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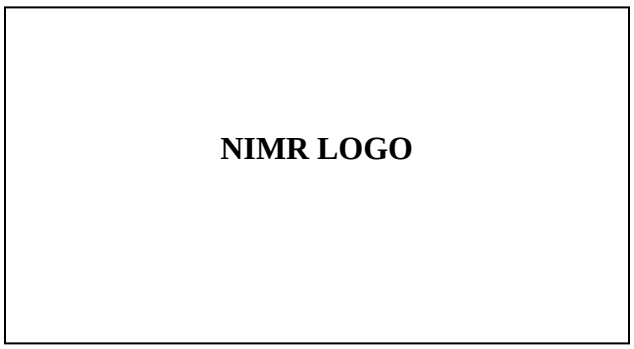

MANKIND AND TUBERCULOSIS: THE STORY YESTERDAY, TODAY AND TOMORROW

DISTINGUISHED GUEST LECTURE (INAUGURAL)

BY

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NIMR DISTINGUISHED GUEST LECTURE SERIES: NO. 1

Tuesday, 15th November 2010

1.0 Why Tuberculosis?

I am sure some of you in the audience will be asking, why this topic? To set your minds at rest, I have decided to talk on tuberculosis for the following disturbing reasons:

- Effective preventive and treatment interventions have been available for the control of TB for over 60 years, yet the disease still remains a global serious public health problem today.
- There was a resurgence of new cases of TB globally in the early 1990s and the World Health Assembly declared TB a global Public Health Emergency, in 1993 and in the same year recommended the DOTS strategy to help control the disease in the various countries. Several countries have since adopted and implemented this DOTS strategy, yet new cases of TB are still occurring in both the developed and developing countries.
- The world is at the verge of losing the battle to TB as current global control global efforts are being significantly retarded by the raving HIV/AIDS and the emergence of MDR and XDR-TB. Global TB morbidity and mortality rates are getting increasingly disturbing, even in the 21st century.
- Every 20seconds someone dies of TB around the world.
- "TB any where is TB every where"
- These unacceptable developments and statistics have put TB on the global health priority and a health topic that should be discussed at any given opportunity

2.0 Straying into the Field of Tuberculosis

My journey into the field of Tuberculosis was quite accidental and an exemplary case of giving close ears to the words of the elders.

After my Ph.D programme in the University of Glasgow, Scotland, I returned to the country in 1979 to resume duties with the Nigerian Institute of Medical Research, Lagos, In my post-graduate studies, I worked on Bordetella Pertussis (Whooping cough) and had hoped to continue in this area on my return to the country. However, on resumption I discussed my career plans in research with the then Director of the Institute, Professor Cyril Enweonwu. After a lengthy discussion, he suggested to me to consider the option of working on TB instead of whooping cough. He informed that TB was a more serious public health problem in the country than whooping cough at that time. My subsequent review of the literature, showed that in as

much as the disease was a serious problem in the country, available scientific data on the epidemiology, clinical management and the overall burden were very minimal. There were obvious information gaps that needed to be filled on TB in the country. The need to fill these information gaps informed my conviction to work on TB. I returned to inform the Director about this and finally got his approval to work on Tuberculosis. This was how I stayed into the field of tuberculosis. My goal was to contribute to understanding the true epidemiology as well as reducing the burden of the disease in the country. This was to be achieved through generating valuable information and data that will inform improvements in control interventions and enhance evidence-based policies and strategiesfor its containment.

With this approval, I then fully settled down to my research duties in the institute. After having decided to work in this area, my initial task was to set up a laboratory for tuberculosis in the institute as there was none when I arrived. With adequate support from management, I set up the first TB laboratory in NIMR with capacity for microscopy and culture in late 1981. Though this was indeed a small laboratory, it marked the beginning of my research career in the field of tuberculosis which spanned 30 years this year. With the able support of a few younger and dedicated colleagues, some of whom are here present- Dr. Onwujekwe and Dr. Onubogu. I ventured into TB Research.After having navigated in this field for this period,it is my singular honour and delight to share with you today my experiences, aspirations, challenges and contributions to the control of tuberculosis in Nigeria.

In making this presentation I will like to focus on the following areas:

- **High lights of the historical landmarks for TB**
- **TB Pathogenesis and Global Epidemiology**
- **TB control globally and in Nigeria within the following periods:**
- **1980-1990**
- **1991-2010**
- **2011 and beyond**

Under each period, relevant issues relating to global advancement in case detection, diagnosis, pathogenesis, epidemiology as well as clinical care and management will be discussed.

3.0 HISTORICAL LANDMARKS

Tuberculosis is an ancient disease which dates back to the early dynastic times; around 3700 BC. The eminent Greek physician, Hippocrates gave an excellent description of the disease between 460 and 377BC. Since then the disease has been with mankind and significant efforts have been made globally, over the past several centuries, to control and contain the disease. Today abundant information on the diagnosis pathogenesis, global epidemiology, and clinical management are available and TB is now curable.

Efforts to come to this stage of effective control and treatment of TB were enormous. In this presentation, I will like to share some of these important remarkable development and achievements. Since these will essentially be for information and records, I have decided to reflect them in Appendix I.

4.0 Brief Pathogenesis and global Epidemiology

4.1 Pathogenesis of TB

Within the 20th Century, Scientists and researchers succeeded in clearly eliciting the pathogenesis, of tuberculosis. A brief description of the various aspects of the disease process, through exposure, transmission infection and active disease is herein presented.

Figure 1

- Pulmonary tuberculosis is caused by the bacterium, Mycobacteruim tuberculosis.
- Tuberculosis is spread from person-to-person through the air

- When a person with active case of TB coughs or sneezes, he creates infectious aerosol containing droplet nuclei. These are tiny microscopic droplet containing TB bacteria which are released into the air
- When susceptible individuals inhale these droplet bacilli, they become infected. When these droplets are inhaled, the tubercle bacilli are usually deposited in the lower lung zones.
- One active case of TB has the potential of infecting 10-12 individuals annually.
- Once a susceptible individual is infected with the tubercle bacillus, a local inflammation reaction develops in the lung and this is usually asymptomatic. Subsequently one of three things may occur:
    - The infection may remain dormant in the lungs if the immune system of the individual is intact. The bacilli will not multiply and this will remain a latent infection.
    - The bacilli will multiply if the immune system is low or compromised and the infection will progress to an active disease
    - The bacilli can get into the lymphatic system or blood stream where they can spread to other parts of the body and cause miliary or extra pulmonary disease

Risk Factors

The risk factors for pulmonary TB include: close contact of persons known or suspected to have TB; people including children from areas with high incidences of TB; residents and employees of high-risk congregate settings; health care workers who serve high-risk clients. HIV infection is now the greatest risk factor.

Symptoms of Active TB

The major symptoms of active pulmonary TB are: prolonged productive cough for upwards of 2-3 weeks, pain in the chest, night sweat, fever chills, weight loss; loss of appetite and blood stained sputum.

Other types of Tuberculosis

Though this presentation is essentially focused on pulmonary tuberculosis, it will be in-complete if other forms of tuberculosis are not highlighted. Mycobacterium strains can infect other organs of the body apart from the lungs. These are referred to as extrapulmonary tuberculosis. These other strains of infecting mycobacterium are often referred to as atypical mycobacterium.

Frequency of different forms of extra pulmonary tuberculosis, as documented in literature showed that 42% are within the lymphatic organs, 21% (pleural); 11%(Bone/Joint) 7%(genitourinary); 5%(Meningeal); 4%(Peritoneal) and 10%(others). Essentially the atypical Mycobacteria strains include M.Kansasi, M Xnopi, M.Ulcerans

TB CONTROL IN NIGERIA 1980 - 1990

Initial Challenges of TB Control in Nigeria

By 1981, adequate diagnostic tools had become available globally for the detection of active cases of the disease. Effective drugs for the cure of the disease were also available. Using these tools several countries across the world were able to articulate and implement well organized TB control programmes which helped to improve the situation in their communities. The strategic thrust of most countries was to detect active cases and provide effective treatment. Most countries implemented active case finding initially but subsequently resorted to passive case finding and organized chemotherapy. By the late 1970s and early 1980s after effective drugs were in place most countries were able to establish Coordinated National TB Programmes for the control of the disease in their countries.

However at this time in Nigeria, there were no formal or organized national strategies for TB control in the country and TB care wasessentially the responsibility of the state governments. A few of the Infectious Disease Hospitals (IDH), which were inherited from our colonial masters across the country and some missionary hospitals for served as chest clinics where new suspected TB cases were referred to and, for diagnosis and treatment Diagnosis of a case of TB was essentially based on clinical symptoms and chest X-ray findings because capacities for sputum microscopy and culture were very minimal. When cases were diagnosed, patients had to pay for their TB drugs. Several short and long term regimens were implemented often not in accord with the standard recommended regimens and with minimal supervision or follow-up. Affordability of treatment was a great issue, as it was greatly influenced by the patients financial capacity. Also because the stock of drugs in the health facilities was often minimal or not often available, a significant number of patients bought their drugs from pharmacies or road side chemists. A good number of patients also patronized the traditional healers.

These haphazard diagnostic and treatment practices were bound, to encourage under-detection of active cases in the communities, misdiagnosis of cases, faulty prescription, inadequate drug intake as a result of poor finances of the patients and stock out of drugs, treatment failure, relapse and resistance. Under situations like this there is bound to be continuous transmission of the infection the communities. These were the initial challenges I observed and which I thought should be addressed to improve the level of TB care. However because the capacity of our new TB laboratory in NIMR at that time was small, we decided to start our contributions to TB controlwith Lagos and gradually scale up to other states. Our first contribution was to provide microscopy and culture back-up services to the six chest clinics in Lagos State. This was to help enhance their case-detection rates and minimize misdiagnosis. These services were provided from early 1982 and it indeed laid the foundation for organized laboratory services for TB in LagosState.

Subsequently, we commenced some research studies to examine the possible impact of the erratic nature of TB care on diagnosis Clinical Management and drug resistance. In conducting these studies we also attempted to generate some data or information on the burden and epidemiology of the disease.

Impact of Diagnosis

Inadequacy in the laboratory component of the health care delivery system in Nigeria and other developing countries in the early and late 1980s resulted in the diagnosis of tuberculosis being based mainly on clinical symptoms and radiological features. However, it was long documented that the microbial spectrum of the etiologic agents of respiratory infections span from viruses, through bacteria to fungi. Furthermore, pulmonary diseases with symptoms clinically and radiological indistinguishable from those of pulmonary tuberculosis were shown to be caused by these other bacteria and fungi agents as well as strains of atypical mycobacteria (KilPaterick et al 1978, Osogbaka 1984, Tsukamera and Ohta 1980).

Quite a number of patients who were diagnosed in Lagos and other parts of the country at that time, based on Clinical Symptoms and X-ray were reported as not responding adequately to treatment (Gutmann, et al, 1983). There was therefore the probability that these cases may be infected with

other agents but were misdiagnosed for tuberculosis and therefore not responding to anti-TB drugs.

Furthermore only 3% of case-detection of true TB cases were recorded at that time using clinical symptoms and chest x-rays. To examine the true situation in Lagos, we conducted some studies in the six Chest Clinics in the state. The six Chest Clinics were located one in each of the then six Local Government Areas of Lagos state namely, Lagos Island, Yaba, Ikeja, Apapa, Ojo and Epe. In the first study, which was carried out between January and December 1984, we decided to examine the case detection rate based on microscopy and culture; then to determine the various strains of Mycobacterium involved in pulmonary infections in the state. Sputum samples were obtained from randomly selected 668 patients who had presented at the six Chest Clinics with symptoms of broncho-pulmonary disorders.

