EVIDENCE BASED PUBLIC HEALTH POLICY AND PRACTICE

To control and beyond: moving towards eliminating the global tuberculosis threat

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For 10 years the World Health Organisation has had a single answer to the deadly threat of tuberculosis (TB)—provide treatment to smear positive patients and watch them take it. In contrast with confident statements about how global TB would be brought under control when directly observed therapy, short course (DOTS) was introduced, TB continues to rise worldwide. The introduction of selected multiple drug resistant TB treatment programmes, ''DOTS-Plus'', although important, also focuses on therapy for active TB. HIV endemic countries in particular have experienced tremendous increases in TB despite having DOTS programmes. A critical review of recent epidemiological data and computer models shows that the present international strategy of concentrating on providing treatment for smear positive TB, DOTS and DOTS-Plus, is likely to have only a modest impact on population based TB control. Effective global TB control will require strategies that go beyond relying on treatment of people with active disease.

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In 1993, the World Health Organisation declared tuberculosis (TB) a global health emergency. One third of the world's population was believed to be infected with TB, and 7.5 million new TB cases and 2.5 million TB deaths occurred each year. One in four preventable adult deaths worldwide was attributable to TB.[1] WHO also introduced directly observed therapy, short course, or DOTS, as the global TB control strategy.[2] This strategy includes five major components: political commitment to support TB treatment, the passive detection of active tuberculosis by the use of sputum microscopy, direct observation of short course therapy for treatment, ensuring a regular supply of medicines, and the reporting of programme performance and treatment outcomes.[3] By implementing these components, WHO believed that DOTS could reduce TB deaths by half over the next decade and control the global TB epidemic. Nearly a decade later, TB cases worldwide continue to rise.[4]

The failure to reduce the number of TB cases globally has been attributed to a lack of support, not of science.[5] With sufficient political commitment and resources, many believe that DOTS alone can effectively control global TB.[6] Yet recent data show that DOTS at best leads to modest declines in TB case rates[7] and in some regions is unable to contain TB at all.[8] Control is defined here as the progressive decline in the incidence and prevalence of a disease in a population ultimately leading to its elimination. After almost 10 years of a control strategy that has done little to reduce or to eliminate TB, global TB control needs to be reassessed.

IS TREATMENT SUFFICIENT TO CONTROL TB?

DOTS refers to both an approach for treating active TB and a strategy for reducing the prevalence of TB in populations. Although the origins of DOTS have been debated,[9] case finding and treatment of active TB form the theoretical rationale for the use of DOTS as a strategy to reduce TB prevalence in populations. Using Netherlands data from the 1950s to 1970s, Karel Styblo concluded that TB control programmes must be based on the diagnosis and treatment of active TB cases and that chemoprophylaxis (also known as preventive therapy or treatment of latent TB infection), had essentially no role in population based TB control.[10] The Netherlands data Styblo used to reach these conclusions were based on ''intensive'' active population based case finding and treatment of all bacillary cases.[10] DOTS, in contrast, relies on passive case finding with the goal of detecting 70% of smear positive cases and curing 85% of those detected.[11] The problem of relying on DOTS is underscored by the numbers. DOTS proponents assume that effective treatment for 60% (0.7×0.85) of smear positive cases will produce progressive declines in global TB.[12] Moreover, only 44% of all TB cases are smear positive.[13] The premise that TB can be eliminated by treating 26% of all TB cases (0.60×0.44) has not been demonstrated.

TB epidemiology today differs substantially in many regions from that studied by Dr Styblo to reach his conclusions concerning the primacy of case finding and treatment over prophylaxis. Dr Styblo concluded that chemoprophylaxis had ''very little, if any, impact on the time of eradication of tuberculosis in the population because the present risk of tuberculosis is very low…''[10] In many HIV endemic countries, this assumption is no longer true. Among HIV infected persons with latent TB infection, the risk of active disease is as much as 3%–10% per year[14 15]; in one group of South African gold miners, the annual rate of active TB is 2.5/100.[16]

Abbreviations: TB, tuberculosis; DOTS, directly observed therapy, short course

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Value of improving TB treatment programmes

Fewer than 25% of TB patients are thought to receive effective treatment.[6] About 50% of untreated TB patients eventually die from their disease. Effective treatment reduces TB mortality rates to under 5%,[17] shortens morbidity, decreases transmission to others, and reduces the prevalence of drug resistant disease.[18] For these reasons, effective TB treatment programmes need to be expanded so they are available to all TB patients.

