Tuberculosis in Children and Adolescence in North Norway

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Emiru Fufa Kanaa

Kull 2011

Veileder:

Professor Claus, Klingenberg

Institutt for klinisk medisin

Seksjonsoverlege ved barneavdeling, UNN

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Preface

After receiving information on 5th year medical school thesis, I started finding what I am going to write. I had an Idea of writing about children and contacted my adviser, but my idea had some difficulties regarding measuring variables and ethical consideration. I was happy to get consent from professor Claus Klingenberg, Consultant in Pediatric at University Hospital in North Norway (UNN) to advice me on this project. After some meeting, we found that it will be unrealistic for this short time thesis. Professor Claus had a project on childhood tuberculosis for children under15 years treated at the university hospital. I grasped at once because I had experience in tuberculosis. When I was a fifth and sixth-grade student, I had a classmate who had tuberculosis. We sat together every day for more than 6 hours on the same bench all the working days. Neither my teachers nor I was aware of the communicable nature of tuberculosis. My father was diagnosed with tuberculosis when I was in ninth-grade, and he received 60 injections and took his drugs daily at the local clinic. No free day for treatment and I was following him when I was not at school. My father recovered and lived 30 more years. Unfortunately, my younger brother, Endalu, contracted tuberculosis at age 8 and did not survive the prolonged treatment. I supposed the literature gives me what went wrong. I know there was no word on child-friendly treatment and diagnostic work-ups in those days for poor Ethiopian families. I have lived and worked, in overcrowded places including refugee camps Kakuma, Kenya. I cannot reason out how I escaped tuberculosis in Ethiopia and Kenya. So writing on tuberculosis was not a mere a reading and writing, but I was emotionally connected because it involved my family and close friends.

My greatest thanks goes to all my friends and families who encouraged me under this strenuous process. I was encouraged by my daughters Nabek and Nanae, who also asked me why I won`t be a physician while I was working as a nurse.

My greatest gratitude goes to Professor Claus Klingenberg, who has made me to rethink and gain knowledge about an old disease which still exists. Professor has taken a good deal of precious time to assist me shape and sort my ideas on this Paper. I am ever thankful for his guidance and advice to write this paper.

Abstract

This objective of this thesis is to gain knowledge in tuberculosis in children and adolescent for ten years period from 01.01.05- 31.12.14 at the University Hospital of North Norway. The study was to answer the following questions: the number patients treated for latent and active tuberculosis in 10 years period of, the debut age for symptoms and treatment, the diagnostic methods the choice of treatment and follow-ups. Retrospective study method is used. Data is collected for 24 variables designed to answer the relevant question. There were 240 patient journals were studied. 13 of them 240 were excluded because of the age limit.

Results: The main findings were (1) Most of the tuberculosis among children in North Norway is latent tuberculosis. (2) The majority of the children with tuberculosis are born foreign born Children (3) Patients with tuberculosis disease were treated adequately (4) IGRA used a diagnostic methods.

Conclusion: Futher study is needed to change the current practice of tuberculosis manangement at UNN and future study should have access to DIPS patient electronic journals at other hospitals in the region and get the access of contacting the local primary care when needed. Some modifications of the variables are also necessary

Project process

Four weeks were used to make a proposal for the project. The project design was constructed because my adviser. My adviser applied to ethic committee so that I get permission to access to electronic patient journal at University Hospital –UNN; The plan was to collect data in 2015 before departure to the five the year practice in community and at local hospitals. Because we are delayed to get permission to get access to data, I could not do with the data collections until March 2016. My Adviser has tried to get the permission; we got the patient list from microbiology department.

I read about the topic between summer 2015 and March 2016 when I district practice. Though I was trying to work on the theoretical del, my lack of experience in this writing has hampered me.

After getting the access to data in t March 2016, I submitted proposed variable to my adviser. I worked on finding the variable in the course of reading. My adviser modified the variables, and I started to collect data. After some days in data collection, I found that most of the patients did not have documentation. Some had only some test result. I was frustrated because my design and planning were facing obstacles. There came a dilemma on how I can proceed with few data. My adviser was helpful and advised me to make use of what I get from data.

While working with data, my computer refused to accept with SPSS, and it stuck for more than a week. After solving the problem, I kept on writing and trying to analyse the little data I had. Finally, I had a draft which my adviser read it, and I got comments on what I have to focus. I was happy to be in track, but suddenly my Endnote program become corrupted, and I had inconveniences with the literature. Much of my aid was spent on the technical aspect of the thesis, and it has affected my chances using time on the contents, and I could contact my adviser as I was supposed, and I could not be through the writing

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1 Introduction

1.1 Short Overview

When Robert Koch found the Mycobacterium, the world believed that threat caused by tuberculosis is comes to end. The years after then great discovery were followed by finding treatment for tuberculosis. The world must wait many years for the coming of streptomycin and other treatment. Parallel to progress in medicine, the social and economic development also advanced. The combination biomedical therapy and living status started to reduce the strength tuberculosis infection. Tuberculosis started declining the western countries until 1980. There was little engagement with the research society after finding four drugs for tuberculosis. The beginning of HIV-infection shifted the direction of tuberculosis disease. No more decreasing but increasing cases. The globalization and immigration have mobilized Tuberculosis across the different region. There is no country without tuberculosis today.

Tuberculosis is everywhere, though the poor countries who have more cases. The incidence of tuberculosis was increasing in Africa and Asia, but in East European countries drug resistant was emerging. With increased globalization, Norway is also expected to share the burden of tuberculosis. Tuberculosis in Norway was very low, by the begging of 1990. But now there are 324 in 2014 in the total population. How the disease in North Norway the last ten years? This thesis attempts to describe tuberculosis in children and adolescent in North Norway for the last 10 years. I propose to find situation by retrospective study method where I utilize the existing the literature-to present the theoretical background of tuberculosis and analysing data from University Hospital of North Norway from 01.01.05 - 31.12.14. I think u descriptive statistic will beneficial in analysing the data to come to end result.

1.2Terminology and abbreviations

Mycobacterium (Mtb): Mycobacteria are immobile, slow-growing rod-shaped gram- positive bacteria. It also displays some properties of gram-negative bacteria. Their thick cell wall and its nature displays colour when stained and washed by alcohol. The name acid-fast is given to because the especially colour remains after washing it with alcohol.

Mycobacterium tuberculosis complex (MBTC): Are subspecies of Mycobacterium, which consists groups, which cause disease in humans and other mammals. Mycobacterium tuberculosis (MT) and Mycobacterium Africanism and Mycobacterium bovis are the most common cause of tuberculosis in human (1).

Interferon-γ (INF-γ) release assay (IGRA): blood tests that detect the interferon-γ (INF-γ) release from a patient's CD4+ T lymphocytes after stimulation by antigens found on the M tuberculosis complex.

Directly observed therapy (DOT): means directly observed therapy where the health worker attends when the patient takes his tuberculosis medication. This program was later extended to have five components: commitment to increase and financing. Increased and Case detection qualified persons and standardized bacteriology services, standard with monitoring, support of patient and drug supply

Latent tuberculosis (latent TB): infection with Mycobacterium tuberculosis without any symptoms. The only sign of the infection is a positive reaction to tuberculin skin test or interferon gamma assay. The person cannot spread TB bacteria to others (CDC).

Active tuberculosis (TB disease), and the person has symptoms like a bad cough, pain the chest, coughing up blood or sputum, weight loss. The person usually feels sick and may spread the bacteria to others.

Interferon-γ (INF-γ) release assay (IGRA): blood tests that detect the interferon-γ (INF-γ) release from a patient's CD4+ T lymphocytes after stimulation by antigens found on the M tuberculosis complex

Multidrug-resistant tuberculosis (MDR-TB) is a type of disease caused by resistant type of mycobacterium. It tuberculosis exhibits high-level resistance to both isoniazid and rifampicin, with or without resistance to other anti-TB drugs (25)

2. Theoretical Background of Tuberculosis Infection and Disease

2.2 Epidemiology

Tuberculosis is a prevalent infectious disease in countries with low socio- economic status. The majority of the Africa, Asia, East Mediterranean regions and south-America are the countries with low income per capita. The vulnerability to tuberculosis infections scales up with the chronic debilitating disease, crowding, and poverty, but HIV is the significant single factor for TB progression in Sub Sahara regions of African (1). The measurements for tuberculosis burden include examining the prevalence, distribution and incidence of the tuberculosis disease. The World health Organization (WHO) has estimated collected data from 205 countries which accounts for 99% of the world population (2). In 2014, WHO estimated 9.6 million cases of tuberculosis disease Approximately, 58 % of these were from South East Asian and East Mediterranean region. Africa bears 28 %, but as high as 281 per 100 000 and the global average is 131. The prevalence declined by 42 percent, and the incidence halved in many regions(3). Out of the total incidence: 890 000 were men, 480 000 women and 140 000 were children. 12.6% were HIV-positive. Furthermore, the report notified 1.5 million deaths in 2014(2). The case notification delivered only 6 million cases covering only 66% of the estimate, and 37% had no record of diagnosis and treatment.
MDR-TB is emerging, and the estimate 480 000 cases. The diagnostic methods detected only 123 000 patients. There are 2 billion people infected with tuberculosis. About 5 -10% have a risk of developing TB disease in lifetime, and about 9 million people develop tuberculosis disease every year(4).