The sputum samples were screened for acid-fast bacilli (AFB) by ZN microscopy and culture on LJ slopes Results showed that sputum samples from 126 (19%) of the patients studied were positive for AFB by microscopy while 104(15%) were positive by culture. A further identification of the 102 Mycobacterium isolates showed that 87(85%) were strains of M.tuberculosis, 6(6%) as M.avuim; 4(4%) were M.bovis; 4(4%) were M.kansasii and 1(1%) were M.fortuitum (Idigbe et al 1986). Our Study documented that with additional laboratory services, TB case detection rates in these Chest Clinics were significantly improved from initial levels of 3% to between 15%-19% . without laboratory support, these Chest Clinics just detected highly clinically suspected cases based on clinical symptoms and X-ray, cases of TB.

However, with the provision of culture services, data from this study not only confirmed cases of TB but highlighted the involvement of strains other than M.tb in pulmonary infections amongst these patients. Of major public health importance was the isolation of M.bovis from some of these patients. The only earlier report of involvement of bovine mycobacterium in human pulmonary infections in Nigeria was that of Alhaji and Schnurrenberger (1977) who documented a 10% incidence rate in four of the northern states of the country. The significant risk of consuming unpasteurized milk was highlighted as M.bovis was reported to be a zoonotic infection transmitted from cattle to man. As at 2006, it was estimated that as much as 13% of the

tuberculosis diseases in humans within a local setting in Ibadan, Nigeria were cause by strains of Mycobacterium bovis (Cadmus et al 2006)

Pulmonary Norcadiosis

As this study was being carried out in Lagos some studies in the eastern part of the country documented the significant involvement of Norcardia strains in pulmonary infections (Njoku-Obi 1980, Osogbaka, 1984). These reports indicated that pulmonary diseases caused by Norcadia in patients were often misdiagnosed for tuberculosis.Similar reports were also documented in some other countries in West Africa.(Murray et al, 1961, Frazier et al 1975). Also of importance is that Chest X-ray of infections with Norcadia were indistinguishable from that of M-TB. Based on these reports we conducted a study to investigate any possible involvement of Norcardia strains in pulmonary diseases in Lagos. Between 1982 and 1986, we studied 320 randomely selected patients who presented in the six chest clinics in Lagos. These patients were clinically diagnosed as suffering from acute TB or chronic bronchopulmonary infections. The patients were diagnosed based on clinical history which included abnormal chest X-ray, persistent cough with the production of purulent sputum and presence of haemoptysis. Sputum samples were obtained from these patients and screened for Mycobacterium as well as for Norcadia stains by adequate microscopy and culture. Techniques results obtained showed that 58(18) were infected by strains of mycobacterium alone, 31(10%) were infected by Norcardia species alone while 9(3%) had mixed infections of Norcadia and Mycobacterium strains. (Idigbe et al 1992).

Table 1

DIFFERENTIATION OF ISOLATES INTO MYCOBACTERIUM AND NORCADIA STRAINS BASED ON BIOCHEMICAL RESULTS

	Controls		Mixed Isolates		Single Isolate	
Mycobacteria						
- Catalase activity	+	-	+	-	+	-
- Niacin production	-	+	-	+	-	+
- Tellurite reduction	+	-	+	-	+	-
- Nitrate reduction	-	+	-	+	-	+

- Number of Isolates	-	-	3	6	7	51
- Strains identified	AM	MT	AM	MT	AM	MT
Norcadia **Hydrolysis of**:						
- Caesin	-	+	-	+	-	+
- Tyrosine	-	+	-	+	-	+
- Xanthine	-	-	-	-	-	-
Number of Isolates			7	2	23	8
Strains identified	NA	NB	NA	NB	NA	NB

(*Idigbe et al, 1992)*

AM - Atypical Mycobacterium
MT - Mycobacterium tuberculosis
NA - Norcadia asteroids
NB - Norcadia brazilliensis

A pertinent observation was the concomitant occurrence of pulmonary norcadiosis with pulmonary tuberculosis in some of the patients. This was found not to be unusual as cases of such mixed infections have earlier been reported in Nigeria and other countries (Hosty et al 1961; Osogbaka, 1984). The TB cases responded adequately to treatment with Isoniazid, Rifampicin para-amino salicylic acid and streptomycin. The patients with Norcadia infection also responded adequately to treatment with co-trimoxizole, a sulphonamide. The patients with mixed infections of Mycobacteria and Norcadia strains responded adequately to the anti-TB regimen in addition to co-trimoxizole. This study further documented the involvement of Norcardia strains in pulmonary infections in Lagos as has earlier been reported in Nigeria and other African countries. The overall findings highlighted the usefulness of microscopy in the routine diagnosis for TB and further strengthened the need to add microscopy to X-ray and Clinical symptoms in the diagnosis of TB and other respiratory tract infections.

Clinical Management: Short vs Long Term Treatment Regimens

The first half of the 20th century witnessed the discovery of new anti-TB drugs which finally made TB a curable disease. Earlier attempts at using just a single drug in the treatment of TB met with serious challenges of the emergence of resistant strains of the bacilli. Later, clinical trials showed that the resistant problem could be resolved by treating a case of TB with a combination of drugs. A combination of streptomycin, Isoniazid and para-aminosalicylic acid (PAS) or Thiacetazone was found to be effective but this combination has to be used for periods of 12-months or more. Streptomycin + Isononiazid + PAS or Thiacetazone for the first two months followed by Isoniazid + Thiacetazone for 10 months. This long course regimen though cheap and effective had serious challenges mainly compliance to drug intake as well as the risk of interrupted supply of drugs. This regimen was reported to be associated with high rates of default, treatment failure, loss to follow-up and emergence of resistance (Springett VH, 1971)

With the discovery of Pyrazinamide, Ethambutol and Rifampicin, shorter course combination regimens were developed. With these short course regimens, TB can be treated for periods of 6-8 months. Isoniazid + Ethambutol + Pyrazinamide + Rifampicin for 2 months followed by Isoniazid + Rifampicin for 4 months or Isoniazid + Ethambutol for 6 months. These short-come regimens though more expensive were effective and had higher adherence rates, and lower treatment failure rates as well as lower rates of loss to follow-up.(East African Medical Research Council, 1980).

In the 1980s and 1990s, there were no nationally coordinated TB control programmes in several developing countries. Furthermore, there were no recommended, standardized treatment regimens adapted for use in most of these countries. As a result, most countries especially the developing world were using both the long and short term regimes in the management of cases. Because patients had to pay for their drugs, treatment regimen was essentially dependent on the patient's financial capacity.

This situation was not different in Lagos at that time as both treatment regimens were used. However, there were no available data on any of the indicators for treatment outcomes for the two treatment regimens, to determine how effective they were. To generate relevant information in this area we conducted a study in Lagos between 1983 and 1986 to evaluate treatment outcomes of the long term as against short term treatment regimens administered on patients over this period 300 patients who were

accessing treatment in four of the six chest clinics in Lagos were enrolled for the study after consents were obtained. 172 of these patients were on short-course regimen and 128 were on long-course regimens. The patients were followed-up all through the duration of treatment and for one year after the completion of treatment. The sputum conversion, cure, failure and death rates as well as loss to follow-up were estimated for the patients in the two arms of treatment. Result obtained as reflected in Table 2.

The results showed a cure rate of 90% amongst patients on short course regimen as against 64% in patients on long term regimen. Also treatment failure rate of 10% was recorded for the short-course arm as against 36% in the long term arm. Furthermore, higher mortality and loss to follow-up rates; of 23% and 14% were recorded for patients on long term treatment as against 10% and 3% respectively in patients on short-term regimen. Alli et al 1987. The study documented that the short-term treatment regimen had better treatment outcomes with lower rates of treatment failure and loss to follow-up. It also documented the superior effectiveness of short course-chemotherapy and highlighted the urgent need to adopt the short-course treatment regiment under the National Tuberculosis programme in the country.

Table 2A

SPUTUM CONVERSION RATES AND TREATMENT OUTCOMES IN GROUPS OF PATIENTS ON SHORT AND LONG-TERM CHEMOTHERAPY

SPUTUM CONVERSION RATES				
Time of Conversion after initiation of treatment	**8 months Regimen 2SHPR/6HE n = 148**		**1 month 2SHT/10HT n = 81**	
	N	%	**n**	**%**
≤ 60 days	86	58	32	40
61 - 90 days	47	32	20	24
Non-Conversion after 90 - 120 days	15	10	29	36
TOTAL	**148**	**100**	**81**	**100**

TABLE B

OUT COME AT THE END OF TREATMENT AND FOLLOW-UP

SPUTUM CONVERSION RATES				
Treatment Outcome	**8 months n = 172**		**12 months n = 128**	
	N	%	**n**	**%**
Cure	133	90*	52	64*
Failure	15	10*	29	36*
Death	18	10**	29	23**
Loss to follow-up	**6**	**3****	**18**	**14****
TOTAL	**172**		**128**	

Alli et al, 1987

Impact on Drug Resistance

Critical observations from our earlier studies stimulated further interest to investigate the possibility of resistance amongst treated patient. Several of the patients failed to sputum convert even after 2-4 months of intensive phase of treatment. Quite a number of patients did not respond to treatment even after 8 months. They were also some patients who were classified as chronic cases of tuberculosis or bronchopulmonary infections.

Whether treatment is with short or long course regimen, it had been documented that resistance can still occur if patients are inadequately managed. Wrong prescription of regimens, treatment with poor quality drugs, irregular intake of drugs have been identified as some of the causes of resistance. These factors existed abundantly within the TB care strategies implemented in Lagos in the 1980s and early 1990s. In 1970, the first major outbreak of drug resistant TB was reported in the USA (Aeras 2011). Since after this report, several other studies have documented outbreaks and cases of drug resistant TB in various countries of the world. High rates of acquired resistance to isoniazid and streptomycin were reported in such countries as Korea (Carpenter et al 1982); Pakistan (Aziz A et al, 1986) Sierra – Leone (Gibson J., 1986), and Saudi-Arabia (Al Orainey et al 1989). The higher

rates of resistance to these drugs were ascribed to the more widespread use of the two drugs in the initial therapy of tuberculosis. These were the drugs that were also more commonly used for TB treatment in Lagos at this time (1980s)

The conventional method to test for drug resistance TB is by the DST (Drug Susceptibility Test) method on solid (Lowenstein-Jensen) medium. Before 1981, capacity for DST in the country was virtually minimal or non-existent. As a result there were no data on drug resistant TB in the country in the 1980's and early 1990's. However, by 1981, when the TB laboratory was established in NIMR, we were able to also establish some capacity for DST. This was essentially with the support of the University of Glasgow, Scotland and Institute Pasteur, Paris (France). With this capacity we decided to conduct the first study on acquired drug-resistant TB in Nigeria using Lagos as a pilot state. Between 1987 and 1990, a total of 96 TB patients of both sexes (between 18 and 55 years) with definitive histories of anti-TB treatment for 9-12 months and were still smear positive; were identified and registered for the study. These patients were recruited from the six chest clinics in Lagos.

Sputum samples were obtained from the patients and cultured on LJ slopes. The resultant isolates were subjected to susceptibility testing to anti-TB drugs (INH, STM, PAS, EMB, RIF) by the proportion method using LJ Scopes. The results obtained are reflected in Table 3.

