



REVIEW

Drug-resistant tuberculosis in the European Union: Opportunities and challenges for control

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SUMMARY

Tuberculosis (TB) is a leading cause of death globally. TB had been considered conquered in Europe but has re-emerged as a significant problem, partly because of poor TB control programs and the link with HIV infection, migrants and other vulnerable populations, but also because a mood of complacency led to declining investment in research and public health infrastructure. In the European Union (EU), efforts initiated by the European Academies Science Advisory Council (EASAC) now assess how research can better inform policy development and indicate the gaps and uncertainties in the scientific evidence base.

A growing number of *Mycobacterium tuberculosis* (*Mtb*) strains are now resistant to the first-line anti-TB drugs, necessitating use of second-line drugs which are more expensive, less effective and more toxic. The presence of extensively drug-resistant (XDR) TB in the EU illustrates that there are problems with TB management and control. In the EU, the aggregated rate of notified TB is approximately 18 cases per 100,000 population (range 4–120 cases/100,000 in different Member States). The highest rates are found in Eastern European countries. Only about half of EU countries routinely perform drug susceptibility testing linked to notification of TB cases. It is important for the European Commission (EC) to network regional reference laboratories to support molecular epidemiology and exchange of data via creation of interactive international databases of *Mtb* genotypic and phenotypic information. EU countries should help develop TB laboratory services by investing in training and provision of assistance to maintain quality control in neighbouring Eastern European countries. Improved TB care necessitates research across the spectrum to include fundamental and epidemiological science, research and development (R&D) for new drugs, diagnostics, vaccines, and operational research. Total R&D investment in TB by the EC and Member States is low by comparison with the USA despite Europe being on the frontline of the epidemic. Thus, alternative funding models for targeting TB research priorities by the EU are required.

Increasing the visibility of TB as a priority issue for the EU requires the scientific community, with the academies of science, as appropriate, to communicate to politicians, healthcare providers, funders and the public at large about the current threat posed by drug-resistant TB. Any global strategy for TB control must also take into account measures to address the social, environmental and economic issues which are inextricably linked with TB. The academies conclude that, overall, the EU has failed so far to respond sufficiently to the global TB threat but can still draw on considerable strengths in its science. The EU also has a humanitarian responsibility to support TB control in developing countries. It remains very important for the EC that neither biomedical research nor investment in health services should become a casualty of the current economic recession.

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1. Introduction and background

Tuberculosis (TB) has a long history as a leading cause of death throughout the world. It persists as a major public health problem with significant economic impact. Worldwide, approximately 8 million people develop active TB every year, with about 1.7 million

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dying from the disease.¹ TB had been considered conquered in many developed countries but has re-emerged as a significant problem, partly because of the link with HIV infection and its concentration in migrant and other vulnerable populations, but also because a mood of complacency led to declining investment in research and public health infrastructure, resulting in sub-optimal infection control.^{2–4}

Recent efforts initiated by the European academies of science assess how research can better inform policy development and uncover gaps and uncertainties in the scientific evidence base. In the European Union (EU), the European Academies Science Advisory Council (EASAC) recently published a wide-ranging report on drug-resistant TB,⁵ the latest in a series of reports on infectious diseases. EASAC comprises all of the national academies of science of the EU Member States, and was created to enable them to collaborate in providing policy advice to EU policy-makers. The report was produced by a Working Group comprising experts nominated by the academies, supported by an open call for evidence; the draft report was subject to independent peer review according to standard EASAC procedures. The added value of multilateral activity by EASAC, is to deliver robust advice to reach policy audiences at the EU level, where funding decisions are made. We draw on some of the analyses and conclusions from the latest EASAC report on the important issues for TB research, surveillance, healthcare delivery and TB control in Europe.