With ineffective treatment programmes, TB, particularly drug resistant TB, can increase. In the 1980s, New York City TB programmes failed to adequately follow up and cure patients with active TB.[19] These programme failures contributed to a multiple drug resistant TB (MDR-TB) epidemic characterised by extensive nosocomial transmission that cost hundreds of lives and in excess of one billion US dollars to be contained.[20 21] MDR-TB is a global problem,[22] and data demonstrate that standard DOTS treatment programmes are inadequate for the treatment of multiple drug resistant disease.[23] The failure of DOTS treatment programmes to adequately cure MDR-TB has lead to the creation of ''DOTS-Plus,'' or DOTS plus therapy with second line agents for MDR-TB in selected situations.[24]

Given the lack of a highly efficacious vaccine to protect susceptible people from TB infection, effective treatment programmes are an essential component of current global TB control efforts. DOTS and DOTS-Plus treatment programmes that improve patient outcomes should be expanded. However, that does not mean that the present international focus on expanding effective treatment programmes to the exclusion of other approaches such as preventive therapy, the existing DOTS and DOTS-Plus strategies, is optimal or sufficient for reducing the global burden of TB.

Limitations of treatment as a TB control strategy

TB may seem unusual among infectious diseases because of characteristics like its long latency period. Yet, while infectious diseases vary in their epidemiology, pathogenesis, and availability of treatments, concepts gleaned from past eradication programmes are applicable to TB elimination efforts.[25] Control is a prelude to elimination.[2] Successful control programmes to date have relied on protecting susceptible people from acquiring disease regardless of whether effective treatments did[26] or did not exist.[25] The present global strategy for TB control, in contrast, is based on preventing people with active TB from transmitting disease. The lack of historical precedents for this approach is worrisome for the successful control and ultimate elimination of TB with this strategy.

There are additional reasons to be concerned that DOTS is inadequate as a TB control strategy. Firstly, even in well run DOTS programmes, TB transmission can still occur in a high proportion of cases by the time the index case is identified.[27] The initial symptoms of TB are non-specific; even when a sputum smear is ordered, the sensitivity of this test for detecting active TB is only 55%–74%.[28 29] Patient delays in seeking care and healthcare worker delays in recognising and starting treatment for TB also contribute to transmission.[30]

A second limitation of DOTS is the inadequate attention to smear negative cases. Although smear positive patients are more infectious, smear negative patients can and do transmit TB infection to others.[31] An estimated 56% of all prevalent TB cases, or 9.1 million people worldwide, have smear negative TB.[13] Assuming the transmission data from San Francisco are representative of smear negative TB patients globally, smear negative people may be responsible for about 1.4 million new TB cases annually. An estimated 2 billion people have latent TB infection.[13] They are and will continue to be an important source of new TB cases, yet DOTS does not prevent these cases from occurring.

The most convincing evidence of the failure of DOTS as a strategy to reduce the global burden of TB comes from sub-Saharan Africa. In the face of the spreading HIV pandemic, DOTS programmes have seen substantial increases in the number of TB cases despite maintaining reasonable treatment completion rates.[8 32]

Needs of millions unmet

Despite widespread evidence that DOTS is failing to contain TB in sub-Saharan Africa,[32] WHO officials recommend expanding DOTS to control TB in this region.[33] Yet there are no current epidemiological studies to support this DOTS only or DOTS first approach. Moreover, under a fully implemented DOTS programme by 2010, WHO models estimate that there would still be about 160 million TB cases and 50 million deaths over a 23 year period.[12] Imagine the outcry if WHO said that after fully implementing the global polio vaccination programme, there would still be 160 million cases of polio over the next 20 years. A TB control programme in which 75% of TB cases and deaths still occur is clearly an inadequate goal.