TABLE – INCIDENCE OF DRUG-RESISTANCE AMONG THE THREE GROUPS OF PATIENTS WITH VARIOUS TREATMENT DURATIONS

	Number of Patients with Resistant Strains in each group				
DRUG	**1**	**2**	**3**	**Total**	**Percentage Resistance (%)**
- INH	15	14	7	36	38
- STM	12	11	5	28	29
- PAS	7	6	3	16	17
- RIF	1	1	-	2	2

- EMB	1	1	1	3	3
Resistance to one drug	14	13	6	33	34
Resistance to two drugs	6	5	2	13	14
Resistance to three or more drugs	3	3	2	8	8
Total resistance to one or more drugs	23	21	10	54	56
Total percentage of resistance per group	44	70	71	-	-
Total number of patients per group	52	30	14	96	-

Idigbe et al 1992

Group 1 - Continuous treatment for minimum of 6 months
Group 2 - Treatment for 6 – 12 months
Group 3 - Treatment for over 12 months

The drug susceptibility patterns of the 96 isolates showed that 34% were resistant to one drug, 14% to two drugs, 8% to three drugs while 56% were resistant to one or more of the drugs tested. Resistance to INH was most common (38%) followed by STM (29%), PAS (17%), EMB (3%) and RIF (2%). Resistant patterns also differed based on duration of treatment. More resistant cases were recorded in those who had 12 months regimen than those who had 6-8 months regimen (Idigbe et al, 1992). Similar observations had earlier been reported in India and Kenya where the incidence of acquired drug resistance in patients with definitive history of previous treatment increased with duration of treatment (Indian Council Medical Research, 1969, East African British Medical Research Council, 1978, Swai et al, 1988). This study first documented the rate and pattern of acquired TB drug resistance in any group of patients in the country. In our conclusion we proffered that the problem of acquired resistant TB in Nigeria can be minimized with the introduction of affordable modalities for better supervision of drug taking and an adoption on a nation-wide level of effective short-course regimens. However, to successfully implement such programmes which are usually expensive, there must be adequate political and financial commitment on the part of the Federal and State governments as well as other international organizations. This is to ensure a regular supply of primary anti-TB drugs, closer government control, effective

distribution of these drugs, total involvement of health personnel up to rural community level, intensified health education programmes for patients, medical and paramedical staff as well as the entire public. The short-course treatment regimens were finally adopted on the national level in Nigeria in 1993.

4.2 Global Epidemiology

Global Epidemiology

Tuberculosis (TB) is an ancient disease that mankind has been battled with over the past several centuries. The disease is believed to have been present in humans for thousands of years. Skeletal remains show that pre-historic humans (4000BC) had tuberculosis, and tubercular decay had been found in the spines of Egyptian mummies (3000-2400 BC).

During the 17th century, exact pathological and anatonomical descriptions of tuberculosis began to appear. The earlier references to the infectious nature of tuberculosis also appeared in 17th century Italian medical literature. Due to the variety of its symptoms, TB was not identified as a unified disease until 1820s and was not named Tuberculosis until 1839 by J.L. Schonlein. In 1882 Robert Koch discovered the tubercle bacilli and proved it is the infectious agent that causes tuberculosis.

The incidence of tuberculosis increased dramatically in Europe and North American during the middle ages and Renaissance era displacing leprosy. The incidence peaked between the 18th and 19th centuries as field workers moved to the cities seeking for jobs. The progressive increase in incidence was linked to the prevailing socio-economic conditions (overcrowding, poor nutrition, lack of hygiene and sanitation, deprived medical Care) that prevailed during the early years of unfolding industrial revolution. It was reported that of the 1571 deaths in the English city of Bristol between 1790 and 1776, 683 were due to Tuberculosis (William Woolcomber 1925). TB death rates in the village of Holycross in Shrophire between 1750 and 1759 were 1 in 6, ten years later 1 in 3. In the metropolis of London 1 in 7 died from tuberculosis at the dawn of the 18th Century. By 1750, the problem grew to 1 in 2. In the United States. TB accounted for more deaths in New York and New Orleans between 1810 and 1815.

With the development of preventive strategies and curative drugs in the 19th and early 20th centuries, several countries commenced the implementation

articulated strategies for the control of TB in their various communities. With these strategies, TB was brought under control in most of the developed and some of the developing countries. However in the late 1980's and early 1990s, a global upsurge of TB was reported (WHO 1992). New cases of TB were emerging from the developing countries and also in the developed country where hitherto TB had been thought to be under control. The World Health Assembly WHA declared TB a global emergency in 1993 and recommended for countries to adopt the DOTS strategy. This strategy has been adopted by several countries over the years but new cases of TB are still emerging. The HIV pandemic and the emergence of Multi-drug resistant TB have been identified as the main factors driving the upsurge of new cases.

Today, TB is still a major Public health problem, despite the fact effective tools for diagnosis and drugs have been available for the effective cure since the past 50 years. The WHO estimated that as at 2010, approximately 2 billion people globally, about one third the world population are infected with the TB bacilli (WHO, 2010). This translates to the fact that 1 in every 3 people in the world is infected. Each year 9 million people develop active TB globally and an estimated 2 million die. Shockingly, every 20 seconds, some one dies of TB around the world. TB has become the leading infectious killer worldwide. In 2010, TB was responsible for more than 5 times as many deaths as all natural disasters combined (Global TB Alliance, 2010). More people in South Africa die from TB each year than graduate from college. About one third of more than 42 million people with TB are also infected with HIV and TB is the leading cause of death amongst people living with the virus.

Presently, there is more TB in the world than ever before and resistance to the available drugs are growing. About 75% global burden of TB are within 22 countries of Africa, Asia and part of Eastern Europe. These are referred to as the high burden TB countries. Poor and erratic clinical management of some TB cases across the world have led to the emergence of cases of multi-drug (MDR-TB) and Extensively Drug resistant TV (XDR-TB). Every year, half a million new MDR-TB cases emerge and more than 130,000 people die of MDR-TB globally. In some locations over 20% on new TB cases are now MDR-TB and up to 10% of MDR-TB cases are XDR-TB. XDR-TB has been reported in at least 46 countries of the world. About half of global MDR-TB cases are in China and India.

Thus despite the huge armameutum presently available, the future of global TB control is still very gloomy as cases of primary infection with MDR-TB and XDR-TB are emerging and new cases of HIV infectious are also emerging. New vaccines are urgently needed to enhance prevention of infection. New potent drugs with shorter treatment duration are also needed to scale up MDR-TB treatment and reduce its spread.

TB Control In Nigeria: 1991-2010

The significant landmark in this era was the establishment of a National TB Control Programme in the Country. The era also witnessed an enhanced involvement and support from partners and international organizations for TB programmes in the country.

A National TB Control Programme

Between 1982 and 1990, significant efforts were made to establish structures and strategies to facilitate a nationally coordinated of TB control programme in the country. In February 1991 the Federal Government of Nigeria formally established the National Tuberculosis and Leprosy Control Programme (NTBLCP). The NTBLCP was established within the Department of Public Health in the Federal Ministry of Health. This is headed by the National Coordinator supported by other relevant support staff. Similarly, the State Tuberculosis and Leprosy Control Programme (STBLCP) was established within the Department of Public Health in the respective State Ministries of Health. This was headed by the State TB and Leprosy Control officer. At the last tier of government, a Local Government TB and Leprosy Control Programme was equally established in each Local Government Area. This was headed by the Local Government TB and Leprosy Supervisor (LGTBLS).

Coordination was top down where the National Coordinator, oversees the activities of the State Coordinator and the State Coordinator in turn oversees the activities of the Local Government Supervisor. In the same breath, reporting was bottom up; where the Local Government Supervisor reports to the State Coordinator and the State coordinator reports to the National Coordinator. This was the beginning of a nationally coordinated TB control Programme in the country.

Goal and Targets

The goal of the NTBLCP is to reduce significantly, the burden of Tuberculosis by year 2015 in line with the Millennium Development Goals) (MDGs) and the Stop TB targets.

Targets

The targets for tuberculosis control are:

- To detect at least 70% of the estimated infectious (smear positive) cases in the country.
- To achieve treatment success rate of atleast 85% of the detected smear positive cases
- By 2015 reduce TB prevalence and death rates by 50% relative to 1990 level.
- By 2050, eliminate TB as a public health problem

- To achieve these targets the NTBLCP adopted the strategy of "Directly Observe Treatment Short-Course" (DOTS) in 1993.

Diagnosis

Under the NTBLCP, diagnosis of TB rests mainly on the identification of the tubercle bacilli by sputum smear microscopy. Microscopy is carried out essentially in the microscopy centres and some other laboratories across the country Sputum production is difficult in children therefore diagnosis is based on clinical findings (especially failure to thrive or weight loss), family history of contact with smear-positive case, X-ray examination and tuberculin testing, culture (if available) and lack of response to broad spectrum antibiotic treatment.

Treatment

When a case of TB is detected through positive AFB microscopy, the individual is referred to the nearest DOTS centre for treatment with the appropriate regimen, after the patient must been have properly classified. Effective treatment is achieved through Directly Observed Therapy Short Course, where the patients swallow their drugs under the supervision of a health worker or designated treatment supporter (family or community member. Therefore health workers should ensure that patients receive treatment in health facilities closest to the patient's homes.

Types of Treatment Regimens

The following are the recommended regimens under the National Programme for the treatment of categories 1 and 2 patients.

- Category 1 regimen for Adults 2 RHZE/6EH or 2RHZE/4RH for treatment of new cases
- Category 1 regimen for children cases (CAT.1)
- Category 2 regimen for Adults 2SRHZE/IRHZE/5RHE for retreatment of relapses. Failure, RAD and others. (CAT 2)
- Category 2 regimen for children 2SRHZE/IRHZE/5RHE for retreatment of relapses, failures, RAD and others (CAT. 2).

Expansion of support for control activities in Nigeria

The era witnessed the coming on board of various partners, organizations and institutions into the TB arena in the country. These included CDC, USAID, WHO, KNCV,CIDA, FHI, IHVN, HARVARD, PEPFAR, GLOBAL FUND, TB-CAP, TB-CARE, DAMIAN FOUNDATION, GERMAN TB AND LEPOSY FOUNDATION

The support and activities of these partners greatly expanded and strengthened various components of TB programmes in the country. Today TB diagnosis and treatment in Nigeria are free.

Current TB Situation in Nigeria

Despite the fact that a National TB Control Programme was established in 1991 with various programmes being implemented across the country, the diseaseis still constituting a serious public health problem. Although the exact burden of TB in Nigeria is not known at the moment the WHO in 2009 estimated an incidence for all forms of tuberculosis to be 311 per 100,000 population and prevalence of 546 per 100,000 population (WHO 2009). These figures placed Nigeria 4th amongst the 22 High Burden countries in the world over 75% of global TB cases. Nigeria also ranks 1st in Africa amongst countries with the highest burden of TB.

As at the end of 2002 only 21 out of the 36 states and the FCT were implementing the DOTS strategy. However, with assistance from CIDA, USAID and other partners, there were rapid DOTS expansion programmes across the country that by the end of 2004, DOTS centres were in place in all the 36 states and the Federal Capital Territory (FCT). The number of LGAs implementing DOTS varied from state to state. As at December 2009, there were 3459 functional DOTS centres across the country. This was still at the level of 56% from the WHO DOTS expansion target which stipulated 1

DOTS centre per 25,000 population. Equally as at December 2009, there were 969 TB microscopy centres in 670 LGAs which translates to 86.% LGA coverage. Case-detection rate was 30% as at 2010 and this was abysmally low compared to the 70% WHO target. The treatment success rate was 82.5% still short of the 85% target. The implication of a case-detection level of 30% is that 60%-70% of active cases within the communities are still not being detected. These constitute a huge pool of index cases that continue to transmit the infection. New active cases of TB are still emerging in the country and case notification rate have been on the increase over the past several years, figure 2 this upsurge has also been closely linked to the growing HIV epidemic and the emergence of MDR-TB coupled with poor DOTS implementation programmes.