Treatment of TB is possible but is complicated requiring four drugs over 6–9 months. A consequence of this treatment scheme, is poor patient compliance. There is a growing number of *Mycobacterium tuberculosis* (*Mtb*) strains, which are now resistant to the commonly used first-line anti-TB drugs rifampicin and isoniazid, multidrug-resistant (MDR) TB, necessitating use of complicated treatment schedules comprising second-line drugs which are more expensive, less effective, more toxic, and can necessitate up to 2 years treatment. Reports published since 2006 document the worldwide emergence of extensively drug-resistant (XDR) TB; resistance to isoniazid and rifampin plus resistance to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). XDR-TB is now found in at least 54 countries globally, including some in Europe.^{6,7} A recent global survey shows regional and national variation in the magnitude and trends of drug-resistant TB.² Countries of the former Soviet Union report the highest prevalence of resistance. Originally XDR-TB was thought to be limited to HIV-positive individuals but it is now known to occur equally in HIV-negative persons. This is of great significance for public health, and its existence reflects the failure of science and policy-makers to contain TB.^{8,9}

Although two decades have elapsed since the WHO declaration of TB being a 'global emergency', no new effective diagnostic, treatment or preventive measures have emerged or been translated into TB management. The Global Stop TB Strategy (http://www.stoptb.org/resource_center/assets/documents/The_Stop_TB_Strategy_Final.pdf), endorsed by the Stop TB partnership, supported by a network of national and international organisations with a secretariat hosted by WHO, has set the year 2015 as target to reduce the global burden of TB by half relative to 1990 levels. The strategy proposes to eliminate TB by the year 2050 as a global threat (reduction to an incidence rate of <1 TB case per 1 million inhabitants). The Stop TB Partnership's Global Plan 2006–2015, was costed at 56 billion USD over 10 years but, at that time, only about 45% of this cost was thought likely to be funded. The cost has since grown significantly to reflect the need to more vigorously address the ominous spread of MDR- and XDR-TB epidemics globally. This need is particularly urgent in Eastern Europe, as well as in China and India, and requires use of the currently

available evidence base to improve TB health service delivery and to develop new drugs, diagnostics, biomarkers and vaccines.

The following sections in our paper are structured to describe: (i) The nature of the problem in terms of current disease in the EU; (ii) TB R&D priority areas as defined by the EASAC Working Group; (iii) Options for collecting the evidence to satisfy the key EU policy requirements in order to achieve better control of TB; some of which relates to research strategy but also encompass issues for patient data collection, for raising awareness about TB, and for promoting innovation to develop new diagnostics, therapeutics and vaccines; (iv) Options for the EU in building global coordination of necessary strategies; and (v) The particular challenges represented by XDR-TB.

2. The current TB situation in Europe

In the EU, the aggregated rate of notified TB is approximately 18 cases per 100,000 population¹⁰ but with a considerable range, 4–120 cases/100,000 in different Member States. The highest rates are found in Eastern European countries. MDR-TB cases have been reported in most of the EU and cases corresponding to the definition of XDR-TB in at least 17 Member States even though systematic monitoring is lacking.^{2,3} There have been significant failures in control of drug-resistant TB in countries bordering the EU (e.g., Russia and other countries of the former Soviet Union). Some success has been seen within the EU, for example in Baltic States, where high levels are now stabilising because of substantial political commitment, public health investment and changes in medical practice. These demonstrable achievements have inspired public health efforts in other Member States, even before their MDR-TB rates reached such critical levels (e.g., the UK¹¹). According to the European Lung Foundation (<http://www.european-lung-foundation.org/index.php?id=77>) treating TB costs more than 2 billion euros annually in the EU but this figure does not take into account the substantial economic burden associated with lost employment and premature death, nor yet the rapidly increasing cost of tackling drug-resistant TB that is likely to bring new budgetary pressures for many countries in light of the current economic crises.