About 500 000 children which corresponds 6% of the total tuberculosis case in 2011 according to the 2012 WHO report. Out of this 327000 children fell sick. The estimate done by collecting data from countries, which have disaggregated data for adults and children. Data From some countries are used to estimate tuberculosis in countries where there is no data for children. The investigators also assumed that the collected data covered for 66% of the actual incidence. The approach was direct and unequivocal but bears some difficulties. Missing data

was extrapolated to estimate for lacking reports, and this has got inherent uncertainty (6).Since case identification was structurally and resources demanding, mathematical modelling was designed to estimate the burden of disease in children.

Another way of estimating the burden of tuberculosis in children is mathematical modelling. Peter et al. used mathematical modelling to estimate the burden of childhood tuberculosis in 22 with high burden nations(6). The incidence was higher in this study than the WHO methods. The study is unique because it bypassed the tuberculosis case notifications. The process demanded working out the exposure of Mycobacterium infection using community and household model. In community model, the prevalence of disease and reporting data was used to estimate the impact to the strength of Mycobacterium infection.(6) A statistical method called gamma distributions accounts for the unreliability of the prevalence in this study. The group assumed linear associations between the force of infection and prevalence combining with annual risk and prevalence of smear positive tuberculosis. The UN population estimate of children 0-1, 1-2, 2-5, 5-10, and 10-15 multiplied the strength of disease. The prevalence of infection and odds of avoiding infection was found by using computer program (6).

However, identifying the exact number of children remains difficult because of the following aspects of childhood tuberculosis. The essential reasons are:

- TB disease in children frequently presents with non-specific clinical features.
- A larger proportion of paediatric cases are extra pulmonary form of TB resulting in a different clinical presentation.
- Children with pulmonary TB are more likely to have the paucibacillary diseases, which commonly result in a negative sputum smear microscopy and culture.
- Microbiological diagnosis is often difficult in children because of the problem of obtaining specimen, as younger children are not able to produce sputum.
- For culture-negative children with TB there is no universally applicable and validated clinical diagnostic algorithm.
- Smear or culture negative cases are not reported in many countries due to the lack to national surveillance systems(7).

2.3 The microbiology of Mycobacterium

The genus Mycobacterium is a slow-growing intracellular parasite with many subspecies. The most important ones are the Mycobacterium tuberculosis complex, Mycobacterium laprae, Mycobacterium Bovis and nontuberculosis mycobacterium. The subspecies Mycobacterium

complex is known to cause tuberculosis in humans. These bacteria reside in host immune cells and reproduce inside the immune cells. It takes 12-24 hours to replicate under favourable conditions(8) Mycobacterium has a unique cell wall. The cell wall in Mycobacterium is strong and impermeable that it protects against chemical compounds and drugs (8). The outer layer the cell consists of long chain mycolic acids, and the inner layer is made up of two thin layers. Next, the outer layer is made up of peptidoglycans, and the inner is called arabinogalactan. The cytoplasm membrane is connected to lipoarabinomannan(8). This is better explained by the following figure

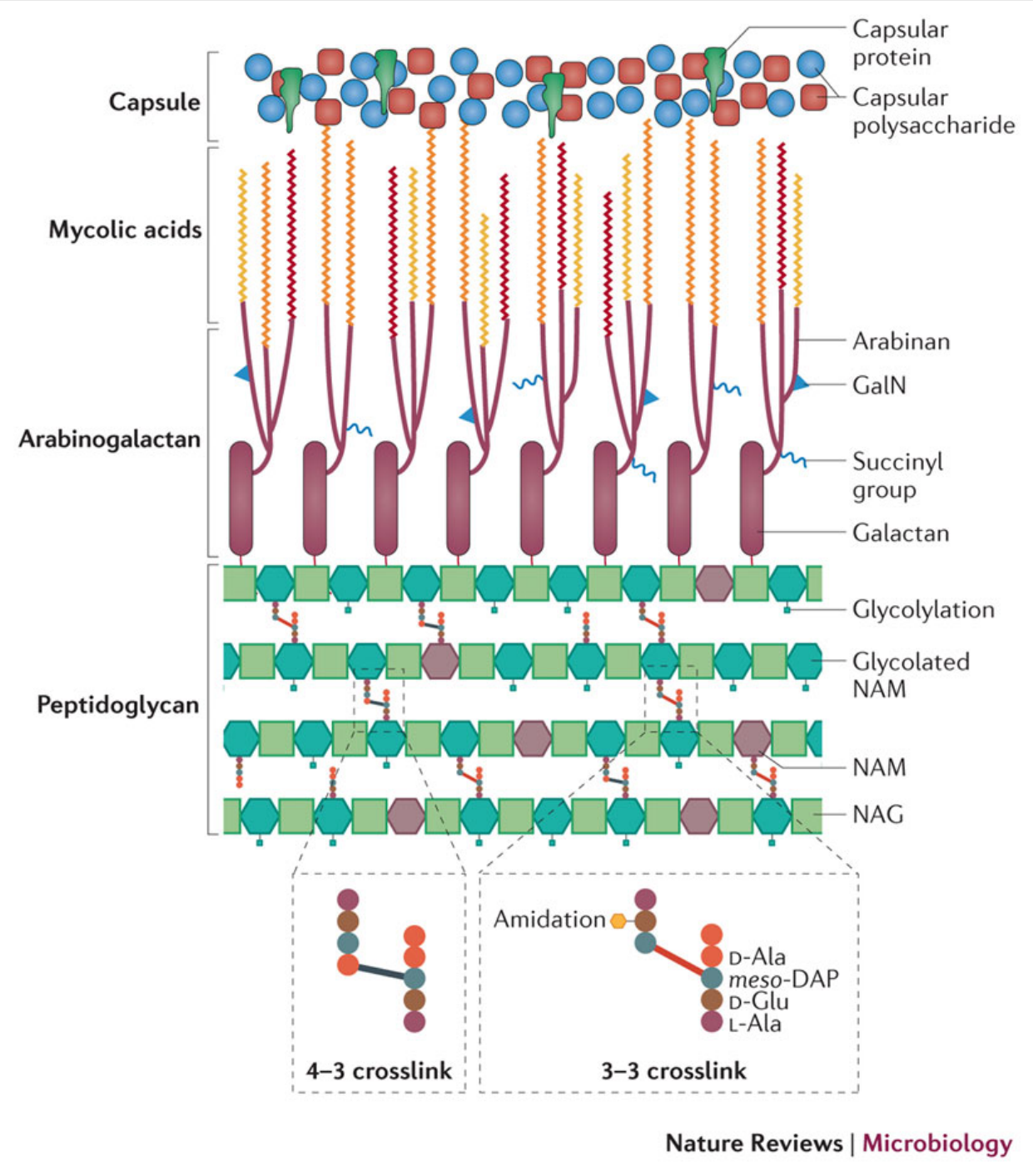

Figure1:1 Cell wall of Mycobacterium tuberculosis of Mycobacterium consisting of Peptidoglycan,Arabinogalactan,Mycolic acid and Capsule (9).