PREVENTION NEEDS TO ACCOMPANY TREATMENT

Epidemiological evidence accumulated over decades supports the use of combined prevention and treatment strategies for TB control. In one of the most successful population based control efforts undertaken, TB treatment and community wide isoniazid prophylaxis led to a 50% decrease in the rate of new infections over a six year period among Eskimos in Bethel, Alaska.[10 34] The rise and subsequent control of TB in New York City is another example. Although New York's success has been attributed by some primarily to DOTS,[35] improvements in infection control practices in hospitals, homeless shelters and correctional facilities, changes in treatment regimens, improvements in diagnostic methods, and expanded use of preventive therapy also were used to reverse this TB epidemic.[21]

Computer simulation models of population based TB control show that combinations of treatment and prevention approaches are more effective than strategies based on treatment alone.[36]

Models also show that the combined use of treatment for latent and active TB is more effective at reducing TB in HIV

Key points

- Although directly observed therapy, short course (DOTS), the World Health Organisation's global control policy, has been in place for 10 years, the global burden of tuberculosis (TB) continues to rise with millions of cases and deaths each year.
- Recent epidemiological and modelling studies suggest that combinations of prevention and treatment strategies are likely to be more effective than DOTS for controlling TB.
- Improving TB control worldwide requires approaches that go far beyond the current WHO programme of treating smear positive TB patients.
- A combined approach of expanded chemoprophylaxis for HIV negative and positive people, population based prevention strategies for drug sensitive TB and MDR-TB, and treatment accompanied by improved surveillance is needed.

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infected populations than current strategies,[37] and widespread treatment of latent TB infection in HIV infected persons in Africa has been recommended.[38] How treatment of latent infection might best be used for TB control in HIV endemic areas is unknown. Limited projects have been undertaken.[39] What is needed however, are studies of sufficient size and scope to re-examine the role of preventive therapy in population based TB control, particularly in HIV endemic settings. These types of studies have been undertaken to examine the impact of sexually transmitted disease treatment for HIV prevention[40]; similar designs should be used to examine the impact of population based treatment of TB infection on TB control.

APPROACHES NEED TO FIT LOCAL EPIDEMIOLOGY

There is no evidence to indicate that one TB control strategy is universally applicable, and mounting evidence that it is not. Yet there remains only one global TB control strategy—DOTS. In Peru, with low rates of HIV, DOTS has resulted in high cure rates and modest declines in TB incidence.[7] In Botswana, where almost 40% of the adult population are HIV infected,[41] there has been a pronounced increase in TB despite maintaining high treatment compliance rates with DOTS.[8] In parts of Russia where MDR-TB is prevalent, DOTS has had low cure rates and no demonstrable impact on incidence.[42] Instead of a single global strategy, control programmes must be developed that consider key epidemiological characteristics such as TB, HIV, and MDR prevalence as well as available resources.

BETTER SURVEILLANCE IS NECESSARY TO ASSESS SUCCESSES AND FAILURES

WHO collects TB case notifications and treatment outcomes to assess global control efforts.[4] Treatment outcome data are essential for assessing treatment programme performance, but they do not necessarily show whether TB is successfully being eliminated in a population. A number of sub-Saharan African TB programmes have rising caseloads despite maintaining consistent treatment outcomes.[8] For many TB high burden countries, there are no good data on the incidence or prevalence of TB cases or deaths. Years after instituting of one of the best DOTS programmes in the world, officials were uncertain whether TB was being controlled in Peru.[7 43] Some at WHO have proposed complex models to assess DOTS or argued that the absence of control groups makes it hard to evaluate the impact of DOTS.[43] However, when good surveillance data exist, demonstrating the introduction of effective control interventions is straightforward.[21 26] Surveillance data need to be gathered so that the effectiveness of TB control and elimination strategies can be assessed.

RESEARCH TO FILL TOOL GAPS

More effective vaccines, rapid inexpensive tests to better diagnose latent TB infection and smear negative TB, and shorter, safer, inexpensive treatments for active and latent TB are needed.[44] Advances in any one of these areas would be important, and research in all these areas must be actively pursued. Field studies to optimise the use of existing tools in different epidemiological settings also need to be undertaken. One of the important lessons from the smallpox eradication programme is the value of ongoing research to improve control efforts.[25]

CONCLUSIONS

Despite almost 10 years of DOTS, much of the world remains no closer to achieving control of TB. In sub-Saharan Africa and parts of Eastern Europe, TB has increased over the past decade. In response to this lack of progress, WHO and others have called for further expansion of DOTS. Even where DOTS programmes have led to declines in TB incidence, the benefits have been modest.

The time has come to re-evaluate TB control strategies. There are those who may argue that we understand how best to control TB, and the primary problem is implementation.[33] This simplistic answer fails to recognise both past experience from other successful infectious disease control efforts[25] and the reality that, in some parts of the world, TB continues to rise despite well run DOTS treatment programmes.[8 38]

The failure of DOTS as a TB control strategy does not mean this approach is without benefits. DOTS programmes that improve treatment outcomes and prevent the emergence of drug resistance should be developed further. However, controlling TB will require much more than treating people diagnosed with smear positive disease. To substantially reduce TB worldwide, we will have to do much more than connect the DOTS.