Figure 2

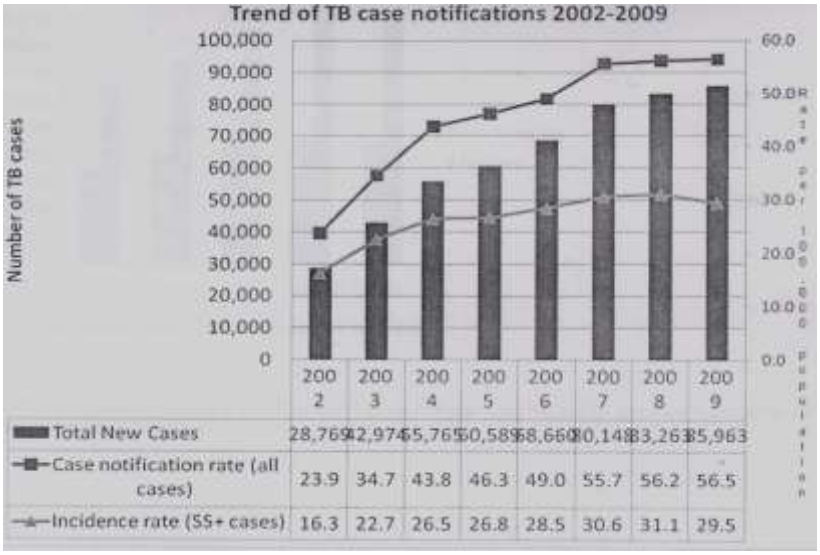


Figure shows the trend of total case notification rate for all cases, the total number of new cases and the incidence rate of sputum smear positive cases

Figure 3

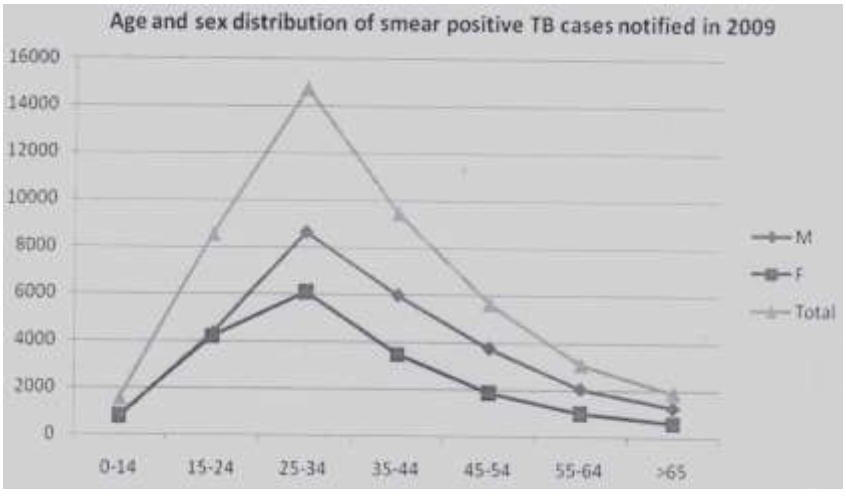


Figure shows the Age and sex distribution of smear positive TB cases notified in 2009.

Global Resurgence of Tuberculosis

With the development of effective drugs and regimens for the cure of tuberculosis in the early 1970s several countries across the world embarked on various strategies to control the disease. These strategies produced excellent results and by the 1980s, several reports indicated that the disease had been brought under control in most of the developed and a few of the developing countries (Luma, JC 2005). Case notification rates stabilized in some countries and actually declined in a few other countries. Thus prior to the 1990s, control efforts helped to reduce the burden of tuberculosis to a minor health problem especially in the developed countries.

However, by the early 1990s, a global resurgence of new cases of tuberculosis was reported. (WHO, 1999). New active cases were reported in the developing countries and even some developed countries where hitherto TB was presumed to be under control. Theough this increase was not too significant in several of the developed countries, it was quite enormous in countries of Africa, South-east Asia and the Western Pacific Region, (figure 4). The WHO African Region contains only 11% of the worlds population, but contributed 27% of the global total of notified TB cases in 2003. more than 34 African countries have notification rates of atleast 300 cases per 100,000 population compared to less than 15 per 100,000 population in developed countries. (WHO, 2005).

Figure 4: Trend of Notification rates for smear positive TB cases by WHO Region: 1993-2003

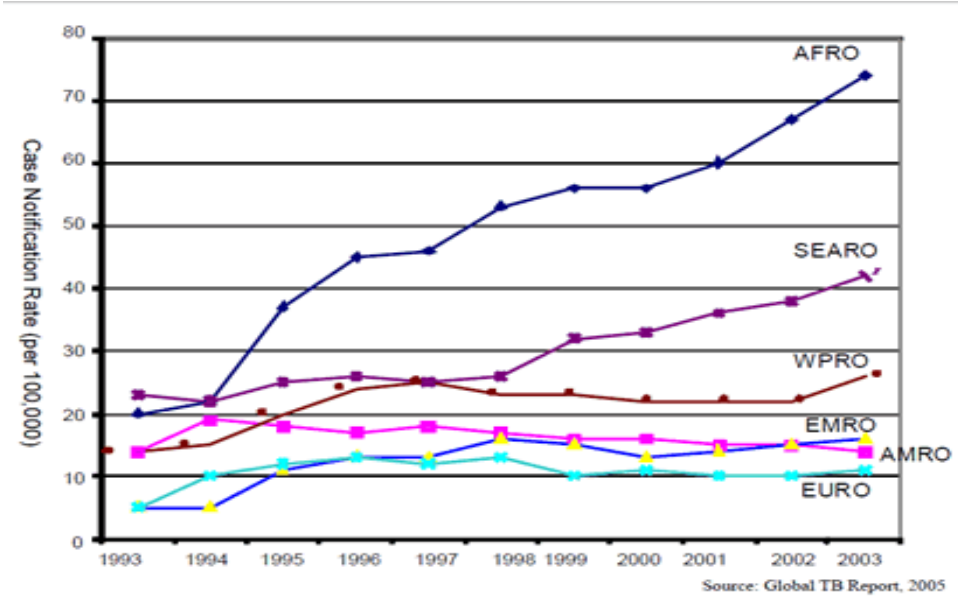
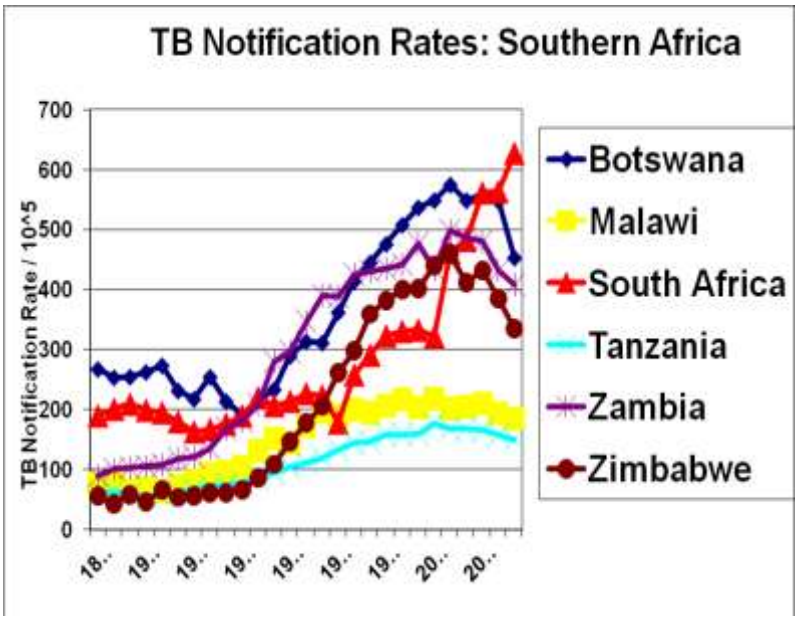


Figure 5

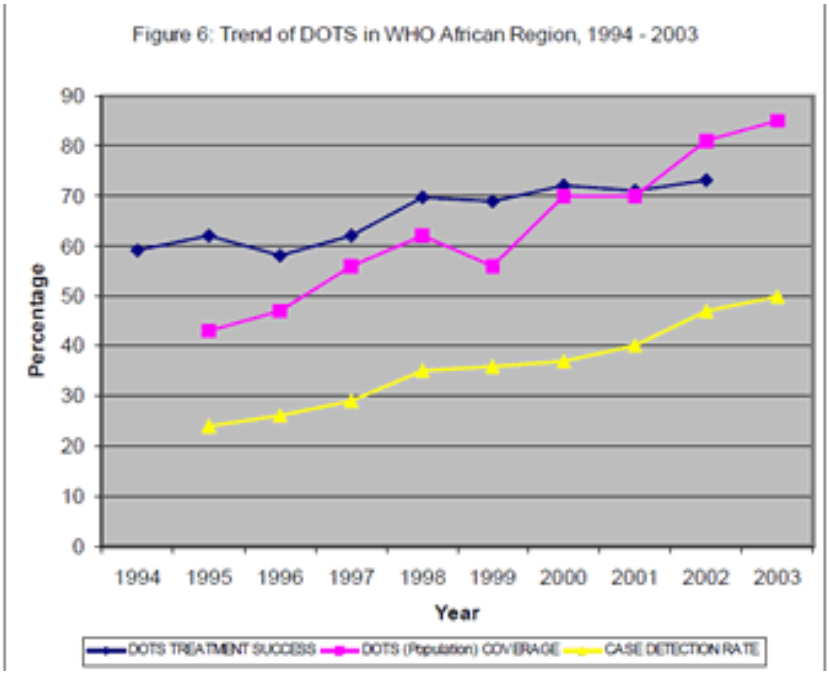


The progressive increase in the global morbidity and mortality rates associated with the resurgence of TB prompted the World Health Assembly to declare TB a global public health emergency in 1993 (WHO 1993). There was therefore an urgent need to reinvigorate and strengthen TB control programmes across the world to arrest the global upsurge. The subsequent WHO recommendation to strengthen global control programmes was for countries to strive to detect at least 70% of new smear positive cases intheir communities and ensure an effective cure of at least 85% of these detected cases. To achieve this, the WHO in 1993, recommenced that National TB programmes adopted the strategy of "Directly Observed Therapy Short Course" (DOTS).