Mtb has five secretory systems labelled ESX1-5.and they have different functions: ESX1 plays a role for the safety of Mycobacterium (8). Mtb comes into the host cell by as phagosome. But it has to translocate from the phagosome to cytoplasm to avoid the enzymatic killing in phagosome. ESX1 plays a significant role in this translocation(8). Besides these, ESX1 also produces ESAT -6 and CFP -10. These are immunologic molecules The new immunological detection of mycobacteria uses these proteins(8). ESX3 is essential for securing the mycobacterium with Iron and Zinc, and these are minerals paramount for the growth of Mycobacterium (8). Besides these secretory elements, the cell wall has Mycobacterium adhesions proteins. These proteins may be necessary for establishing of contacts between the host and mycobacterium. (8)

Another feature of Mycobacterium is that it the capability to go into dormancy under unfavourable conditions. Some proteins are regulating the survival of Mycobacterium in dormancy when the host immune cells contain the MTB (8). These proteins help mycobacterium to reduce: the metabolism level, change of metabolic pathways and stopping of replication favours survival in un favourable en environment where there is no nutrients and oxygen (8)

Mycobacterium coughed as tubercle droplet from the persons having pulmonary or laryngeal tuberculosis through a cough and sneezing. The droplet comes in other person and passes all the way to alveoli (10). In the alveoli, they will be engulfed by macrophages. Usually, the engulfed phagosome is fused to the lysosome. The enzymes in the lysosome digest and kill the phagosome. Mycobacteria inhibit the fusion by several mechanisms. The tubercles are expelled as tubercle droplet from the persons having pulmonary or laryngeal tuberculosis through a cough and sneezing**.** The droplet comes in and passes all the way to alveoli. In the alveoli, they will be engulfed by macrophages and the fused to lysosomes. The enzymes in the lysosome digest and kill the phagosome. Mycobacteria inhibit fusion by several mechanisms(10).

2.3. Pathogenesis of Tuberculosis Infection

Mtb transmits by aerosol from an infected person when the person coughs. The Mycobacterium reaches the alveoli after passing through the upper respiratory ways. Both the innate and the adaptive immune system fight against Mtb. The professional phagocytic cells in lungs, including macrophages, macrophages, neutrophils, monocytes, and dendritic are not

effective because they are inhibited largely even though not exclusively(10). The likelihood of transmission of Mtb depends on factors several factors. Some of these are the number of organisms breathed out from an infected person, the number of pathogens, and the dimension of the space and its ventilation, the duration a person breathes in the contaminated air, and presumably the immune status of the vulnerable(11).

Only 5-10% of people infected with latent TB progress to tuberculosis disease of which the majority develop it within five years after infection (4). Most of the infected individuals clear the infection by the innate immune system(2) . When tubercle bacilli come into the alveolar, macrophages engulf and kill it. However, if killing by macrophage failed, the Mycobacteria translocate themselves into the cytoplasm where they can persist and reproduce (14). Mtb modulates transport and maturation of phagosome, so it can circumvent lysosomal restriction, killing and degradation. Moreover, Mycobacteria impede the antibacterial effects of macrophages by inhibiting the fusion lysosomes and phagosomes (16). The inhibition of phagolysosome favours the proliferation of mycobacteria for the first three weeks resulting in many tubercle bacilli in macrophages of alveoli. Despite this, the infected individuals experience some common cold symptoms. No typical symptoms because Mtb has no endotoxins or exotoxins (2).

Mtb uses the ESX I –VII system to optimize spreading from cell to cell. ESX system promotes the necrotic death of infected phagocytes and recruit phagocytes. They proceed to the new phagocytes so that they can grow and expand their population (12). Mtb also inhibits the host cell's apoptosis so that survival of cell allows large number bacteria to accumulate in a single cell before they are released by cell death (12).

The genetic build-up of the persons is critical on how the infection develops. Patients who lack the "natural resistance-associated macrophage protein 1 (NRAMP 1), develops the disease without an effective immune response. RAMP is a trans-membrane ion-protein in endosomes, and lysosome plays a significant role in killing the microbes. Persons with variant alleles for NRMP have indicated vulnerability for tuberculosis (10)

The adaptive immune system functions in three weeks after infection. Immunologic test like tuberculin skin test is measurable after 42 days. The dendritic cells reach the lymph nodes and then present antigen to the naive CD4+ T cells, with sometimes laps with proliferation, differentiation of effector T- cells and transportation to lungs (16). The involvement of Mtb

antigen-specific regulatory cells may also lead to the delayed priming of CD4 and CD8+ T. Dendritic cells transport Mycobacterium antigen to lymph nodes and presents antigen to the naive the CD4+, and CD4 proliferates and in the lung lymph nodes(10). Macrophage secrets interleukins –I2 and it influences CD4+ under groups TH1 to secrete interferon gamma (IFNγ). IFNγ is secreted by CD4+, and plays a significant role in activating macrophages (10).

The activated macrophages secrete tumor necrosis factor alpha (TNFα) and expresses inducible nitrogen oxide synthase gene(10). TNFα in turn recruits monocyte, which proliferates and differentiates to epithelioid histiocytes . Epithelioid histiocytes are essential for the granuloma response. Inducible Oxide nitrogen synthase increases nitrogen oxide at the infection sites has an anti-microbial effect. It also generates reactive oxygen intermediates and free radicals for the destruction of mycobacteria cell wall and other structures, including DNA (1). The result of activation the immune system is to kill or arrest by forming granuloma. Individuals, who have defects in TH1 response, IL-2, IFNγ, TNFα or production of nitric oxide end up with badly developed granuloma, which can release may prevent escaping of Mycobacteria. If the granuloma is not optimal, Mtb can progress to disease. The person with incompetent TH1 disposed to get the mycobacterial infection(4). The outcome of the primary infections are induced hypersensitivity with resistance to Mycobacterium, foci of the scar with viable bacilli with a tendency to reactivation under diminished host defence mechanism(10).

Progressive primary tuberculosis is very common in persons with HIV-positive (1). The host reaction clears the infection. It may also contain the Mycobacterium. In the latter case, the immune systems prevent replication of Mycobacterium. But under some circumstances, the Mycobacterium could replicate and escapes the immune system (5). If the Mycobacterium escapes the immune system and replicates, the infection progresses to active tuberculosis disease. In the scenario where the host immune has contained and prevented replicating it becomes the latent infection. The latent infection can progress to TB disease when diminishes the host's immune system by any factor. Immune suppressed individuals having latent infection taking Anti –TNF has 25 times increased the risk of de developing TB (13).

