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Prevention starts with cure, and does not end there

TB epidemiology and social change - a historical outlook

Social causes of tuberculosis were apparent to health observers long before Robert Koch in 1882 discovered the germ that is a necessary factor in the causal web of the disease (Rosen 1974). TB flourished in urban slums and in other crowded, impoverished, and socially deprived places in the 18th century, and it continuous to flourish there in the 21st (Rieder 1999, Grange 1999, Marmot 2004, WHO 2005, Lönnroth et al 2006).

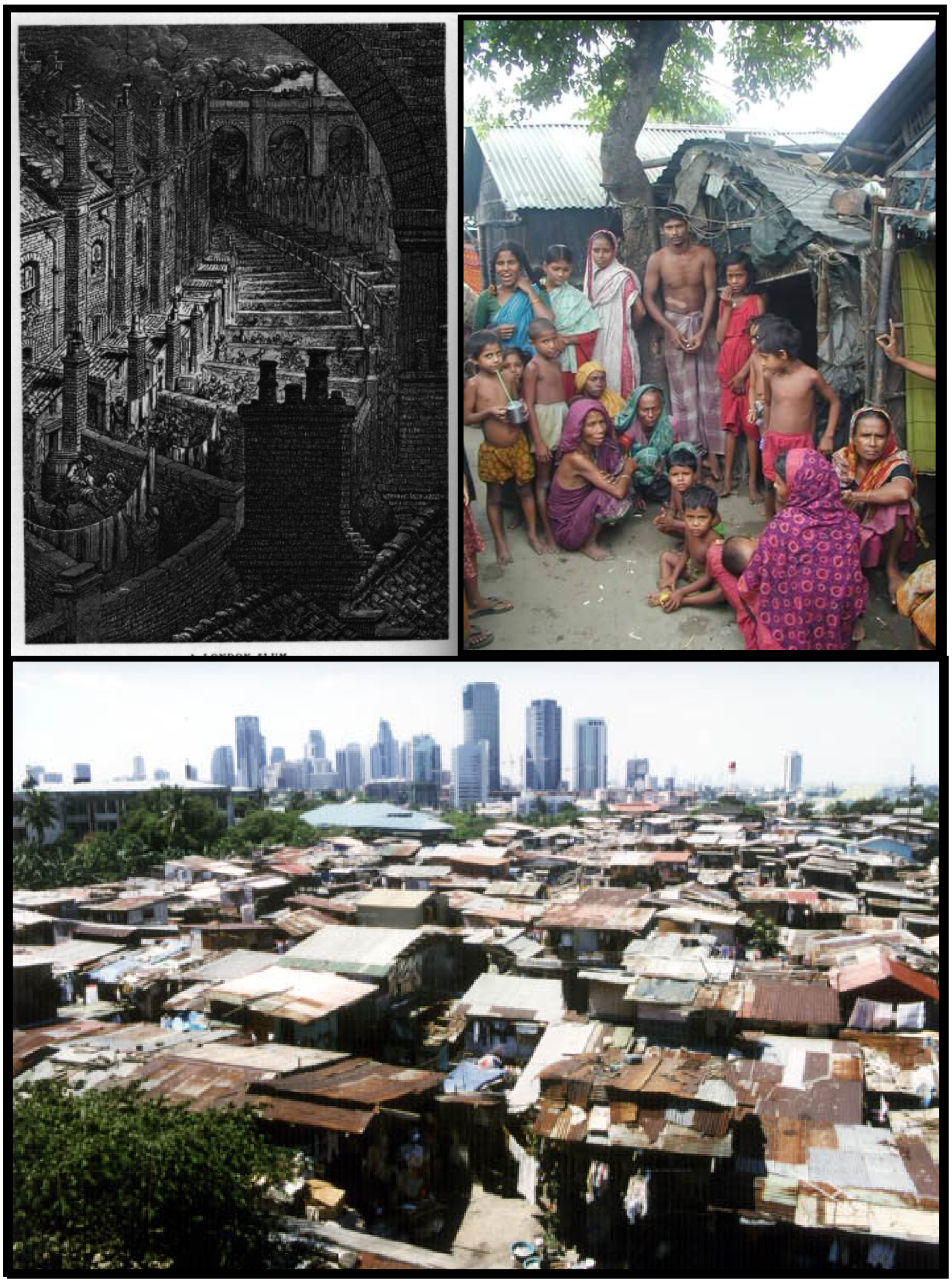

Figure 1. Slums in London, India, and The Philippines

Epidemiological data on TB morbidity and mortality prior to the 20th century is of questionable validity and comparability. However, some broad trends have been identified with a reasonable level of certainty. There seem to have been an increase in TB incidence starting in the 17th or 18th century, peaking at different times between the mid-1700s in Great Britain to the beginning of the 1900s in Japan. From these trends, a temporal association has been suggested between increased TB incidence and rapid industrialization and urbanisation. A plausible explanation is increased transmission due to migration, increased population density and crowded living conditions, especially in urban slums (Rieder 1999, Aparicio 2002, Shimao 2005, Grundy 2005). This lead, at the peak of the epidemic, to TB death rates close to 1% per year in some urban areas, which is several times higher than the TB death rates currently experienced in high HIV burden countries in Africa (figure 2).

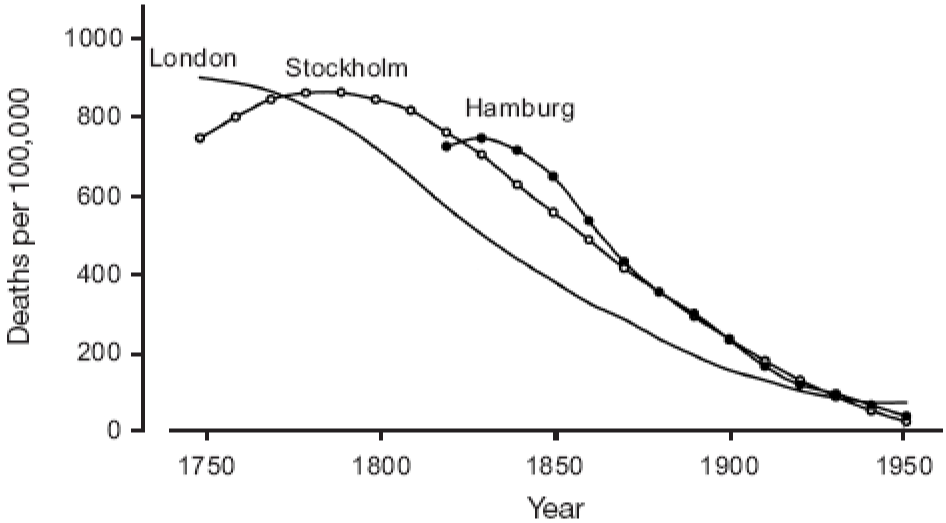

Figure 2. Tuberculosis deaths modelled from available data. (Source: Rieder 1999, reproduced from Grigg 1958).

