I. Epidemiology Refresher

1. The TB Chain of Transmission

First, let us examine the tuberculosis chain of transmission. At birth, people are uninfected. Following contact with an infectious TB person, uninfected individuals may become infected. About one third of the world’s population is currently infected. Most infected people develop a latent infection, and remain in the latency state for many years. At a certain point in time, they may reactivate their old infection, and develop either reactivated infectious TB, or reactivated non-infectious TB.

TB patients who are not diagnosed and treated may die. However, even if they do receive treatment, treatment might fail. The major reasons for TB treatment failure include drug resistance and poor compliance. Furthermore, once patients are cured, either spontaneously or through treatment, they might develop another TB episode.

2. Important TB Indicators

A number of indicators help us assess the burden of both infectious and non-infectious tuberculosis.

a. Incidence, Prevalence, and Disease Duration

Incidence and prevalence rates are two key indicators. The Incidence rate is defined as the number of new TB patients, divided by the population, and expressed per 100,000 population. The prevalence rate, on the other hand, measures the number of existing cases at a certain point in time. This number is also divided by the population size, and expressed per 100,000 population.

Let us examine the relation between incidence, prevalence, and disease duration over a period of several years. We observe that when disease duration is shorter, the number of prevalent cases is reduced given a constant number of incident cases. Prevalence can be lower than incidence. In a stable-state epidemic, one can typically observe a simple relationship between prevalence, incidence, and disease duration.

b. Notification Rates

Notifications are defined as the number of cases notified to the national TB-programmes. They are expressed per 100,000 population, so that countries with different population sizes can easily be compared. We usually distinguish between all forms of TB and smear-positive TB.
c. Case Detection Rate

The case detection rate is a rather complicated concept, which serves as an indicator of the coverage of the surveillance system; that is, the proportion of TB cases that are actually notified to the authorities. The case detection rate is defined as the notifications rate divided by the incidence rate. Not all new TB cases are diagnosed and notified. Some cases are detected by private practitioners, or even hospitals, which do not report them to the national TB programme.

d. Cure Rate

The cure rate is defined as the proportion of smear-positive patients who completed their TB treatment, and were confirmed as smear-negative at the end of the treatment.

e. Fatality Rate

The TB case fatality rate is defined as the proportion of patients who die during the course of TB treatment, regardless of the cause of death.

f. Mortality Rate

Lastly, the TB mortality rate is the number of TB deaths expressed per population.

3. Estimations of TB Incidence

Estimating incidence is a complex, uncertain task. While we know the number of notifications, we do not know how many cases are not being reported each year. Estimating incidence directly is highly impractical, as it requires repeated surveys. Since tuberculosis is a rare disease, an extremely large sample size would be necessary for such surveys to produce meaningful results. In fact, measuring TB directly is such a logistically-complex and costly endeavour, that it was never implemented on a large scale.

Thus, TB incidence is usually estimated indirectly, using one of the following four formulas. The first formula defines incidence as the number of notifications divided by the case detection rate. In order to assess the case detection rate, we typically ask experts to estimate the coverage of detection system in their country. Naturally, these estimates are imperfect and imprecise.

The second way to estimate incidence is to divide prevalence by disease duration. Unfortunately, while the prevalence rate can be estimated directly, estimating the duration of disease is difficult.

The third way is through the use of tuberculin surveys. Tuberculin surveys allow to measure the prevalence of infection. The prevalence of infection is then translated into an annual risk of infection, or an ‘infection incidence’. Incidence of disease is estimated by multiplying the annual risk of infection by a constant, called a Styblo ratio.

In the 1970s, the Styblo ratio was estimated at 50, suggesting that a 1% annual rate of infection would translate into 50 smear-positive cases per 100 000 population. Unfortunately, this rule does not hold true in most settings. Since we do not know the true Styblo ratio, it is extremely difficult to use this method. We must also deal with uncertainties relating to the measurement of the infection itself. Namely, tuberculin positive reactions might be due to
past BCG vaccination or to exposure to environmental mycobacteria. It is thus difficult to
determine whether a positive reaction is really due to an infection.

A fourth approach is to estimate TB incidence through the mortality data. Incidence is thus
obtained by dividing the number of deaths by the TB fatality rate (the proportion of TB cases
dying from the disease). Again, it is difficult to assess how many patients die during the
course of the disease. Particularly, we do not know the case fatality rate of unnotified and
untreated cases.