Several countries have since adopted and implemented the DOTS strategy with various success rates. Figure 6, shows the trend of DOTS in WHO African Region between 1994-2003. the figure showed that DOTS coverage increased from 43% in 1995 to about 85% in 2003. however case-detection rate was still at a level of 47% and treatment success rate stalled at the level of 70%. While some countries in the region have since improved their case-detection and treatment success rates, these rates are still very low in some other countries (Nigeria inclusive)

Figure 6

Figure: Trend of DOTS in WHO African Region, 1994-2003



Earlier surveys on TB in the country even though based on tuberculin testing confirmed a high prevalence of TB in the country (WHO 1958, Pust et al, 1973). A few clinical studies aimed at the bacteriological confirmation of open cases of the disease reported no significant change in Ibadan from 1968-1975 (Alausa et al, 1977) while a 21% incidence rate was reported in Lagos in 19 82 (Idigbe and Onwujekwe, 1983). However, in view of the reported global upsurge in case-notification rates in several countries in the late 1980s and early 1990's we decided to conduct a retrospective study to determine the trend of the disease in Lagos between 1982 and 1992. The study involved a detailed review and analysis of available clinical records of the six chest clinics in Lagos State within the period. Results showed that the incidence of pulmonary tuberculosis in these clinics increased significantly from 21% in 1982 to 42% in 1992. (Idigbe et al 1995). This study though based on clinical records from chest clinics in Lagos strongly suggested that the burden of TB in the state and possibly in the country was on the upsurge as has been reported in various communities in other developed and developing countries (WHO, 1991). National data showed that as at 2009 the total number of new cases and the incidence rate sputum smear positive cases were still on the increase (FMOH, 2010). Apart from weak health

infrastructure and poor implementation of some components of the program HIV and MDR-TB were other factors.

The Challenges of HIV/AIDS and MDR-TB

The two main factors identified as significantly responsible for the resurgence and global upsurge of new cases of TB are the HIV/AIDS pandemic and the emergence of MDR-TB. The adverse impact of HIV and MDR-TB on global TB control has been enormous and some highlights, on these serious threats are herein presented.

Impact of HIV/AIDS

Global Perspectives

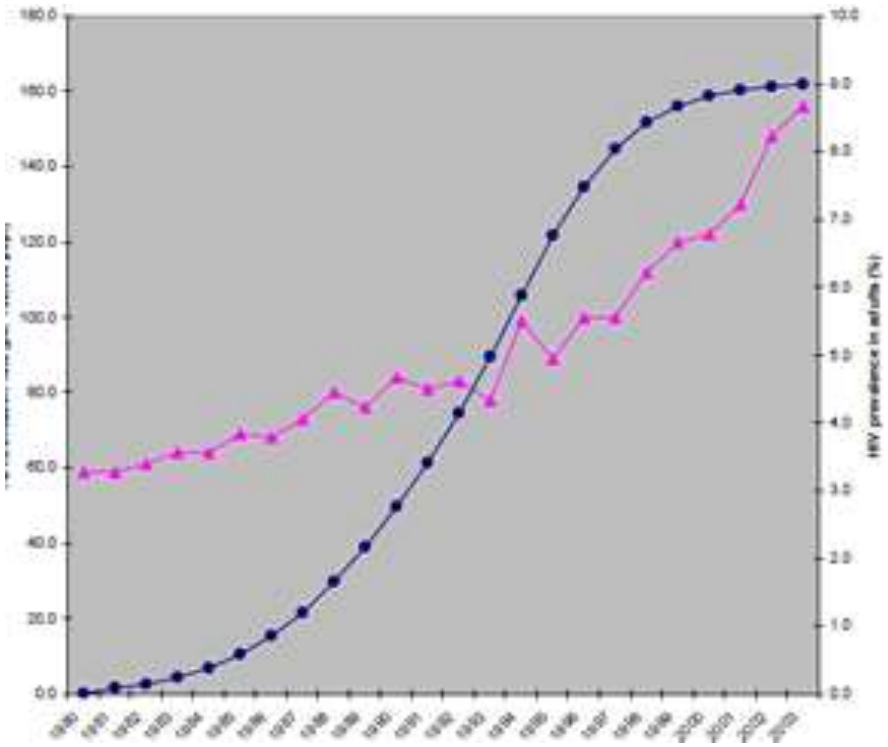
Earlier descriptions of the Acquired Immunodeficiency Syndrome (AIDS) in Europe and the USA did not mention TB as one of the manifestations of the disease. An association between HIV infection and TB was first recognized when AIDS was discovered among Haitans and intravenous drug abusers in the USA (Sunderam et al 1986). Since then, several studies have clearly indicated that the rapid growth of the HIV epidemic in many countries has also been matched with a dramatic rise in the estimated number of new cases of TB (Chaisson and Slutkin, 1989; Mcleod et all, 1988). HIV has now been documented as the most important risk factor for TB incidence and death. On the other hand, it has also been documented that TB co-infection enhances the multiplication of HIV and accelerates the progression of the infection. Because each speeds the progress of the other, the alliance between TB and HIV has had the greatest impact in regions of the world where the two infections are on the increase, particularly Africa and Asia.

It was estimated that over 33 million people were dually infected with HIV and TB worldwide in 2009 (WHO 2010). The combination of these 2 infections in one patient has grave implications for public health services. HIV accelerates the natural progression of latent TB to active disease by lowering cell-mediated immunity. It has been documented that an individual who is HIV positive and infected with latent. TB is 30 times more likely to develop active TB than an individual with latent TB but HIV negative HIV makes TB diagnosis difficult since co-infected patients more often have negative smear microscopy and chest X-ray features that are often uncharacteristic of TB. HIV has also impacted on the clinical management of TB as the cheap anti-TB drug Thiacetazone has been dropped because of resultant adverse skin reaction (Stephen-Johnson’s Syndrome) when used in

HIV co-infected patients. The use of streptomycin is also being highly regulated because of the possibility of HIV transmission through the use of unsterilized needles or syringes. Furthermore drug-drug interaction between some anti-TB and antiretroviral drugs, has created some problems for the parallel treatment of TB and HIV.

HIV/TB patients are also more likely to develop adverse reactions to treatment, increasing their chances of interrupting drugs and chances of developing MDR-TB. Currently, tuberculosis is the leading cause of death among HIV infected patients and accounts for one third of HIV/AIDS associated deaths worldwide. Approximately, 35% of all TB patients in sub-saharan Africa are dually infected with HIV compared to the global average of 8%. In some countries in sub-saharan Africa, up to 70% of patients with active TB are also HIV positive. Figure 6 shows the step increase in TB notification across the continent occurred about five to six years after the increase in the HIV epidemic The dual epidemics are of also growing concerns in Asia where two-thirds of TB-infected people live and where TB now accounts for 40% of AIDS deaths ( ).

Figure 7: HIV prevalence rates in adults and TB notifications rates, WHO African Region, 1980 -2003



To enable countries contain the emerging problems of TB/HIV co-infections, the WHO has recommended that countries establish a joint planning at National levels for collaborative TB/HIV activities between the NTP and NACP. The strategies of the 3Is were also recommended: Intensified case-finding; Isoniazid prophylaxis and Infection control. The thrust is to prevent TB infection in those infected with HIV and prevent HIV infection in those with TB infections. Eastern Europe and the former Soviet Union now have the fastest growing HIV epidemic and is a factor that is exerbating the problems with MDR-TB epidemic in these regions. The overlap of HIV/TB co-infection with MDR-TB and XDR-TB is a tremendous public health challenge that is reversing all the gains that had been made in controlling both TB and HIV/AIDS.

The Nigerian Situation

After the first case of HIV/AIDS was diagnosed in Nigeria in 1986, the disease, spread so dramatically that by 1991, cases had been diagnosed in all the states of the country. Between 1991 and 2008, new cases emerged and the prevalence rate in the country increased progressively. However,the prevalence stabilized between 2007 and 2009 and showed a slight drop in 2010. also from 1991, there was a progressive increase in the number of new cases of TB in the country (Figure 2)

However, despite the clinical evidence linking TB and HIV/AIDS in other countries (Elliot et al, 1990), available data on the prevalence of HIV infections in TB patients in Nigeria were indeed very scantly in the late 1980s and early 1990s.

Again at this point, we made some efforts to generate some information on any possible interactions between both infections in the country.We conducted a study to examine the prevalence of HIV infection among TB patients seen in Lagos, between 1989 and 1991, 536 patients who presented with symptoms of brochopulmonary disorders were randomly selected from the six chest clinics in Lagos. Venous blood and sputum samples were obtained from these patients and screened for HIV anti-bodies and AFB respectively. Of the 536 patients, 13 (2.4%) were diagnosed positive for HIV while 523 (97.6%) were negative. Also 88(35%) were AFB positive while 348(65%) were AFB negative.

When the HIV and AFB results were correlated we established a 5.3% HIV seroprevalence rate amongst the AFB positive patients (Idigbe et al 1994). This pilot study documented some interaction between HIV/AIDs and TB infections in a Nigerian community. on all our several visits to the chest clinics, we observed that quite a number of patients seen at the clinics were prison inmates. This observation prompted another study on HIV and TB in the three prisons in Lagos(Ikoyi, Kirikiri and Badagry). In this study we established a TB/HIV co-infection rate of 28% amongst the prisoners studied.(Idigbe et al 1997).This rate was significantly higher than the 5.3% rate earlier reported in the Chest Clinics. and suggested a higher TB and HIV infection rates in congregate settings like prisons. This highlighted the need to expand TB and HIV services in Nigerian prisons. A similarly high level of interaction (32.8%) of the two diseases was also recorded in a hospital setting in Ibadan (Awoyemi et al 2002). The various HIV sentinel surveys in the countryhave equally documented co-infection rates of between 2.3% and 32% between 1991 and 2008 (FMOH, 1989).

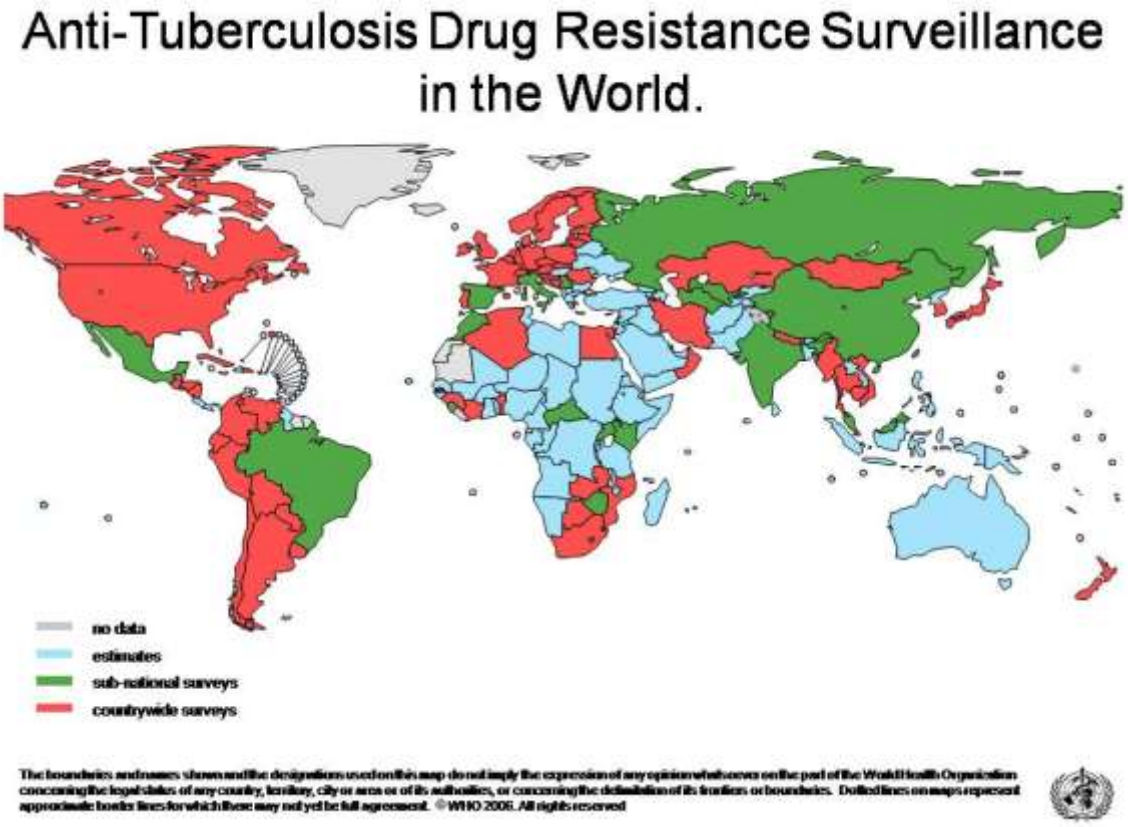
Several other studies, carried out in different other States of the country have also confirmed the association netween HIV and TB infections. Data from these studies showed a progressive increase in the levels of interaction; from of the 6.1% in 1992 through 28.6% in 2006, 44% in 2007 to 53% in 2008 with various communities (Anteyi EA et al (1996); Onipede et al (1999); Salami and Oluboyo (2002); Odaibe GN et al (2006); Lawson L et al (2008) Pennab et al (2010)

The interaction between HIV and TB is still a growing problem which is seriously impacting adversely on not only the efforts to control both diseases but on the overall health system in the country. Nigeria has since 2006, adopted and commenced the implementation of Joint HIV/TB programmes and the implementation of the 3Is (Intensive Case-Finding, Isoniazid Preventive therapy and Infection Control) for the control of the HIV/TB co-infection.