Throughout the 20th century, TB incidence declined steadily in most industrialized countries, with the exceptional peaks during the two world wars. This was a period of economic growth, social reform, gradual poverty reduction, improved living conditions as well as great medical and public health advances. The relative importance of these factors has been debated. Some have suggested that the decline until the1940s was exclusively due to improved living conditions and nutritional status in the population, and virtually ruled out any impact of medical and public health interventions before chemotherapy became available (McKeown). Others have argued, on good grounds, that the introduction of sanatoria and other mechanisms to isolate infectious cases as well as pasteurization of milk also had a significant impact on the trends (Wilson 2005, Grundy 2005, Lienhardt 2001).

The discovery of the biological agent of TB during the early 1880s was an outstanding advance in the understanding of transmissible diseases, and marked the beginning of the germ theory era. As a result of this discovery the control of TB based mostly if not exclusively on the biological understanding of the disease was strengthened. Meanwhile, the environmental interventions preached during the 1800s were progressively discarded. This model for TB control received a final boost with the discovery in the 1940s and 1950s of drugs that cure the disease. and lead the path towards the paradigm of "prevention starts with cure". The expanded pharmacopeia of anti-TB drugs in the 1950s and 60s helped accelerate the decline in TB incidence in countries that had equipped their health system to deliver the recent medical advances to those in need. But this was not only a period of rapid medical and health care advances. The 1950s and 1960s were also a time of both rapid economic growth and accelerated welfare reforms in many industrialized countries (International Monetary Fund 2000, Navarro et al 2006).