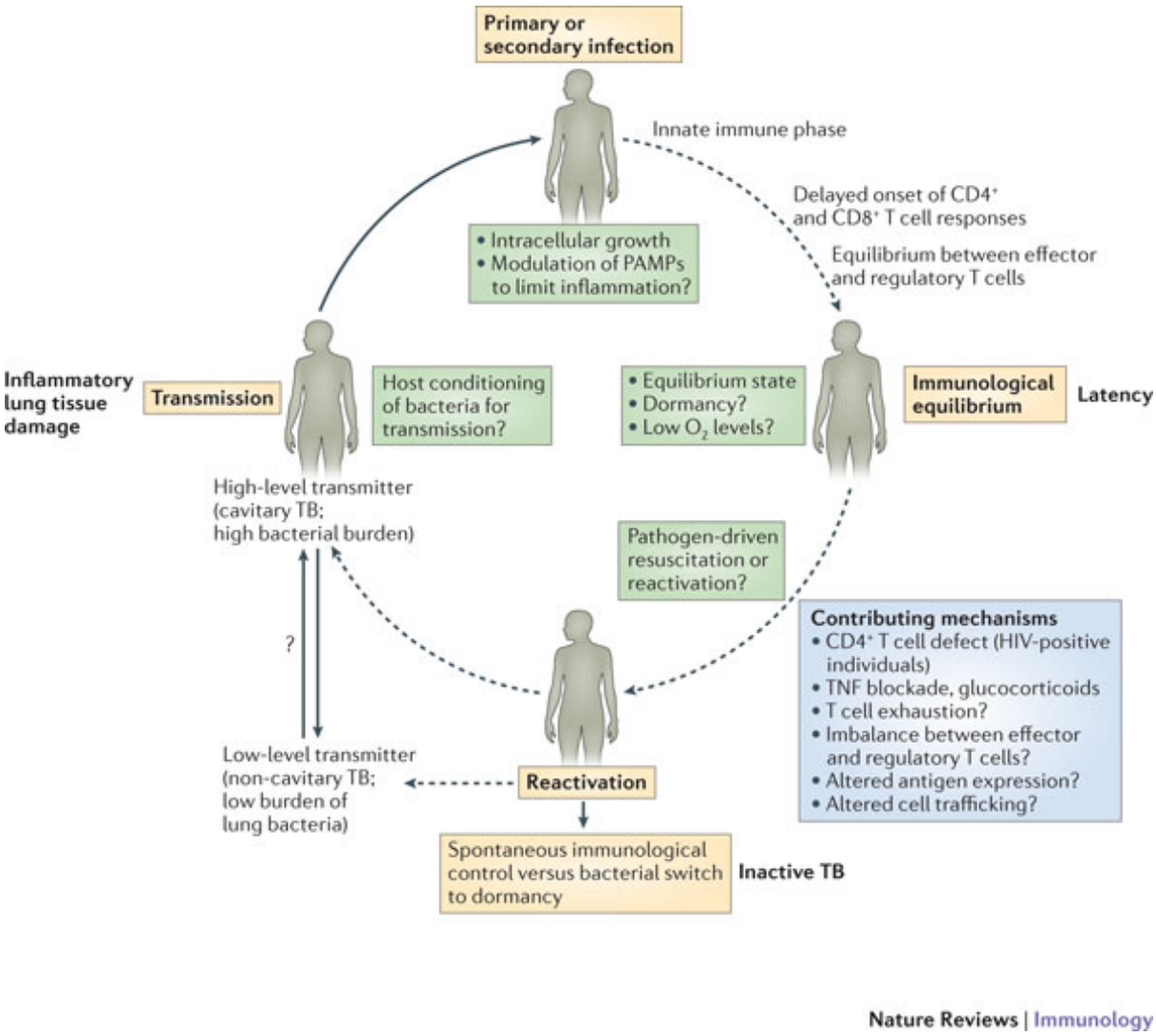

Figure 2.2 Shows the primary infection, latency, reactivation and transmission of Mtb (12).

2.5 Tuberculosis in Children

2.5.2 The manifestation to of tuberculosis in children

The adult standard for tuberculosis such as smear positive and case notification has obscured and caused the under-diagnosing and under-reporting of tuberculosis in children (14). Even before the era of chemotherapy, the need for accurate case definition, risk stratifying, and spectrum of disease pathology in children has concerned the experts(15) As the diagnosis and treatment is advancing, the awareness for childhood tuberculosis is increasing.

There significant differences between tuberculosis in children are: the spectrum of disease, risk factors, clinical factors and diagnostic results depends on age. (7) Tuberculosis in children is quite different from adult tuberculosis in both pathophysiology and clinical presentations.(16) One major characteristic of tuberculosis in children is that children are

susceptible for progression from latent to active disease is higher because of the differences between the immune system protection mechanism in children and adults.(17) Children also have a higher risk for extrapulmonary dissemination like meningitis and death. (16) Not all of the latent infections progress to active tuberculosis. Some factors like the maturity of the immune system, vaccination, give protection tuberculosis. The virulences of Mycobacteria are among other factors, which determines the impact of infection. Malnutrition and immune suppressive disease also shape the outcome of infection with Mycobacterium. HIV. TB in children expresses itself in the form of pulmonary and extra pulmonary tuberculosis. The most common forms of extra pulmonary TB in children are

- Peripheral lymph
- Millary TB
- Tuberculosis meningitis
- Pleural effusion
- Abdominal TB
- Osteoarticular TB
- Pericardial TB.(18).

Central nervous involvement is most common in children under three years and HIV-infected children. (19) Co-infection of TB and HIV is very common in African countries than in developed countries.(16) In co-infected children, TB manifests itself in the form of acute and severe pneumonia causing death. Hence, this makes the case notification demanding to know if the child dies of HIV or TB. A third of mortality in children infected with HIV is caused by Mtb.(19)

The clinical manifestation of tuberculosis depends on the proliferation site of mycobacteria, and this can happen in the spine, hips, the gastrointestinal tract, but about 85% cases take place in pulmonary.(4) So important to visualize the symptoms given the patients symptoms that come if the proliferation occurs in lungs. For example extrapulmonary TB like abdominal tuberculosis gives pain in the abdomen. The most common symptoms from in pulmonary tuberculosis consist of

- A chronic cough,
- A night sweat
- Blood tinged sputum,
- Weight loss,
- Shortness of breath,

- Fever, chest pain, pleurisy,
- Cloudy patches and pleural effusion can in the chest radiograph. (4)

These symptoms are not specific and can appear in many other respiratory infections.

2.5.3 The Clinical Methods in Children

The clinical methods in childhood tuberculosis management include the identification of risk factors, identifying clusters of symptoms, laboratory work out and treatment according to the existing national and international guidelines(18). This integrated approach is necessary because of the unspecific presentation of tuberculosis in children. A child can contract the infections from older children, caretaker, and parents who have on-going infections. Both exposure time, the likelihood of infection, the proximity of to the infectious agent and the susceptibility of the child is detrimental in acquiring the infection(16). Poverty has a significant role in the transmission of tuberculosis because the children stay in an overcrowded place and poor housing condition (16). The risk of infection varies for children according to their age. The risk is higher for children under five years, but decreases between 5-10 and then increases from 10 years(16). This is believed to due to the immature immune system for children.

Mtb infection in children is a good indicator of on-going or recent infection in community(7). Because of children stay at kinder garden and at school, a single infectious can put the others exposed. The Therefore, targeting children tuberculosis is essential for eradicating tuberculosis disease. Mycobacterium passes from smear positive patient to another person through tuberculosis bacilli The Mycobacterium reaches the alveoli after passing through the upper respiratory ways. If the Mycobacterium passes the immune system in the mucosa of the upper respiratory system, it will pass to the macrophage. Macrophages are professional effectors and kill the Mycobacterium. In addition to the effector functions, the Mycobacterium also recruits the monocytes to the infections site. The destiny of the Mtb is decided by the effector activity of macrophage, the recruitment of monocyte to the infections site and the antigen presentation by the dendritic cell to naïve T cells (16).These activities may be reduced in infants and predisposes them to extra pulmonary infections. The characteristic features of tuberculosis in children are its paucibacilliary nature, types of disease and diagnostic challenges (14). Besides this, getting a quality specimen for laboratory diagnosis is not easy with children. The WHO has outlined an approach for diagnosis of TB in children. Among these are: careful history taking, clinical examination, tuberculin skin test,

X-ray bacteriological confirmation and also includes other relevant investigations and HIV testing in high prevalence setting(18).

2.6 Current Challenges and Strategies for Multidrug-Resistant Tuberculosis

Multidrug-resistant tuberculosis (MDR-TB) is tuberculosis due to Mycobacterium, which exhibits high-level resistance to both isoniazid and rifampicin, with or without resistance to other anti-TB drugs (20). MDR-TB –plus is a term used to denote if the resistance is the same monster as for these two but has additional resistance to other first drug lines or second line drug resistance (20). The risk factors for developing MDR –TB, one must examine the patient's factor, the caregiver factor, the drugs factor and the Mycobacterium factors. According to the National tuberculosis program the most important risk factors and when to suspect MDR-TB are the history of contact with the MDR-TB patient, interruptions of anti tuberculosis treatment, culture positive after five months of treatment with anti-tuberculosis and history of adherence problem. Adherence to the treatment regime determines the bioavailability of bactericidal and sterilizing drugs. Regular drugs administration, cares for continual disruption of Mycobacterium tuberculosis. In addition to these, the presence of guidelines and the care- givers preference to use it also shapes the treatment and the fate of Mycobacterium to become MDR-TB

The known mechanism for Isoniazid chromosomally is mediated lose of catalase-peroxidase, a mutation in mycolic acid synthesis and regulators of peroxidase response. Resistance to rifampicin comes from reducing binding to RNA –polymerase, clusters of mutations at rifampicin and reduced cell permeability(21) Mutation in KatG or InhA gene gives resistance to isoniazid, while it is mutations in *rpo* genes gives resistance to rifampicin(22).

The diagnosis of MDR-TB necessitates the identification of Mycobacterium in culture and drug and susceptibility testing(22). The nucleic acid polymerase based test called The XprtMTB/RIF is also suggestive for MDR-TB. The assumption behind this is that due to the rifampicin is a marker for 90% of case of MDR-T while rifampicin monoresistant is under 10% (22). The responsibility for avoiding MDR-TB is should be addressed factors with the patients, mycobacterium, drugs and the health worker who treats and the system promoting.