There are signs that the EU policy landscape is changing. The origin of that change can be traced back to the EU Programme for Action in 2001 (<http://www.europa.eu.int/eur-lex/en/com/cnc/2001/com20010096en01.pdf>) but concrete actions are more recent now that the European Commission (EC) with the European Centre for Disease Prevention and Control (ECDC) and EU Council Presidencies acknowledge the importance of taking a better coordinated approach in TB surveillance and control. There is evidence of a new commitment to understanding and managing the threat of TB, accompanied by some new allocation of resources worldwide.^{12–14} However, there is concern that the economic recession could complicate efforts to tackle the public health challenges as well as raise doubts as to whether additional funding promises will be kept. It remains highly important to continue making the case that neither biomedical research nor investment in health services should become a casualty of the recession.¹⁵

3. Collecting the evidence: defining EU TB priority areas

TB research and development in Europe fulfils all the criteria for an EU "Grand Challenge"^{16,17} an agreed societal need, feasible goals, an excellent base of research and industrial capability with viable prospects for implementation of research advances. The priorities for R&D and associated actions in public health in this area are discussed in detail in the EASAC Report and include:

- (i) Improving the quality and performance of all national TB programs at point-of-care.
- (ii) Improving TB data collection and use of databases across the EU;
- (iii) Creation of an international database of *Mtb* strains. Characterising the determinants of *Mtb* strain resistance and fitness, including infectivity, growth and transmissibility;
- (iv) Identifying novel TB drug candidates and lead targets by analysing structure–function relationships in-vivo, in-vitro and in-silico;
- (v) Developing new, shorter, more effective treatment regimens for drug-resistant TB;
- (vi) Exploring host–pathogen interactions in order to understand why only a small proportion of infections progress to clinical disease;
- (vii) Developing new, more sensitive and specific diagnostic tests for drug-resistant TB to help identify all cases of MDR- and XDR-TB;
- (viii) Identifying targets for new vaccines and developing new scientific approaches to improve vaccine formulation and delivery, applicable to all geographical areas;
- (ix) Drawing on advances in genomics, transcriptomics, proteomics and metabolomics to identify and validate biomarkers of disease activity;
- (x) Utilising epidemiological and modelling data to evaluate the socio-economic consequences of drug resistance and of public health control measures, including immunisation strategies;
- (xi) Instituting large-scale population studies together with other clinical and translational research to delineate the risk factors for contracting and transmitting TB and to assess current clinical practice and inform better clinical decision making. For example, characterisation of the rapid emergence of TB drug resistance, often in the context of HIV/AIDS, in Eastern Europe needs to establish if a circulation of counterfeit treatments has compounded the effects of the social determinants and sub-optimal infection control protocols;
- (xii) Forming an effective network of European TB researchers. The collaborative networking of the main European academic groups within the EU-FP7/PAN-NET proposal funded by the EU on the MDR issues provides an opportunity to promote quality training, laboratory services, research and data dissemination in Europe.^{3–6} This important venture will facilitate the advancement of the research priorities described.

4. Strengthening TB data collection and use across the EU

The EASAC review⁵ indicates that only about half of the EU countries routinely perform drug susceptibility testing linked to notification of TB cases. A lack of quality control, particularly for standardised testing for resistance to second-line drugs, with the potential for case-referral bias, creates uncertainties in the evidence base which can therefore only be used with caution to inform policy making. The ECDC Framework Action Plan¹⁸ outlines the priorities for strengthening data collection, developing laboratory techniques, integrating epidemiological data and creating algorithms for detection of disease clusters. This plan does not yet fully cover those aims, which may become essential for mandating the reporting of national surveillance data to the ECDC, to create the evidence base to steer national TB management plans. What can be capitalised on now is the opportunity to use standardised methodologies for more consistent generation and sharing of drug susceptibility testing and *Mtb* strain typing data, informed by agreement on the minimum data set required for case definition. This collection of typing data, if it can be transposed from its present research focus to become the responsibility of the health

services, is vital for several reasons – to characterise the changing patterns of drug resistance, to define the frequency and pattern of mutations and, thereby, improve on current diagnostic capabilities, and to track outbreaks. The potential value of an EU TB Reference Laboratory Network has been reviewed recently.¹⁹ EASAC recommends that it may be more cost effective for the EU to create networked regional Reference Laboratories to support molecular epidemiology and facilitate standardisation of analysis and exchange of data, rather than contend with the consequences of uncoordinated decisions by each EU Member State in setting up centres of excellence.