The highest TB rates recorded in history were thus in settings were there was rapid urbanisation coupled with very dire living conditions for the disadvantaged. These were times of economic growth brought about by the industrialization, but also times of extremely uneven wealth distribution and limited social reform. The most rapid decline in TB incidence and death rate recorded in history were, on the other hand, in settings experiencing economic growth coupled with social and health sector reforms and medical advances.

Progress in TB control in the industrialized countries over the past centuries was thus brought about by advances on several fronts at the same time - medical and public health advances, as well as economic and social advances. History should teach us that future progress of TB control should rest on the same pillars (Jaramillo 1999). Rapid urbanisation and inequitable economic growth are developmental patterns presently common in many high TB burden countries. Weak health systems are a ever-present phenomenon in the developing world. Should and could these challenges be factored into global, regional and national TB control policies? What would it mean in practice for countries and national TB programmes (NTP) to apply a broader perspective on TB control, including strategies to address also the upstream drivers of the TB epidemic?

From downstream risk factors to their upstream determinants

To make explicit what the focus of preventive interventions might be, it is necessary to disentangle the determinants that are proximate or downstream and therefore within the domains of traditional public health programmes and health care workers, from those that are distant and upstream, and therefore possible to influence mainly by policy makers outside the health sector.

The tentative framework presented in figure 3 identifies the different stages of TB disease development and highlights two broad biological and environmental mechanisms through which known risk factors for TB are most likely to operate. It then considers three levels of upstream determinants that influence exposure to these risk factors.

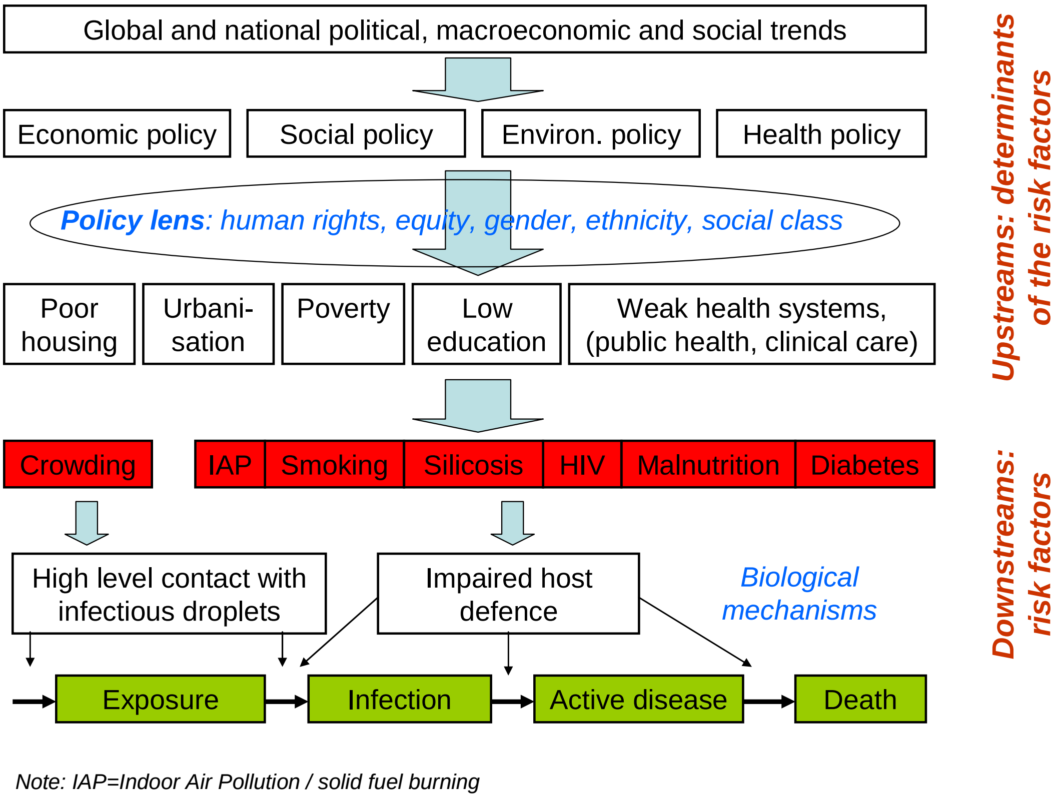

Figure 3. Framework for downstream risk factors and upstream determinants of TB

This framework is not comprehensive, but focuses on risk factors that lay outside the current domain of conventional TB control. Thus, the framework does not consider social determinants of access to medical interventions to prevent and treat TB, a topic that has been thoroughly addressed elsewhere (WHO 2004, WHO 2005). It is obvious that early and effective curative treatment of infectious individuals will reduce the level of contact with infectious droplets in the community as well as reduce TB mortality. Vaccination and preventive treatment will influence the risk of progress from exposure, through infection and active disease, to risk of death. What this framework highlights is that there are others factors too that influence this chain of events, and which may modify the effect of the medical interventions.

