Tuberculosis

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"There is a dread disease in which death and life are so strongly blended that death takes the glow and hue of life, the gaunt and grisly form of death which sometimes moves in great strides, or sometimes at a tardy pace, but slow or quick, is ever sure and certain".

(Charles Dickens, Nicholas Nickelby)

In 1820 John Keats the great English poet, 24 years old, coughed a spot of bright red blood and said: "It is arterial blood. I cannot be deceived. That drop of blood is my death warrant. I must die." He died within a year.

The 1900s: the century when TB was to have been conquered.

January 1900 was a time of optimism regarding the control of TB. Koch had described the bacillus 18 years earlier and in 1890 he declared that his immunotherapy using a precursor to tuberculin would both cure and prevent the disease (turned out to be wrong). The sanatorium movement was flourishing in Europe and beginning to appear in North America.

Calmette and Guérin finally succeeded in developing a vaccine in 1921 after 13 years of weakening a bovine TB bacillus. This was used to vaccinate billions of people around the world.

By 1952 there was an effective triple therapy for TB lasting 24 months with PAS, streptomycin and isoniazid. This cured over 90% of TB patients. Much later the period of treatment was shortened to 6-8 months by the addition of rifampicin and pyrazinamide.

However the 1900's ended with dark clouds gathering as multi-drug resistant TB emerged and as it became clear that there was an absolute increase in TB in many parts of the world fueled by cut-backs in public health and the appearance of HIV as a strong co-factor.

Today some speak of a triad of diseases that have links with each other, namely

TBC ------STD
\ /
HIV

One third of the population of the world is infected with the Tubercle bacillus i.e. >2 billion. There were an estimated 9 million who were ill with TB and 1.5 million (**2013**) who died that year as a result of TB. There were 8.8 incident cases in **2010** of whom 3,2 million were women. In the total prevalence of those ill with TB 13% are co-infected with HIV. TB is currently the biggest killer of people with AIDS. Less than 5% of new and previously treated TB patients were tested for multi-drug resistant TB in most countries in **2010**. There were estimated to be 480 000 cases of MDR-TB in **2013** of whom an estimated 9% had an extreme resistant strain XDR which in practice in most settings is not treatable. During **2011** 6 months after being endorsed by WHO the new X-pert MTB/ RIF rapid molecular test for MDR-TB was available in 26 of the 145 countries eligible to purchase this at special cheap prices.

On average a patient with "open" TB not on treatment will infect 10-15 others/ year.
In the USA the lowest incidence of TB was in 1985. Since then there has been an increase each year with 21% increase in the annual number of reported cases over this time.
In Malawi the number of TB cases increased by 160% over 5 years. In Zambia 66% of all TB patients were HIV-positive. In Zimbabwe reported TB cases rose from 5000 in 1986 to 35 000 in 1997.
Of all cases of TB in the world, 95% are in developing countries where 98% of all TB deaths occur. 22 countries have 80% of all cases and all are poor countries. It is the economically productive age group (15-50 years) that is hardest hit with 80% of cases being in this group. Thus TB is often caused by poverty and in turn leads to poverty. India has the largest number with 23% of the total, but the highest prevalence is in Sub-Saharan Africa
It was estimated that 90% of all patients with active TB would seek help at a health institution because of their symptoms but recent surveys (2013) in 5 high incidence countries (not least Nigeria) suggest that this is a gross overestimate. Because of the link between poverty and TB, as absolute numbers of destitute increase globally so the numbers with active TB will also rise. Alleviation of poverty is the long term solution for the TB problem world-wide.

History
Over the last 200 years it is estimated that 1000 million people have died of TB throughout the world.
TB was common in Egypt 4000 B.C and described by Hippocrates (460 BC where almost all died) and in the Bible as the Wasting disease or phthisis.
It was treated in India 3000 years ago with fresh air up in the mountains, good food, rest and later when the acute stage was over horse riding and sunshine.
Europe was primitive in its attempts at treatment and what was very popular was to try to get the reigning monarch to touch the person afflicted (it was called the "King's evil"). Thus on one Easter Sunday King Louis XIV touched 1600 TB patients on one day! The result is not recorded!
One treatment that was used was tying a trout to the chest of a patient with the skin of a freshly killed cat! Another treatment was soaking a piece of meat in the patient's urine and then feeding this to a dog! Romans bathed in human urine or ate wolf's liver or drank elephants blood to be cured!

TB was rare in African villages living in isolated groups in the forest but when they were taken as slaves to the New World and then freed, they moved into slums in cities where many died of TB.
At the beginning of the 1800s it is estimated that 7 million people died each year world-wide of TB and 50 million had active TB.
Franciscus Sylvius de la Böe of Amsterdam in the mid-1600's was the first to describe the tubercles

in the lungs and other organs in those with consumption,
In 1867 Budd in Bristol came with the theory that TB must be caused by an air-borne infective agent since one open case of TB could infect a whole ship's crew during a long sea journey.

On the evening of **24th. March 1882** Robert Koch presented evidence that TB was caused by a bacillus that he had managed to stain with his new method and demonstrated in a microscope.
On the **30th. October 1944** the first active anti-TB medicine was tried on a human patient. This was the drug **para-amino-salicyclic acid (PAS)** at Sahlgrenska Hospital in Göteborg (Jörgen Lehmann).
On **20th Nov 1944** the first patient was put onto **Streptomycin** at Mineral Springs sanatorium under the Mayo Clinic, USA (Schatz and Waksman).
On the 1st. May 1947 the first patient was tried on Conteben and in **May 1952** the first patient was treated with **isoniazid** at Sea View Hospital, USA (Fox and Domagk). This turned out to be the most important anti-TB drug of all time (it had been synthesized in 1912 by the Czech chemists Meyer and Mally).
At the beginning of the 60s Rifampicin was introduced into TB treatment in 1972..
During the rest of the 60s and 70s no new TB medicines were discovered.
In 1985 the first definite case of **Multi-Drug-Resistant (MDR)** TB was found in a Korean woman in Denver, USA.
In 1990 there was an explosive outbreak of MDR in New York and Florida. This was related to the down-sizing of the Public Health sector in the Reagan era with the down-sizing of TB programmes nationally. Similar devastating consequences were seen in the former Soviet Union as this broke up and TB programmes were down-sized. This led to WHO proclaiming TB as being a Global Health Emergency in 1993. MDR TB increased globally from **274 000 in 2000** to **480 000 in 2013** (5% of the global case burden of TB), and of these an estimated **9% had XDR** which is not treatable in most settings.

A serious outbreak of MDR-TB took place in Russian and Ukrainian prisons. Prisoners tried in every way to avoid the extreme working conditions of labour camps by being sick for as long as possible in the prison hospitals. If they were sick with TB they tried to be prolong their illness with poor compliance by hiding the drugs in their mouths after taking them and then surreptitiously spitting them out afterwards.

In **2005-2006 MDR-TB** was diagnosed in 221 out of 1539 patients recruited within a 15-month period at Tugela ferry, Kwa-Zulu Natal, South Africa. Of these 221, **53** had **extensively drug resistant TB (XDR-TB).** 55% of the patients had never been treated for TB and 67% had had a recent hospital admission. All 44 patients with XDR-TB who were tested for HIV were positive and **52 out of 53 patients with XDR-TB died**, with a **median survival of 16 days from the time of diagnosis.** Genotyping of isolates showed that 85% of patients with XDR-TB had similar strains (Ghandi 2006).

XDR-TB has been diagnosed in 6 continents and their treatment outcome has been considerably worse than that of other MDR-TB. By definition **XDR-TB** has to be **resistant to at least two primary drugs always involving isoniazid and rifampicin simultaneously** (as in MDR-TB) and **additional resistance to any fluoroquinolone and to at least one of the three injectable aminoglycosides: capreomycin, kanamycin and amikacin (Raviglione 2007)**. The cost of expensive and prolonged treatments of MDR or XDR-TB will cause ethical dilemmas in poor countries. Here only 48% of MDR are treated to completion and, as said above, in most settings XDR is untreatable.

By 2020 it is estimated that TB and HIV infection will account for 82% of all adult deaths due to infectious diseases (up from 60% in 1990).

The Organism

Mycobacterium tuberculosis (with close relatives: M. bovis and M. africanum and the rare M. canetti and M. microti) are all together members of a single species, the **Mycobacterium tuberculosis complex.** The TB bacillus is non-motile, non-sporulated, usually slightly curved bacillus with the highest lipid content in the wall of all bacteria. It is 2-4μm long and 0.3-0.5μm in diameter. It reaches the alveoli in aerosol droplet nuclei that are 2-10 μm in diameter. Especially those 5 μm or smaller are small enough to reach the alveoli but big enough to get stuck there and not to bounce out again. Bigger nuclei often get trapped in the mucosa of the upper respiratory tract and are eliminated by the mucocilliary defence mechanism before they can establish themselves. Lipids constitute more than half of the dry weight of the mycobacteria. The surrounding envelope has a plasma membrane, a cell wall and an outer capsule-like layer. The cell wall has an unusual high number of cross-links with 70-80% of peptidoglycan cross-linking in the wall. The fatty acids are called mycolic acids with long chains making it extremely stable to antibiotic attack from outside and resistant to staining and to immune factor attack. Outside of this is an extra pseudo-capsule increasing its resistance. Ethambutol and dimethyl sulfoxide alter or fray the surface architecture of the cells increasing their susceptibility to antibiotic and immune factor attack. The cells divide every 12-24 hours which is extremely slow (most bacteria divide in 15-60 minutes although Mycobacterium leprae takes 11 days!).

