knowledge, attitudes, and practices (KAP) of private medical practitioners in Eldoret on the management of TB. Specifically, they aimed at establishing the knowledge of the doctors regarding;

i. The recommended schedule of sputum collection as per the Kenyan guidelines.
ii. The criteria used for the diagnosis of tuberculosis, both in adults and children.
iii. The regimes recommended and used for the treatment of TB in children and adults.

The National Leprosy and TB Programme at the time recommended regimes such as 2RHZ/4RH, 2RHZE/6HE, 2RHZ/6HE and 2SHRZE/1RHZE/5HRE. These regimens were used by 9(19.6%), 2(4.3%), 0% and 0% of the doctors respectively. The rest used un-recommended regimens [36].

None of the interviewees had appropriate knowledge on all the areas of diagnosis, treatment, case recording, and follow up.

Their conclusion was that most doctors were not aware of the correct diagnosis and treatment of TB and many used un-recommended treatment regimes, and recommended that continuing medical education on clinical management of TB patients was needed for doctors in private practice.

From the above study, it can be inferred that only 24% of the patients under the care of the doctors at Eldoret were likely to receive a prescription with the correct regimen as recommended. The dosage calculation was however not tested in this study to enable us to compare with our results which show that only 20% of the patients actually received the correct dosage.

In Somalia, a study carried out by Suleiman et al [37] revealed even more disturbing results. Fifty three doctors were interviewed in. Of these, 32 (64%) had treated TB patients during the previous year, but only 1 had notified the authorities, 33 (66%) knew the most important symptoms and 32 (64%) identified sputum smear microscopy as the most important diagnostic test. Only 4 doctors prescribed the correct regimen and only 7 advocated DOTS. The conclusion was that few doctors follow national treatment guidelines. The reason was not established.

The studies above, together with our study demonstrate clearly that the treatment of tuberculosis in the various areas of study is not optimal. The degree of inaccuracy differs from 93% in Somalia, through 80.4% in KNH to the different percentages as discussed in the study by Diop et al above.

It would be of great importance to do similar studies on the knowledge, altitude and practice among the doctors working in the paediatric wards of KNH and to compare the outcome with the other studies. This could possibly shed some light on some of the factors that contribute to the in-appropriateness of dosing as demonstrated in our study.

Previous studies have always demonstrated a better performance in the public hospitals as compared to the private practitioners. Vandan, N et al [39] conducted a study to assess the knowledge of doctors in the public and private sectors regarding TB control and management. The study was done in India, which tops the list of 22 high-burden tuberculosis (TB) countries. The study used a self-reported questionnaire based on the operational guidelines. One hundred and forty-one doctors were recruited through census sampling; all were registered with the Chest Physicians Association and treating TB using allopathic medicine, and 71% had specialized medical education for treating TB. Public sector doctors demonstrated better knowledge of drug regimens for sputum smear-positive and sputum smear-negative TB than private sector doctors. Sixty-six (84%) doctors from the public sector and 41 (66%) doctors from the private sector reported the same drug regimen for TB as mentioned in the guidelines. Statistical analysis indicated that doctors in the public sector had 2.1 times better knowledge than private sector doctors (odds ratio 2.1; P=0.05). The high levels of knowledge elicited here could be due to the fact that a large number of the doctors had specialized training in the management of TB.

It would be expected that KNH, a National Teaching and Referral Hospital would perform better than was found in our study.

Each of the four paediatric wards of KNH had at least one copy of the Kenyan National guidelines on the management of tuberculosis displayed on its notice board. It would have been our expectations that all the doctors refer to these charts as they write the prescriptions for the anti-tuberculous drugs. From the results of this study, it is evident that this did not happen. We were not able to establish the reason for this failure to utilize guidelines.

The error in dosing was found to be both in over- and under-dosing as shown in table 8b.

The danger of over-dosage of individual anti-tuberculous drugs is their toxicity, in particular hepatotoxicity due to rifampicin, isoniazid and pyrazinamide and optic nerve toxicity due to Ethambutol. From the study, 38.1% and 40.2% of the patients received an overdose of Rifampicin and Isoniazid respectively. Children are known to suffer fewer adverse effects to anti-TB medications as compared to adults, possibly the reason why there was no alarming presence of clinically evident adverse drug reactions. Of note, however, is that due to the WHO advocacy for higher dosage of the two drugs above, the incidence of overdosing as per the WHO Sept 2009 recommendations is much lower at 8% and 1% for rifampicin and isoniazid respectively. This is however no reason for complacency on the adherence to guidelines.