The downstream risk factors

Downstream risk factors include those that directly increase the level and duration of exposure to infectious droplets. This includes, apart form contact with an infectious individual, crowding and poor ventilation, in households, in health care settings, in workplaces, in public transportation, in prisons, etc. Downstream risk factors also include those that directly impair the host defence through reducing the ability to clear the airway from bacilli (damaged clearance of secretion of the tracheobronchial mucosal surface), or through impairing the innate and/or cell-mediated adaptive immune system.

More or less well-established risk factors for the latter include HIV infection, chronic malnutrition, chronic alcoholism, smoking, indoor air pollution (indoor burning of solid fuels without proper exhaust/ventilation), silicosis, diabetes, malignancies, a wide range of chronic systemic illnesses, and immunosuppressant treatment (Rieder 1999, American Thoracic Society 2000, Lienhardt 2001, Cegielski and McMurrey

2004, IUATLD 2007, Lin et al 2007). Genetic factors and age are obviously also important, but will not be discussed further here since they are not possible to alter.

The evidence base for the different risk factors is variable. Moreover, there is a lack of data on the magnitude of the population level impact of the various risk factors. In other words, we still know little about the number of TB cases and TB deaths attributable to the different factors. Such information would help narrowing down the focus of possible preventive interventions. The Population Attributable Fraction (PAF) is a measure that expressed the proportion of disease burden attributable to a specific risk factor. PAF depends on both the relative risk increase associated with the risk factor and the prevalence of the risk factor. Therefore, risk factors with a very high relative risk, such as advanced AIDS and advanced silicosis (which increases the risk of TB 30-100 fold), may have a lower PAF than, for example, malnutrition and smoking, which have lower relative risks but much higher prevalence. The so called "prevention paradox" reflects the fact that prevention often need to focus more on low risk, high prevalence risk factors than on high risk, low prevalence factors.

In a recent analysis, applied to the 22 High TB Burden Countries (HBC, countries that together suffer 80% of the estimated global TB burden), WHO has attempted to estimate PAF for a number of downstream risk factors. Table 1 summarizes the preliminary results (WHO 2007).

Table 1. RR, prevalence and population attributable risk of risk factors TB, in 22 high TB burden countries (source: WHO 2007)

	Relative Risk for active TB disease (range)	**Weighted prevalence in 22 HBCs**	**Population Attributable Fraction (Range)***
Silicosis	30.0 (25.0-35.0)	0.05%	1.4% (1.2-1.7)
HIV infection	10.0 (7.0-13.0)	1.1%	8.9% (6.1-11,5)
Malnutrition	4.0 (2.0-6.0)	17.2%	34.1% (14.7-46.3)
Diabetes	3.0 (2.0-4.0)	4.7%	8.7% (4.5-12.4)
Smoking	2.8 (2.0-3.9)	24.9%	30.3% (19.3-41.6)
Crowded living	2.0 (1.5-3.0)	30.0%	23.1% (13.0-37.5)
Indoor pollution	1.5 (1.2-3.2)	71.1%	26.2% (12.4-61.0)

*Note that sum of PAFs should normally be >100%, since most causal pathways requires presence of two or more risk factors simultaneously or in sequence, e.g.: crowding for exposure level, smoking to impair airway clearance functions, and malnutrition to impair the cell mediated immune system

These rough estimates suggest that malnutrition, smoking, indoor air pollution and crowded living conditions are more important risk factors than HIV/AIDS, on a global scale. Though the analysis is preliminary and the figures indicative only, it provides a starting point for better understanding of what areas of preventive interventions might be relevant to explore further. It also provides a starting point for modelling both impact of historical change of these risk factors on historical TB incidence trends as well as possible impact of various interventions to reduce the exposure to these risk factor in the future. For example, one can postulate questions such as how much TB incidence would decline if malnutrition was halved, or if smoking prevalence was brought down 25%, and so on.