Drug is increasing is also increasing in Europe as well as in other countries and poses a public threat and the key to stop this treatment is to better detection and management is the key to stop MDR-TB (23). There were 480 000 new cases of MDR in 2014 and only one third of this

is detected and reported by WHO (2) . The most challenging aspects of MDR-TB are: delayed diagnosis, increased risk transmission, expensive treatment, prolonged treatment, ineffective treatment, and poor outcomes. The loss of Isoniazid and rifampicin has severe consequences on public health. The first line ant-TB are isoniazid, rifampicin, pyrazinamide and ethambutol or streptomycin has a cure rate of 95% in the first two months and a conversion of an infectious case into a non infectious case in 2 weeks(22) Furthermore, their bactericidal profile is different in killing the tubercle bacteria which is metabolically inactive for most of the time to become the multidrug resistant.(22) Isoniazid is best bactericidal drug and while rifampicin is the best sterilizing drug.(22) A resistance to isoniazid extends treatment with rifampicin an ethambutol to 9-12mothes and resistance to rifampicin extends the treatment to 18 months, with pyrazinamide the first two moths.(22) The burden of management and duration of medication is much more than the 6 months short course treatment in drug susceptible tuberculosis disease. The infectiousness of the case is also longer in community and in hospital with drug-resistant tuberculosis(22)

One of the strategies for preventing new drug-resistant cases is by adhering to the guidelines. The WHO recommends initial treatment of tuberculosis disease with 4 drugs for six months (isoniazid, rifampicin, pyrazinamide and ethambutol, the last to are given for two months(22). If culture is positive after treatment in fifth or sixth months of treatment, an additional treatment for eight months is recommended, but with relapse other eight months is recommended(22). The treatment regime is different for multidrug resistant. WHO recommendations for the treatment of multidrug-resistant with a minimum of five drugs, and including on injectable until culture negative result and a minimum of three drugs for a minimum of 9 months for or extensively drug-resistant tuberculosis include second-line drugs and a treatment duration of 18–24 months or longer(22). Prognosis for drug-sensitive TB is 95%, it is 70% for drug-resistant tuberculosis. The problem treatment for with MDR-TB is associated with delibliteting and drugs side effect. The outcome of therapy may be that patients are cured proven by consecutive culture results, some times the patient completes the treatment without the evidence of negative culture, sometime the treatment fails and some time death is the outcome

There still a challenge of testing the MDR-TB because the majority of the countries use the smear positive and treat patients without the drug susceptibility test and the drug

susceptibility takes a long time, and there is discordance among the different methods (24). Implementation of these guidelines results in a wide range of treatment regimens that are dependent on the availability of drug-susceptibility testing, cost, physician preference, and drug availability in developing countries.

The strategies for combating MDR-TB are different in developed and resource-poor countries. In resource poor countries DOTS-plus program is recommended (22). The DOTS-plus program includes supporting the monitoring drug resitance, national TB program, and drug availability at affordable price through the Global TB Alliance (22). The focus for developed countries in combating MDR-TB

- -Treatment by physicians experienced in treating complex cases with drug-resistant organisms.
- Treating infectious cases as inpatients and in facilities with full negative pressure ventilation.
- Management of cases in collaboration with national/regional mycobacteriology services utilizing drug susceptibility data (22).

But the overall strategy for drug resistant suggested by the WHO: Early detection and high quality treatment of drug-susceptible TB, elective implementation of infection control measures , Strengthening and regulation of health systems an addressing underlying risk factors and social determinants (25).

2.6 Improvement in diagnostic tests

The diagnostic methods for Mycobacterium tuberculosis have been difficult because of lack methods which can identify Mycobacterium with high sensitivity and sensitivity. We can identify Mycobacterium by identifying Mycobacterium itself in sputum, through the identification of the host immune reaction, part of the structure of Mycobacterium and by observing the changes it causes, and finally by the clinical cluster of symptoms where. There are also methods of identifying the drug susceptibility of the Mycobacterium. Interferon-gamma Release assays a method, which measures the host immune reaction in whole blood.

2.6.1 Interferon Gamma Release Assay

Interferon Gamma Release Assay (IGRA) is one of the newest diagnostic methods for detecting the mycobacterium by host immune response in whole blood. It is an immunological method developed after tuberculin skin test. The T-cells produces interferon gamma when it detects the immunogenic molecules produced by the Mycobacterium. There are two types of assay: Quantiferon –TB gamma test and T-spot.TB Assay. Quantifieron TB detects ESAT-6, CFP-10 and TB7.7. T-spot Tb detects ESAT-6 and CFP-10. The IGRA measures the INF-gamma and T-spots count the number of cells releasing the interferon. The hypothesis is that the white blood cells of the infected patient reacts to Mycobacterium by delayed type hypersensitivity and produces interferon gamma. IGRAs should be 0,35 /ml in the blood sample. Interferon gamma binds to ESAT-6. Some of the advantages of this test are that it does not depend on the person who is analyses it. The measurement is objective alike the tuberculin skin test which needs an identifying and grading of risk factors to interpret the test. Another advantage is IGRAs does not cross react with BCG but can react with another mycobacterium. The disadvantage is that this test cannot differentiate between latent and active tuberculosis.

Though the IGRA and TST test the immunological s, the result of the two tests shows concordance and dis-concordance. The superiority of IGRA to TST is its ability to distinguish between Mycobacterium tuberculosis and non tuberculosis mycobacterium and it shows no cross-reaction with BCG (26). However, the IGRA has shown a better resultant in patients having co- infection with HIV and in populations with BCG vaccination. However, the use of IGRA is not recommended for investigation of active tuberculosis because the positive result does not exclusively indicate active TB infection and the negative result does not exclude the presence of activeTB ((26). There are three approaches to using IGRA as a guideline. What is known and agreed is that IGRA has increased sensitivity in immunocompromised individuals and in BCG-vaccinated. The approaches are as follows:

- Two-step approach of TST first, followed by IGRA,
- IGRA only, replacing the TST
- Both and IGRA together. Either TST or IGRA*, but not both* (26).

The rationale behind the choice is not clear, and no metanalysis shows preference for TST or IGRA. While the IGRA shows the latent infection, it does not predict the extent of progression of latent to active TB. Another limitation for IGRA that is has sensibility of 24% in children below five years (27, 28).

2.6.2 Polymerase chain reaction

Polymerase chain reaction (PCR) shows part of the Mycobacterium structure particularly DNA. It tests the DNA structure of the Mycobacterium test by amplifying nucleic regions that are unique to Mycobacterium (29). PCR is an alternative method for testing mycobacterium since it is usually very few bacilli in specimens collected from children. The paucibacillary nature of paediatric tuberculosis is the underlying reason for smear negative sputum and extra pulmonary. The limitation of this test is that it does not distinguish between latent and active tuberculosis. Besides this, the negative result does not exclude the active extra pulmonary tuberculosis, and neither does the positive confirm active tuberculosis.

PCR is a rapid test, and this facilitates the treatment initiation. Because of the ability of the PCR to amplify small sample by using primer, it can be used in situations where diagnosis of tuberculosis is difficult for example in extra pulmonary, negative smear microscopy, and scare specimen(30). The PCR is used when for diagnosis for rapidly identifying DNA from M. tuberculosis, when the sputum smear is negative, and when there is a need to distinguish between Mtb and non tuberculosis mycobacteria and to identify resistance to some anti-mycobacterium.(31). According to Kumar PCR can be used in the following situations.

- Diagnose TB in difficult samples with negative microscopic examination, negative culture, or with scarce sample;
- Determine if the organisms in the sample are M. tuberculosis or atypical mycobacteria;
- Identify the presence of genetic variations like a mutations or deletions known to be associated with resistance to some anti mycobacterial agents (29)

2.6.3 XPERT MTB/RIF

Xpert MTB/RIF is another nucleic acid test based methods of detecting Mycobacterium and determining rifampicin resistance. The Rapid diagnosis of MDR-TB may improve the treatment outcomes. A rapid test can shorten the delay in treatment since the treatment is initiated based on evidenced presence of Mycobacterium and its drug susceptibility (32).The most used conventional methods for drug susceptibility test is the solid LJ culture method which takes about 4-8 weeks and it is usually done at the referral laboratories.

The rapid tests developed are compared with this culture medium as a standard. The culture medium has a sensitivity of 80-90%. The improvement in drug resistance is rooted in the

molecular and nonmolecular methods. The nonmolecular methods depend on the observation of growth in culture media. Sincne the mycobacteria grow slowly, this method takes at least a week or more. The molecular methods are improved PCR methods. In this section, one example of each approach is presented

Xpert MTB/RIF is an automated nucleic acid amplification test. It is a fully automated, self-enclosed system bypasses the need for infrastructure for processing DNA materials for further PCR analysis(24). The method detects both Mycobacterium and its drug susceptibility to rifampicin. The test has a sensibility 92.8%, 72.5% for smear positive and smear negative specimens respectively and has 99.2% specificity for detecting Mycobacterium DNA. The sensitivity drops in immunocompromised patients to 95% in smear positive and 55% I negative smear(33). The paucibacillary of the specimen make it difficult to obtain DNA material even though it can amplify. Xpert MTB/RIF increases detection rates in smear negativesamples(24)(24)(22)(21)(21)(21)(21)(21)(21)(21)(21)(21)(21)(21)(21)(21)(21)(21)(21)(21)(21)(21)(21)(21)) but the drug susceptibility test is limited to rifampicin. (19) The test scores were high in detecting Mycobacterium DNA.