One organism is enough to cause disease (compare typhoid where 10^6 organisms are needed) but it is likely that the infecting dose is important and droplet nuclei often contain 1-10 bacilli and 5-200 may be more likely to cause disease. One cough from a patient with open TB can release 3000 droplet nuclei with TB bacilli. Transmission is usually indoors where poor ventilation may allow the droplet nuclei to hang around for many hours.

The organism is difficult to stain and heat is needed which drives the very strong stain through the waxy outer coat made of glycolipids and lipids. Once it has been stained neither acid nor alcohol can destain it (Acid and Alcohol Fast Bacilli - AAFB). The essential diagnostic tool is direct staining of sputum smears for AAFB with the Ziehl-Neelsen staining method, unchanged since soon after Koch's discovery. Culture of the organism is unavailable in most low-income-countries and is on the same culture medium, a solid egg-based Löwenstein-Jensen medium that was used 1886!

Pathology

The bacilli are swallowed by alveolar macrophages which are transformed into epithelioid cells that form “giant cells” and in turn form a tubercle. Here in the acidic centre there is not much proliferation of the bacilli.

The body responds with a TH1, **Type 1** cell-mediated immune-response, whereby the bacilli are captured into phagosomes. These melt together with lysosomes and super oxide anion and hydrogen peroxide are released together with nitric oxide leading to peroxynitrites which may be lethal to the bacilli. Activated CD4 cells produce IL-2, IL-12 and interferon-γ. **Tumour necrosis factor-**α is produced by macrophages and all three promote intracellular killing of bacilli.

However a **Type 2** reaction also occurs with IL-4, 5, 6 10 and 13 release which causes necrosis in the tubercles so that the liquid contents break through to an airway, are coughed up, a cavity is formed

where the bacilli proliferate rapidly since air enriched with CO_2) enters the cavity, neutralizes acidity and provides oxygen for the bacilli to replicate. Each cavity 2 cms in diameter can produce 10^8 bacilli per cavity worsening the illness. Local granulomas are made more stable with better control of the enclosed TB bacilli within them by low oxygen concentration and nutrients, and the local production of
TNF-α and NO. Increasing the production of NO by boosting the substrate, arginine, needed for its creation by giving daily supplements of groundnuts may improve the outcome of treatment. However TNF--α in the presence of type 2 cytokines has the opposing property of causing tissue damage. An excess of TNF--α accounts for several of the symptoms of active TB with fever, lassitude and wasting. Patients treated with an anti-TNF--α drug, thalidomide show rapid symptomatic relief and weight gain.

These two immune processes, Type 1 and Type 2 usually develop in parallel but at differing rates.

Clinical varieties

1. Primary TB. This is usually in children where the first tubercle (usually in the lung tissue) causes enlargement of the nearest lymph node. This combination of a tubercle in the lung and the accompanying enlarged lymph node is called a **Ghon complex** (or Ranke's Complex) after 3-8 weeks. It can either heal, or go into a latent resting phase or can spread. The risk of spread is greatest during the first 3-5 years and especially the 1st year. Only a few older children risk developing lung cavities and so most will have a paucibacillary illness and less likely to develop resistance to treatment unless initially infected with such a strain. These children cannot spread the infection to others. The risk of a child infected with TB becoming ill is greatest if the bacterial load is great, the host immune response is weak or immature (especially when Vitamin A deficiency is present) and certain factors within the bacilli that make it more virulent. Spread is via the airways to other parts of the lungs, or by blood spread to the meninges to cause TB meningitis, or to the intestinal system, kidneys or bone. This blood spread has its highest risk in young children over the first 3 months after infection It may become a very widespread infection in someone with poor immune response due to HIV or after measles where it causes miliary TB. There may also be TB pleurisy in the first 3-4 months by spread directly from the primary focus or by blood spread. The primary complex resolves after up to 3 years and if quiescent is replaced by a stable granuloma with scarring showing calcification in due course.

2. Post primary TB. This may be an awakening in a latent tubercle when there is some disturbance in the immune response (recent "finger-printing" with DNA of the bacilli suggests that a secondary new infection on top of the original one occurs in some 40% of post-primary TB). The TB bacilli usually spread via the airways to other parts of the lungs. There is a delayed-type hypersensitivity (DTH) reaction (based on Type 2 immune response with IL-4 prominent) with central necrosis in the tubercles (looks like soft dry cottage cheese, caseation necrosis, because of the extremely high fat content when TB bacilli are breaking down).
Over 80% of TB is localized to the lungs and this is the form of the disease that is of public health interest since this is the form that is infectious.

Effect of Tuberculosis on Nutrition
In both adults and children the awakening of a hidden TB infection to become active almost always leads to some degree of malnutrition. Much of this is due to one of the signal substances, Tumour

Necrosis Factor-α (TNF-α) sent out by the body's immune system when the infection spreads. This is the same substance that causes much of the weight loss in someone with cancer. TNFα has a series of effects on appetite, metabolism and the body's tissues so that more food is needed to remain in positive balance. If food intake is not increased the body weight goes down. Fever increases the turnover in the tissues also leading to loss of weight.

Effect of Nutrition on Tuberculosis
TB bacilli are kept in check by the body's immune system. When this is damaged by malnutrition, especially Vitamin A deficiency, the bacilli are likely to spread and to cause active disease.

Paediatric TB
Of all cases of clinical TB, 5-15% (some estimates in South Africa suggest a higher figure of 15-20%) are in children and the younger children are especially at danger. They will often develop consolidation and pneumonia without cavitation. There is a period from 5 years to puberty where TB is not usually a great danger, the "protected safe school age"unless severe malnutrition, HIV, measles or other factors damage the immune system.
Making a diagnosis of TB in a child, especially in low-income-countries with extreme limitations in resources, is difficult and usually the diagnosis is presumptive. This is because the symptoms are usually vague and non-specific: malaise, loss of weight, or failure to grow, fever, and sometimes (but not always) a cough.

In least developed countries (LDCs) 20% of children who present with Protein-Energy-Malnutrition may have TB. Looked at the other way round, 90% of children ill with TB are malnourished. A simple screening method for malnutrition is to measure ***mid-upper-arm circumference*** (MUAC) which normally remains almost unchanged from the age of 1-5 years. Normal circumference at this age is around 16.5 cms. There is one cut-off point which is at **13.5 cms and below this the child is moderately wasted.** A second level which shows **severe wasting is if the circumference is below 12.5 cms**.

Diagnosis of TB during childhood when resources are scarce

1. Sputum examination in children is difficult and only of use in older children who are the least likely to fall ill with TB. There induced sputum production using inhalation of 5% saline increases the diagnostic value.
2. TB culture from gastric lavage. This is a difficult procedure, takes at least 6 weeks for the culture and is often negative. Where there are no culture facilities it is of course not possible. ***A possible alternative for the child is to swallow a string linked to a capsule, and culture from its contents when withdrawn,*** but young children find this difficult.
3. Culture from laryngeal swabs. This is easier with somewhat better results where culture facilities are available.
4. Chest Xrays are of limited value in small children with TB.
5. Chest Xray Tomography is somewhat better but unlikely to be available in low-income-countries. Here thoracic lymphadenopathy can be seen better.
6. Bronchoscopy with aspiration under direct vision. This is difficult to do even in ideal circumstances and is dangerous when done under inadequate resources.
7. Biopsy of cervical lymph nodes. There are only a few who will be diagnosed in this way. If done the node should be bisected immediately after removal and if it shows caseation necrosis the

diagnosis is made in 75% of cases by just eye inspection but of course should be confirmed by a pathologist.
8. Mantoux testing. This is of some use but is likely to be negative in the presence of TB in those who are malnourished (the majority of TB patients), or in those who are HIV positive, in post measles children and in severe TB such as miliary TB and TB meningitis, all the most urgent group.
9. The accelerated BCG test. Give a normal dose BCG vaccination and read the resulting swelling after 4-6 days. If the swelling is more than 15 mm then the child has almost certainly active TB. If it is between 10-15 mm there is a strong suspicion of active TB. This will be positive even after measles, in malnutrition and in severe disease such as TB meningitis or miliary TB.