The answer would depend on the baseline prevalence and PAF. To illustrate the relevance of performing this type of analysis across settings with different prevalence of exposure, figure 4 shows three different PAF patterns for three of the WHO regions.

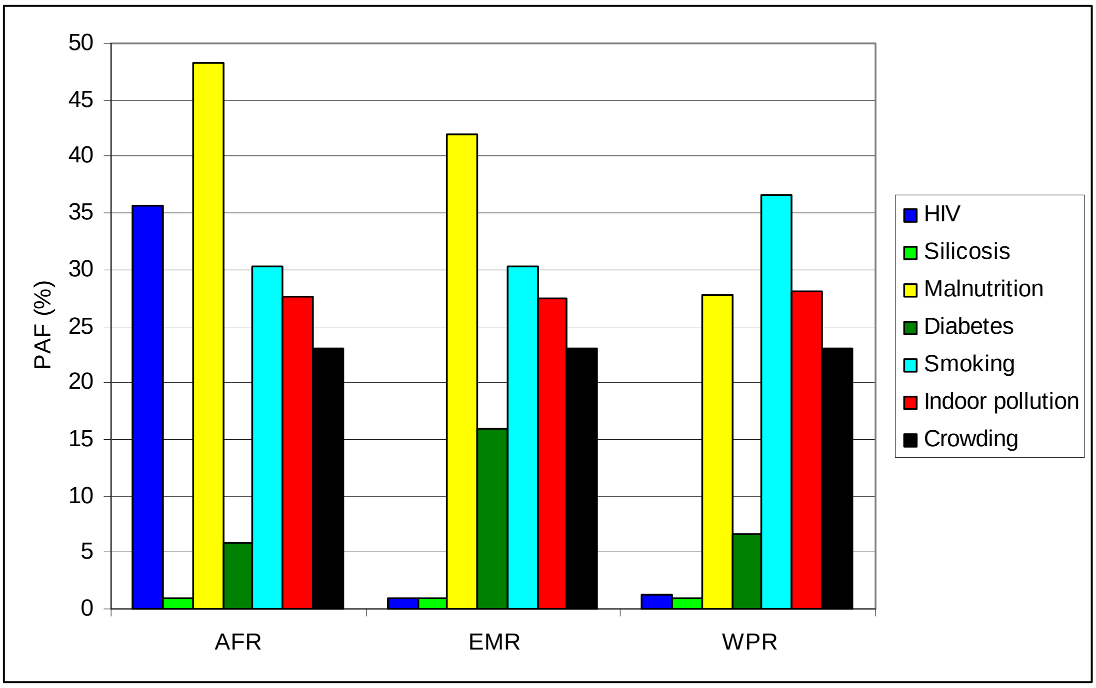

Figure 4. Population Attributable Fraction in thee WHO regions (Source: WHO 2007)

The analysis suggests, as expected, that HIV/AIDS is a much more important risk factor in the African Region (AFR), than in the Eastern Mediterranean Region (EMR) and the Western Pacific Region (WPR). However, it also suggests that malnutrition is more important than HIV and that all risk factors except diabetes and silicosis are important in AFR. It is plausible that high TB burden in Africa is a result of a high combined population exposure to several risk factors, not just HIV. In EMR, it is interesting to note that malnutrition seem to be the most important factor, while diabetes at the same time seems to be a relatively more important risk factor than in the other regions. In WPR, "environmental" risk factors - smoking, indoor air pollution and crowding - seem to dominate. If these regional estimates are roughly correct, they would indicate somewhat different foci for preventive interventions in different regions.

The upstream determinants

Identifying and quantifying the downstream risk factors is also a step towards better a understanding of why socioeconomic status is such as strong predictor of TB (figure 5). Many studies from different countries and from different time periods (from the 1830s onwards) have shown that the risk of TB is many-fold higher among people from low socioeconomic groups, compared to those from higher socioeconomic groups (Rosen 1974, Rieder 1999, Lienhardt 2001, Hinman et al 1976, Enarson et al1989, Tupasi et al 2000, Cantwell et al 1994, Marmot 2004).

