Joining forces to develop weapons against TB: together we must

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New approaches are needed to tackle the current and impending disaster of TB. First, its lethal combination with HIV will continue unless the detection and treatment of both infections improve simultaneously. The double impact of TB and HIV is keeping large numbers of people trapped in poverty and disease which reinforce each other. This phenomenon is not limited to sub-Saharan Africa and other long-standing HIV hot spots; it now threatens countries where TB was barely on the radar screen 10 years ago, such as those in the former Soviet bloc. Current efforts to organize joint TB and HIV strategies are of paramount importance, as is the development of new tools. For example, faster-acting anti-TB drugs, effective against latent as well as recognized infection, would dramatically improve the situation of co-infected patients and their contacts.

Second, drug-resistant TB is a result of inconsistent or partial treatment with existing drugs, due to a large extent to the long regimen they require. It is alarming to note the presence everywhere of strains resistant to at least one anti-TB drug. The rise on every continent of strains resistant to all major anti-TB drugs is a disastrous and explosive trend. This deadly form of multidrug-resistant TB (MDR-TB) defies today's therapeutic toolkit. Adjusting strategies and improving access to second-line drugs are among the initiatives under way, but ultimately it is only new therapies that will break the drug-resistant cycle.

Tremendous progress in TB control has been achieved since 1992, when the last World TB Congress was held. There are great success stories behind the annual WHO statistics on expansion of DOTS, the directly observed treatment short-course. Yet only a quarter of TB patients worldwide receive proper treatment under DOTS. Progress is severely hindered by the lack of new diagnostics and faster-acting medicines. Currently, treatment under DOTS demands a combination of at least four drugs administered for at least six months. The logistics involved in providing directly observed treatment for such a long period make DOTS expansion as daunting as it is essential. New agents are badly needed to reduce treatment duration, frequency and supervision.

The prospects for TB control even in countries with low endemicity are now in question. In the USA, data for 2001 from the Centers for Disease Control revealed a setback in the march towards TB elimination for the first time since the outbreaks of the early 1990s. The downward trend continues, but the annual rate of decline in TB case-loads slowed from its previously steady 7% to 2%. The rise in TB incidence in 20 USA states last year points to new challenges for treating remaining cases, despite success with existing tools so far.

The good news is that scientists are mobilizing to develop three new weapons with which to counter-attack: better diagnostics, better and faster-acting medicines, and a vaccine. For the last few decades, research and development (R&D) efforts have been unfocused, with little stimulus from market forces. But now new initiatives are leading to powerful cutting-edge research, as can be seen from the work on new medicines.

The present class of anti-TB medicines was introduced 30 years ago, and our current goal is to have a new drug in production by 2010. There is much that can be built upon in the work of the intervening years. In addition, new methods such as combinatorial chemistry, and research breakthroughs such as the genome sequencing of *Mycobacterium tuberculosis*, open up new avenues for the pursuit of novel compounds. Derived through target research, these new classes of compounds are priorities, as medicines are needed which can both withstand the test of resistance and ensure shorter treatment regimens.

The most publicized work being done now is on developing existing compounds which show promise. The quinolones, some already in use in the fight against MDR-TB, such as ofloxacin, could contain additional members ready to include in the roster of tuberculosis therapies. Recent encouraging findings from animal model studies indicate that moxifloxacin and gatifloxacin could have valuable sterilizing effects, and human studies are in the planning phase. The most promising lead compound seems to be PA-824, which displays both bactericidal and sterilizing effects.

The context of this research is changing too. A handful of multinational pharmaceutical companies are adjusting their strategies towards TB, including GlaxoSmithKline, AstraZeneca and Novartis. As a result of an encouraging report on the economics of TB research published last year (*1*), medium-sized pharmaceutical and biotechnology companies in developing and established economies are busy screening their libraries for compounds for anti-mycobacterial activity. More details on research in progress can be found in the news section (pp. 518–523).

These trends are encouraging, but they also highlight the gravity of the scientific challenges we now face, and the urgent need for the public and private sectors and all concerned to join forces and work together worldwide. Despite the difficulties of doing so, the result will be more and better options in the end than any one group could find on its own. For us this means increasing the number of candidates for new medicines, diagnostics and vaccines. The call for closer collaboration should be the dominant theme of this year's World TB Congress. Only by working together can we make the scientific innovations needed to transform TB control and help to save the lives of millions of people. ■

1. *Economics of TB Drug Development.* New York: Global Alliance for TB Drug Development; 2001.

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