Controversy over diagnosis of TB in children
a. The Purists. They insist on AAFB in the sputum or a positive culture from gastric lavage or indisputable Xray changes or a positive lymph node biopsy.
b. Pragmatists. In a setting with plenty of TB and plenty of malnutrition: give all PEM children nutritional resuscitation for 1 week. If no improvement investigate carefully for a hidden infection (especially urine and stool tests and careful clinical examination). If negative give a broad spectrum antibiotic (e.g. chloramphenicol + metronidazole) for 5 days. In severe malnutrition give this from the start since many of these children (70%) have an unsuspected bacteraemia.
If still no improvement 3 weeks after admission give a trial of TB treatment using specific treatment that has no other effect e.g. isoniazid + pyrazinamide. If there is dramatic improvement add rifampicin.
If no improvement after 2 further weeks test the mother for HIV.

Making the diagnosis of TB in children using a clinical points system	**Points**
Cough for 4 weeks (excluding whooping cough)	1
"Pneumonia" not improving after 3 weeks treatment	1
Unexplained fever more than 3 weeks	1
Malnutrition rehabilitated with food as outpatient - no change	1
Malnutrition rehabilitated with food as inpatient - no change	2
Onset of PEM after age of 3 years	3
Onset of PEM after age of 4 years	5
Measles followed by prolonged ill-health for 2 months	2
Family member sputum positive for AAFB	4
Cervical glands enlarged, rubbery, painless	4

Interpretation of clinical points system
1 or 2 points - further control after 1 month
3-4 points - refer if possible for further investigation
5 - start TB treatment.
NB malnutrition after 4 years in the absence of famine is almost certainly due to active TB.

Thus there are three practical instruments that can be used in order to make a diagnosis of TB in a child. None of these are perfect, all have theoretical and scientific weaknesses but at present we have nothing better to take their place. All three have been used in many units in low-income-countries and have been found to work in practice and to identify the children who otherwise would have died without a diagnosis being made.
These three instruments are:

1. Using BCG as a diagnostic instrument
2. Using a flow treatment model for all malnourished children
3. Using a points-scoring chart to identify probable TB patients

Diagnosis of Pulmonary TB in Adults when resources are scarce (usually post-primary and constituting 90% of all TB)

History

Fever, night sweats, malaise and weight loss are prominent. Cough (more prominent in the morning) for more than three weeks, initially dry but later with purulent or mucous sputum (yellow, not thick or smelly). Less than 1/4 have blood which is usually streaky but occasionally copious and this increases the likelihood of TB. Cough with haemoptysis (blood in the sputum) is more common in HIV+ patients.

Examination

Lighter skin in some Africans. Thin, **MUAC↓**. Below 23 cms in men or 22 cms in women is significant. Febrile. Tachycardia out of proportion to the fever. Pallor.
Enlarged lymph nodes especially in the supraclavicular fossa.
Sometimes crepitations and bronchial breathing over the affected area of the lung.
Signs of pleural effusion in some (stony dull on percussion, absence of vibrations when holding lightly with the palm of the hand when the patient says "99"). Trachea not midline (normal is very slightly to the right).

Investigation

The essential diagnostic tool is direct staining of sputum smears for AAFB with the Ziehl-Neelsen staining method, unchanged since soon after Koch's discovery. The minimum number of bacilli that are needed to be detected by standard smear are 5000-10,000 bacilli per ml sputum. This will identify 50-70% of all "open" TB cases. **Induced sputum test** with inhalation of 5% saline will improve this level. Staining with auramine O in the fluorochrome procedure makes reading the smears much quicker and easier, but the slides have to be read with a fluorescence microscope and have to be read within 24 hours as the fluorescence fades with time. This method is not available where it would be most useful, in poorer countries. Improved sensitivity is possible with **household bleach and centrifugation of sputum,** a simple and cheap addition and has the added value of sterilizing the sputum but then culture samples have to be removed first where this is available.

The method: An equal amount of household bleach (5% NaClO) is added to the sputum sample in a screw cap tube and the tube is shaken for 30 seconds. Then, the tube is left on the table top for 10-15 minutes at room temperature and then hand shaken for 30 seconds, every five minutes. An equal amount of distilled water is then added and the tube centrifuged at 3000 rpm for fifteen minutes. The supernatant is discarded and the pellet is suspended in a few drops of the remaining fluid. Smears are prepared from the suspended sediment.
The Sodium hypochlorite (NaClO) solution: The "Rheachem" bleach (or other make) is purchased, with the stated chlorine concentration as 5%. To prevent the reduction of the chlorine activity due to a repeated exposure to air, each 5 L bottle is decanted after it is opened into a 25ml brown glass bottle for daily use and the remaining solution which remains unused at the end of the day is discarded.

Ref. Improved Diagnosis of Pulmonary Tuberculosis using bleach Microscopy Method. Preeti B Mindolli, Manjunath P Salmani, and Prashant K Parandekar. J Clin Diagn Res. 2013 Jul; 7(7): 1336–13385

A PCR method to identify the bacilli more easily is a method for the future in countries with scarce resources. Another possibility is the use of the firefly luciferase where a virus carries the enzyme into the TB bacillus lighting it up and making it easier to see. If an anti-TB drug is effective against TB the light goes out.
Culture of the organism is unavailable in many low-income-countries and, when possible, is on the same culture medium, a solid egg-based Löwenstein-Jensen medium that was used 1886! Newer quicker methods include liquid culture methods such as the BACTEC radiometric method.

PPD is used to look for latent and even active TB but has serious problems of sensitivity and specificity (see p.14). Its main use is in children under 5 who are not malnourished, not post-measles and not suffering from overwhelming TB e.g. miliary TB, TB meningitis or severe pulmonary TB where those sick with TB will be PPD negative. These are the most important of all children to diagnose quickly.
Some help can come from the newer tests for interferon-γ of which there are two in use: Ellispot (T SPOT-TB) assay or Quantiferon TB Gold Assay. They have advantages over PPD as they are not influenced by previous BCG vaccination but **cannot differentiate between latent and active TB.** It is unlikely that they will be of much use in low-income-countries, even if they were affordable. The majority will have been exposed to TB infection and are therefore latent carriers. Its use in children is still being evaluated.

In Tanzania rats have been trained to identify sputum from "open" TB patients by smell and one trained rat can screen 1000 sputums in a day. There are plans to develop an electronic "nose" to detect the smell that is characteristic of Pulmonary TB.
Derided as dirty, dangerous and diseased, if there is one creature that tops the list of people's most hated animal, it is the rat. But rats are clever, and usually trainable. In Tanzania, they have been taught to detect patients with tuberculosis by detecting early signs in human saliva. What would take a human scientist a whole day to diagnose the disease takes a rat a mere seven minutes.
BBC Earth's Extraordinary Animals series visited the social enterprise Apopo in Tanzania to see how the rats are trained, and discover what makes a rat's sense of smell so superior. A rat makes about eight sniffs a second compared with two for humans. Rats also smell in stereo, distinguishing two similar odours with one sniff. And around one in every 100 of a rat's genes is involved with odour detection, compared with one in 1,000 in humans.

Two new molecular diagnostic kits used on sputum give a TB diagnosis with very high sensitivity and specificity within 60-90 minutes but the cost is high unless their purchase is financed.
A chip is being developed at KTH Stockholm with the hope that it may even detect single molecules of TB when coughed upon.

If you strongly suspect pulmonary TB but find no AAFB in the sputum, Xray the lungs. A normal Xray virtually rules out active lung TB except in a few (5%) HIV positive patients.

Typical Xray findings of active TB: soft shadows that are irregular, especially in the upper

lobes and often initially in a pyramid with the base towards the lung periphery and the apex looking at the hilar area. Cavities without fluid levels are highly significant. If followed over a period of time shadows and cavities will increase in size in active TB. Cavities are prominent in early HIV infections with TB but less prominent in late HIV disease. Over 90% of those with cavities are smear positive for AAFB and if these are not found, consider another diagnosis e.g. lung abscess or carcinoma. Extensive shadows suggest active disease.

N.B. Chest Xray is not the best way of diagnosing pulmonary TB since it can be mimicked by other lung diseases. However it is of value in following progress in a difficult case. In a setting of extreme resource scarcity, good TB programmes can still be run without Xrays provided there is a good laboratory for Ziehl-Neelsen staining of sputum which identifies those most likely to spread the bacilli to others.

Treatment

Without treatment 55% of adults sick with TB will die of their disease. After 5 years 55% will be dead, 25% will be healthy (self-cured) and 25% will have chronic infectious TB. With standard treatment, more than 95% will recover (of course if they have MDR-TB or are HIV positive the long-term prognosis is still grim). Treatment is not cheap and 6 months standard treatment for an adult will cost US$13 per person. However the World Bank estimates that because of the impact for good in controlling spread of the disease in the community this treatment is one of the most cost-effective interventions in improving health in a country. Each TB patient treated successfully will save the country 4 times the cost of treatment in prevention of spread. Multi-drug resistant TB costs 100 times as much and has poor prognosis even if treated for 18-24 months. In some former Soviet-Union countries one quarter of all TB patients have MDR-TB. Extreme multi-drug resistant TB: XMDR-TB is defined as TB resistant to at least rifampicin and isoniazid plus any quinolone plus at least 1 of the 3 injectable drugs used in TB treatment - capreomycin, kanamycin and amikacin. The prognosis of the first group described in Tugela Ferry was extremely grave with 52 of 53 dying with a median survival of 16 days from the time of diagnosis. All who were tested for HIV were positive. 85% of them had the same strain of TB.