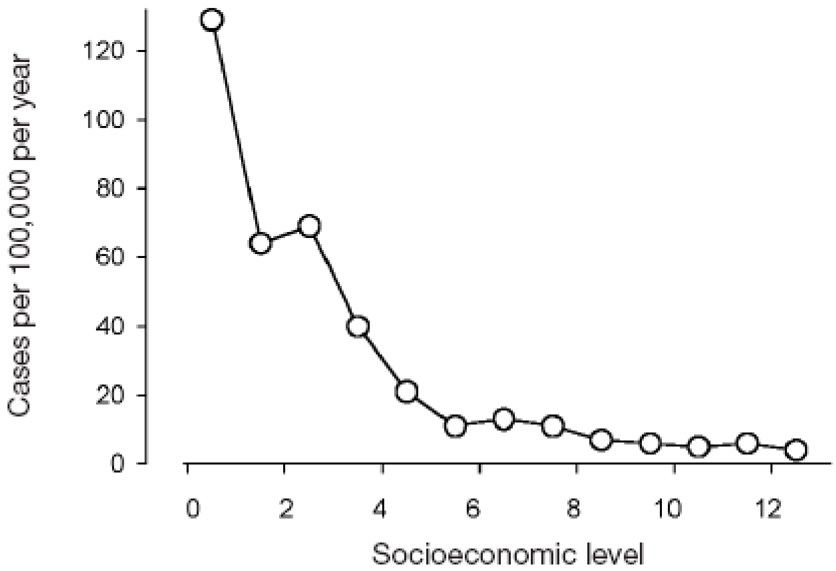

Figure 5. Incidence of tuberculosis by socioecomomic group, New York State, 1973. (Source: Hinman 1978, in Rieder 1999)

Low socioeconomic status translates into increased risk for disease through multiple mechanisms (Marmot 2004). For TB, possible pathways include higher likelihood of crowded and poorly ventilated living conditions, limited access to safe cooking facilities, malnutrition, lower level of awareness of healthy behaviour, higher risk of occupational exposure to silica, and limited access to quality health care services. Indeed, all factors listed in table 1 follow a social and economic gradient, where those from lower social classes, with less education, with less income, and with lower living standard, are more likely to be exposed (References to be added).

Social inequities in health and absolute levels of poverty, malnutrition, poor housing, and low education are influenced by a complex mix of social and economic determinants on local, national, and international level. Broader development patterns, industrialization, urbanisation, globalization and international economic and social policy trends influence health and health care directly and indirectly (Dahlgren and Whitehead 2006, Raviglione 2006). This pattern of multifactoral and multilevel TB causality narrows down the control strategies, both those that address the specific risk factors and those that tackle their common upstream determinants. The paradigm of "prevention starts with cure" may need to be replaced by one where "TB control is the result of prevention and cure" (Jaramillo, 1999).

Taking the preliminary analysis forward

Considerable work remains to be done to better measure the contribution of different determinants to the TB epidemic and devise the most appropriate strategies. To this end, the WHO (Stop TB Department together with other departments including Tobacco Free Initiative, Public Health and Environment, Chronic Diseases and Health Promotion, and Nutrition), and several partner organizations, including US CDC, have started a project to further address the issue. The purpose of the project is to first refine the quantification of the population-level impact on the TB epidemic of various risk factors, then identify reasons why transmission and incidence trends are not developing as anticipated. Thereafter, the project will identify the linkages with upstream determinants for the different risk factors, and finally explore possible interventions to address both downstream and upstream risk factors.

This work is linked to the work of the Commission on Social Determinants of Health which was launched by WHO in 2004 (WHO 2006). Recently, the Priority Public Health Conditions Knowledge Network (PPHC-KN) was formed under the commission. The Stop TB Department at WHO is the Secretariat for the subgroup of the PPHC-KN working on TB. The aim of the PPHC-KN is to identify social determinants and relevant strategies to address them, and then to advocate for countries and international partners to implement those strategies. In this work, the analysis of determinants of the TB epidemic is but one piece of information that will inform the recommendations on what type of social change is required to improve public health.

