Tuberculosis: where are we going?

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In the 17th century John Bunyan described tuberculosis (TB) as, 'the captain of all these men of death'. In the late 20th century the World Health Organization (WHO) pronounced it a 'global emergency'. Whether described by poetry or prose, TB has been the leading global infectious cause of morbidity and mortality for more than 500 years. New directions are required to combat the disease but we need to remember where we have come from before we decide how to progress.

Sixty years ago there was no effective treatment for TB. In 1946, 51,289 cases were reported in the UK: 42,173 (82.2%) with pulmonary disease and 9,116 (17.8%) with extra-pulmonary disease.[1] Those with advanced pulmonary disease had a 50% five-year survival rate,[2] although a rapid death was inevitable if miliary, pericardial or meningeal disease intervened. Many retreated to Alpine sanatoria to find a cure, which inspired some (notably Thomas Mann, who wrote *The magic mountain* (1924) after his experiences in a sanatorium in Davos, Switzerland), but cured no one. Then, in the mid-1940s, came the simultaneous but independent discoveries of two compounds active against *Mycobacterium tuberculosis* – streptomycin and para-aminosalicylic acid (PAS). The assessment of these two drugs for the treatment of tuberculosis was a defining moment in medicine. The need for a rapid, authoritative, unbiased assessment was paramount and the chosen methodology, the random assignment of control and experimental treatment regimens, would become a cornerstone of clinical research. The British Medical Research Council (MRC) performed the first trials, comparing streptomycin with bed rest for acute progressive bilateral pulmonary tuberculosis[2] and showed that streptomycin reduced six-month mortality and improved bacteriological and radiological cure rates. Resistance to streptomycin developed, however, in 35/41 patients and after five years the number of deaths in the streptomycin group (53%) was only slightly less than in the controls (63%). Urgent strategies were required to overcome the problem of resistance and in 1948 the MRC started a trial comparing streptomycin alone, PAS alone and the two in combination. It demonstrated unequivocally that combined therapy reduced the risk of developing a resistance.[3]

Consistent and complete cures only became a reality in 1952 with the addition of isoniazid to these two drugs, although a treatment programme of at least 12 months was required. Ethambutol replaced PAS (which caused frequent side effects) and led to a better-tolerated regimen.[4] But reductions in treatment length only became possible with the addition of rifampicin, when the term 'short-course chemotherapy' was coined.[5] A remarkable series of trials performed by the MRC Units in East and Central Africa defined the limits of short-course chemotherapy and demonstrated that complete cure could be achieved following six-months treatment.[6] They discovered that pyrazinamide (a drug that was initially discarded due to fears of hepatic toxicity) in combination with rifampicin and isoniazid was a key component of the regimen. Further trials in Hong Kong, Singapore, Madras and Algeria showed that the best results were achieved after an 'intensive' phase of two months of rifampicin, isoniazid and pyrazinamide followed by a 'continuation' phase of four months rifampicin and isoniazid.

By the late 1970s the best drug combinations and the duration of the treatment had been worked out. In the 1980s the total number of notified TB cases in the UK fell to just over 5,000 a year,[1] one tenth of the figure 40 years earlier. Optimism was rampant and there was even talk of sending TB the way of smallpox and banishing it to the history books.[7] Amid this collective glow of satisfaction, however, the seeds of our current problems with TB were sown. In 1986, the MRC tuberculosis trial units closed. In 40 years they had delineated the measures necessary for successful TB control, the optimal drug regimens and the importance of directly observed therapy (DOT). Two subsequent events suggest the closure of these units was premature. The first was predictable – the increasing prevalence of drug resistance and resulting treatment failures. The second, the arrival of HIV, was not predictable, although by 1986 it was already clear that TB and HIV had a special relationship.[8]

For a decade the developed world lost focus on the challenges presented by TB; systems of disease control and prevention were disbanded, clinicians lost basic skills in diagnosing and treating the disease and research into novel diagnostic and therapeutic approaches fell away. Our backs turned, tuberculosis continued to plague the poorest people on the planet and crept back into the life of the developed world.

Have we turned this problem around in time? Patients with multi-drug resistant tuberculosis (defined as resistance to *at least* rifampicin and isoniazid) are considered incurable with conventional

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regimens and, in many countries, are left untreated.[9] Other drugs exist, but to date there have been no randomised controlled clinical trials to evaluate these regimens. HIV threatens all tuberculosis-control programmes and presents special problems in clinical management.[10] Adverse drug events are more common in this group and standard regimens may be less efficacious. In particular, regimens that do not contain rifampicin have shown a high frequency of failure and relapse.[11] Antiretroviral therapy introduces new problems when used in combination with anti-tuberculosis drugs: protease inhibitors and the non-nucleoside reverse transcription inhibitors interact with the rifamycins and immune reconstitution can cause paradoxical clinical worsening of the disease.[12] The best clinical management of these problems is uncertain, particularly in poorer countries.