The aim of TB treatment is four-fold:

1. to cure the individual patient, **2.** to prevent death, **3.** to prevent relapse of the disease, **4.** to stop transmission to others.

The tubercle bacilli behave as if they occupy three "compartments"

1. those replicating rapidly on the walls of the cavities,
2. those replicating less rapidly in anoxic and acidic solid lesions and
3. those in a dormant or near dormant state within dense lesions or macrophages.

In drug-sensitive TB of all of the standard anti-TB drugs ***isoniazid*** is the most important and effective and acts primarily against the rapidly replicating bacilli in the walls of the cavities. **It kills 95% of the organisms during the first two days of treatment** but then its bacteriocidal role is supplemented by ***rifampicin*** and ***pyrazinamide*** which are very effective against the more slowly replicating bacilli in anoxic and acidic solid lesions . These two are essential for a sterilizing effect of treatment. ***Pyrazinamide*** seems important for killing the intra-cellular organisms especially in the period 2-14 days after starting treatment. ***Rifampicin*** is only slightly less effective than isoniazid and has less of a resistance problem. It is the most effective against the bacilli in a dormant or near

dormant state within dense lesions or macrophages. ***Ethambutol*** which is a bacteriostatic drug is added to try to reduce the risk of resistance and has its extra value with the widespread emergence of resistant strains. It may also enhance the activity of other TB agents by increasing mycobacterial cell wall permeability. Rifampicin and Pyrazinamide are essential in **sterlizing** the body from TB. Below will be given the short-course TB treatment of new cases with or without smear positive results. Relapsed cases, those with treatment failure and defaulters are much more difficult, expensive and complicated to treat.

Short-course therapy (WHO Recommendation) NB each country may have its own TB drug recommendations. Successful treatment shows often early with **MUAC⇑**

Smear-positive TB

2 months treatment with 4 drugs: Ethambutol (E) (or Streptomycin), Rifampicin (R), Isoniazid (H) and Pyrazinamide (Z) followed by

4 months of 2 drugs: Rifampicin and Isoniazid (2 EHRZ/4 HR). **NB.** HIV+ need 7 months

Alternative: 2 months treatment with 4 drugs as above, followed by 6 months treatment with Isoniazid and Ethambutol (2 EHRZ/6 EH (or Thioacetazone instead of Ethambutol if HIV level in community is very low) This is cheaper than the first alternative (less Rifampicin is used) but longer with more follow-up.

Smear-negative TB

2 months treatment with 3 drugs: Rifampicin, Isoniazid, Pyrazinamide followed by 2 months treatment with Isoniazid and Rifampicin. This method is not yet adequately tested in HIV+ patients.

New combination drugs: **RIMSTAR**=RZHE, **RIMCURE**=RHZ, **RIMACTAZID**=RH

Dosages of TB drugs		**DOTS**	
Drug	**Daily dose: mg/kg**	**3 times/week dose: mg/kg**	**2 times/week**
Isoniazid	5 (4-6) mg/kg	10 (8-12) mg/kg	15 mg/kg
Rifampicin	10 (8-12) ¨	10 (8-12) ¨	10 mg/kg
Pyrazinamide	25 (20-30) ¨	35 (30-40) ¨	45 mg/kg
Ethambutol	15 (15-20) ¨	30 (25-35) ¨	45 mg/kg
Streptomycin	15 (12-18) ¨	15 (12-18) ¨	15 (12-18) mg/kg
Thioacetazone	3mg. ¨	-	

These drugs have the following shelf-life stability under proper storage conditions after the date of manufacturing:

5 years: isoniazid, ethambutol, thioacetazone

3 years: rifampicin, pyrazinamide, streptomycin.

There is some evidence that the 3 times or 2 times a week regimens are **somewhat slower and less effective than the daily treatment.**

There are at least 10 new or repurposed TB drugs in late phase clinical trials that have the potential to shorten the treatment of drug-susceptible TB and improved the treatment of MDR-TB. results from 3 trials of 4-month regimens of drug-susceptible TB are expected between 2012 and 2013 and 2 trials of new drugs for treatment of MDR-TB are expected in 2012. (***See separate document***).

In TB meningitis, TB pericarditis and Renal TB treatment there is a place for adjunct treatment with steroids to reduce local damage and improve outcome.

MDR treatment will depend on drug sensitivity tests but generally it will have a backbone of a fluoroquinolone such as moxifloxacin, and aminoglycoside such as capreomycin with two or 3 additional drugs not previously used. New drugs may soon be available - see below. Remember successful treatment shows often early with **MUAC⇑.**

If resistance testing is impossible give the standard quadruple TB treatment and **if within 2 weeks there is no increase in MUAC there is very likely a resistance problem.** If possible get help with resistance testing or treatment from elsewhere but if not possible change the treatment to include Moxifloxacin and a good aminoglycoside such as capreomycin

XDR-TB treatment (usually not possible in most poor settings) depends also on sensitivity tests but generally will have a backbone of PAS and capreomycin to which other drugs are added. These may include linezolid, amoxicillin/clavulanate, clarithromycin, clofazimine and dapsone which all have weak antimycobacterial effects. The new drugs below will play a major role. Moxifloxacin was an independent predictor of survival in XDR-TB even if resistance to ofloxacin had been shown. High dose isoniazid may also have a role even when resistance has been shown by standard tests. Surgical resection of localized MDR lesions has a role in some patients.

TDR Total Drug Resistant TB (where the bacilli are resistant to the 12 accepted anti-TB drugs) has been described from India, Italy and Iran. The term is controversial and not widely accepted.

HIV/AIDS and TB

The two diseases are strongly synergistic. There were 8.8 million incident cases of TB in **2010**, of which 13% were HIV positive.

TB is the commonest opportunistic cause of death in HIV.

TB in the presence of HIV tends to take on features of paediatric TB as the HIV infection progresses. There is a trend towards more sputum negative cases, more extra-pulmonary presentations e.g. pleural effusion, pericardial effusion, lymph node involvement. However pulmonary TB is still the largest group. Even within the lung tissue there is a trend of involvement of the lower lobes as well as upper lobes with less cavitation and more widespread disease and in at least 5% no infiltrates show on Chest Xray.

The results of treatment of HIV+ TB patients is generally satisfactory and yet 20% die within 1 year of starting TB treatment.

If possible start TB treatment 1 month before starting HAART (Highly Active Anti-Retroviral Therapy) if the CD4 level is below 100 or if 2 months before, it is between 100-200. If it is above 200 wait with HAART until the TB treatment is over if possible. This is to reduce the risk of Immune Reconstitution Inflammatory Syndrome (IRIS). Use Rifabutin 150 mg/day instead of Rifampicin to minimize interactions with HAART. If needed used efavirenz at a higher dose of 800mg/day and not nevirapine as NNRTI and use nelfinavir as a protease inhibitor.

By 2020 TB and HIV infection may account for 82% of all adult infectious disease deaths.

WHO recommends three I's in those with both HIV and TB:

1. **I**ntensify TB case-finding and ensure quality TB treatment.

2. **I**nitiate TB prevention with isoniazid preventive therapy and earlier initiation of ART in line with WHO and national guidelines.
3. **I**nfection control for TB in health care and congregate settings ensured.

Planning a district programme for TB Control

Look at the possibility of integrating it into an on-going home-based-care programme or starting such a programme that reaches out into the homes with regular follow-up visits.
Have as the four main priorities of the programme:

1. Adequate **treatment of all cases of TB discovered** (and especially following through all "open" TB). Try to improve the rate of detection by better investigation of all adults who cough for more than 3 weeks especially if they have a MUAC below 23 cms in men or 22 cms in women.
Start the phased programme of treating all malnourished children who do not respond to nutrition rehabilitation within 3 weeks of admission.

2. Build up a **reliable system of laboratory investigation** of sputum samples to carry out direct Ziehl-Neelsen staining looking for Acid and Alcohol Fast Bacilli (AAFB). This is initially far more important than hoping for the establishment of a TB culture service which may never be established or if it is, may be very inconsistent.

3. Build up a **reliable system of consistent drug supply** for the programme. Have these drugs available at every health facility. If there are problems of drugs being misused or disappearing into the local market try to limit all follow-up drugs to those that are only used for TB treatment e.g. Pyrazinamide, INAH, and Ethambutol (Rifampicin and Streptomycin can easily be sold for treating STIs). There is an advantage of using only the already combined versions i.e. **RIMSTAR**=RZHE, **RIMCURE**=RHZ, **RIMACTAZID**=RH. These are less likely to be used for STI or other needs.