The planned next steps of this work are:

- Conduct a detailed analysis of routine TB surveillance data (case notifications, treatment outcomes) from selected countries, down to district level, to determine precise trends in transmission and incidence;
- Further review of the literature on the various risk factors for TB, with special attention to review articles;
- Identification of possible need for new systematic reviews of the available evidence, and commissioning of such reviews if necessary;
- Obtain better data on prevalence of exposure for some of the risk factors;
- Develop a model for analysing interactions between the various risk actors in light of assumed causal pathways;
- Refine the PAF estimates, based on above steps;
- Develop an analytical framework for the identification of possible interventions which are not yet part of the Stop TB Strategy;
- Conduct mathematical modelling to evaluate present and future risks to TB control programmes, coupled with an assessment of the potential impact of (a) the current Stop TB Strategy in the face of newly-identified risks, and (b) interventions that address new risk factors specifically, going beyond the current strategy.

The expect outputs of this work include a series of technical reports, scientific publications and policy papers, including:

- <u>February:</u> Discussion paper (present) sent for comments to ROs and COs
- <u>April</u>: Paper presented at a symposium on risk factors for TB, to be held at the annual TB Surveillance and Research Unit (TSRU) meeting, KNCV, The Hague.
- <u>July</u>: Draft paper on the social determinants of TB, as a contribution to the work of WHO's Commission on the Social Determinants of Health, to be finalized by end 2007.

- December: Draft report on drivers and determinants of the TB epidemic, setting out the implications for the Stop TB Strategy, the Global Plan to Stop TB, and the Millennium Development Goals.

Some thoughts on possible implications for TB control policies and practices

A Stop TB Strategy in evolution

The DOTS strategy was developed in the early 1990s, after decades of TB control neglect (Raviglione and Pio 2002, WHO 1994). Realizing that the best available medical technologies were not used optimally (if at all) in most parts of the world, the logical response was to devise a strategy that ensured that at least some health care system elements were in place to enable effective delivery of those essential technologies.

Underpinning the strategy is an epidemiological model which predicts that detecting at least 70% of the incident cases of highly infective TB and treating at least 85% of the successfully, would result in rapidly declining incidence (Styblo and Bumgarner 1991, Dye et al 1998, Borgdorff et al 2002). This model does not include assumptions about other driving forces of TB epidemics, though HIV has been considered in some of the modelling exercises (Dye et al 1998, Stop TB Partnership 2006). Implicitly, the approach to control TB through DOTS does not rely on improvement in the upstream factors that drive the TB epidemic. It certainly does not say that socioeconomic development or other approaches to prevent TB were unimportant. But it suggests a way forward that is independent of such development. In a sense, it is an attempt to find a short cut by focusing on actions to ensure appropriate diagnosis and treatment (Etzioni and Remp 1972). In light of stagnant economic and social development or inequitable economic growth without social reform in large parts of the developing world during the 1980s and 90s, this could be considered by some a rational and pragmatic approach. But then, pragmatism has its limitations when addressing global health concerns.

Some ten years after the DOTS strategy was launched, the new Stop TB Strategy was developed in response to a number of challenges that had not been sufficiently tackled through DOTS, notably the challenges of MDR TB and the intersecting epidemics of TB and HIV, as well as the challenges of weak health systems and reliance on imperfect medical technologies, some of which are century-old (WHO 2006). The new strategy, while building on DOTS, broadens the scope of TB control considerably. In particular, it emphasizes the need to "think systems" and go beyond the domain occupied by conventional tuberculosis control efforts: passive case detection and treatment of TB by health staff in public health care facilities through a number of new components such as contributing to health systems strengthening, empowering people with TB and communities and engaging all health care providers, public as well as private. The new Strategy also pays a lot of attention to mechanisms for improving access to quality TB services for the poor (WHO 2005). The latter is aimed to increase real coverage and case detection, but is also an expression of the strategy's emphasis on the human rights perspective of TB care and control.

The main thrust of the new strategy is to create better mechanisms for equitable delivery of quality assured medical technologies, and promote development of new technologies. The strategy does however emphasize that wide implementation of appropriate TB diagnosis and effective treatment is but one aspect of TB control. It highlights the upstream determinants and argues that advocacy is needed for social development in order to control and eventually eliminate TB. What is missing are details on which the most important risk factors and socioeconomic determinants are, and how to address them.