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REFERENCES

1 **Raviglione MC**, Snider DE Jr, Kochi A. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. *JAMA* 1995;**273**:220–6.
2 **Enarson DA**. Controlling tuberculosis—is it really feasible? *Tuber Lung Dis* 2000;**80**:57–9.
3 **Raviglione MC**, Pio A. Evolution of WHO policies for tuberculosis control, 1948–2001. *Lancet* 2002;**359**:775–80.
4 **World Health Organisation WH**. *Global tuberculosis control. WHO Report 2001*. Geneva: World Health Organisation; 2001 2001. WHO/CDS/TB/2001.287.
5 **Reichman LB**. Tuberculosis elimination—what's to stop us? *Int J Tuberc Lung Dis* 1997;**1**:3–11.
6 **Blanc L**, Floyd K, Norval PY, *et al. Global DOTS expansion plan. Progress in TB control in high-burden countries, 2001*. Geneva: World Health Organisation; 2001. WHO/CDS/TB/2001.11.
7 **Suarez PG**, Watt CJ, Alarcon E, *et al*. The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru. *J Infect Dis* 2001;**184**:473–8.
8 **Kenyon TA**, Mwasekaga MJ, Huebner R, *et al*. Low levels of drug resistance amidst rapidly increasing tuberculosis and human immunodeficiency virus co-epidemics in Botswana. *Int J Tuberc Lung Dis* 1999;**3**:4–11.
9 **Mitchison DA**. The origins of DOT. *Int J Tuberc Lung Dis* 1998;**2**:863–5.
10 **Styblo K**. *Epidemiology of tuberculosis*. Vol 24. The Hague: Royal Netherlands Tuberculosis Association, 1991.
11 **Maher D**, Chaulet P, Spinaci S, *et al. Treatment of tuberculosis: guidelines for national programmes*. Vol WHO/TB/97.220. 2nd ed. Geneva: World Health Organisation, 1997.
12 **Dye C**, Garnett GP, Sleeman K, *et al*. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. *Lancet* 1998;**352**:1886–91.
13 **Dye C**, Scheele S, Dolin P, *et al*. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA* 1999;**282**:677–86.
14 **Whalen CC**, Johnson JL, Okwera A, *et al*. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. *N Engl J Med* 1997;**337**:801–8.
15 **Selwyn PA**, Sckell BM, Alcabes P, *et al*. High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. *JAMA* 1992;**268**:504–9.
16 **Churchyard GJ**, Kleinschmidt I, Corbett EL, *et al*. Mycobacterial disease in South African gold miners in the era of HIV infection. *Int J Tuberc Lung Dis* 1999;**3**:791–8.
17 **Cohn DL**, Catlin BJ, Peterson KL, *et al*. A 62-dose, 6-month therapy for pulmonary and extrapulmonary tuberculosis. A twice-weekly, directly observed, and cost-effective regimen. *Ann Intern Med* 1990;**112**:407–15.
18 **Kim SJ**, Bai GH, Hong YP. Drug-resistant tuberculosis in Korea, 1994. *Int J Tuberc Lung Dis* 1997;**1**:302–8.
19 **Brudney K**, Dobkin J. A tale of two cities: tuberculosis control in Nicaragua and New York City. *Semin Respir Infect* 1991;**6**:261–72.
20 **Frieden TR**, Sherman LF, Maw KL, *et al*. A multi-institutional outbreak of highly drug-resistant tuberculosis: epidemiology and clinical outcomes. *JAMA* 1996;**276**:1229–35.