4. Introduce the WHO **Directly Observed Treatment Short course** (DOTS) with a network of community health workers who administer and supervise thrice weekly doses of isoniazid, rifampicin, pyrazinamide and ethambutol for 6 months. A recent modification of DOTS is Patient-centred DOTS where the patient decides who will be their supervisor.
Between 1995 and 2012 **55 million were treated in DOTS programmes of which 46 million with success** and these treatments saved almost 7 million lives,
There is value in changing terminology within DOTS programmes: ***compliance*** has an authoritarian flavour where conflict may emerge. ***Concordance*** is a more neutral word.

Less important than the above but also worthwhile are the follow up of family contacts especially those with symptoms, and trying to track down absconders from treatment.
BCG immunization: of little use in the community control of TB but of value in individual prevention in children of TB meningitis and miliary TB. (however in Sweden BCG in an earlier era prevented probably 80% of TB even in adults).

Completely useless in community control of TB are mass miniature radiography, yearly chest xrays and asking for Xrays prior to employment (this is of value to an employer but has no impact on TB levels in the community).

New vaccines

There is now increasing evidence that during the 230 successive passages in the laboratory that were weakening the M. bovis strain so that it would not be pathogenic, the protective immune-stimulating effect was also weakening. There is also evidence that since 1921 when BCG was launched, strains of the vaccine have been chosen that cause less local reactions and thereby almost certainly give less protective effect. It may be that the 80% protective effect in early studies in Sweden was an effect using a more immunogenic strain.
Two new ideas are being explored to make BCG more effective as an immune-stimulant. The one is to combine it with a virus e.g. a pox virus to boost the previously primed T-cell response against intra-cellular pathogens. The other is to use the membrane-perforating listerolysin to construct a recombinant BCG which will allow the agent to escape from the phagosomes of infected host cells. This improves the access of mycobacterial antigens to the major histocompatibility complex Type 1 pathway thus resulting in a better CD8 + T cell stimulation. Another idea is to add a sub-unit vaccine (based on key antigens of the TB bacillus) to the BCG vaccine to get better immune-stimulating effect. Many pure sub-unit vaccines are under development. There are 9 vaccine candidates in phase I or phase II trials and it is hoped that at least 1 will be licensed by 2020. STOP-TB/WHO hopes that 20 different vaccines will be undergoing clinical trials by 2015.

New medicines

The first new drug combination for treating TB was shown to kill more than 99% of patients' TB bacteria within 2 weeks. It was a combined TB therapy with **drug 1: PA-824**, a new novel TB candidate combined with **drug 2: moxifloxacin** and **drug 3: pyrazinamide**. This involved 85 patients at two centres in South Africa. However only 15 patients were on this combination and 3 had to withdraw because of side-effects. Some preclinical data suggests that this combination could **treat MDR-TB in 4 months (yet to be confirmed)**. If confirmed this would slash the cost of MDR-TB therapy by 90% and eliminate the use of injectables. It could also mean that all TB patients could get the same treatment while awaiting resistance results which would decide the length of the treatment. Where these are not available 4 months treatment for all may be adequate in the large majority. In New Zealand another drug: TBA-354 is being developed. It is a counterpart of PA-824 and may be even better.
One of the most radical new drug in 40 years is a diarylquinoline that acts on an entirely new mycobacterial target, the proton pump of ATP synthase.
Another exciting new drug is OPC-67683, a nitro-dihydr-imidazooxazole derivative that inhibits mycolic acid biosynthesis is highly active in mice against TB. Pyridomycin is another potential anti-TB drug which is being assessed for MDR-TB treatment. 2 other new TB-drugs are in phase 3 trials, 8 drugs in phase 2 and 9 drugs in phase 1 trials.
Soon trials start of an ultra-short 2 months treatment schedule.
There is early evidence that high dose Vit D may enhance TB treatment. **(See separate document for further detail)**

The great controversy - PPD and latent TB

1. What does PPD measure and how useful is it? Some who are latent carriers and many who are BCG vaccinated never become PPD positive.
2. How much use is there in treating latent PPD and with what?
It is known that in **pre-school converters** (converting from PPD- to PPD+) **5% will some time develop active disease, in adolescents 1 in 110 , and in adults 1 in 1000 will do so.**
The total number of people who are infected with TB world-wide is 2 billion. Of these around 10%

will sometime during their lifetime become sick with TB (apart from those with HIV where 50% will become ill with TB). At least half of this number will become sick within 2 years of being infected.
3. Traditionally isoniazid alone has been used for up to 1 year. Now the evidence is clear-cut: 6 months is enough but with such treatment the number who become sick during their lifetime is reduced by 60% i.e. from 5% after the first 2 years of infection to 2%. All are agreed that those under 5 years are the priority. **After 35 years there is no benefit of isoniazid treatment.** The controversy is in the ages between 5 and 35.
4. The alternatives: since isoniazid is the illogical choice for getting rid of latent TB (its main effect is in actively replicating bacilli especially in the cavities) a trial in the US was made of the logical choice i.e.the "sterilizing" drugs, a combination of pyrazinamide and rifampicin for 2 months. This resulted in a significant number of side-effects, some of them severe and the method was abandoned. In the UK a 4-month combination of rifampicin and isoniazid was tested. Later the same combination for 3-months showed equally good results.
5. A special category of patients who are being prepared for anti-TNF-α therapy for various auto-immune diseases will benefit considerably from TB prophylactic therapy if they are latent carriers. Otherwise they could become ill with TB during their therapy with anti-TNF--α

Smoking and TB

Studies in India show that smoking may contribute to half of the deaths due to TB in men. Smoking is the cause of 1/4 of all deaths in midldle-aged men.

A new textbook about TB is downloadable free at the following address: http:// www.TuberculosisTextbook.com/download12.htm

Breaking News 2013

Prediction from the Global Fund: By 2015 we will have halved the mortality rate for TB since 1990

Tuberculosis results in an estimated **1·7 million deaths each year** and the worldwide **number of new cases (more than 9 million) is higher than at any other time in history**. 22 low-income and middle-income countries account for more than 80% of the active cases in the world. Due to the devastating effect of HIV on susceptibility to tuberculosis, **sub-Saharan Africa has been disproportionately affected and accounts for four of every five cases of HIV-associated tuberculosis.** In many regions, highly endemic for tuberculosis, diagnosis continues to rely on century-old sputum microscopy; there is no vaccine with adequate effectiveness and tuberculosis treatment regimens are protracted and have a risk of toxic effects. Increasing rates of drug-resistant tuberculosis in eastern Europe, Asia, and sub-Saharan Africa now threaten to undermine the gains made by worldwide tuberculosis control programmes. Moreover, our fundamental understanding of the pathogenesis of this disease is inadequate. However, increased investment has allowed basic science and translational and applied research to produce new data, leading to promising progress in the development of improved tuberculosis diagnostics, biomarkers of disease activity, drugs, and vaccines. The growing scientific momentum must be accompanied by much greater investment and political commitment to meet this huge persisting challenge to public health.

The TB Alliance has received a grant from the United Kingdom's Department for International Development (DFID) to support the advancement of new tuberculosis cures that have the potential to save millions of lives. DFID's investment in the TB Alliance builds on previous grants and comes at a crucial time, as several treatments in the organization's pipeline are in late-stage testing and are poised to deliver near-term impact. These projects show promise to markedly improve TB therapy, including drug-resistant TB, pediatric TB, and HIV/TB co-infection.
DFID's grant to TB Alliance funds the development of urgently needed new TB regimens that can tackle the global TB pandemic and the work to ensure these treatments obtain maximal uptake. Support for TB Alliance's efforts are part of DFID's total investment of £138 million over the next five years into nine public-private partnerships to support the development of innovative new drugs, vaccines, insecticides, diagnostic tools, and microbicides to prevent, diagnose, or treat some of the world's most deadly and neglected diseases.
Today, complex TB drug regimens must be taken for six to months to 2 years or even longer. These lengthy and demanding treatment programs with their associated side effects prove overly burdensome for many patients, frequently resulting in erratic or inconsistent compliance which can lead to drug resistance, treatment failure, or death. TB kills 1.7 million people each year, according to the World Health Organization (WHO) and disproportionately impacts impoverished and vulnerable populations.
Since its establishment, the TB Alliance and its partners have developed the largest pipeline of new TB drugs in history. "We are extremely grateful for DFID's sustained and generous support of improved TB therapy," said Mel Spigelman, MD, President and CEO of TB Alliance. "TB Alliance is excited about the promise of our pipeline, and it is donors like DFID that make it possible to transform scientific promise into new tools that can improve the health and prosperity of people around the world."
India: TB Alliance, an international non-profit organization which develops better, faster-acting, and affordable TB drugs, has announced that it has granted a license to and is working with the Open Source Drug Discovery (OSDD) programme of Council of Scientific and Industrial Research (CSIR) to develop and commercialize a promising new tuberculosis (TB) regimen for use within India. CSIR is an Indian governmental institution, which provides scientific and industrial R&D that maximizes the economic, environmental, and societal benefits for the people of India.
Each year, **TB affects 2.3 million people in India, which has the highest rates of TB in the world.** Today's current TB treatments are growing increasingly resistant to available drugs and new tools are urgently needed. The license enables CSIR to undertake the research that is urgently needed to advance this late-stage development program in India. This is the first Indian-sponsored clinical research of a novel TB regimen.