The advantages of molecular methods are they are rapid, high sensitivity and specificity, can be standardized to field use, and the disadvantages are they cannot eliminate the need for culture, a limited number of drugs for resistance and work better with smear positive than smear negative. (24) Since the majority of tuberculosis patient live in poverty, this technology has limited impact for diagnosis unless it is standardized for field use. There are other more advanced methods for nucleic acid amplifications methods. Genotype MTBDR plus tests rifampicin and isoniazid. The test for second line drug resistance necessitates Pyro sequencing for drug resistance identification. Because the molecular methods show results long after treatment, nonomolecular methods should be used for monitoring of treatment.(34)

The progress is advancing in nonmolecular methods. One of the promising tests is the Microscopic observation of drugs susceptibility assay (MODS), a method endorsed by WHO. MODS depends on the growth of Mycobacterium grows slowly it take more time compared to the molecular methods, but still more rapid compared to the LJ culture medium. The method uses microplates with containing Middlebrook 7H10 liquid medium used for incubating the specimen and allocating some wells for growth and some for controls. (24)

An expert observes the culture with intervals. Growth only in wells without drug indicate drug susceptive. A growth of Mycobacterium in both drug containing and without drugs assures drug-resistant tuberculosis (24). The sensitivity of the MODS for detection of Mycobacterium ranges from 87%-98, the sensitivity and specificity for rifampicin are 98%, and 99% respectively while the sensitivity and specificity are for high-level isoniazid resistance is 90% and 98% respectively(24). MODS has capacity to test suseptibity for many drugs simultaneously unlike the molecular methods. The drawback of this MODS is the probability of contamination because it uses liquid media. MODS requires high-level laboratory infrastructure and competence(24)

The result of MODS was indifferent in HIV-negative and positive. Another important aspect of MODS was its ability exclude MDR-DR rapidly which is a great benefit because co-infection of TB and HIV overpowers the patients within a month leading to death within 60 days and 60% the TB patients with HIV are smear negative-TB which delays the diagnosis and treatment initiation (35). With MODS, every specimen type can be used: sputum, gastric aspirate, and CSF. The median time for MODS was seven days compared to 35 days in LJ culture, but the recommendation is up mycobacterium grows slowly (32).

2.7 Improved treatment for latent and active TB

Treatment of active tuberculosis extends from 6-8 months. And it is resource demanding since the practice of DOTS is used in guidelines. of high-risk countries, and treatment of latent infection is a key for preventing future active tuberculosis**.**

2.7.1 Improved treatment for latent infection

This section is devoted to the treatment latent and active tuberculosis respectively. Mostly, new active tuberculosis emerges from latent infection(36). Therefore, treating latent tuberculosis is equivalent to eliminating the seedbeds of future tuberculosis. Initiation of latent treatment serves the children with latent protects other from potential infection. The purpose of latent tuberculosis is to eliminate the infection in individuals before the latent becomes the active infection and to prevent transmission to the community in the future.

The convention treatment for latent infection is that isoniazid is given with DOTS for nine months. Rifampicin is given for nine months in cases of resistant to isoniazid or existence of contraindications(27) .

The treatment of tuberculosis with tuberculosis chemotherapy takes a long time as long as 6-8 months. The problem of adherence is related to this prolonged duration of therapy. A combination of 3 months isoniazid and rifampicin is as effective as nine moths isoniazid. Nowadays, the CDC recommends nine moths of isoniazid without DOTS, six moths with twice weekly DOTs and DOTS observed weekly f isoniazid and rifapentine (37). The WHO has suggested the following alternatives: sixth months or nine months isoniazid or three months of rifapentine plus isoniazid or 3-4 isoniazid of rifampicin, or 3-4 rifampicin(38)

2.7.2 Improved treatment for active tuberculosis disease

According to the WHO the objective of the treatment of tuberculosis is to:

- Cure the patient of TB;
- Prevent death from TB disease or its late effects;
- Prevent relapse of TB;
- Prevent the development and transmission of drug-resistant TB;
- Reduce transmission of TB to others;
- Achieve all this with minimal toxicity. (18)

Thus, a priority for drug development has been for new tuberculosis drugs that will shorten regimens. Potent sterilizing medications that can shorten treatment duration to 2 months or less would improve adherence, and reduce program supervision and distribution costs. Furthermore, drugs that would reduce both total lengths of treatment and frequency of drug intake would be ideal. The reason for prolonged treatment is the nature of the mycobacteria that it goes into dormancy, and the medication is more effective when the mycobacterium is active. Mycobacterium has a tendency to undergo dormancy up to 100 days under conditions of anaerobiosis and nutrient depletion. Their ability to undergo dormancy is the reason why the treatment takes long time as the antituberculosis drug are most effective when Mycobacterium is in active phases (39).The four of the most effective first-line oral drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) must be taken together during the first two months of treatment, and two (rifampicin and isoniazid) for a subsequent four months in the continuation phase.(40) The lengths of the treatment pose a problem of adherence. Though the first line drugs are effective, they need an effective management like DOTS. DOTS is effective way to increase the adherence problem and reduce mortality, reduce the risk of drug-resistant tuberculosis.

Until recently the maximal dos of rifampicin used is 450-600 mg. There is a call for evaluation for higher doses of rifampicin and HIGHRIF2 passed the safety, tolerability, and pharmacokinetics of 900 mg and 1200 mg doses of rifampicin in combination ratios with the standard regimen components over to months (15). Pyrazinamide can be used to kill persistant ones. The current drug combinations have attempted to decrease the either the total duration of treatment or the number DOTS administration.

A combination of moxifloxacin, ethambutol, rifampicin and pyrazinamide for two months and moxifloxacin and 900 mg rifapentine for two months with the purpose of reducing with to months, and moxifloxacin for two months and followed by the weekly dose of moxifloxacin and 1200 mg rifapentine for four months. This reduces the frequency of drugs administration. (41)

Chapter 3: Methodology

3.1 Introduction to methodology

The objective of the project is to gain knowledge in children and adolescents treated for active or latent tuberculosis at the University Hospital of North Norway from 01.01.05-31.12.14. The project is expected to contribute to knowledge:

1.The number of patients having active and latent tuberculosis during the study period.

2. Debut age for symptoms / treatment

3. Diagnostic methods

4. The choice of the treatment

5. The following ups of the patients

In addition to these, the project gives insight for qualities of active and latent tuberculosis management in children under 15 years at UNN.

3.2 The setting of the research

The research is done in at the University Hospital of North Norway (UNN). Norway has a low incidence of tuberculosis. The yearly incidence of TB disease in Norway is about 324. Most of the children having tuberculosis actually came from foreign-born because of the family unifications and other aspects of immigration. Data was collected patient electronic journal (DIPS), for patients admitted to the hospital or had consultation at Polyclinic department. The study was retrospective study. The study is done at University Hospital of North Norway. Because of the socio- economic status, it is nearly possible to follow up individuals and manage with diagnostic labs and radiographs as much as needed. There is no stretching on the resources

3.3 The overall Study design

The study is a retrospective study patients journals concerning barn and adolescent with tuberculosis. A retrospective study is a non-experimental study done on pre-existing records. It investigates a phenomenon, a situation, problem or issue that has happened in the past (31). The advantage retrospective studies are it is done on the available data and does not require interventions. The drawback is the existing data may not be detailed enough because the data is taken to serve other purposes than a project that emerges later. Participant recalling can also be if data does not exist (42). The researcher must decide the time frame and inclusions

criteria. In this study, there is no control and the purpose is to collect information on the existing to understand the trends of the case in the future. Retrospective identifies the qualities of the work done the past. The data was collected according to the following criteria. The children included in this study are based on the following criteria.

a) Must have been admitted or consulted at the poly clinic at Department of UNN at day care clinic Within 01.01.2005 - 31.12.2014
b) The age of the children must be Fra 0-15 year.