5. Creation of international database of *Mtb* strains

It is equally opportune to determine how best to create international databases of *Mtb* genotypic and phenotypic information²⁰ to improve understanding of the relationship between molecular variation and clinical consequences, including exploration of the historical and geographical origins of outbreaks. While there is still much to be done at the EU level, there are also opportunities for wider international coherence. For example, the Broad Institute (Boston, USA) with support from the NIH has made strong efforts in compiling TB databases and there are additional activities in the USA (<http://www.tbdb.org>) that provide potential partnering opportunities for the EU. Such database systems must have interactive interfaces to make full use of the information in the database: accessible for both country-level and Europe-wide surveillance as well as by the individual clinician treating a patient. Additional potential utility resides in more extensive databases to clarify the interplay between the genetic make-up of the bacterial strain and of the patient.²¹ Recent research has confirmed a role for host genes in susceptibility to TB, relating to the control of innate and acquired immunity, but studies on larger groups are needed to determine the inter-relationships between *Mtb* polymorphisms, host polymorphisms and disease characteristics.²¹ Investment in research and modelling to improve a shared understanding of the determinants of micro-epidemics to provide new routes to their control is required.²² Policy-makers need to understand that TB diagnosis can only be part of an integrated strategy that includes care and treatment irrespective of the legal status of the individual.²³ Research on TB molecular epidemiology in the EU will benefit from genotyping of archived samples in the migrant countries of origin; public health in the EU will benefit from efforts to improve the health of vulnerable populations worldwide.

6. Raising awareness of TB as a public health issue

Increasing the visibility of TB as a priority issue for the EU requires the scientific community, with the academies of science as appropriate, to communicate to medical practitioners, politicians and the public at large about the current threat posed by TB, its causes and the potential future impact if drug resistance is not managed effectively. Many medical practitioners in the EU lack awareness about TB and it is necessary to provide better support in their initial training and retraining programmes, based on a common set of teaching standards for TB basic and clinical science, epidemiology and disease management, so as to facilitate the uniform adoption of standards of TB care.²⁴ One of the impediments to raising the broader public profile is that TB has an inaccurate image and stigma, perceived only as a disease of poor countries, where immediate action is not important by contrast, with HIV, swine flu or SARS. The misconceptions need to be corrected and a more active role be taken by the scientific community to inform political dialogue. However, the challenge for providing evidence-based advice should not be under-

estimated: attempts to integrate multiple initiatives have proved controversial in the past.

7. Alternative funding models for sustainable research and development

Continuing health challenges for improved TB care necessitate research across the spectrum to include fundamental science, clinical medicine, research and development (R&D) for new drugs, diagnostics and vaccines, as well as operational research.²⁵ Investment in basic TB research may now be declining^{26,27} and the most recent data suggest that a trend for increasing total R&D investment is decelerating (<http://www.treatmentactiongroup.org/publication.aspx?id=2486>). R&D spending on TB in Europe in total, by the EC and EU Member States is low by comparison with the USA despite Europe being on the frontline of the epidemic.²⁸ EU Member States must recognise their responsibility to act immediately. It is now time for the EC to examine alternative funding models for targeting TB research priorities, whereby leading researchers would be encouraged to combine their joint expertise to bid for funding to be allocated for a much longer period than is the present case, to support research and capacity-building sustainability and flexibility. However, continuity in collective research programmes would need to be accompanied by a mechanism to encourage new researchers and new ideas. If successful, the model should lead to development of infectious disease research centres to incorporate multi-competencies spanning several specialities: microbiology, immunology, infectious disease epidemiology, molecular biology, field experience, social sciences, mathematical modelling, functional and structural genomics and drug discovery among others. Such virtual centres will have an important role in increasing training in translational research, relevant to the range of initiatives proposed recently.²⁹