CSIR will assume responsibility for the development and commercialization of the PaMZ regimen in India. This regimen, which consists of the **novel compound PA-824, a fluoroquinolone, moxifloxacin, and pyrazinamide** has shown potential to shorten treatment, including for some forms of drug-resistant TB. The TB Alliance has licensed the treatment regimen to CSIR in India and, if successful, CSIR agrees to make the treatment available to the people of that country at the lowest cost possible. -

CSIR-OSDD will initiate a Phase 2b trial, which is an 8-week trial to test efficacy of the PaMZ regimen. If the results of that trial are successful, CSIR-OSDD will then invest in a Phase 3 trial—a significant undertaking that will determine if the regimen could be introduced for the benefit of patients in India.

If successful, the results of this research will pave the way for the development of a simple, safe and patient-friendly regimen. Currently, TB treatment lasts 6 months and MDR-TB can last up to 30 months and includes one injectable. The **PaMZ regimen shows promise to reduce treatment time for drug-sensitive and many forms of drug-resistant TB to 4 months.**

The first new drugs to supplement current TB treatments are on the precipice of introduction. Two new drugs, **bedaquiline** (Janssen) and **delamanid** (Otsuka) have been or are projected to be approved to treat MDR-TB on top of the current background regimen. This is a first step in improving TB treatment.
However, the true transformation of TB treatment will come by delivering new regimens that are shorter, simpler, and safer, and because they are novel, can treat both drug-sensitive and drug-resistant TB. The TB drug combinations currently under development show promise to drastically reduce the length, cost, and complexity of treating various forms of TB, enabling the necessary scale-up of treatment to defeat the pandemic.

Present treatment of TB 6-30 months
Drugs in trials Hope is 2-4 months
Ultimate Goal 7-10 days

Childhood Tuberculosis: TB is among the top 10 causes of illness and death among children. TB is commonly passed from adults to children within the same family and household. Current estimates indicate **500,000 new cases each year** and more than **64,000** deaths. However, many children with TB go undiagnosed, so experts suspect the number of children suffering from TB is even larger. In some particularly hard-hit countries, **children represent 20-40% of the TB caseload.**

TB Vaccine: The phase 2b clinical trial of the TB vaccine candidate **MVA85A** is historic, the first efficacy study of a **novel BCG booster tuberculosis vaccine in infants.** Although the trial showed little evidence of efficacy in the population studied, it has added a tremendous amount of scientific knowledge to the field, and helped establish an infrastructure that enabled not only the conduct of this trial, but also many studies yet to come.

Pyrazinamide (PZA) is an incredibly important sterilizing agent in the treatment of tuberculosis and is **considered responsible for reducing the duration of treatment from the previous 9-12 months, to the current short-course of 6 months** produced by the standard regimen (HRZE).Beyond its contribution in the current first-line regimen, the TB Alliance, through its ongoing novel regimen development program is finding that PZA is critical to any treatment shortening regimen, including those that contain newer agents currently in clinical development. PZA has the ability to synergize with other drugs and this synergy drives the treatment-shortening potential of experimental regimens, such as PaMZ (PA-824 + moxifloxacin + pyrazinamide) currently under clinical development. However, resistance to PZA is on the rise, creating potential problems for PZA-containing regimens in development. Yet, there may be ways to circumvent this resistance. Investigating whether this is possible is the focus of a 1-year, $250,000 grant from the US NIH ACTG.
The mechanism of **PZA resistance** is mostly due to **mutations in an intrinsic mycobacterial pyrazinamidase (PncA)**, an enzyme that hydrolyses pyrazinamide to its active form, pyrazinoic acid (POA). If we can deliver POA without depending on pyrazinamidase, then theoretically we can overcome PZA resistance and we can extend the life of this amazing drug.

The method proposed in this research utilizes another intrinsic mycobacterial enzyme, a **beta-lactamase, to hydrolyze synthetic beta-lactam-POA conjugates, and deliver POA into the pathogen without utilizing PncA**. We will take advantage of this powerful enzyme to deliver POA. This kind of approach has been used in cancer chemotherapy to deliver drugs specifically to tumor cells.
Furthermore, since this delivery method would take a more direct path to the target, it has the potential to reduce toxicity to the patient. If successful, this technique could be applied to the delivery of additional TB drugs to further reduce toxicity and increase efficacy. This exciting program is the first step in finding out whether such innovations are possible.

With the rise of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) around the world, it is crucial that treatment providers identify what they are treating within a much quicker timeframe. To this end, the partnership between FIND and TB Alliance will seek to introduce new and better drug regimens by **developing tests that can detect resistance to crucial TB drug components.**
Currently, few drug-resistant patients in lower-income countries are correctly diagnosed. Drug-resistant TB is often "found" by determining a patient's reaction to first-line treatment, which means that by the time they are identified as having drug-resistant TB, patients have become even more resistant than they were prior to their latest therapy. By developing a new arsenal of diagnostics that complement drug regimens in development, health care providers will be able to modernize their approach to TB management and treat patients with drugs to which they will respond right from the start.
"It's not enough to just detect the presence of TB. We need to know the resistance patterns of the disease we're confronting," said Philippe Jacon, CEO of FIND. "Oftentimes, the testing for drug resistance takes days or even weeks, and doctors are left to guess at the proper course of treatment to prescribe. Our work with TB Alliance will help refine this approach, making TB treatment more efficient, effective, and responsive."
Indeed, FIND and partners have been making great strides in the development of technologies that can diagnose resistance to vital medicines for the treatment of TB and these tools are now being made available to the populations who need them most. In December 2010, FIND's collaboration with Cepheid resulted in the endorsement by WHO of **Xpert MTB/RIF®,** a molecular test that **detects the presence of TB, including rifampin resistance for MDR-TB, in less than 2 hours.**

This trial builds on the TB Alliance's two-week New Combination 1 trial, or NC-001, initiated in 2010, which was the first study to test novel TB drugs in combination. The newly launched Phase II trial, New Combination 2 (NC-002), advances the regimen of new TB drug candidates **PA-824 and moxifloxacin in combination with pyrazinamide,** an existing antibiotic commonly used in TB treatment. NC-002 treats patients for two months and will take place at 8 sites in **South Africa, Tanzania, and Brazil,** and will advance global capacity for TB trials along with the new innovative approach to TB drug development.
A novel approach to discover the first new tuberculosis (TB) combination drug regimen cleared a major hurdle when **Phase II clinical trial results found it could kill more than 99 percent of patients' TB bacteria within two weeks** and could be more effective than existing treatments, according to a study published today in the Lancet. These results add to a growing body of evidence that the new regimen could reduce treatment by more than a year for some patients.

Breaking News September 2015

37 million lives saved since 2000 WHO Global Tuberculosis Report 2014

KEY TB FACTS

In 2013, 9 million people fell ill with TB and 1.5 million died from it, including 360 000 among people who were HIV-positive.

In 2013, there were an estimated 480 000 new cases of multidrug-resistant TB.

3 million people who fall ill with TB still unreached every year
MDR-TB crisis detection, waiting lists for treatment and quality of care

Global strategy and targets for tuberculosis prevention, care and control after 2015 **VISION**
A world free of tuberculosis
– zero deaths, disease and suffering due to tuberculosis
GOAL
End the global tuberculosis epidemic

Reduction in number of TB deaths compared with 2015 (%)		**Year**	**Reduction** fr 2015
		2020	35%
		2025	75%
	SDG	**2030**	**80%**
		2035	**90%**

Reduction in TB incidence rate compared with 2015 (%)			
		2020	20% (<85/100 000)
		2025	50% (<55/100 000)
	SDG	**2030**	**80% (<20/100 000)**
		2035	**90% (<10/100 000)**
TB-affected families facing catastrophic costs due to TB (%)			**Zero**

PRINCIPLES

1. *Government stewardship and accountability, with monitoring and evaluation*
2. *Strong coalition with civil society organizations and communities*
3. *Protection and promotion of human rights, ethics and equity*
4. *Adaptation of the strategy and targets at country level, with global collaboration*

PILLARS AND COMPONENTS

1. INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION

A. Early diagnosis of tuberculosis including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups

B. Treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support
C. Collaborative tuberculosis/HIV activities, and management of co-morbidities
D. Preventive treatment of persons at high risk, and vaccination against tuberculosis

2. BOLD POLICIES AND SUPPORTIVE SYSTEMS
A. Political commitment with adequate resources for tuberculosis care and prevention
B. Engagement of communities, civil society organizations, and public and private care providers
C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality
rational use of medicines, and infection control
D. Social protection, poverty alleviation and actions on other determinants of tuberculosis

3. INTENSIFIED RESEARCH AND INNOVATION
A. Discovery, development and rapid uptake of new tools, interventions and strategies

B. Research to optimize implementation and impact, and promote innovations
To sustain progress beyond 2025 and achieve the SDG* 2030 and End TB 2035 targets, additional tools must be available by 2025. In particular, a **new vaccine** that is effective pre- and post-exposure and a **safer and more effective treatment for latent TB infection** are needed to reduce the number of new TB cases arising from the approximately 2 billion people worldwide who are infected with M. tuberculosis, as well as **better diagnostics and safer and easier treatment including shorter drug regimens for TB disease.** For new tools to be available by 2025, greatly enhanced and immediate investments in research and development are required.