The participants were identified through ICD-10 with diagnosis code A15-19 tuberculosis from the electronic patient journals (DIPS) and positive INGRA analysis in the same period from department microbiology department of NUN

3.5 Ethical consideration.

The person protection board (PIVOT) granted the permission to access the electronic patient journals after application. My access is limited to UNN. The project did not involve direct patient contact, and no individual consent is applied. It was unnecessary to apply to regional committee of medical and health research (REK). The patients were allocated codes when entered into the database and it is not possible to recognize the identity of the patients.

3.6 Data collection

All the possible information about the patient was collected by standardized sets of data from DIPS. The data was collected on the statistics program (SPSS). Code is allocated to all the participants All of the participant were given a code number to be annonymized. The variable thought to give us more information about the sample were divided in to three: the variables for risk factors of getting tuberculosis infection, variables for identification of tuberculosis infection and variables for treatment and follow ups.

3.6.1 the variables for risk factors for tuberculosis infection

The following variables were considered. Age, sex, age for diagnosis, the origin of the patient, continent, born in Norway, arrival age in Norway, Bacilli Chalmette Guerin (BCG) tuberculosis in household, type of tuberculosis. The origin is classified as the country of birth and region from which the participants were grown and lived. Born in Norway is denoted as a person born I Norway or not Norway. Tuberculosis is transmutable and identification of this could make a suspicion of infection. BCG was given as a vaccine in many countries and

protected children against tuberculosis meningitis and extra pulmonary tuberculosis. It has reduced capacity to protect against pulmonary tuberculosis.

3.6.2 Variable for identification of tuberculosis

The following variables were used in diagnostic workups and were entered to give us information on the identification of Mycobacterium. These include: Interferon gamma assay (IGRA test), IGRA titer, X-ray, gastric lavage, Sputum, Polymerase chain reaction (PCR), Tuberculosis culture and Mantoux(Tubeculin skin test). The identification of mycobacterium is in children is difficult because of the paucibacillary and the following test were considered to increase the possibility of identifying tuberculosis infection. Mantoux test is usually done at the health stations. It was given a positive if tit is above 5 mm. And this was checked by IGRA. The cut point for IGRA was sett up to be 0.35 u/ ml. Chest X-ray is used in many respiratory diseases and it also shows the presence to TB.

3.6.3 Type of TB tuberculosis treatment and follow up

The following variables were used to categorize tuberculosis infection and treatment

Type of tuberculosis was one for Latent TB infection. In latent tuberculosis, the infection is identified, but the patient has no symptoms of tuberculosis. 2-Active pulmonary: in this case the patient has symptoms of tuberculosis infection in the lungs, and it is identified by the one the above tests 3. Extra pulmonary TB disease: the patients may be having tuberculosis pleura, lymphatic glands, the bone or in the abdomen he treatment was given give a coded 1 for no treatment, 2 for treatment for latent tuberculosis with isoniazid and rifampicin for three months, 3 for treatment for active tuberculosis of different regime, 4 for the treatment of active TB for 6 months and 5 for treatment for more than 6 months. The follow-ups were classified as zero for no follow-up and two clinically healthy during the follow-up.

3.7 Data analysis

The data is analyzed by using the SPSS analytics methods, and the descriptive statisticis used. Descriptive statistics describes the mean, median standard deviations, and frequencies. The data was analyzed to give an answer to the research objectives. The results were bepresented in the form texts, tables.

4. Result

The expectation was to get necessary documentation on the patients to be available to perform the research. There were 240 patients were identified by the ICD diagnose and IGRA test. We define all who had positive IGRA test have latent TB. Most of the patients had data on fewer variables. 13 of the 240 participant was e excluded from the study because they because they were above 15 years. It is worth to mention that the documentations for patients who were admitted to the UNN or had a consultation at polyclinic had satisfactory documentations on patient background and all the diagnostic workups. The Norwegian Surveillance communicable disease (MSIS) were filled and reported to the Institute of Public Health for patients treated for latent and TB disease. The forms were filled and reported by physicians attending the patient. The template was so standardized and summarized typical test for tuberculosis risk factors, and treatment.

Some of the patients did no have complete data, because they were referred data to the laboratory and had not had consultation with the physician at the paediatric department. They were followed at their respective hospitals.

The higher proportion children tested for tuberculosis were not from Norway. 88% of the participants were born in foreign countries. The proportion from Africa was much higher and followed by Asia, Eastern Europe and other regions. The distribution of infection was higher in male than the female. The male constituted 68% to 46 % female.

Country of birth	
Norway	27 (12%)
Outside Norway	200 (88%)

Table 4:1 the table shows the comparison between the Born in Norway and Born Abroad.
The ratio of the male participant to the female was 1,45. It was 20% higher among male participants (not shown here).

Debut age for symptoms was estimated to be close to the time when IGRA test was taken. The youngest patient was 0.2 year, and the oldest is 15 year. The mean for debut was 9,7 years and the mode was 11 years. Standard deviation was 4.3.

	Number	Percentage		
< 5 år	23	10.1		
5-10 år	48	21.1		
11-15 år	80	35.2		
Unknown	76	33.4		

Tabel 4:2 Debut age for latent and TB disease symptoms.

The male data showed there were male than female. The ratio of female to male was 1.44

	Number	Percent
Female	93	40.97%
Male	134	59.03%

Table 4.3 Table shows the proportion of female and male.

There were diversities of tuberculosis including latent tuberculosis, active tuberculosis, extra pulmonary and some are unknown. The extra pulmonary and pulmonary are combined together and considered as TB disease.

	Number	percent
Latent TB	207	91.2%
TB disease	6	2.6%
No TB	14	6.2%
Total	227	100%

Table 4:4 the proportion of latent and TB disease

The study found out the IGRA was the most frequently used test. Mantoux was specially used in primary Sputum smear and PCR, LJ culture were used in few cases. Montoux test and IGRA were used most frequently. The mean value for IGRA titer was 6.9 and the mode was 10 and the highest value of 32.

	TB disease N=6	Latent TB N = 209?	
IGRA	Mean (SD)	Mean (SD)	
Mantoux test positive	7/8	140/200.	

Figure 4.5 Table showing IGRA showing the IGRA test against all sorts of TB

	Number	Percent
IGRA positive	211	92.5 %
IGRA negative	14	6.16 %
IGRA not tested	2	0.8 %

Figure 4:6 IGRA test in both gender

Besides the IGRA test, mount box was also most used in the initial part of the diagnostic workups. It was mostly taken at the primary health care, at health stations. Mantoux was used as a screening test. The primary health services used Montoux above 15 to be an indication for referring to the hospital

.

Some of he participants received no treatment, some received for three months treatment and others were treated latent for 6 months. Very few were treated for active tuberculosis for 6 month. None of the participants revived treatment for more than 6 months.

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	Number	Percent
Latent TB	207	
No treatment	150	72.98
RIF-INH 3 month	51	24.17
Other regimen	6	2.8
TB disease	6	
6 month standard	6	100
Other regimen	0	0

Table 4:6 showing the treatment received by the participant

Patients with TB disease

	Patien1	**Patient2**	**Patient3**	**Patient4**	**Patient5**	**Patient6**
Age	2.5	14	14	15	14	
PTB	Yes	No	No	No	No	Yes
EP TB	No	Yes	Yes	Yes	Yes	No
Region	Africa	Africa	Asia	Africa	Africa	Africa
DOT	Yes	Yes	Yes	Yes	Yes	Yes
Complete follow up	Yes	Yes	Yes	Yes	Yes	Yes

Table 4.7 Shows characteristics of TB and follow-ups

The participants were followed up in the course of treatment.

All the patients got information and were followed for both side effects of drugs and culture conversion. However, few needed a close monitering All were found to be clinically healthy at the control.

5: Discussion

The summaries of the main findings of the study are as follows.

1. Most of the children had latent tuberculosis
2 Most of the children with latent tuberculosis or tuberculosis were not from Norway
3. All of the children with TB disease have got adequate treatment
4. IGRA test was mostly in diagnostic methods

I shall discuss these finding under by giving dividing them in to subtitles.

5.1The predominance of latent tuberculosis children North Norway

The data used in this study showed that there only 13 who where born I Norway. The variables used in this could not identify if those in Norway had parents from high-burden countries .Our data showed that 207 out of 227 (91%) had latent tuberculosis. The data from MSIS revealed that there were 774 who started preventive treatment and there were 324 new cases of TB disease in general population (43) . There are more cases of latent tuberculosis in general populations than tuberculosis TB disease.