Awareness has grown, however, over the last five years and there are now reasons to believe a 'way forward' can be found. Strategies to improve or replace the 85-year-old BCG vaccine are being developed. For example, a modified vaccinia virus expressing an *M tuberculosis* antigen (antigen 85A) substantially boosted *M tuberculosis*-specific T cell responses when given to BCG vaccinated individuals,[13] although whether this will result in enhanced disease prevention remains unproven. New assays threaten the 120-year monopoly of the tuberculin skin test and the Ziehl-Neelsen (ZN) stain over the diagnosis of latent and active tuberculosis. Recent data suggest two new commercial assays (QuantiFERON-TB gold and T-SPOT.*TB*), based on the detection of interferon γ produced by T cells in response to *M tuberculosis* specific antigens, are more accurate than the skin test at diagnosing latent infection.[14] Tests using nucleic acid amplification techniques, such as the polymerase chain reaction (PCR), have proved more effective than a ZN stain for the rapid diagnosis of pulmonary tuberculosis;[15] although they have performed disappointingly in pauci-bacillary extra-pulmonary disease, such as tuberculous meningitis, in whom rapid diagnosis and treatment is critical to survival.[16] These molecular techniques are also being successfully used for the rapid detection of drug resistance – especially rifampicin resistance – and overcome the three-month delay in treatment decision-making created by conventional drug susceptibility testing.[15] There is also clear evidence of a resurgence of clinical and pharmacological research into the treatment of tuberculosis. Old questions, such as the use of adjunctive corticosteroids for the treatment of tuberculous meningitis, have been answered;[17] and, for the first time since the introduction of rifampicin in the 1970s, new drugs are entering clinical trials. The fluoroquinolone antibiotic moxifloxacin is highly active against *M tuberculosis* and may have a role in shortening treatment to less than six months.[18] Controlled trials examining this question are underway. More exciting still is the development of novel anti-tuberculosis agents such as R207910, a diarylquinoline that selectively inhibits mycobacterial ATP synthase,[19] and PA-824, a nitroimidazopyran that inhibits the synthesis of proteins and cell wall lipids.[20] Both demonstrate potent bactericidal activity in murine models of disease and the results of the first human treatment trials are eagerly awaited.

The 'way forward' has begun with these advances, but what will truly revolutionise the prevention and management of tuberculosis? Firstly, a vaccine that, unlike BCG, provides prolonged protection against pulmonary TB in children and adults. Secondly, a treatment regimen that cures TB in less than a month: longer treatment regimens will always fail in the face of human nature and our reluctance to take tablets for six months. And thirdly, the greatest challenge of all, to ensure universal access to new therapies, diagnostics and drugs. To achieve these breakthroughs will require sustained and unsurpassed cooperation between scientists, clinicians, and politicians.

References

1 Health Protection Agency. www.hpa.org.uk/infections/topics_az/tb/epidemiology/table1.htm
2 Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *BMJ* 1948;2:769–782.
3 Fox W, Sutherland I. A five-year assessment of patients in a controlled trial of streptomycin, para-aminosalicylic acid, and streptomycin plus para-aminosalicylic acid, in pulmanoary tuberculosis. *Q J Med* 1956;25:221–43.
4 Doster B, Murray FJ, Newman R, Woolpert SF. Ethambutol in the initial treatment of pulmonary tuberculosis. *Am Rev Respir Dis* 1973;107:177–90.
5 Fox W. Whither short-course chemotherapy? *Br J Dis Chest* 1981;75:331–57.
6 Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946-1986, with relevant subsequent publications. *Int J Tuberc Lung Dis* 1999;3:S231–279.
7 Horne NW. Eradication of tuberculosis in Europe – so near and yet so far. *Eur J Respir Dis Suppl* 1983;126:169–73.
8 Raymond CA. Increase in AIDS-associated illnesses focuses new attention on an old nemesis. *JAMA* 1986;256:3323–5, 3330.
9 Farmer P. The major infectious diseases in the world – to treat or not to treat? *N Engl J Med* 2001;345:208–10.
10 Small PM, Fujiwara PI. Management of tuberculosis in the United States. *N Engl J Med* 2001;345:189–200.
11 Perriens JH, Colebunders RL, Karahunga C *et al*. Increased mortality and tuberculosis treatment failure rate among human immunodeficiency virus (HIV) seropositive compared with HIV seronegative patients with pulmonary tuberculosis treated with 'standard' chemotherapy in Kinshasa, Zaire. *Am Rev Respir Dis* 1991;144:750–5.
12 Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis* 2005;5:361–73.
13 McShane H, Pathan AA, Sander CR *et al*. Recombinant modified vaccinia virus Ankara expressing antigen 85A boosts BCG-primed and naturally acquired antimycobacterial immunity in humans. *Nat Med* 2004; 10:1240–4.
14 Ferrara G, Losi M, D'Amico R *et al*. Use in routine clinical practice of two commercial blood tests for diagnosis of infection with Mycobacterium tuberculosis: a prospective study. *Lancet* 2006;367:1328–34.
15 Drobniewski FA, Caws M, Gibson A, Young D. Modern laboratory diagnosis of tuberculosis. *Lancet Infect Dis* 2003;3:141–7.
16 Thwaites GE, Caws M, Chau TT *et al*. Comparison of conventional bacteriology with nucleic acid amplification (amplified mycobacterium direct test) for diagnosis of tuberculous meningitis before and after inception of antituberculosis chemotherapy. *J Clin Microbiol* 2004;42:996–1002.
17 Thwaites GE, Nguyen DB, Nguyen HD *et al*. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004;351:1741–51.

18 Nuermberger EL, Yoshimatsu T, Tyagi S *et al*. Moxifloxacin-containing regimens of reduced duration produce a stable cure in murine tuberculosis. *Am J Respir Crit Care Med* 2004;170:1131–4.

19 Andries K, Verhasselt P, Guillemont J *et al*. A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis. *Science* 2005;307:223–7.

20 Stover CK, Warrener P, VanDevanter DR *et al*. A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. *Nature* 2000;405:962–6.