The WHO 2014 Global tuberculosis report—further to go Lancet Zumla et al Jan 2015

In May 2014, the World Health Assembly officially approved the Draft Global Strategy and Targets for Tuberculosis Prevention, Care and Control after 2015.1 The target of the strategy is the elimination of tuberculosis as a public health threat by 2035. This target is ambitious, but the commitment to the end of tuberculosis is laudable. The recently published 19th WHO global tuberculosis report 2014,2 provides an opportunity to think once again on the global tuberculosis strategy, and

to assess just how much further effort is needed before global tuberculosis control can be achieved.

Previously,3 we declared that the 1·3 million deaths per year from tuberculosis reported in the 2013 WHO global tuberculosis report was unacceptable in the 21st century. The latest 2014 WHO global tuberculosis report has revised its estimates of new tuberculosis cases worldwide from previous years, and now shows that almost half a million more cases of tuberculosis occurred worldwide than in their 2013 estimate.4 Of an **estimated 9 million people who developed tuberculosis in 2013, 1·5 million people died (deaths up from 1·3 million estimated in 2012).**

The 2014 WHO report also states that the problem of drug-resistant tuberculosis is worsening, with an estimated **480000 new cases of multidrug-resistant (MDR) tuberculosis in 2013.** This number too might be an underestimate, since estimates for the true burden of drug-resistant tuberculosis across sub-Saharan Africa, Asia, and eastern Europe are impaired by the fact that drug-resistance testing and treatment services are generally unavailable at most health-care facilities.5,6 Perhaps even more concerning was that, **of the nearly half a million estimated cases of MDR tuberculosis worldwide, only 136 000 cases were officially diagnosed.** The outlook for these patients is bleak, with **treatment completion rates remaining at 48**% and a widening gap between people who are diagnosed and those who receive treatment. Furthermore, **9% of people with MDR tuberculosis are estimated to have extensively drug- resistant (XDR) tuberculosis—ie, nearly 50000 people worldwide** have a form of the disease that, at present, cannot be treated.

The i**ncreased revised estimates in the 2014 report** arise from a series of studies in five high-burden

countries: Gambia, Laos, Nigeria, Pakistan, and Rwanda. One of these countries, **Nigeria,** was reported to have a Jan 2015 **tuberculosis diagnosis rate of about 50**% —ie, only half of all people with tuberculosis were notified that they had the disease. 2 After the prevalence study, it was estimated that just 16% of all patients with tuberculosis were notified by the national treatment programme. Results from a similar study in Indonesia2 showed that prevalence had been substantially underestimated and the number of cases could be nearly one million more than were previously estimated. The report states that the rate of progress against the disease has remained largely unchanged. The number of new cases has decreased by roughly 1·5% each year between 2000 and 2013. At these present rates of progress, the target of elimination by 2035 seems remote.

So what can be done by the global community to accelerate progress to achieve global targets? First, many cases of tuberculosis are clearly not officially diagnosed or treated. The so-called missing 3 million continue to be a major driver of the epidemic. This challenge was the theme of World Tuberculosis Day 2014.7 People with active

tuberculosis who are not treated can transmit the disease to others, while people who are treated unofficially, outside national tuberculosis programmes, are at increased risk of developing drug-resistant strains of the disease. As the revised data and other studies suggest,8,9 the more tuberculosis is looked for, the more is found. Therefore, approaches are needed that look for tuberculosis more thoroughly, and diagnose more people as soon as possible, allowing them to receive the appropriate high-quality treatment. Fully funded projects like TB REACH, which has a proven record of piloting innovative ways to diagnose and treat great numbers of people, would be a good first step.

If the gap between those who are officially diagnosed and those who are ill can be closed, transmission reduction can begin, and progress against the disease can be accelerated. The fight against HIV has adopted a powerful message of treatment as prevention—this is even more appropriate in the fight against tuberculosis. This effort must be led by the countries with the heaviest tuberculosis burdens; donor countries can provide financial and technical assistance, strengthen health systems, and help to identify innovative methods to reach patients, but these efforts must be locally led. If the search for and treatment of patients must be done at the local level, what more can donor countries do to help defeat the disease? The answer is simple: more resources are needed for proactive screening, and new ways to diagnose, prevent, and treat tuberculosis should be identified. A report by the Treatment Action Group,10 released on the same day as the Global tuberculosis report 2014,2 shows how little is invested in tuberculosis research and development, compared with what is needed. The 2014 Report on Tuberculosis Research Funding Trends10 revealed that total global investment in tuberculosis research and development was about US$675 million. Although this amount might seem substantial, it is barely a third of the estimated $2 billion needed to develop new drugs, vaccines, and diagnostics.

In October, 2014, the All Party Parliamentary Group on Global Tuberculosis published a report11 investigating the failure to develop much-needed new drugs for neglected diseases—including tuberculosis—that affect millions of people but represent a relatively small financial market. The report made clear that the commercial market had failed with respect to these products. Treatment Action Group's report10 estimates that, in 2013, spending on tuberculosis by pharmaceutical companies was just $99 million. This total is the lowest since Treatment Action Group started reporting research spending in 2005.

Where markets fail, governments must intervene, and the UK is a global leader in this field. The UK Prime Minister launched a commission12 into the failure of markets to develop new antibiotics, and much of the commission's work will be equally relevant to failures to develop new tuberculosis drugs. The Department for International Development13 has committed £150 million over 5 years for product

development partnerships—non-profit organisations that seek to develop treatments for diseases that do not attract attention from pharmaceutical companies. Nonetheless, these investments are small compared with both the resources needed for, and the potential rewards of, for example, a new tuberculosis or HIV vaccine. The future challenge is to convince other countries to invest more in research and development for global health.

Breaking News MDG revised report July 1 2015

•• Between 2000 and 2013, tuberculosis prevention, diagnosis and treatment interventions saved an estimated 37 million lives. The tuberculosis mortality rate fell by 45 per cent and the prevalence rate by 41 per cent between 1990 and 2013.

Latent TB

There are several treatment regimens currently in use:

- 9H — isoniazid for 9 months is the gold standard (93% effective).
- 6H — Isoniazid for 6 months might be adopted by a local TB program based on cost-effectiveness and patient compliance. This is the regimen currently recommended in the UK for routine use. The U.S. guidance excludes this regimen from use in children or persons with radiographic evidence of prior tuberculosis (old fibrotic lesions) (69% effective).
- 6 to $9H_2$ — An intermittent twice-weekly regimen for the above 2 treatment regimens is an alternative if administered under Directly observed therapy (DOT).
- 4R — rifampicin for 4-months is an alternative for those who are unable to take isoniazid or who have had known exposure to isoniazid-resistant TB.
- 3HR — Isoniazid and rifampin may be given daily for three months.
- 2RZ — The two-month regimen of rifampin and pyrazinamide is no longer recommended for treatment of LTBI because of the greatly increased risk of drug-induced hepatitis and death.[33]
- **Probably the best:** 3HP - **three-month (12-dose) regimen of weekly rifapentine and isoniazid.**[34][35] The 3HP regimen has to be administered under DOT. A self-administered therapy (SAT) of 3HP is investigated in a large international study.[36]

Evidence for treatment effectiveness

A 2000 Cochrane review containing 11 double-blinded, randomized control trials and 73,375 patients examined six and 12 month courses of isoniazid (INH) for treatment of latent tuberculosis. HIV positive and patients currently or previously treated for tuberculosis were excluded. The main result was a relative risk (RR) of 0.40 (95% confidence interval (CI) 0.31 to 0.52) for development of active tuberculosis over two years or longer for patients treated with INH, with no significant difference between treatment courses of six or 12 months (RR 0.44, 95% CI 0.27 to 0.73 for six months, and 0.38, 95% CI 0.28 to 0.50 for 12 months).[37]

A Cochrane systematic review published in 2013 evaluated four different alternatives regimens to INH monotherapy for preventing active TB in HIV-negative people with latent tuberculosis infection. The evidence from this review found no difference between shorter regimens of Rifampicin or weekly, directly observed Rifapentine plus INH compare to INH monotherapy in preventing active TB in HIV-negative people at risk of developing it . However the review found that the shorter Rifampicin regimen for four months and weekly directly observed Rifapentine plus INH for three months “may have additional advantages of higher treatment completion and improved safety." However the overall quality of evidence was low to moderate (as per GRADE

criteria)and none of the included trials were conducted in LMIC nations with high TB transmission and hence might not be applicable to nations with high TB transmission.[38]

Treatment efficacy

Main article: tuberculosis treatment

There is no guaranteed "cure" for latent tuberculosis. "People infected with TB bacteria have a lifetime risk of falling ill with TB..." [7] with those who have compromised immune systems, those with diabetes and those who use tobacco at greater risk.[7] Although many doctors and professionals may speak of Isoniazid and other TB treatment drugs as a "cure," in the strictest sense it is not. This is because while the drugs applied to latent or active Tuberculosis are effective, they are not 100% so; every bacteria has a chance to be resistant to the drug in question. When the appropriate treatment is applied to an active case of Tuberculosis and is deemed successful, the patient is "cured" in as much as the patients symptoms will subside - the Tuberculosis itself is not gone, but merely reverted to its latent state.

