

Editorial

World TB Day 2010 – New innovations are required for enhancing the global fight against Tuberculosis: the ‘Captain of all these men of death’

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Despite the availability of inexpensive and effective treatment for more than 60 years, tuberculosis (TB) remains a major global health threat (WHO Report 2009a). This is a telling and shameful indictment of the current world order. The pace at which scientific understanding has advanced over the past few decades has been unacceptably slow. Also, researchers have, in general, failed to take into account the complex interaction of factors that sustain the global TB epidemic with the factors that have led to the failure of the global community to get rid of one of the worst scourges that has affected humanity for centuries. Tuberculosis continues to be one of the top three causes of death from infectious diseases, after HIV/AIDS and malaria, causing more than 1.8 million deaths every year (Dye *et al.* 2008).

Over the past decade, the international community has become more aware of the seriousness of the threat of TB to human health. Despair is gradually, although with faltering steps and many setbacks, being replaced by hope (Grange *et al.* 2009; Zumla *et al.* 2009). Definite signs of progress in the scaling up of TB diagnostic and treatment services worldwide have been witnessed over the past decade, and almost all countries have adopted the Stop TB strategy of the World Health Organization (WHO), including DOTS (WHO 2009a). Although these achievements are important, the global control of the TB epidemic remains elusive. There is epidemiological evidence that the number of new cases of TB are levelling out in Asia and China, even though the TB-disease burden remains at a very high level (Dye *et al.* 2009). By contrast, the disease continues to spread relentlessly in high HIV-endemic sub-Saharan African countries. TB also contributes substantially to morbidity and mortality in children under the age of 5 in endemic areas (Marais *et al.* 2009). It is, however, heartening that it has at last been recognized that children make up a significant proportion of the TB disease burden in sub-Saharan Africa (Donald *et al.*

2007; WHO Report 2007). The global emergence of multidrug-resistant and extensively drug-resistant (XDR) TB further compromises efforts to control the disease (Gandhi *et al.* 2006; Schaaf *et al.* 2009). Without substantially stronger domestic and international commitment to TB control, the number of TB cases will continue to rise, especially in HIV-endemic areas. Creative new strategies and pragmatic new approaches are urgently required if the epidemic is to be brought under control.

TB is the most common cause of death among HIV-infected individuals in Africa (Lawn & Churchyard 2009). To reduce this risk, direct strategies to prevent TB such as Isoniazid-preventive therapy (IPT) as well as indirect measures, including antiretroviral therapy (ART) and co-trimoxazole prophylaxis, to improve the immune status of those infected with HIV need to be scaled up urgently (Churchyard *et al.* 2007; WHO Report 2008). Data from observational studies and a randomized control trial support the early integrated use of ART in patients with TB to reduce mortality. Earlier initiation of ART at higher CD4 counts will greatly reduce the incidence of TB in HIV-infected populations by reducing the risk of overt disease after infection and improving both the effectiveness and durability of IPT. The longstanding call for integration of TB and HIV services should now be heeded by all governments of developing countries (Harries *et al.* 2009). Such integration will facilitate provider-initiated HIV testing of all TB suspects and patients and their families, thereby allowing prioritization of HIV-infected TB patients for ART initiation and provision of co-trimoxazole.

The prevalent misconceptions among both the community and health care workers who maintain the stigma associated with HIV and TB need to be addressed by means of education. A concerted effort is required to empower individuals with TB co-infected with HIV, so that they are able to play a key role in shaping current and future health

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care strategies and interventions. Attention to the demonstrated adverse effect of tobacco smoking on TB-associated mortality is also required and it therefore, makes sense to introduce smoking cessation interventions into integrated TB-HIV programs (Pai *et al.* 2007).

Progress in TB control has been greatly hindered by a lack of sufficient funding dedicated to priority areas that have been defined *many times* by international specialist and advisory groups, especially the need for better TB diagnostics, vaccines, drugs and shorter treatment regimens (Donald *et al.* 2007; Cobelens *et al.* 2008; Fauci & NIAID Tuberculosis Working Group 2008; Chaisson & Harrington 2009; Dheda *et al.* 2009). Perhaps, the most striking shortcoming of current TB control efforts is the inability of health care workers to make an accurate diagnosis of TB in a large proportion of patients, particularly in HIV-infected individuals and in children. While several new diagnostic tests are in the pipeline, an improved, rapid, cheap, practical point-of-care test is still eagerly awaited. The major problems associated with current TB therapy are the long duration of treatment that complicates administration, reduces adherence and increases the likelihood of acquiring drug resistance; high rates of resistance to standard first line therapy and the emergence of XDR TB and the frequency of toxic side effects, together with pronounced drug–drug interactions especially with rifampicin. These shortcomings emphasize the need for the development of new drugs and treatment regimens. Large-scale financial investment, both from non-profit agencies and industry, is required to advance new products to human clinical trials. As BCG vaccination has not had a major impact on TB control, the development of new, globally effective, TB vaccines is a major research priority. Development of a novel effective vaccine is, however, complicated by the fact that previous natural infection seems to offer little protection against future TB; most individuals in endemic areas have been primed with BCG or environmental mycobacteria, or they are latently infected with *M. tuberculosis*. In addition, malnutrition and HIV-infection affect the efficacy and safety of vaccines, especially living attenuated ones.

The past few years have seen a modest increase in financial support for the development of new methods for the diagnosis, prevention and treatment of TB (Agarwal *et al.* 2009), but this work has not yet delivered any new products that have been proven to be more useful than currently available ones. With recent increases in research funding for TB by the Gates Foundation, EU, USAID, NIH, Global Alliance for TB Drug development and EDCTP, the next decade may well see the introduction of a new generation of rapid, cheap and more accurate diagnostic techniques and, new more powerful, shorter treatment

regimens. Any new tools for disease control will, however, have to be delivered through the inadequate health care systems in developing countries which bear the major burden of TB and TB/HIV/AIDS disease. Patients in many TB-endemic areas find it difficult get adequate health care. Without strict attention to the medical and management skills required, together with effective training of health care workers and laboratory personnel who deliver health services to the community, TB programs and patients will not benefit from any new advances in TB care. New scientific breakthroughs will be of no practical value if they are not made available at well-functioning points of care in TB-endemic areas, and if there is not a serious commitment by the governments in the developing countries. Inadequate commitment to TB control by governments of many developing countries is to a large extent responsible for poor program performance.

The recently created ‘TB Research Movement’ initiated by the Stop TB Coordinating Board and the Stop TB Advisory Group (STAG) involves TB researchers, program managers and end users in attempts to link advances in basic research with new policy changes and optimal implementation (WHO-STOP TB Research Movement 2009b). The individual contribution of these factors may be minimal, but at the population level, their combined impact may be considerable and remains relatively unexplored. A better understanding of the relevant social determinants affecting the prevalence of TB and the involvement of the community and especially the families of the patients will help to broaden the emphasis from an exclusive focus on developing newer technological interventions to a more holistic health care approach to vulnerable communities. This will require an interdisciplinary approach, including research on how best to measure government commitment and how to identify cost-effective funding models in liaison with donor agencies so as to assure the best return on investment. Investment in capacity building, together with ongoing training and operational research to determine the factors that lead to the failure of TB programs, is essential if service delivery and any new tools are to be implemented with optimal efficiency.

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