EDITORIAL

Tuberculosis: A re-emerging enemy

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Journal of Molecular and Genetic Medicine (2006), 2(1), 87-88

(Published 24 November 2006)

Tuberculosis (TB) is one of the oldest diseases known to the mankind; it is also a leading cause of death among adults, and kills almost 500 children each day worldwide. More than 90% of TB-related deaths occur in developing countries. TB was declared global emergency by the World Health Organization (WHO) in 1993, with around 8-10 million new cases of the disease each year and over 2-3 million deaths worldwide (WHO Report, 2005).

Nearly one third of the world's population are latently infected with *Mycobacterium tuberculosis*, which produces the disease in immuno-compromised individuals, such as those with HIV infection. Consequently, large regions of sub-Saharan Africa, Asia and Eastern Europe, where HIV is prevalent and/or general populations have low immunity due to social deprivation and poverty, are particularly vulnerable, and have seen a considerable rise in cases of TB during the past decade. TB cases have also been increasing in the USA and Western Europe since the 1990s. This trend is likely fuelled by recent, increasing migration of populations from Eastern European countries to Western Europe. After years of complacency and stagnation recent years have seen revitalization of the TB research, recently with a particular helping from Bill and Melinda Gates Foundation.

PROGRESS IN TB VACCINE DEVELOPMENT

The Bacille-Calmette-Guérin (BCG) vaccine is health worker's oldest weapon against TB, and is still the only commercially available TB vaccine. It has been successfully used to limit the disease in many countries through extensive neonatal immunisation programmes. However, perhaps due to genetic differences in different populations, environmental factors (*e.g.*, high prevalence of environmental mycobacteria) or the type of strain used in vaccine preparation, BCG vaccine affords highly-variable immune protection against pulmonary TB (see Doherty and Anderson, 2005). BCG vaccine protection also lasts only for 10 to 20 years (*e.g.*, Sterne et al, 1998). A recent study exploring revaccination of Brazilian children aged 7-14 showed that it did not provide substantial additional protection (Rodrigues et al, 2005), stressing the need for developing improved vaccines. Currently, there are some 200 or so new candidate vaccines in development. One such vaccine is being developed by Adrian Hill and colleagues at the University of Oxford, aiming to enhance the immunogenecity and protective efficacy of BCG (McShane et al, 2004), was recently granted the orphan drug status by the European Commission (Lang et al, 2005). This vaccine is a recombinant modified vaccinia virus Ankara expressing the antigen *85A* gene from *M. tuberculosis* (MVA85A) and is currently in Phase 2 clinical trials in South Africa. Orphan drug status is generally granted for rare and serious, life-threatening diseases and where the drug is unlikely to generate sufficient financial returns on investment. This status offers substantial incentives, including free scientific advice from the European Agency for the Evaluation of Medicinal Products (EMEA) and an exclusive market in the EU for 6-10 years, and thus opens the door for the development of other medicines for diseases with poor expected financial returns.

ADVANCES IN TB CHEMOTHERAPY

Once an individual has been infected, the second line of resistance against TB is chemotherapy, which has been clinically available for almost 60 years. However, more and more emerging strains of *M. tuberculosis* are resistant to currently available antimicrobial drugs, further weakening our defences. While treating non-resistant *M. tuberculosis* is challenging, resistance to antimicrobial drugs poses a further danger.

Current recommended treatment for active TB comprises a minimum of six months antibiotic treatment, with isoniazid and rifampicin being the front-line agents (others include ethambutol, streptomycin and pyrazinamide). An *M. tuberculosis* strain resistant to both these agents is termed multidrug- resistant (MDR), with or without resistance to other antimicrobials (Sharma and Mohan, 2006). A

recent report by the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) (WHO/IUATLD Report, 2004) suggests the prevalence of multidrug-resistant TB (MDR-TB) in participating countries was 1.1% for new cases and 7% for previously treated cases. MDR-TB requires treatment with second generation antibiotics that are less effective and more toxic. A relatively recent and worrying development is the emergence of 'extremely-drug- resistant TB' or XDR-TB (with resistance to three or more of the six classes of second-line antibiotics), with a fresh and the largest ever outbreak of XDR-TB reported in Kwa Zulu-Natal Province of South Africa (Cohen, 2006). XDR-TB has been identified in almost all regions of the world with high prevalence in Asia and Eastern Europe.

While several new TB vaccines are in the pipeline, the recent upsurge in TB research has also attracted considerable attention in the arena of new antibiotic development, as well as the discovery of new drug targets (Zhang et al, 2006). Andries et al (2005) have made a promising new development in the front of antibiotic development, and have identified a diarylquinoline (DARQ), R207910, that potently inhibits both drug-sensitive and drug-resistant *M. tuberculosis in vitro* (minimum inhibitory concentration 0.06 mg/ml). In mice, R207910 exceeded the bactericidal activities of isoniazid and rifampin by at least 1 log unit. Other promising candidates include new fluoroquinolones, rifamycin derivative (such as rifapentine, rifabutin and rifalazil), oxazolidinones and nitoimidazopyran. Even some anti-fungals are being considered for TB therapy; for example, azoles, phenothiazines and riminophenazine derivatives like clofazimine show good anti-TB activity are good candidates for further evaluation (Zhang et al, 2006). However, considering that no new antibiotic against TB has been introduced for almost past 40 years, and one of the most favourite drugs, R207910, is only in Phase 2 clinical trials, it may be some time before we see another new drug in the clinic.

The immense global health and economic threat posed by TB and its resistance to drug enforces the need for ever greater and concerted global efforts to develop new defences against this enemy. A failure to act now could cost heavily on future generations.

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