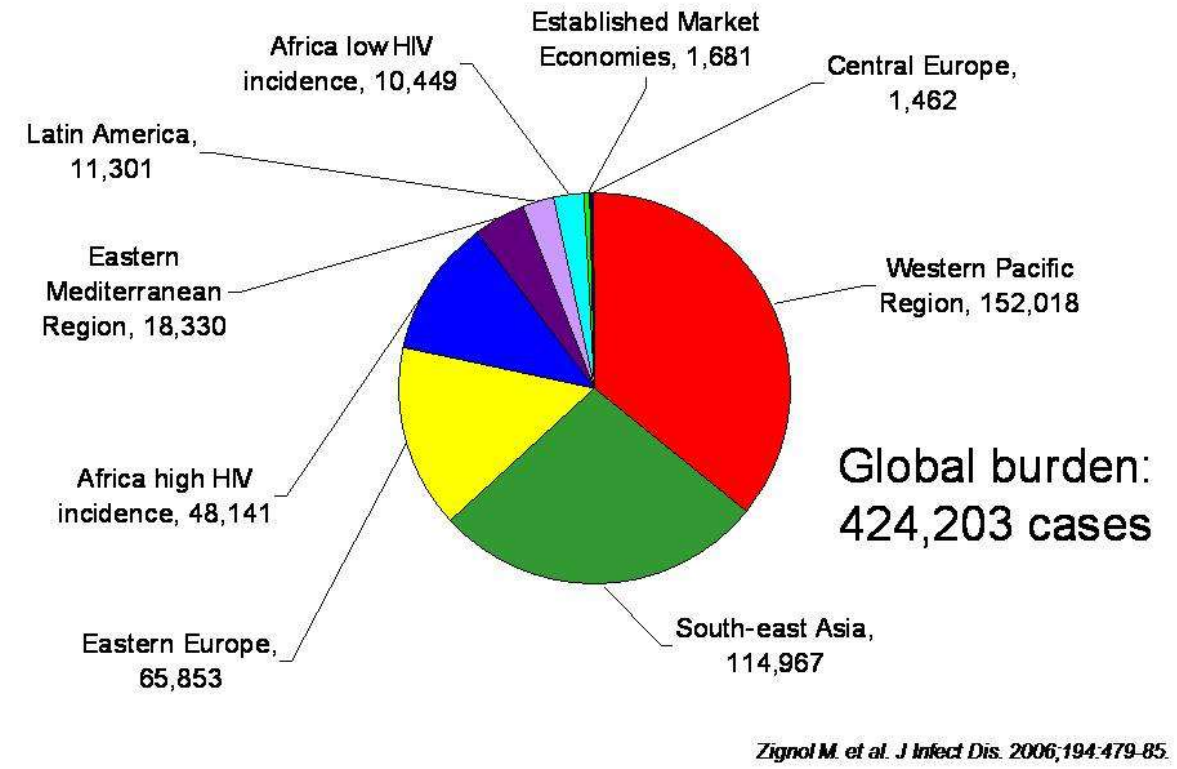
Impact of MDR and XDR-TB Global Perspectives

Another important factor that was associated with the resurgence of new cases of tuberculosis in the early 1990s was the emergence of cases of multidrug resistant TB, (MDR-TB). An outbreak of TB (MDR-TB) among hospitalized patients with AIDS **BR**…, Tokars JI, Grieco MH et al, 1992). Multi-Drug, Resistant TB is a case of TB that is resistant to Isoniazid and

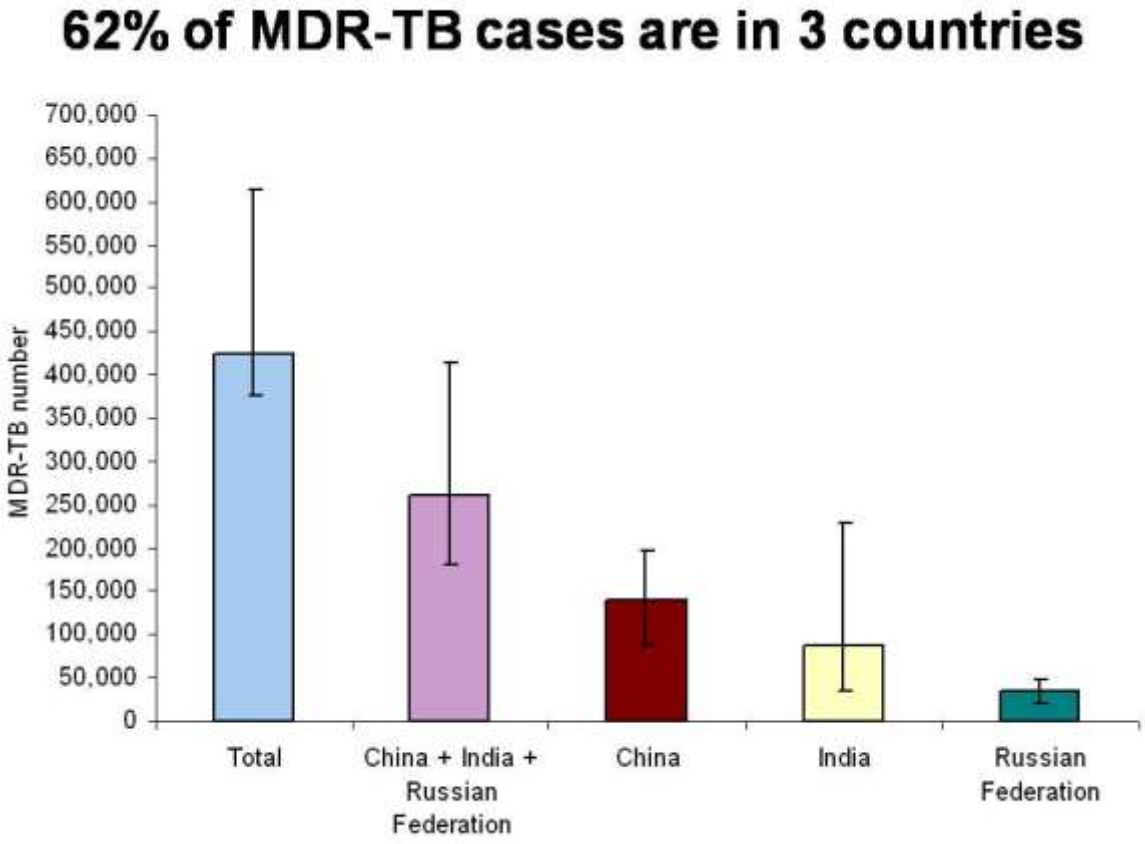
Rifampicin, the two most powerful first line drugs used in the clinical management of TB. MDR-TB is fostered by poor or faulty provider prescription, treatment with low quality first line drugs and irregular drug supply that interrupts patients medication. Also patients may themselves stop taking their drugs because they felt better or that the six to eight months course of treatment is so long and stressful.



By 2006, cases of MDR-TB had been reported in virtually all countries of the World and the global incidence was estimated between 500,000 new cases annually with a global prevalence estimated to be 2-3 times the incidence (WHO, 2008).



As at 2009, 62% of global MDR-TB cases were in China India and Russia.



Conventionally, DR and MDR-TB was diagnosed by the Drug susceptibility Testing (DST) using solid or liquid medium. Presently most of the developing countries have no capacity for DST. The implication of the lack of capacity for DST in most of the developing countries, is inability to diagnose MDR-TB cases in their various communities. In settings or communities where undiagnosed cases of MDR-TB exist, transmission of resistant strains of the bacilli will occur.

MDR-TB is basically transmitted the same way as the susceptible TB. Equally, a case of active, undiagnosed MDR-TB has the potential of infecting 10-12 susceptible individuals a year in the community. With time, this will lead to mini or localized epidemics of MDR-TB in such communities. To be able to break this chain of Transmission, cases have to be promptly and accurately diagnosed and treated. Because MDR-TB cases are already resistant to most of the effective first line drugs, these cases can only be treated with adequate regimen of second line drugs. If not treated or inadequately treated, cases are often fatal.

To halt the growing global incidence of MDR-TB the WHO recommended the DOTS plus strategy to diagnose and treat MDR-TB. The strategy involves diagnosing MDR-TB thorough quality assured drug susceptibility testing (DST) and treatment of patients with second line drugs under proper case management conditions. However, this strategy is still associated with several challenges, as a result global incidence of MDR-TB is still increasing.

Several mini epidemics have been reported in various countries (WHO, 2006). However a major outbreak has not occurred, but it may only be a matter of time before small outbreaks begin to merge into a global epidemic. Unless other efficient and affordable tests are available for its early diagnosis, undiagnosed cases will continue to transmit the infection in the various communities. This will pose huge challenges that will undermine global TB control efforts.

With enhanced efforts from the Stop TB Partnership and the global health community significant improvements have been made in the area of prompt and effective diagnosis of MDR-TB. The conventional solid medium DST is still in use; in addition the following new diagnostic tools have also been developed, the liquid culture technique using the BACTEC 960 MGIT machine, the bacteriophage-based test (FAST Plaque TB-RIF), the PCR based techniques, the Hain Line-probe assay and quite recently the GeneXpert technique. Capacity for Solid medium DST is still very limited in most developing countries. The Bactec liquid culture and the Hain line probe assay are therefore more commonly used presently. The costs are still unaffordable by most developing countries but generally these have led to improved diagnosis of MDR-TB cases globally. The Genexpert which determines resistance to Rifampicin in less than 2 hours and has a potential of evolving into a point of Care tool is still being rolled out in some developed and developing countries.

Another area that is also posing some serious challenges is the Clinical management of cases of MDR-TB. Cases of MDR-TB cannot be treated effectively with first line anti-TB drugs. Mortality rates are quite high with patients surviving only for a few weeks or months. Cases can only be treated effectively using second line drugs. The course of treatment takes much longer (18-24 months), its efficacy is lower and toxic side effects are higher. The treatment is specialized, complex, expensive and should only be undertaken at recognized centres. The complexity of the management of

patients is an indication for the treatment to be carried out exclusively by very experienced medical staff.