We have passed the year when the World Health Assembly TB control targets were supposed to have been met, and at least two things are worrying. The first is that few countries have actually reached the targets (WHO 2007). The second is that among those who have, there is no consistent evidence that it has had the expected impact on the TB epidemic. Recent analysis of the global, regional and national trends of TB incidence suggest that DOTS and the new Stop TB Strategy have not had the anticipated impact on TB transmission and incidence, notably in Asia where many countries have greatly improved TB diagnosis and treatment in recent years. This leads to questions about the epidemiological model itself, as well as about what is happening with the trends of other risk factors that are influencing the TB epidemic. Another observation that leads to the same set of questions is that the TB incidence trend seem to have declined in some settings well before access to quality assured TB diagnosis and treatment had improved. This might therefore be the appropriate time to consider reverting to a TB control approach that has a sound historical foundation: that prevention should start with both cure and prevention (Jaramillo 1999).

Potential implications for practice

So, what are the possible interventions, and what is the possible role for NTPs and Stop TB Partners? Should NTPs get involved in HIV prevention and treatment, smoking cessation, actions to reduce indoor pollution, nutrition programmes, diabetes care and prevention, etc? Which are the other partners and sectors that should be involved in TB control, in its broader sense? In fact, secondary preventive interventions are already happening as part of TB programme implementation, particularly with regards to HIV/AIDS, but also targeting smoking, alcohol abuse, and malnutrition. The new Stop TB Strategy included a component of TB/HIV collaborative activities, which also opens up for involvement in HIV prevention, both secondary and primary. Some programmes provide nutritional support to poor patients, others are involved in initiatives to tackle alcohol abuse. Smoking cessation by NTP is currently being piloted as part of a Practical Approach to Lunghealth (PAL) initiative. Contribution to health systems strengthening is another components of the new Stop TB Strategy which provides an entry point for contributing to public health programmes and improved clinical care of the conditions that increase risk of TB or adverse TB outcomes, especially through contributing to improved primary health care.

The required practical steps that NTPs could take in this field need to be explored further in light of: (1) more detailed analysis of the PAF of the different risk factors in countries; (2) effectiveness and cost-effectiveness of the available interventions to reduce them; (3) possible complimentary role that NTPs can play to support other programmes and the general health system; and (4) capacity of and competing demands on NTP.

Should NTPs also be involved in addressing the upstream determinants, and contribute to improved housing, poverty reduction, improved educational level, etc? Well-performing NTPs are already contributing to poverty reduction through curing poor people with TB at a subsidised cost. This has microeconomic as well as macroeconomic implications (Dholakhia 1996, Dye and Floyd 2006, WB study). Furthermore, NTPs in several countries are already engaged in the development of Poverty Reduction Strategy Papers, and similar processes (WHO 2007). What else can be done? To answer this question, it is important to distinguish contributions in terms of direct action from contribution in terms of providing intellectual ammunition for social change. Public health experts are in a good position to provide policy makers with the evidence of links between health and social change. Therefore, the most constructive contribution by NTPs towards addressing upstream determinants may be to talk with policy makers and argue that decisions in the field of economic development, social welfare reform and environmental policy, has bearing on the TB epidemic, and might determine if TB will be controlled or not in the future. Similarly on regional and global level, Stop TB Partners could do more to highlight the importance of addressing social and economic determinants.

The establishment of links between public health problems and socioeconomic conditions has been very important for driving social change in the past, (Rosen 1974, Marmot 2004, Dahlgren and Whitehead 2006). The more forceful the messages from public health experts, the more likely the action by policy makers. The potential role that physicians and other health professionals can play is well illustrated by the influence of the German surgeon and pathologist Rudolph Virchow. Virchow, who helped uncover social determinants of health in 19th century Germany, used slogans like "medicine is a social science, and politics nothing but medicine on a grand scale" when actively working to translate his ideas into social and health policy through direct political action. Similar processes by his colleagues in other countries, helped shape the landscape of social change and labour and environmental legislation in Europe and elsewhere in the 19th and 20th century (Rosen 1974).

Political commitment, the first element of DOTS and the new Stop TB Strategy, not only concern commitment from Governments to invest in and support TB diagnosis and treatment only, but also commitment from all social and political actors to address the upstream drivers of the TB epidemic. Advocacy for such type of political commitment is more effective when done jointly across public health programmes and across partnerships working on different public health conditions that share common upstream social determinants.

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