A retrospective study done in at paediatric hospital karoniska Institute showed that they're mere more latent Tb among foreign born abroad and resettled in Sweden. 309 children had symptoms associated with tuberculosis. And 197 of these had latent tuberculosis while there were five TB disease cases. There were 197 children for children treated for tuberculosis symptoms of 309 (44) Preventive treatment was given to children who high risk of latent progression to TB disease. Most importantly, they were treated to prevent disease, but it also reduces the number of persons who can develop the potential infectious disease (45). FHI recommends treatment latent infection with Isoniazid 6 months or isoniazid and rifampicin for three months (34).

5.2 Comparing tuberculosis in born in Norway and foreign-born children in North Norway.

There were only few children who are born in Norway. Only 12% were native from Norway, even this group there more who are born I Norway but not have parents from abroad. Most of the children with latent tuberculosis or tuberculosis were not from Norway. The majority came from Africa and followed by Asia. A study done on the management of latent tuberculosis in Norway with a sample of 721 participants showed that 84% of the participant

were born abroad, 39% came from Africa, 34 % came from Asia. 16 % were from Norway. The FHI report for 2014 indicates that the foreign-born children infected with tuberculosis were high-burden countries. Among the 774 who started preventive treatment, 80% were born abroad, and 23% were born in Norway (43). Those born in Norway had one or both parents were born I Norway. Tuberculosis was decreasing continuously among the born in Norway and increasing among the foreign born from 2007-2014.

Out of 325 patients for Tb disease were 22(7%) born in Norway, 175(54%) from Africa and 96 (29.6%) from Asia and 25(8 %) from Europe outside Norway. TB had shown decreasing trend among the born in Norway and was increasing among the foreign born from 2002 (43). Data from MSIS confirms that TB disease was rising in foreign-born persons consequentially from 2007-2014 (34). Norway has an incidence of 7/ 100 000 inhabitants and 350 new cases every year (43). A retrospective paediatric study from in Sweden for year of 2000-2009 followed 147 TB patient: 61 % of them came from abroad, and 38 % were born in Sweden from families came from high burden countries and only one child was born to both Swedish born parents (46). Similar retrospective study is done in Denmark for 2000-2009 (34). There were 323 children treated for TB disease. 79.6% were from high- burden countries and 20.4% from born I Denmark. It is clear from this that TB in Denmark is lower, and this is attributed to the strict immigrations rules (47). These studies supports that the high proportion of tuberculosis I North Norway is attributed to the fact that there 11% in north Norway have one or more foreign origin

In my understanding, the low latent infection in Children born in Norway is the result of child vaccination program, well-regulated infections control program. For the foreign-born children, the underlying factor is the infection in their respective country, and lack of immunization, and inadequate health services. It is also notable that the children born in Norway are screened if there is suspicion, but all of foreign born are obliged to screening law.

Most of the children with latent tuberculosis were not from Norway Only 12 % were native Norway. The majority came from Africa, and followed by Asia. The FHI report for 2014 indicates that the foreign born children with tuberculosis was high. Out of 325 patients for Tb disease were 22(7%) born in Norway, 175(54%) from Africa and 96 (29.6%) from Asia and 25(8 %) from Europe outside Norway.

In order to understand the why the number of foreign-born children have higher proportion; we have to understand the Norwegian infection control program for tuberculosis. All the children who were born in high-risk countries are screened within a short time after arrival in Norway should undergo tuberculosis testing.(45) According to the public health institute, all the asylum seekers or other persons planning to stay for more than three months in Norway must be tested for tuberculosis infection (45) Any other who have the risk of infection and where there is medical suspicion of infection are required to be examined(45). The native Norwegian are screened if there is suspicion of infection or exposed. 97% of the Norwegian children are vaccinated through the child vaccinations program(43). Every municipality has tuberculosis control program as part of infection disease control program, and municipal health officer can trace contacts to find the source of infection or to find the person infected in case of suspicion (45). Norway has an incidence of 7/ 100 000 inhabitants and 400 new cases every year(45) From this point of view, the native Norwegian has little risk factors and it is screening is unnecessary. The Norwegian children are also safeguarded by laws in that all persons who have been in countries with high tuberculosis endemic regions with more than three months and works with health services, teaching and all kinds jobs related to children have to submit a certificate from the health services.

Most of the participants that we had enough documentation, more than 50%came from Africa including east and West Africa. East African countries like Ethiopia and Eritrea and Somalia are highly represented. Some central and West African Countries had also some cases. Data from MSIS confirms that most of TB disease patient comes from Africa. This also indicated by the Norwegian Institute of Public health that number of patients in general population comes from Africa followed by Asia consequentially from 2007-2014(45).

5.3The adequacy of treatment of childhood tuberculosis in North Norway

All Six patients had TB disease were given six- months treatment, with Isoniazid, rifampicin. Ethambutol and pyrazinamide were also provided in the first two months of treatment. The drug administration was that monitored by DOTS and according to the guidelines of FHI.

The out comes that all of them were clinically health at tend of treatment. All of the six patients were clinically healthy at the end of treatment. Those with active tuberculosis were followed up by culture. Those who start treatment received advise information on the treatment, procedures and DOTS. The same drug regime is recommended by WHO national

plans for active tuberculosis in children (18). Norway had a treatment default rate zero according to the joint European Centre for Disease Control and WHO(48). The FHI institute also recommends treatment with four drugs treatment with DOTS program.

The control of the treatment is done by the clinically and by laboratory tests. The literature shows that interferon gamma can be seen up to 6 months after finishing of the treatment. IGRA test has shown different results both by decreasing and increasing after the start of treatment. 70% for Quanti-FERRON and 46 % for T-SPOT.TB remained positive after 6 months (49) .

The treatment approach was that some of them got no treatment, some of them get treatment for three months and some of them for 6 months. Preventive treatment was given to children who high risk of latent progression to TB disease. Most importantly, they were treated to prevent disease, but it also reduces the number of persons who can develop potential infectious disease(45). FHI recommends treatement latent infection with Isoniazid 6 months or isoniazid and rifampicin for three months (45)

5.4The preference for diagnostic methods -IGRA

IGRA test was performed on IGRA (225/ 227), and 211 of there positive. The mean value for IGRA was 9,7, and the mode was 10. The value was smaller among the children under four years of age. IGRA was lower in lower age groups 0-5 år. The immature immune system, s and malnutrition affect IGRA. The Norwegian public health institute recommends two-step step test. Fist Mantoux test but individuals with positive Mantoux test should be tested with IGRA to detect tuberculosis. As from 2014, it is optional to use TST or IGRA or both. IGRA was tested to be effective in countries with low tuberculosis incidence. According the meta analysis in 2011 there was no difference in use of TST and IGRA, it is also notble that there was no differences in measurement of INFgama in latent and TB disease in children (50) .The metaanalye showed IGRA had a sensitivity of 83-84, and specificity 91-94% for latent infection. The majority of the study was collected from the low endemic countries. There are discordances and concordances between TST and IGRA. There were cases some patients were TST+/ IGRA− and IGRA + /TST− and it is recommend TST should be used in TB endemic (49) . Two of the 6 patients who had TB disease had had negative IGRA test. . There is no clear cut documentation for choose of IGRA than TST,

may be the practical aspect of IGRA has influenced the decision, which does not require the children to come twice for the test.

IGRA test has shown different results both by decreasing and increasing after the start of therapy. 70% for Quanti-FERRON and 46 % for T-SPOT.TB remained positive after six month(49) IGRA mostly used to diagnose latent infection, but I was also a supplement for active tuberculosis diagnostic. In this study, there are only very few who had immunosuppression. IGRA was tested to be effective in countries with low tuberculosis incidence.

Limitations

The size of the sample and the missing documentation are the main factors for limiting the use of this study for decision-making. But was the first study done on this area in recent years on children and adolescent tuberculosis. The low incidence of tuberculosis in North Norway limits the use this result for other regions.

Conclusion

The study shows that the current management of paediatric tuberculosis at UNN follows the national guidelines adequately. . Children born in North Norway have little risk for Tuberculosis infections. It is unnecessary to screen children in born Norway unless suspicion. The current screening for foreign-born children should continue. The future study must have access to other hospitals, cooperate with the tuberculosis coordinator and have the accessibility to get more information, for example from a pharmaceutical register in addition to laboratory and DIPS. I also recommend that may be some more variable included like the origins of the family. Further study is needed to change the current practice of childhood tuberculosis in North Norway.

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