To facilitate access to second line drugs for the treatment of MDR-TB cases, the Green Light Committee (GLC) of the WHO Stop TB partnership was established in 2002, with the triple aim of preventing the misuse of second line drugs, promoting access to quality assured drugs and providing technical assistance to countries implementing DOTS plus. The GLC has been able to negotiate price reductions of up to 95% for the most expensive second line regimens and several countries have commenced organized treatment programmes for MDR-TB

As the world was battling to cope with MDR-TB, cases of Extensively Drug Resistant TB (XDR-TB) were reported in several regions of the world in 2006. XDR-TB is defined as Tuberculosis (TB) caused by TB bacilli that are resistant to atleast INH and Rifampicin among the first line drugs and to at least three of the six main classes of second line drugs. In some countries, over 20% of new TB cases are now MDR-TB and up to 10% of MDR-TB cases are XDR-TB. Cases of XDR-TB have now been diagnosed and reported in over 46 countries in the world. To combat this threat, WHO in October 2006 convened a Global XDR-TB Task Force in Geneva. The Task Force has developed a Global MDR-TB and XDR-TB Response plan. It is anticipated that the full implementation of this plan will save lives of 134,000 people affected by MDR-TB and XDR-TB annually (WHO, 2010).

MDR-TB in Nigeria

The WHO in 2008 estimated an MDR-TB prevalence of 1.9% among new smear positive cases and 9.3% among retreatment TB cases in Nigeria. There were mere estimates as data on MDR-TB in the country were indeed very scanty. Available data were the cases of resistance to three or more anti-TB drugs reported by the NIMR laboratory in 199 the 28 cases reported by the Zankli laboratory Abuja between 2006 and 2007 and the 29 case reported by the Damiah Foundation in 2007-2008 and the 12 cases reported by NIMR 2008-2009. With the growing incidence of MDR-TB globally the WHO advocated for all countries to strive to estimate the magnitude of the problem in their countries and developed effective structures for surveillance to be able to track the disease and plan effective control strategies. This call informed the expressed need to address the issue of MDR-TB in the country and set up structures to implement the DOTS plus strategy

MDR-TB Notification in Nigeria, 2006 – 2009 (Limited Data)

Reporting Institutions	Notified MDR-TB Cases				Total
	2006	2007	2008	2009 (Jan-Jun)	
Zankli Medical Center Abuja	12	16	9	10	**47**
NIMR, Lagos	0	0	9	3	**12**
DFB	0	29	5	O	**34**
Total	**12**	**45**	**23**	**13**	**93**

In 2007, Nigeria was successful with the Global Fund Grant to address the challenging issues of TB in the country. One of the major activities of focus under this grant was MDR-TB. However, at that time, there were no structures or strategies in place in the country to facilitate the implementation of this Global Fund activity. In the last quarter of 2006, I convened a meeting to stimulate a national discourse towards establishing structures and strategies for control of MDR-TB in the country. The meeting was held in NIMR and was duly attended by the National Coordinator of the TB Programme and the various stakeholders on TB in the country. At the end of the 2-day meeting, the consensus was to establish policies and structures for adequate administrative, diagnostic and Clinical Management for the control of MDR-TB in the country and a road-map was developed.

As a follow-up to the NIMR meeting, the Honourable Minister of Health set up a National Technical Committee for MDR-TB in the country in 2007. The committee which is comprised of various partners and stakeholders was charged with the responsibility of providing support and direction in programme planning, implementation, monitoring and evaluation of MDR-

TB activities in the country. I had the honour of being appointed the Chair of this committee; and currently still serving in this capacity.

The committee commenced work after its formal inauguration and has been able to accomplish the following:

- Developed national guidelines for the Clinical national and programmatic management of MDR-TB in the country.
- Developed a four year strategic plan for MDR-TB in the country
- Developed significant human capacity for the management of MDR-TB in the country.
- Doctors, Laboratory personnel, National and State programme managers have been trained on clinical and programmatic management of Drug-resistant TB as well as on Good Laboratory Practices
- With the support of partners, a 25 bed MDR-TB ward for the management of MDR-TB cases was established at UCH Ibadan by the Damuan Foundation. FHI has also established two MDR-TB treatment wards in the Mainland Hospital Yaba and the Specialist Hospital, Calabar.
- The committee applied and obtained approval for second line anti-TB drugs from the Green Light Committee of the Stop TB partnership.
- Over 50 patients with diagnosed MDR-TB have undergone or still undergoing treatment with 2nd line drugs at UCH.
- The Committee, working with the NTBLCP and with the support of the CDC, WHO and other partners conducted the first National MDR-TB survey in the country in 2009

The First National MDR-TB Survey in Nigeria

Like in many other developing countries data on MDR-TB were not readily available because of lack of adequate capacity for the diagnosis of cases. Capacity for DST, the converntinal tool for the diagnosis of MDR-TB was not available in many countries because of the cost essentially and the stringent requirements of WHO for infection control.

With the drive to turn around this situation and establish capacities for MDR-TB diagnosis in the country, I applied for and obstained a grant from the WHO and the Ford Foundation. With this grant, we were able to significantly expand and enhance our facilities for DST at the NIMR TB Laboratory. With this capacity established we were able to conduct

surveillance studies on MDR-TB in parts of South Western zone of the country.

We could still not conduct a national survey at that time because of our limited infrastructure to cope with a huge work load Also the fact that only one or two other laboratories in the country had capacities for DST. These capacities were also limited with regards to the number of samples that can be handled.

However, in 2006, the WHO endorsed a new molecular biology based diagnostic tool for detecting MDR-TB cases. This is the Line-probe assay developed by Hain Lifesciences in Germany. The technique can detect resistance to Rifampicin and Isoniazid directly from AFB smear positive sputum samples. With the technique, you do not need to work directly with the live bacilli and the infection control requirements are not as stringent as for DST. Moreso, results can be obtained within 24-48 hours. Thus a case can promptly be diagnosed and placed on treatment.

With the WHO approval of this technique efforts were made to establish this capacity in the NIMR TB Laboratory. I applied for and obtained a grant from the International Association of Nation Public Health Institutes (IANPHI) at Emory University, Atlanta. With this grant we were able to set up Capacity for the Hain Line-probe assay in NIMR in 2007. Laboratory personnel were trained and we commenced surveillance for MDR-TB in the country. Subsequently, capacity for the Hain assay was also set up in the TB laboratory in Zaria. With capacity of the Hain Assay in NIMR (South) and Zaria (North) and liquid culture at the Zankli Laboratory the National MDR-TB Committee thought there was enough capacity for a National survey for MDR-TB in the country.

A protocol was developed, different categories of clinical, laboratory and data management staff were trained. With this the first ever National MDR-TB survey was conducted in the country using the Hain Line-probe assay, with the support of the CDC and WHO. This was the first national MDR-TB survey globally, using the Hain Line-probe assay techniques.

Since then cases of MDR-TB in the country are being diagnosed in the NIMR, Zaria and Zankli laboratories. This has enabled the country set up facilities for diagnosis of suspected cases and improved surveillance of MDR-TB. The NIMR laboratory receives smear positive samples from

across the country for MDR-TB tests. This has improved diagnosis and surveillance and the quarterly reports from our laboratory and other Laboratories are usually forwarded to the National Programme office.

Quite recent studies established a 6.5% MDR-TB prevalence rate amongst TB patients seen in three State of South Western Nigeria between 2007 and 2009 (Idigbe et al in press). Lawson est al (2011) established an 8.0% MDR-TB prevalence rate amongst some culture positive cases diagnosed in Abiya, Ibadan and Nnewi between 2009-2010. on our recent studies in NIMR also established an MDR-TB prevalence rate of 4.8% amongst HIV positive patients seen in a DOTS centre in Lagos (Onubogu et al in press)

MDR-TB is still a maturing public health problem in the country as primary transmission and new cases are rapidly emerging in many communities. Urgent efforts must be put in place to control the spread. If allowed to spread will spell disaster and will reverse national and global gains that have been made in the control of TB over the decades. There must therefore be enough commitment and political will from Government to fully roll out the WHO recommended DOTs plus strategies to be able to stem the threat of MDR-TB in the country. It is indeed a time bomb waiting to explode if not defused at this time.

Policies and Health Systems Strengthening

In the last several years Nigeria witnessed the coming of board of several International organsiations and partners in support of TB programmes in the country.

The funding support for TB programmes increased several hundred folds in the past 2 decades and various partners supported different components of the control programme. All these supports were spread across the country from the states to the LGA.

In as much as these various supports were welcome, and helpful to the country, there was very minimal coordination of these efforts by the national programme. The resultant effect was that most of these supported programmes were running in parallel and most often not really addressing the areas of needs of the National programme but driving the agenda of the funding partners. Huge resourses were being invested in TB control but the expected results were not being achieved.

To effect a more Coordinated Control, the Honourable Minister of Health set up a National Inter-Agency Committee for TB control in Nigeria in 2002. The committee was to develop structures and strategies that will bring the various partners and stakeholders together with the National programme, to share areas of support and evolve coordinated action plans that will minimize duplication of efforts, even geographical spread of support and enhance national outputs while addressing the areas of need and priority of the national programme. I was appointed the Chair of this committee in 2004. This committee had representatives from all partners and stakeholders and within two years it came up with well articulated structures and strategies for operation such that the national programme had adequate coordination of their various activities.

The committee recommended the establishment a "Planning Cell Committee". This is to comprise of all the partners and other stakeholders supporting TB programmes in the country. The committee is to be headed by the National Coordinator. The Federal Ministry of Health and the national Programme must be informed on all funds coming in for support of the national TB programme. Subsequently, the National Programme and the funding partners will work together to come up with a workplan that will be in line with the strategic plan for TB control in Nigeria. The Planning Cell Committee is also to meet quarterly during which each partner will give a report of their activities. Through this medium, the National Programme and the various partners will be well informed of all activities going on in the area of TB control in the country. The Honourable Minister of Health approved the establishment of the Planning Cell Committee in 2006. Since then the committee has been meeting regularly and this has achieved a well coordinated support for TB control at the National and State levels.

At various times I had served in various National Committees on TB in the country. These include the National Committee on Networking of TB laboratories in the country; the WHO monitoring Committee on the implementation of DOTS in the management of Pulmonary Tuberculosis in Nigeria, National Technical Committee on Routine Surveillance for MDR-TB, and the Nigerian Stop TB Partnership. Through these various committees, I have been able to contribute to several National policies which have positively enhanced the control of TB in the country.

Strengthening health systems for TB control was another area of concern in the early 1990s and 2000's. The laboratory plays a very vital role in TB

control as that provides a definitive diagnosis of a case of active TB. However, laboratory services for TB in the country have been very weak, as a result earlier cases of TB were detected based on Clinical Symptoms and X-ray features. This was fraught with challenges of under-diagnosis and misdiagnosis. In the late 1990's, the National Programme commenced the establishement of microscopic centers across the country. This was to ensure adequate coverage of the country with regards to case detection. However, these were microscopic centres which only detected AFB in sputum samples. Capacities for culture, identification, DST were only limited to about 2-3 laboratories in the country.

Several Efforts were then made to expand laboratory capacities for TB in the country. In early 2000, NIMR obtained a grant to expand our TB laboratory facilities. With this grant and some further support, I was able to transform the small TB laboratory in NIMR to a National Reference laboratory in 2004. This became the first national Reference laboratory for TB in the country. This laboratory has been providing laboratory back-up services to various components of the national programme as well as support services to various health facilities across the country.

