Interview

Dr Mario Raviglione, Director of the Stop TB Department World Health Organization

Tuberculosis (TB) is a very global disease; there are over 9 million new incidences of TB every year with the vast majority of cases emerging in the developing world. As one of three major diseases associated with poverty it affects the areas where poverty is most prevalent, notably Asia and Africa. While the incidence rate has been slowly declining in the developed world it continues to pose a major health threat to even the most developed nations. To demonstrate the global, and persistent, nature of TB we asked Dr Mario Raviglione, Director of the World Health Organization's Stop TB Department to provide an analysis on the current TB situation in the United Kingdom and comment on what measures should be taken to alleviate the issue of TB in one of the world's richest countries.

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Tuberculosis is still a major global health problem. Can you give us an idea of the scale of the problem worldwide?

Of infectious diseases, tuberculosis is a top killer in the world. There are, we estimate, some 1.7 million people dying of TB every year, including some 380 000 among people living with HIV. Yet incidence of TB is declining, at about 1% per year since the early 2000s globally, but I would like to see this rate decline more rapidly. There is some important decline, for instance, in Latin America at 4% per year but this rate of reduction is not replicated in Asia, Africa and in Europe. While morbidity and prevalence rates are going down, incidence rates still remain high and it is incidence rates that are the ultimate indicator as they show the amount of recent transmission that can be cut, which in turn can help morbidity and prevalence rates decline.

What is the situation in the UK? Are the incidence rates there a concern?

The problems in the UK are similar to those in the rest of western Europe. It is a country which has fairly low incidence rates relative to developing countries but has slightly higher incidence than other western European countries, which are at approximately 10–15 per 100 000 of the population. Three-quarters of cases are those born outside of the country, either recent immigrants or long-term residents born outside the UK. The

peculiarity is that the UK numbers have remained stable or increased slightly in recent years. We used to say in the 1990s that 'TB has no border' and that is still valid. We will not see an elimination of cases of TB in the UK in the foreseeable future until it is under control globally. Therefore, development agencies of rich countries are required to support control of TB in high-prevalence countries in order to reduce incidence rates in their own.

What measures can be taken to improve TB control in the UK?

For the UK and most countries worldwide there are a large amount of vulnerable populations: immigration and flows of population are continuous in our era and so the spread of disease is hard to manage among migrants, particularly the undocumented immigrants, and there are groups that are hard to reach, such as alcoholics, prisoners and socially deprived people like the homeless. Until the focus is on providing better services for these populations then the problem is going to be difficult. So, even in very rich countries like the UK, it is still difficult to treat TB patients belonging to some segments of communities. The future of TB control for middle- and higher-income countries has to involve targeting the high-risk groups, country by country, and targeting them actively rather than waiting for symptoms to arise, because this may cause a diagnostic delay

Figure 1 Tuberculosis case rates by place of birth and ethnic group, England, 2003–2009

of many months and by then it is too late to prevent transmission to others. So, there needs to be a focus on early detection and on the appropriate screening of the vulnerable populations in those at-risk communities.

So, local health authorities' and parliamentary engagement with the issue in the UK just isn't enough?

A lot more can be done. This is proved by the unique situation of an increase of incident cases. Despite similar epidemiological contexts, the UK has the highest rates in Western Europe, with exception to Portugal and Spain, which traditionally have had significantly higher rates but the incidence of which is declining. The necessary measures that are required for TB control that I have already outlined incur active screening of immigrants coming from highly endemic countries. One must recognise that this is a delicate issue for governments because these people can already be stigmatised by native populations. But it is important that immigrants at risk are screened on entry and equally important is education; the

high-risk groups must understand that they are at risk and should seek advice if early symptoms arise. Therefore it is a matter of much broader health promotion and health education approaches. I also must say that in terms of the UK's parliamentary engagement, groups like the TB All-Party Parliamentary Group (APPG) are extremely useful to the cause and may help to mobilise the public and eventually resources.

However, as far as the response is concerned, I have seen less enthusiasm for TB control than, for instance, malaria, let alone HIV. This isn't uncommon; in my view, there isn't one European country that excels in contributing to global TB control.

Incidence, prevalence and morbidity figures in other western European countries are similar to the UK. Are health bodies across Europe employing similar strategies to combat TB, or are there lessons to be learned?