Similarly, under-dosing of anti-tuberculous drugs is equally dangerous. Lower than adequate dosages carry the risk of sub-inhibitory drug concentrations, which might be one of the possible mechanisms responsible for the development of drug resistance. When calculated, rifampicin and isoniazid were found to be under-dosed by 20% and 36% respectively. This was even worse when calculated as per the WHO recommendations, showing an under-dose of 39% and 86% for rifampicin and isoniazid respectively.

From the data collected, those children on management for tuberculosis in ward 3B were more likely to get a correct dosage prescribed compared to patients in the other three wards of the same hospital. The four general paediatric wards are fairly similar in the organizational and management structures. One would thus expect a uniform performance in all aspects of patient management, prescribing habits included. However, there may be factors that we were not able to control for. This could include supplies and variations in personnel in terms of numbers and specialized training. A possible critical factor is the high turn-over rate of doctors in the paediatric wards. This is so because the clinical officers, medical officer interns and paediatric SHOs work on a three month rotational basis. It might thus call for regular continuous medical education and strict supervision of the junior doctors.

When associations were sought between the inappropriateness of the anti-TB dugs dosage and various clinical and demographic factors, none was found. The dosage was not influenced by the age, sex or the diagnosis (pulmonary or extra-pulmonary) of the patient.

7 CONCLUSIONS:

From the results presented above, the following conclusions were made:

1. Of the 97 patients in the study, only 19 (19.6 %) of the patients had the correct dosage for all individual anti-tuberculous drugs prescribed, leaving 80.4% of the patients with inappropriate dosage. In other words, four out of every five paediatric patients on treatment for tuberculosis in the general wards of KNH received inappropriate doses of the anti-tuberculous drugs.
2. The weight of the patients at the beginning of therapy was either not done correctly or it was carried forward during the stay in the ward, thus not correcting for the anticipated weight gain after initiation of therapy. This was demonstrated by the significant difference noted when compared to the weight taken at the time of stay, p value 0.004.
3. Ward 3B performed better than the other three wards, p value 0.038.
4. The inappropriateness of the dosing was not influenced by the age or sex of the patient and neither was it influenced by the severity of the patient's disease.
5. Vitamin B6 supplementation was done in only 16.5% of the patients on isoniazid.

8 RECCOMENDATIONS

From the conclusions above, and based on the observations made at the time of the study, the followings are the recommendations we make;

1. A study should be conducted to establish the knowledge, attitude and practice of the doctors and nurses working in the Department of Paediatrics at KNH. If there are gaps identified, then training sessions should be organized to address them.

2. Another study should be done to establish the serum drug levels of the various anti-tuberculous drugs among the children on treatment for tuberculosis. This would establish the degree of variation, if any, of the serum levels from the recommended therapeutic drug levels.

9 REFERENCES:

1. **Rubin SA**. Tuberculosis—Captain of all these men of death. Rad Clin N Am 1995; 33:619–639.
2. **Marais BJ**, Hesseling AC, Gie RP, Schaaf HS, Beyers N. The burden of childhood tuberculosis and the accuracy of routine surveillance data in a high burden setting. Int J Tuberc Lung Dis 2006; 10:259–263
3. **Donald PR**. Childhood tuberculosis: The hidden epidemic. Int J Tuberc Lung Dis 2004; 8:627–9.
4. Global tuberculosis control: A short update to the 2009 report. "WHO/HTM/TB/2009.426".
5. **Marais BJ**, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Starke JJ,Enarson DA, Donald PR, Beyers N. The natural history of disease of childhood intra-thoracic tuberculosis: A critical review of the prechemotherapy literature. *Int J Tuberc Lung Dis* 2004; 8: 392–402.
6. **Eamranond P**, Jaramillo E. Tuberculosis in children: Reassessing the need for improved diagnosis in global control strategies. Int J Tuberc Lung Dis 2001; 5:594–603
7. **Starke JR**. Paediatric tuberculosis: Time for a new approach. Tuberculosis 2003; 83:208–12
8. **Zar HJ**, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. Lancet 2005; 365:130–4
9. Guidance for National Tuberculosis Programmes on the management of tuberculosis in children. Stop TB, chapter 1: Introduction and diagnosis of tuberculosis in children. Stop TB Partnership Childhood TB Subgroup. Int J Tuberc Lung Dis 2006; 10:1091
10. **Coulter**. J. B. S. Diagnosis of pulmonary tuberculosis in young children. Annals of Tropical Paediatrics (2008) 28, 3–12
11. **Osborne C. M**. The challenge of diagnosing childhood tuberculosis in a developing country. Archives of Disease in Childhood 1995; 72: 369-374.
12. World Health Organization. WHO vaccine-preventable diseases: monitoring system. Global summary; 2006. World Health Organization, Geneva, 2006