II. The Stop TB Strategy

The Stop TB Strategy is based on the DOTS (Directly Observed Treatment, Short-Course)
strategy, which was developed in the 1990’s and adopted by most countries. DOTS focuses
on the detection of smear-positive TB cases through microscopy. Identified cases are then
treated using standardised short-course chemotherapy. A number of methods are used to
ensure patient compliance. The DOTS strategy also promotes a number of supporting
mechanisms, such as regular drug supply and political commitment.

About five years ago, we realised that DOTS alone is not sufficient, since it does not allow us
to control key problems such as HIV-TB, MDR-TB, or TB transmission in prisons. We thus
initiated the Stop TB Strategy, which includes several components aimed at addressing such
challenges.

The Stop TB Strategy also includes components aimed at addressing TB treated outside the
scope of national TB programmes. For example, in China, many TB suspects are assessed in
general hospitals that do not fall under the scope of the Chinese national CDC programme.
These cases are then typically notified to the CDC, and referred to TB dispensaries. It is
extremely important that care providers use methods that are in line with the strategy used at
the national level. We have thus devised a number of strategies, such as the Public-Private
Mixed DOTS, allowing to improve the performance of services provided by non-national TB
programmes.

III. The Millennium Development Goals

The UN has set a number of goals for 2015, called the Millennium Development Goals. Most
of these goals focus on poverty and health, and one concerns tuberculosis. It states that by
2015, incidence should have reverted. The meaning of the somewhat awkward term ‘reverted
incidence’ is that incidence should be declining. Targets were set to monitor progress towards
the goal: aiming at halving TB prevalence and mortality rates by 2015 in comparison to the
1990 rates

Two targets were previously set for 2005. The first is that at least 70% of TB cases should be
notified by DOTS programmes. The second relates to treatment success, which is a
combination of cured patients and patients who have completed their treatment, but have no
bacteriological confirmation of cure. The aim is that 85% of smear positive patients be cured
or have completed treatment.
IV. Estimates of TB Burden

1. Estimate of TB Incidence by Geographical Region

Let us examine the estimated number of new TB cases in different countries in 2006. Since the numbers are directly related to the population size, the highest numbers were observed in China and India. However, the highest rates per capita are observed in Sub-Saharan Africa. The main cause of these high rates is the high prevalence of HIV in that region.

When we examine TB incidence trends, we observe that incidence in a subset of African countries with high HIV rates more than doubled between 1990 and 2003. Incidence levels topped in 2003.

TB incidence in Eastern Europe has also risen in the second part of the 1990’s, until the early 2000s, and then stabilised. This rise was due to two main factors. The first was the weakening of many Eastern European health systems, following the collapse of the Soviet Union; and the second was MDR-TB.

A steady decline in TB incidence has been observed in high-income countries, as well as in Central Europe, Latin America, and the Western Pacific.

2. Factors Influencing TB Incidence

It is interesting to examine the correlates of the average annual change in TB incidence in different parts of the world. For example, in Latin America, TB incidence tends to increase when the proportion of HIV-positive individuals in the general population increases. In high income countries, TB incidence tends to increase when there is a rise in foreign migration. In fact, in Western Europe, a significant proportion of TB cases occur in immigrants. It is noteworthy that the trends in tuberculosis incidence among immigrants tend to reflect epidemiological patterns observed in the country of origin. Finally, the larger health expenditures per capita in a country are, the faster the decline in TB incidence.

3. Global Aggregates

Finally, I would like to show global aggregates of prevalence, mortality and incidence over time. Global TB prevalence has been declining from a level of 300 cases per 100,000 population in 1990 to a level of 220 cases in 2005. Unfortunately, we are still far from reaching the 2015 goal, of about 150 cases per 100,000 population. However, an acceleration in the decline of prevalence has been observed, which we believe is due to improvements in TB control programmes.

Mortality rates, which have been rising due to a combination of factors, including HIV-TB and MDR-TB, are now declining. Global incidence rates, which have been unexpectedly increasing until 2003, have also begun declining.