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21 **Frieden TR**, Fujiwara PI, Washko RM, *et al*. Tuberculosis in New York City—turning the tide. *N Engl J Med* 1995;**333**:229–33.
22 **Espinal MA**, Laszlo A, Simonsen L, *et al*. Global trends in resistance to antituberculosis drugs. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med* 2001;**344**:1294–303.
23 **Espinal MA**, Kim SJ, Suarez PG, *et al*. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *JAMA* 2000;**283**:2537–45.
24 **Gupta R**, Raviglione MC, Espinal MA. Should tuberculosis programmes invest in second-line treatments for multidrug-resistant tuberculosis (MDR-TB)? *Int J Tuberc Lung Dis* 2001;**5**:1078–9.
25 **Henderson DA**. The challenge of eradication: lessons from past eradication campaigns. *Int J Tuberc Lung Dis* 1998;**2**(suppl 1):S4–8.
26 **Wenger JD**. Epidemiology of Haemophilus influenzae type b disease and impact of Haemophilus influenzae type b conjugate vaccines in the United States and Canada. *Pediatr Infect Dis J* 1998;**17**(suppl):S132–6.
27 **Bishai WR**, Graham NM, Harrington S, *et al*. Molecular and geographic patterns of tuberculosis transmission after 15 years of directly observed therapy. *JAMA* 1998;**280**:1679–84.
28 **Isaac-Renton JL**, Puselja BB, Allen EA, *et al*. Microscopic evaluation of sputum specimens submitted for Mycobacterium tuberculosis culture. *Am J Clin Pathol* 1985;**84**:361–3.
29 **Kim TC**, Blackman RS, Heatwole KM, *et al*. Acid-fast bacilli in sputum smears of patients with pulmonary tuberculosis. Prevalence and significance of negative smears pretreatment and positive smears post-treatment. *Am Rev Respir Dis* 1984;**129**:264–8.
30 **Allos BM**, Genshelmer KF, Bloch AB, *et al*. Management of an outbreak of tuberculosis in a small community. *Ann Intern Med* 1996;**125**:114–17.
31 **Behr MA**, Warren SA, Salamon H, *et al*. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. *Lancet* 1999;**353**:444–9.
32 **Cantwell MF**, Binkin NJ. Tuberculosis in sub-Saharan Africa: a regional assessment of the impact of the human immunodeficiency virus and National Tuberculosis Control Program quality. *Tuber Lung Dis* 1996;**77**:220–5.
33 **Bleed D**, Dye C, Raviglione MC. Dynamics and control of the global tuberculosis epidemic. *Curr Opin Pulm Med* 2000;**6**:174–9.
34 **Comstock GW**, Ferebee SH, Hammes LM. A controlled trial of community-wide isoniazid prophylaxis in Alaska. *Am Rev Respir Dis* 1967;**95**:935–43.
35 **World Health Organisation**. *WHO report on the TB epidemic: stop TB at the source*. Vol WHO/TB/95.184. Geneva: WHO, 1995.
36 **Brewer TF**, Heymann SJ, Colditz GA, *et al*. Evaluation of tuberculosis control policies using computer simulation. *JAMA* 1996;**276**:1898–903.
37 **Heymann SJ**. Modelling the efficacy of prophylactic and curative therapies for preventing the spread of tuberculosis in Africa. *Trans R Soc Trop Med Hyg* 1993;**87**:406–11.
38 **De Cock KM**, Chaisson RE. Will DOTS do it? A reappraisal of tuberculosis control in countries with high rates of HIV infection. *Int J Tuberc Lung Dis* 1999;**3**:457–65.
39 **Stop-TB**. TB and HIV: the ProTEST initiative. http://archives.healthdev.net/stop-tb/msg00069.html (accessed 5 Jun 2002).
40 **Grosskurth H**, Mosha F, Todd J, *et al*. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;**346**:530–6.
41 **Masupu K**, Jimbo W, Chipfakacha V, *et al*. *Botswana 2000 HIV seroprevalence sentinel survey amongst pregnant women and men with sexually transmitted diseases*. Gaborone: National AIDS Coordinating Agency, December 2000.
42 **Kimerling ME**. The Russian equation: an evolving paradigm in tuberculosis control. *Int J Tuberc Lung Dis* 2000;**4**(suppl 2):S160–7.
43 **Dye C**. Tuberculosis 2000–2010: control, but not elimination. *Int J Tuberc Lung Dis* 2000;**4**(suppl 2):S146–52.
44 **Miller B**, Castro KG. Sharpen available tools for tuberculosis control, but new tools needed for elimination. *JAMA* 1996;**276**:1916–17.

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Inequalities between developed and developing countries are a serious problem in the field of health research. The Human Development Report 2003 emphasises that 90% of global researching for pharmaceutical drugs goes to diseases that account for 10% of the disease burden in developing countries. Tropical diseases, incidence of HIV/AIDS, and the lack of diffusion existing technologies affect particularly poor countries. Financing of health research and the social use of technology may be two of the main ways to improve global health.

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