Not all European countries have a particularly good record of effort in controlling TB. The majority of industrialised countries like the UK abandoned specialised practices in the 1980s in the false

hope that TB had been conquered. TB treatment is unlike that of other infectious diseases in that most only require antibiotics for a week. TB sufferers require constant support and what we term supervision, because many TB patients are those in poor communities who have more to worry about than just TB. So, unless they receive full support and supervision of treatment then one cannot be sure that they are completing their treatment until cure. In the 1990s, the WHO set up new policies and new standards to address these issues and to help control TB, but like in many other cases in the UK, it was not that easy at the start. It was difficult to convince countries, for instance, to change their notification system or use certain definitions, and particularly to implement standard treatment outcome monitoring. The WHO and the European countries agreed on a common surveillance system, common definitions, and to report treatment results. Today, it is the ECDC (European Centre for Disease Prevention and Control) that takes care of ensuring we can

measure and assess throughout the EU in a standard and harmonised fashion.

WHO recently published updated guidelines for programmatic management of drug-resistant TB. What is suggested in the guidelines and what sparked these changes?

We took the multiple drug resistant (MDR) TB problem seriously in the early 1990s. In 1994, we established the Global Drug Resistance Surveillance Project – and started to implement surveys in countries to establish how bad MDR TB was. We facilitated the connection of laboratories through a network that could exchange strains so that results could be compared using the same methodology. From the mid-1990s, the WHO produced programmatic guidelines because the first data collected suggested that we could not leave the problem to individual physicians or institutions in the country. Until the early 2000s, national programmes did not include the notion of MDR TB and so, in 2001 or 2002, the first manual was published to set out the inclusion of MDR TB in national programmes and provide guidance. This manual was then updated in 2006, and followed by an emergency edition issued in 2008 that responded to the extensively drug resistant (XDR) TB emergence in South Africa. The emergency edition was only supposed to last three years and so the new programmatic management of drug-resistant tuberculosis (PMDT) guidelines, published in the summer this year, takes into account the latest information on the potency of the

regimens and gives some indication on what type of drugs to be used on what occasion. But in reality there is no treatment revolution in these guidelines as we have only a very limited armamentarium of second-line drugs, which in the last decade has not changed because there has not been a new drug developed and put on the market, so the new guidelines provide more sophisticated recommendations on how drugs should be combined, for how long and when.

No new drug has been developed in recent years. But are there any drugs currently in development that excite you?

Two new drugs, perhaps three, may become available in late 2012 or early 2013. And on top of those there are the fluoroquinolones that are not new drugs, but the most advanced fluoroquinolones, moxifloxacin and gatifloxacin, have been found to be active against TB. These have been tested to try to reduce the duration of the regimen for standard TB from 6 months to just 4 months. This might have an implication since, if we find that the clinical trials for these drugs support the notion that adding either of the two fluoroquinolones to isoniazid, rifampicin and pyrazinamide can cut the duration from 6 to 4 months, then we, as the WHO, will make a recommendation to use this new treatment. The other two drugs in development are completely new molecules; they belong to new classes of antibiotics and so should have no similarity with any of the existing drugs, and they shouldn't risk cross-resistance.

These drugs will improve the treatment of MDR TB; perhaps shortening the treatment duration and could possibly further reduce the treatment duration of standard TB. These two drugs could be ready by the end of 2012. So finally we might have the first new drugs developed for TB for 40 years.

And for vaccines? There is a lot of controversy with vaccine efficacy, are there new developments that might improve it?

In terms of vaccines, there are two or three that are entering advanced phase trials. The majority of vaccines in the pipeline today are improvements on the Bacille Calmette-Guérin (BCG); as such I do not have the sense that these will revolutionise the way vaccines work. As we know, the BCG is variable in its efficacy: it is effective in very young children to protect them against the disseminated forms of TB that are common in infancy but not that protective against adult forms of TB. The BCG is the most widely used vaccine in the history of humanity; hundreds of millions of BCGs have been administered in the last 50 or 60 years, yet the fact that it has not had an impact on TB shows how weak the vaccine is. This justifies the WHO recommendation that it should just be used as soon as possible in infancy against the disseminated forms of disease typical of this age. So I am not sure that we will have a revolutionary vaccine in the next few years. I think it might take more time and I don't think we know enough about the immunity and pathogenesis of TB.