We are making some progress towards our goals. Assuming that the current prevalence decline trends will continue, we will probably manage to meet the 2015 prevalence target, of halving the 1990 rates. However, we will be slightly short of the death rates target. We must also remember that the situation is extremely heterogeneous across regions. Africa, for example, where prevalence has increased, will likely be far from the prevalence target in 2015. On the other hand, the Western Pacific region should easily meet both prevalence and death rates targets.
V. Notifications

TB notification rates, which measure the number of cases notified to the national TB-programmes, expressed per 100,000 population, reveals patterns similar to those of incidence rates. Notification rates in Sub-Saharan Africa, and in some Asian countries, such as Cambodia, Vietnam and Bangladesh, are extremely high.

The current global case detection rate is 60%. Significant progress would be necessary before we could reach the global detection rate 2005 target of 70%. While there has been some increase in the number of cases reported under DOTS, this increase has been largely at the expense of non-DOTS case detection rate. In other words, while the coverage of the DOTS programme has increased, the total case detection rate has not been increasing fast enough. Thus, while the 70% target was set for 2005, it will probably be reached only in 2010. The only region that has so far met the target is the Western Pacific region, and some regions, such as Africa, remain far from it.

VI. Tuberculosis Control

Almost all countries have adopted DOTS.

Treatment outcome is one of the most important performance indicators of TB control programmes. Treatment outcomes of HIV-TB patients are consistently poorer than those of HIV-negative TB patients, due to the high death rates of HIV-TB patients. It is crucial to diagnose both TB and HIV conditions as early as possible.

A second important predictor of treatment outcome is history of previous treatment. Patients who have not been treated for TB in the past tend to enjoy better outcomes.

A significant part of the unsuccessful TB treatments are due to defaulting, meaning that some patients quit their treatment before completion.

Finally, there are two regions, Africa and Europe, in which mortality rates are particularly high. In Africa, this is due to HIV and in Europe, to MDR-TB.

VII. Tuberculosis Drug Resistance

1. Surveillance

The first global surveillance project has launched in 1994. To support the project, a network of Supranational Reference Laboratories (SRLN) has been put in place.

The supranational reference laboratories are situated in all regions and provide a number of important services. First, they ensure quality of drug resistance surveillance, through quality assurance programmes provided to national reference laboratories. For example, the supranational reference laboratory that has been working with China for the past decade is located in Hong Kong.

The network also provides on-site support, and helps countries implement surveys on drug resistance, which is an extremely challenging task. It is typically difficult to obtain accurate information on prior TB treatment of patients, which is the single most important predictor of drug resistance TB.
2. **Description of MDR-TB**

MDR-TB is defined as resistance to two essential anti-TB drugs, INH and Rifampicin. The treatment of MDR-TB patients is more difficult, since these two drugs are the most potent anti-TB drugs. MDR-TB patients require treatments that include second line drugs. Such treatments are extremely toxic, typically last for several years, and cause many adverse drug reactions.

High MDR-TB rates in new cases demonstrate an active transmission of MDR-TB in the community. They thus serve as an important indicator of past performance of TB control. MDR-TB rates are significantly higher among patients who have been treated for the disease in the past.

3. **Incidence of MDR-TB**

In the year 2006, there were about 500 000 new MDR-TB patients worldwide, accounting for almost 5% of all new TB cases. The distribution of MDR-TB rates across regions is heterogeneous. In Europe, and particularly in some of the former Soviet Union countries, MDR-TB rates are extremely high.

In Hong Kong, the prevalence of MDR-TB has been slowly declining over the past ten years. This decline is largely due to a well performing TB control programme. Unfortunately, that is not the case everywhere. For example, in the Baltic countries, Estonia, Latvia, and Lithuania, we observe a trend of a slow increase of MDR-TB in new patients. This trend is particularly worrisome when we consider that the overall TB incidence in these countries has been declining.

In Peru, while the general TB notification rate has been declining over the past decade, the rate of MDR-TB among new patients has been increasing despite good performance of TB control. MDR-TB rates are also increasing in South Korea, although the country possesses all the necessary resources to effectively treat TB.

4. **XDR-TB**

Extensively drug resistant TB, or XDR-TB, is defined as MDR-TB, with additional resistance to the most potent second line drugs: fluoroquinolones and one injectable. The treatment of XDR-TB is very challenging and results in poor outcomes.