13. **Trunz BB**, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet 2006; 367: 1173-80
14. **Colditz GA**, Berkey CS, Mosteller F, et al. The efficacy of bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. Pediatrics 1995; 96: 29-35
15. World Health Organization. Report of the meeting on TB medicines for children. July 2008. World Health Organization, Geneva 2008
16. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), second edition. Tuberculosis Coalition for Technical Assistance, The Hague, 2009.
17. **Fox W**. The John Barnwell Lecture. Changing concepts in the chemotherapy of pulmonary tuberculosis. American Review of Respiratory Disease, 1968, 97:767–790.
18. **Tyrrell W F**. Bed rest in the treatment of pulmonary tuberculosis. Lancet, 1956, 1:821–823.
19. **Schatz A**, Bugie E, Waksman SA. Streptomycin, a substance exhibiting antibiotic activity against Gram-positive and Gram-negative bacteria. Proceedings of the Society of Experimental and Biological Medicine, 1944, 55:66–69.
20. **Waksman SA**, Bugie E, Schatz A. Isolation of antibiotic substance from soil microorganisms with special reference to streptothricin and streptomycin. Mayo Clinic. Proc 1944;19:537-48.
21. British Medical Research Council. Treatment of pulmonary tuberculosis with streptomycin and para-amino-salicylic acid: a Medical Research Council Investigation. Br Med J 1950;2:1073-85
22. British Medical Research Council. Treatment of pulmonary tuberculosis with isoniazid: an interim report to Medical Research Council by their Tuberculosis Chemotherapy Trials Committee. Br Med J 1952; 2:735-46.
23. **Newman R**, Doster B, Murray FJ, Ferebee S. Rifampin in initial treatment of pulmonary tuberculosis. Am Rev Respir Dis 197 1; 103:46 l-76.

24. **Sense P**. History of the development of rifampicin. Respiratory and Infectious Disease, 1983, 5:402–406.
25. East African/British Medical Research Council. Controlled clinical treatment of short course (6 months) regime of chemotherapy for treatment of pulmonary tuberculosis. Third report. Lancet, 1974, 2:237–248.
26. **Fox W,** Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. International Journal of Tuberculosis and Lung Disease, 1999, 3:S231–S279.
27. World Health Organization. The stop TB strategy: Building on and enhancing DOTS to meet the TB-related Millennium Development Goals. WHO/HTM/TB/2006.368
28. Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC). The Hague: Tuberculosis Coalition for Technical Assistance, 2006.
29. World Health Organization. Treatment of tuberculosis: guidelines – 4th ed. WHO/HTM/TB/2009.420
30. **Mclleron, H**. Willemse, M ,Werely CJ. Isoniazid Plasma Concentrations in a Cohort of South African Children with Tuberculosis: Implications for International Paediatric Dosing Guidelines. Clin Infect Dis. 2009; 48:1547-53.
31. Ministry of Public Health and Sanitation; Guidelines for TB and leprosy control. June 2009.
32. **Marais, B. J**. Graham, S. M. Cotton, M.F, Beyers, N. Diagnostic and Management Challenges for Childhood Tuberculosis in the Era of HIV. The Journal of Infectious Diseases 2007; 196:S76–85
33. **Alimuddin** Z. et al. The tuberculosis pandemic: Implications for health in the tropics. Transactions of the royal society of tropical, medicine and hygiene (1999) 93,113 - 117.
34. **Williams G**, Alarcon E, Jittimanee S, et al. Best practice for the care of patients with tuberculosis: A guide for low-income countries. Paris, France: International Union Against Tuberculosis and Lung Disease, 2007.
35. **Dye C** et al. Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally. Journal of the American Medical Association, 2005, 293:2767–2775.