8. TB diagnostics

Inadequate diagnosis carries high costs for the patient but also for the clinician, laboratory staff (poor use of resources) and health systems (increasing number of contagious patients). Significant progress is being made in developing novel diagnostics in consequence of the leadership shown by FIND Diagnostics and new funding streams, supported by the Bill & Melinda Gates Foundation, and rapid molecular methods for diagnosis of drug resistance are now under evaluation. It is vital to do more in Europe by coordinating the development of consistent testing methodologies between public sector laboratories, by capitalising on generic advances in the application of technology for provision of cheap, reliable, point-of-care testing, and by continuing to grow public-private partnerships for the application as well as the development of new tests.^{30,31} New discoveries may also lead to non-invasive diagnostic approaches.³² At the same time, it is essential to optimize performance of the older methods, especially microscopy, and to grasp the new challenges for using biomarkers. These include finding diagnostic tools to differentiate between patients with active TB from latently infected healthy individuals, prognostic tools to predict the risk of TB outbreak in those latently infected, and tools to serve as surrogate endpoints for disease in monitoring drug and vaccine trials.

9. TB vaccines

The attenuated live BCG vaccine does not provide adequate protection against pulmonary TB, particularly in adults and, therefore, has limited impact on the control of TB transmission. After a long period of relative neglect in R&D, several candidates are now

in the vaccine pipeline.³³ It is important to focus not only on improving the protective effect of novel vaccines but also their formulation and delivery route, to enable appropriate storage, shelf-life and global distribution, and their utility for HIV-infected individuals, particularly children. Previous EASAC policy advice³⁴ has warned that increasing optimism for a new generation of vaccines can only be sustained if policy-makers act to resolve the funding, regulatory, legislative and other impediments to development in a concerted way. It is also necessary to find the means to evaluate clinical efficacy faster – this requires identifying and using highly predictive biomarkers as indicators of infection and correlates of clinical protection, but it also requires capacity-building to establish additional trial sites and new incentives to attract industry investment. In this context, the recently founded European Tuberculosis Vaccine Initiative (TBVI; <http://www.tbvi.eu/UK/>) is a forward step.

10. Novel TB drugs and drug treatment regimens

The desirable new drugs required should be rapidly acting and potent, able to be used in shorter treatment regimens, effective against drug-resistant TB, safer than existing treatments, and safely co-administered with anti-retrovirals. Despite these hurdles, there are increasing numbers of drug candidates in the discovery and pre-clinical phases. This pipeline is promising and can be attributed in large measure to the activities of the Global TB Alliance, (www.tballiance.org/new/portfolio/html-portfolio.php). More effort is still needed to offset the anticipated high attrition rate in R&D.³⁵ There is need for action to reduce the obstacles and provide incentives to encourage new drug R&D.³⁶ This also includes the development of biomarkers which predict cure, treatment failure or relapse. It is also important to focus on the current therapeutic situation in Europe and to ensure uniform regulation and registration in drug supply so that all second-line drugs used to manage MDR-TB are made available in all Member States. Without this consistency in provision across the EU, it will be impossible to implement the lessons of best clinical practice.

11. Addressing the failings in innovation

The main current diagnostic test for TB in developing countries remains the 125-year-old sputum smear microscopy. No new TB drug has been specifically developed to treat TB in nearly 40 years and there has been no new TB vaccine for nearly 90 years. The current situation confirms that there is continuing need for the EC together with international agencies and philanthropic bodies to encourage the public and private sectors to work in complementary ways to advance the translation of research into innovation and to enable the practical application of novel products to health services even in resource-poor settings. This cannot be expected to be achieved without innovative health financing mechanisms, coupled with efforts to reduce R&D bottlenecks for companies by rationalising regulatory requirements.