XDR-TB has been receiving considerable attention lately, following outbreaks of XDR-TB in South Africa with very high cases fatality rates. So far, XDR-TB has been found everywhere we have looked for it, and I believe that the more we will look for it, and more we will find it. XDR-TB is a man-made problem; it is due to the misuse of second-line drugs. Significant levels of XDR-TB have been found in former Soviet Union countries and the South Korea. I firmly believe that XDR-TB will impose an increasing burden on national TB programmes.

5. **MDR-TB Treatment**

While there has been some improvement in the detection of MDR-TB patients, most of them do not receive adequate treatment. Global progress of treatment programmes for MDR-TB is too slow. A number of countries, such as Latvia, do offer high-quality treatment programmes for MDR-TB patients. However, the cure rates in Latvia are merely 65-70%, demonstrating the difficulty in curing MDR-TB patients.
VIII. Conclusion

In conclusions, we could say that the overall TB disease burden is declining, albeit very slowly. In 2006, 9.2 million new TB cases have been identified worldwide. 14 million prevalent cases were recorded, and 1.7 million people died from the disease.

Progress in case-detection has been significantly slower than we had anticipated when global targets were set. HIV-TB and MDR-TB pose an ever increasing challenge to TB control programmes.

I. Question and Answer Session

Participant

What is the Styblo ratio for all TB cases, not merely the new ones?

Philippe GLAZIOU

We estimate the incidence of all TB cases from the estimated incidence of smear-positive cases, by multiplying it by a factor of about 1.5. We are not favouring, at this point in time, the Styblo method to estimate disease incidence. A recent survey conducted in Vietnam, showed the observed prevalence was 1.5 times higher than previously anticipated using Styblo method.

Participant

What is the MDR-TB treatment based on?

Philippe GLAZIOU

It is based on a combination of second-line drugs, such as Kanamycin, Cycloserine or Fluoroquinololones. One of the principles of the treatment is using at least four active drugs that the patients have not been exposed to in the past. Since we typically do not conduct drug susceptibility testing for all second-line drugs, the treatment regimen is designed based on the patient history of previous treatments.

Qian GAO

What is the strategy to prevent the transmission of primary drug resistance?

Philippe GLAZIOU

The first strategy is to implement sound TB control programmes. For example in China, many patients are treated in general hospitals, where they are provided with costly prescriptions for one month. We must train physicians to use proper treatment programmes, and to utilise the support services of the CDC, in order to track patients who default.

Once MDR-TB emerges, it is important to identify patients whose regular treatment failed, as well as contacts of identified MDR-TB patients. All these people should be tested for drug susceptibility. If they are diagnosed with MDR-TB, they should be put under adequate treatment regimen, to ensure that they are cured as fast as possible, in order to cut the chain of
transmission. Hopefully, a rapid test for MDR-TB will be introduced soon. If it proves to be an effective diagnostic tool, significant effort should be put to ensure that it is widely used.

**Qian GAO**

Many MDR-TB patients are poor. However, merely first line drugs are provided for free.

**Philippe GLAZIOU**

Ensuring free treatment is perhaps the most crucial part of MDR-TB control, since it is clear that MDR-TB would never be controlled if patients are obliged to pay for the drugs. Currently, most patients are required to pay for diagnostics tests and for second line drugs, which are extremely expansive. As a result, patients often select drugs according to their cost, rather than efficacy. However, by taking the inappropriate drugs, they might develop XDR-TB.

In 2000, WHO has initiated low-priced quality-assured drugs treatment programmes. This mechanism allowed a sharp decline of more than ten-fold, in the cost of drugs. Nevertheless, the MDR-TB treatment is still very expensive, so funding must be sought.

**Participant**

On one of the slides presented, it has been noted that TB incidence declines in a population, when the percentage of women who smoke is higher. How do you explain this phenomenon? Was a similar trend observed in men who smoke?

**Philippe GLAZIOU**

I agree that this finding is counter-intuitive, since the fact that smoking increases the chances of developing TB is well documented. A possible explanation is that eastern European countries with high rates of female smokers are more economically developed, and thus have stronger health systems, with lower TB incidence. We did not observe a similar correlation with respect to the proportion of male smokers.

**Olivier NEYROLLES**

Do you believe there is a genuine sex-bias in tuberculosis?

**Philippe GLAZIOU**

The notifications rates of men are higher than those of women. However, we are not sure whether it is due to the fact that men have higher access to healthcare in many countries, or whether men really suffer more from the disease. Men are likely more exposed to infectious cases.