36. **Ayaya SO**, Sitienei J, Odero W, Rotich J. Knowledge, attitudes, and practices of private medical practitioners on tuberculosis among HIV/AIDS patients in Eldoret, Kenya. East Afr Med J. 2003. 80:83-90.
37. **Suleiman BA**, Houssein AI, Mehta F, Hinderaker SG. Do doctors in north-western Somalia follow the national guidelines for tuberculosis management? East Mediterr Health J. 2003. 9:789-95.
38. **Vandan N,** Ali M, Prasad R, Kuroiwa C. Physicians' knowledge regarding the recommended anti-tuberculosis prescribed medication regimen: a cross-sectional survey from Lucknow, India. Southeast Asian J Trop Med Public Health. 2008 Nov; 39:1072-5.
39. **Vandan N**, Ali M, Prasad R, Kuroiwa C. Assessment of doctors' knowledge regarding tuberculosis management in Lucknow, India: a public-private sector comparison. Public Health. 2009;123:484-9.
40. **Diop, H. et al**. Dosages of anti-tuberculosis medications in the national tuberculosis programs of Kenya, Nepal, and Senegal. Int J Tuberc Lung Dis 2002; 6:215–221
41. **Schaaf,HS,** Parkin,D, Seifart, H, Isoniazid pharmacokinetics in children treated for respiratory tuberculosis. Arch Dis Child 2005;90:614-618
42. **Marais, B.J**, Hesseling, A. C. Gie, R. P., Schaaf H. S. The Bacteriologic Yield in Children with Intra-thoracic Tuberculosis. Clinical Infectious Diseases 2006; 42:69–71.
43. World Health Organization. Dosing instructions for the use of currently available fixed-dose combination TB medicines for children -September 2009

10 APPENDIXES

APPENDIX 1; PROFORMA:

1. Biophysical data. (Interview the parent or primary caretaker for information on age of the patient).

   Study Number of patient ……

   Sex (Male/Female) ……

   Date of birth (dd/mm/yy) - (be exact) ……

   Ward ……

2. Weight of patient

   i. At start of treatment ……. kg

   ii. Current weight ……..kg

3. Check the patient's treatment records (TB card or in-patient file and treatment sheet) and extract the following information.

   i. Diagnosis – *circle one.*

      a. Pulmonary tuberculosis

      b. Tuberculous adenitis

      c. Tuberculous meningitis

      d. Others – specify ……..

   ii. Regimen prescribed – indicate the prescription as per the treatment record.

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   iii. Date intensive phase of treatment started ----------

   iv. Date continuation phase of treatment started ----------

   v. Health facility where the treatment was initiated ----------

4. Dose of anti-TB drugs used – check with the parent/caretaker.

   i. Formulation – is it specified? ……..

   ii. Number of tablets per day …….

5. Is patient on vitamin B6 supplementation? Yes/No

APPENDIX 2; CONSENT EXPLANATION FORM

I am Dr. Paul Mutua Musila, a post graduate student doctor at the college of Health Sciences, University of Nairobi carrying out a study on the appropriateness of TB treatment among children in KNH.

The study aims to assess if all children on treatment for TB at KNH are receiving the correct medicine and in the correct dosage or not.

If you agree for your child to be a part of this study, I will take a short history to establish his/her age, date and place where treatment was initiated. I will proceed to weigh your child. I will then proceed to examine the child's medical records to extract further information to assist me in establishing the correctness or otherwise of the prescription.

The benefit of the study is that, if any errors are identified in the prescription, the doctor shall be given a feedback as soon as possible to rectify as per the established guidelines. This feedback will be of help not only to your child but to other children to be treated for tuberculosis in future.

There shall be no further tests done on your child other than what the doctors will already have done. Thus no pain/harm shall come onto your child as a result of been part of the study.

Participation in this study is voluntary. If you decline to participate, your child shall continue to receive treatment in KNH without any form of discrimination.

My contacts are

Dr. Paul M. Musila

P.O Box 8365 -00100 Nairobi

Tel. No. 0722 256 372

If you have any questions later, you are free to contact me or you can get in touch with the Chairperson of the KNH Ethics and Research Committee on telephone no. 2726300 ext 44102.

APPENDIX 3: CONSENT FORM;

I ……., been the parent/guardian of the child serial number ….., hereby do give permission for my child to be enrolled in the study titled '' Appropriateness of drug prescriptions among children on treatment for tuberculosis at Kenyatta National Hospital Nairobi, Kenya''.

All the issues pertaining to the study have been explained to me to my full understanding. I am aware that it is purely on a voluntary basis that my child is getting enrolled and that I can choose to pull out of the study at anytime I deem necessary to do so.

I also appreciate the fact that declining to enroll my child for the study and/or opting out at any stage of the study will not in any way compromise the care, medical or otherwise, that my child is entitled to while on treatment at Kenyatta National Hospital.

Signed, ……

Name - ……

Relationship to child ----------

Signature of witness ----------

Name of witness ----------