A person who has taken the complete course of Isoniazid (or other full course prescription for tuberculosis) on a regular, timely schedule may have been cured. "Current standard therapy is isoniazid (INH) which reduce the risk of active TB by ***as much as 90 per cent*** if taken daily for 9 months." [39] However, if a person has not completed the medication exactly as prescribed, the "cure" is less likely, and the "cure" rate is directly proportional to following the prescribed treatment specifically as recommended. Furthermore, "[I]f you don't take the medicine correctly and you become sick with TB a second time, the TB may be harder to treat if it has become drug resistant." [40] If a patient were to be cured in the strictest definition of the word, it would mean that every single bacterium in the system is removed or dead, and that person cannot get tuberculosis (unless re-infected). However, there is no test to assure that every single bacterium has been killed in a patient's system. As such, a person diagnosed with latent TB can safely assume that, even after treatment, they will carry the bacteria - likely for the rest of their lives. Furthermore, " It has been estimated that up to one-third of the world's population is infected with M. tuberculosis, and this population is an important reservoir for disease reactivation." [41] This means that in areas where TB is endemic treatment may be even less certain to "cure" TB, as reinfection could trigger activation of latent TB already present even in cases where treatment was followed completely.

Once a positive skin test is shown, a patient's body will always react to the tuberculosis test even after treatment. This happens because the patient's immune system has already recognized the tuberculosis bacteria as an invader. It is unnecessary to get another skin test under any circumstances; a person who has contracted TB either in its latent or active form will always get a positive. Blood tests, however, may be effective in determining if there has been any change in a persons diagnosis in cases where reinfection is a possibility, and should be considered if entering a high-risk area.

Breaking News 2015-10-28

Tuberculosis now ranks alongside HIV as the world's most deadly infectious disease, the World Health Organization (WHO) says.

Each accounted for between 1.1 million and 1.2 million deaths in 2014.

The WHO said the tuberculosis figures were unacceptable for a disease that could be cured.

Medecins Sans Frontieres said the statistics were "disheartening" and warned the world was "losing ground" on tackling resistant forms of TB.

The WHO's Global Tuberculosis Report 2015 shows the huge strides that have been made in tackling TB, with the death rate being nearly halved since 1990.

And the number of infections has been falling by 1.5% a year since 2000.
Deaths from HIV/Aids have also been falling rapidly because of improved access to anti-retroviral drugs.
Dr Mario Raviglione, the WHO's tuberculosis director, told the BBC News website: "Tuberculosis and HIV are now competing to be the number one cause of death from infectious disease in the world.
"Tuberculosis now ranks alongside HIV."
Most new cases of TB are in China, India, Indonesia, Nigeria or Pakistan.

Deaths from HIV/Aids have been falling since the mid-2000s, **and stand at 1.2 million a year**.
Overall there were 1.5 million tuberculosis deaths in 2014.
But 400,000 of them are officially counted as Aids deaths as they were in HIV positive patients.
The WHO now considers TB and HIV to be effectively joint top killers.
WHO director-general Margaret Chan said there had been "tremendous impact" since 1990, but added that "if the world is to end this epidemic, it needs to scale up services and, critically, invest in research".
Dr Raviglione agreed, saying that if the international investment in TB matched that of HIV, then "we could have accelerated the decline in mortality".
Resistance
The report also highlights the dangers of tuberculosis becoming resistant to antibiotics.
About three in every 100 new cases of TB could not be treated with first choice antibiotics.
Dr Grania Brigden, from Medecins Sans Frontieres, said it was "yet another year of disheartening statistics" that should "serve as a wake-up call".
She added: "We're losing ground in the battle to control drug-resistant forms of TB, and without considerable corrective action, the vast majority of people with multi-drug resistant TB won't ever be diagnosed, put on treatment, or cured."
The World Health Organization will shift to its End TB Strategy next year, which aims to cut deaths by 90% by 2030.

However here is the sober comment from The Lancet: Richard Horton and Pamela Das
Reviewing research *The Lancet* has published on the global tuberculosis epidemic, one will be struck by how little the situation has changed over the years, and how the same calls to action get repeated from one year to the next. For decades, a piecemeal approach with a narrow treatment focus and a cost imperative has prevailed. The result? A global epidemic of disease. For more than a decade the global tuberculosis incidence rate has declined, but only slowly by about 1·65% annually.1,2 Meanwhile, the worst legacy of this disease has become multidrug resistance.

Global Tuberculosis Report 2015: Executive Summary

The year 2015 is a watershed moment in the battle against tuberculosis (TB). It marks the deadline for global TB targets set in the context of the Millennium Development Goals (MDGs), and is a year of transitions: from the MDGs to a new era of Sustainable Development Goals (SDGs), and from the Stop TB Strategy to the End TB Strategy. It is also two dec- ades since WHO established a global TB monitoring system; since that time, 20 annual rounds of data collection have been completed.

Using data from 205 countries and territories, which account for more than 99% of the world's population, this global TB report documents advances in prevention, diag- nosis and treatment of the disease. It also identifies areas where efforts can be strengthened.

Main findings and messages

The advances are major: TB mortality has fallen 47% since 1990, with nearly all of that improvement taking place since 2000, when the MDGs were set.

In all, effective diagnosis and treatment of TB saved an estimated 43 million lives between 2000 and 2014.

The MDG target to halt and reverse TB incidence has been achieved on a worldwide basis, in each of the six WHO regions and in 16 of the 22 high-burden countries that collec- tively account for 80% of TB cases. Globally, TB incidence has fallen by an average of 1.5% per year since 2000 and is now 18% lower than the level of 2000.

This year's report describes higher global totals for new TB cases than in previous years, but these reflect increased and improved national data rather than any increase in the spread of the disease.

Despite these advances and despite the fact that nearly all cases can be cured, TB remains one of the world's biggest threats.

In 2014, TB killed 1.5 million people (1.1 million HIV-negative and 0.4 million HIV-positive). The toll comprised 890000 men, 480 000 women and 140 000 children TB now ranks alongside HIV as a leading cause of death worldwide. HIV's death toll in 2014 was estimated at 1.2 million, which included the 0.4 million TB deaths among HIV- positive people.1

Worldwide, 9.6 million people are estimated to have fall- en ill with TB in 2014: 5.4 million men, 3.2 million women and 1.0 million children. Globally, 12% of the 9.6 million new TB cases in 2014 were HIV-positive.

To reduce this burden, detection and treatment gaps must be addressed, funding gaps closed and new tools developed. In 2014, 6 million new cases of TB were reported to WHO, fewer than two-thirds (63%) of the 9.6 million people esti- mated to have fallen sick with the disease. This means that worldwide, 37% of new cases went undiagnosed or were not reported. The quality of care for people in the latter category
is unknown.

Of the 480 000 cases of multidrug-resistant TB (MDR-TB)
estimated to have occurred in 2014, only about a quarter of these – 123 000 – were detected and reported.

Although the number of HIV-positive TB patients on antiretroviral therapy (ART) improved in 2014 to 392 000 people (equivalent to 77% of notified TB patients known to be co-infected with HIV), this number was only one third of the estimated 1.2 million people living with HIV who devel- oped TB in 2014. All HIV-positive TB cases are eligible for ART.

Funding gaps amounted to US$ 1.4 billion for implemen- tation of existing interventions in 2015. The most recent estimate of the annual funding gap for research and devel- opment is similar, at about US$ 1.3 billion.

From 2016, the goal is to end the global TB epidemic by implementing the End TB Strategy.

Adopted by the World Health Assembly in May 2014 and with targets linked to the newly adopted SDGs, the strategy serves as a blueprint for countries to reduce the number of TB deaths by 90% by 2030 (compared with 2015 levels), cut new cases by 80% and ensure that no family is burdened with catastrophic costs due to TB.