Again with the Global Fund Round 5 support, NIMR played the lead role in establishing six zonal TB Laboratories (Enugu, Jos. Ibadan, Port Harcourt, Maaiduguri and Kano). Plans were also put in place to establish the state TB laboratories. These efforts succeeded in strengthening laboratory services for TB in the country by creating a network of laboratories from the National through the zones to the states. Today, there is an additional Reference laboratory in Zaria with BSL3 facilities. A state laboratory with BSL3 facilities has also been established in Calabar. In all of these efforts, specific mention must be made of the Zankli laboratory in Abuja. this is a private laboratory that has contributed and still contributing immensely to TB control programmes in the country. By 2009, the TB Reference laboratory in Milan, Italy was appointed the supranational Reference Laboratory for Nigeria. Under this capacity, the Milan laboratory provide external quality assurance and proficiency testing for the National Reference laboratories in the country. Another important stride is that the NIMR laboratory is currently being upgraded to a BSL3 facility through a grant support from the USAID and FHI.

2011 and Beyond

With a number of structures and programmes already in place, the era of 2011 and beyond is expected to produce significant advances in the prevention, diagnosis and management of tuberculosis. After several decades of implementation of global programmes for TB control, a number of challenges and gaps have been identified. There are still no effective vaccines for the prevention of TB, diagnosis, especially in the era of MDR and XDR-TB is still posing a very serious problem in virtually all the developing countries of the world, the anti-TB drugs presently used for Clinical management were developed some fifty years ago, drug-resistant TB has emerged needing management with second line drugs, the disease is still strongly transmitted and new cases are still emerging in both the developed and developing countries.

Without addressing these challenges, the future of effective global control of TB will be jeopardized. In the bold attempt to address these challenges, the WHO set up a number of global organizations with varied objectives of addressing specific problem areas. A number of non-profit public-private partnerships also came on board to assist with addressing these challenges.

These organization include the, Stop TB Partnership, the Global Drug Facility, the Green light committee, the Foundation for Innovative New Diagnostic (FIND) and the Global TB Alliance. The Stop TB partnership was established in 2000 with the aim of realizing the goal of eliminating TB as a public problem and ultimately to obtain a world free of TB. It comprises of a network of International organizations, countries, donors from the public and private sectors, governmental and non-governmental organizations that have expressed an interest in working together to achieve this goal. The Stop TB Partnership have developed a global strategic plan for TB 2005-2015. The strategy is addressing Seven main areas: DOTS Expansion, TB/HIV, MDR-TB, New TB Drugs, New TB Vaccines, Diagnostics as well as Advocacy, Communication and Social Mobilization. All partners across the world are to work together to achieve the following Targets

- 70% of people with infectious TB to be diagnosed and 85% of them cured by 2005
- The global burden of TB disease (deaths and prevalence) reduced by 50% relative to 1990 levels by 2015
- Reduce the global incidence of TB to less than 1 per million population (Elimination of TB as a global public health problem) by 2050.

Nigeria is a member of the Stop TB Partnership and has since commenced the implementation of the various components of the global plan.

The FIND Organization has been working hard to develop simpler, cheaper and effective diagnosis tool that can be accessible and used even in the developing countries. The efforts of FIND led to the discovery of the line-probe assay for testing for MDR-TB. Quite recently a newer device, the GeneXpert has also been developed for diagnosis of MDR-TB cases. This device is quite safe and results are readily available within 4-6 hours. This will help countries to promptly and efficiently diagnose, TB, MDR-TB and Smear-negative TB cases in their communities. Nigeria has just concluded plans to roll out the use of the GeneXpert in some of the laboratories in the country. It is envisaged that this may eventually become a point of care device than can be used even in the hard to reach communities. The NIMR TB laboratory is one of the sites currently evaluating the device.

One of the important organizations which hold the key to the control of TB in the immediate future is the Global TB Alliance for Drug Development. The mission of the TB Alliance is to discover and develop better, faster-acting and affordable drugs to fight TB. Current first line drugs are nearly half a century old and are taken for 6-8 months. Long demanding treatment schedules prove too much for many patients and the resulting erratic or inconsistent treatment breeds drug resistance yielding deadlier, more difficult and expensive to treat disease. There was therefore the urgent need to develop faster-acting agents to treat both drug-sensitive and drug-resistant TB as well as being fully compatible with HIV/AIDS Treatment.

Several drugs have been developed and have undergone various phases of clinical trials. The most promising of all of these drug combinations is the regimen of Moxifloxacin +H+R+Z and Moxifloxacin +R+Z+E. these regimens are presently in the phase III Clinical trial and it is hoped that these regimens can treat susceptible TB in a period shorter than 6 months. Another promising regimen is the combination of a novel TB drug candidate-PA-824, Moxifloxacin and Pyrazinamide. This combination has been shown to have potentials as a single regimen to treat both drug-sensitive TB and MDR-TB in four months. Furthermore, this regimen has potentials for use by TB/HIV co-infected patients, with no anticipated drug-drug interactions with anti retrovirals. Several other candidate drugs and combination are in the pipeline of the Global TB Alliance.

Development of new TB vaccines have also been on the front burner of the Stop TB Partnership. In 2009, at least six different TB vaccine candidates both live and submit vaccines have completed initial phase 1 clinical trials. Three are currently in phase II trials. Assuming that at least one of the first generation candidates successfully completes phase III (efficacy) evaluation, licensure of a new TB Vaccine is anticipated around 2013-2014. Until that time, extensive resources are needed to conduct reliable Clinical trials in developing country settings.

Capacities for Clinical trials for new TB drugs and Vaccines are currently not available in Nigeria. However, we (NIMR) recently obtained a grant from the EDCTP and with this we are fast developing capacities for clinical trials for TB drugs and vaccines in the Institute. Human and infrastructural capacities are being developed and it is hoped that by mid 2012, NIMR should be ready to join the global initiative for drug and vaccine development for TB.

The period 2011 and beyond no doubt will produce newer diagnostic tools drugs and vaccines which will revolutionalize the global control of TB and lead to achieving the Stop TB target of eliminating TB by 2050.

My Joy

Apart from the various humble contributions I must have made towards the control of TB in the country, my greatest joy is to have set up a TB laboratory in NIMR when none existed. Then to see this two-room improvised laboratory grow progressively to become the TB National Reference Laboratory of the country in the mid 2000. furthermore, to eventually see this laboratory evolve to a Biosafety Level 3 (BSL3) Laboratory in 2011.

The initial efforts at setting up the NIMR TB laboratory met with a lot of challenged. The space was quite small as we had only 2 small rooms. We virtually had very few old laboratory equipment when we started. The first incubator and water bath we used were retrieved from pile of discarded equipment lying outside the present TB DOTS Clinic. These were refurbished and made functional for use. The initial set of test tubes and other relevant materials were also retrieved from this pile, property washed and decontaminated. We had no safety cabinet but had to supervise our carpentry department to build one made of wood based on the recommended

dimensions recommended at that time by the WHO. An extractor fan was mounted on the wooden safety cabinet and a UV light was installed. We also designed and produced wooden sloppy trays with wire gauze at the back, which we mounted in our water baths used for cooking solidifying our IJ slopes. We bought some plastic sandwich boxes with which we transported our sputum samples form the Clinics to the laboratory. To ensure reasonable infection control in the laboratory we mount 3 extractor fans in each of the two rooms of the laboratory.

"The journey of a thousand miles, they say, starts with the first steps" from a small 2-room laboratory in 1981 to a BSL3 TB Laboratory 30 years down the line is a dream come true for me. I feel fulfilled and I give GOD all the glory.

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Appendix 1

- 400B.C – The Greek physician, Hippocrates first described the clinical symptoms of TB, then called Phthisis or Consumption
- 1679 – Franciscus Sylvus described the lung modules characteristic of Tb infection which he termed "Tubercles"
- 1722 – Benjamin Marten first suggested that TB may be communicable from one individual to the other
- 1818 – Rene Laennec invented the stethoscope, thereby greatly facilitating the diagnosis of TB
- 1839 – J.L Schonien first used the term "Tuberculosis" for the name of the disease.
- 1859 – Brehmer established the first successful sanatorium for tuberculosis in Silesia, Germany
- 1882 – Robert Koch discovered the tubercle bacilli and proved it is the infectious agent that causes tuberculosis. It was named the Koch bacillus and later Mycobacteruim tuberculosis.
- 1885 – Ehrich developed the Acid-Fast Stain for the diagnosis of TB. This was later improved by Fraziehl and Friedrich Neelsen to produce the Ziehl-Neelsen Stain
- 1885 – Sir Robert W. Philip opened the first TB dispensary in the world in Edinburgh.
- 1895 – Roentgen, discovered the X-ray which became a basic tool for the diagnosis of tuberculosis
- 1907 – Intradermal tuberculin diagnostic skin test was introduced by Chales Mantoux
- 1907 – Friedrich, performed the first thoracic surgery as a clinical management of the disease
- 1908 – Calmette and Guerin began the development of a TB Vaccine at the Pasteur Lab in Lillie, France
- 1920 – The International Union Against Tuberculosis was founded
- 1921 – The resulting Bacille Calmette-Guerun Vaccine-termed BCG was first used in humans by Well-Halle and protected a new born infants in Paris
- 1928 – BCG accepted by League of Nations Health Committee
- 1930 – Several hundred babies accidentally given BCG contaminated with virulent strains. 74 of these children died and several had severe morbidity – "The Lubeck Disaster"
- 1930 – 2009 – Several solid and liquid culture media were developed for the diagnosis. Several serological, biochemical and molecular

biology based tests were also developed. Most globally adopted areculture on solid (IJ) and Liquid (BACTEC) medium

- 1945-1948 – International TB Campaign re-established confidence in BCG and administered BCG to over 8 million children in Europe. Based on the benefits WHO subsequently directed that BCG be integrated as an important component of the expanded Programme on Immunization (EPI).
- 1944 – Waksman and Schatz discovered Strepomycin, the first potent drug against TB. This was followed by the discovery of another drug Para-aminio- Salicylic acid (PAS)
- 1952 – Roche introduced Isoniazid and shown to be highly effective against TB.
- 1960 – Dr John Crofton proposed a combination regimen of Streptomycin, PAS and Isonizid after monotherapy management using each of these drugs resulted in resistance to these drugs.
- 1962-1966 – Three new drugs were discovered in successions: Thiacetazoe (1962); Pyrazinamide (1964), Rifampicin (1966). Various clinical trials over this period with various combinations of available drugs produced various important results.
    - Treatment can be effectively given on an outpatient basis
    - Therapy can also be effective when intermittently given
    - Development of long-term (12-18 months) chemotherapy
    - Developement of short term (6-8 months) chemotherapy

- 1970 – First outbreak of drug resistant TB reported in the USA
- 1988 – 1991 – Global resurgence and upsurge of new cases of TB reported
- 1993 – The World Health Organization declared TB a global health emergency. Directly observed Therapy short course (DOT) strategy was recommended by WHO.
- 1995 – The first recorded outbreak of MDR-TB reported in a London Hospital, HIV unit.
- 2000 -2002 – Several TB Partnerships inaugurate: Stop TB partnership, Green Light Committee, Global Drug Facility, Global TB Alliance.
- 2006 – The Stop TB Partnership launched its Action Plan to Stop Tuberculosis 2006- 2015
- 2007 – The WHO approved the Hain Line-probe assay for the diagnosis of MDR-TB