12. EU global coordination for implementation of proposals and recommendations

The EU is an established leader in funding TB research in Europe. Unfortunately, according to the evidence reviewed by the EASAC Working Group, the amount of EU funding for TB R&D has not increased over the past few years. The quality of R&D outputs from the EU funded R&D is steadily paving the way towards development of new vaccines, drugs and diagnostics for improved delivery of TB services worldwide. A unique opportunity exists for Europe to take up the challenge of translating political will into well-defined pledges and taking a lead role globally, in TB R&D and in the other

efforts to improve disease surveillance and control. Global coordination is warranted in those circumstances where there are common issues affecting countries worldwide or when action is most efficient when taken at the global level. The following considerations may assist in achieving this goal of global coordination:

- a) TB cannot be isolated from other public health issues and the policy priorities for the EU cannot be isolated from the global context. More efficient interactions between the EU developing country governments, intergovernmental organisations (IGOs) and nongovernmental organizations (NGOs) are essential to drive a shared public policy agenda.
- b) TB should be an integral part of other public health issues. The EU agenda on TB cannot be dealt within isolation and must be viewed in the global context. It should aim for better coordination and interactions between all countries in Europe, Russia, China, Asia, Africa and other developing country governments.
- c) There is need to develop a coherent and comprehensive research agenda. In that agenda there has to be a balance between investments in basic research as well as the translational efforts. This needs to be fully integrated with the global research movement.
- d) The EU must invest more in TB R&D and catch up with its US counterparts, particularly the Bill & Melinda Gates Foundation (BMGF) and the National Institutes of Health (NIH). The EC (DG Research) should be encouraged to take a lead in initiating discussion between the various funding agencies and donor countries, with the objective to create better integration and coordination of funding streams, thus enhancing sustainable R&D and infrastructure development programmes with multiplier outputs. More efficient and productive interactions between the EU, EDCTP, NIH, BMGF, WHO, USAID, UK-DFID, World Bank, International Monetary Fund (IMF) and other donors is required to achieve the priority areas stated. The EU should enhance current R&D on TB and develop an evidence base which can be used universally for TB control.
- e) Current research funding is restricted in amount and duration and runs the risk of reversing any gains made when the funded projects are completed. TB programs should be sustainable and continuity of these should be maintained to have any significant outputs. It is important that the EU partners other funders to ensure that productive R&D programs do not close down due to lack of funds.

An encouraging and promising step forward taken by the EC was hosting the International Conference¹⁴ entitled Challenges for the Future: Research on HIV/AIDS, Malaria and Tuberculosis, where all stakeholders from all continents assembled to jointly discuss priorities for R&D on these three killer diseases, and how to best bring them forward to implementation. The consensus report has been published by the EC and recommendations on R&D for all three diseases from the meeting will provide the basis of future R&D investments in Europe and developing countries.

13. Control and prevention of drug-resistant TB

The presence of XDR-TB in the EU illustrates that there are problems with TB management and control in the EU.^{2,3,6} Standard case management is hampered by inefficient diagnostic, treatment and control tools.²⁵ As new tools to facilitate management of XDR-TB are being developed and tested, accessibility to quality diagnostic and treatment services needs to be urgently put in place and existing public health policies should be carefully implemented to prevent proliferation of drug resistance. Meanwhile rapid and early

diagnosis and effective management of XDR-TB provide the best chance of reducing further spread, but prevention still remains an important factor. Attention to public health measures is required to prevent the selection of resistant *Mtb* strains spreading in the community.^{8,17} Even if these tools can be improved, proper case management depends on maintaining high quality patient management in health services infrastructures that are currently of poor quality and in some cases crumbling. Any global strategy for TB control must also take into account measures to address the social, environmental and poverty issues which are inextricably linked with TB.

14. Conclusions

The growing threat of drug-resistant TB presents a major challenge for public health in all of Europe. The best prevention strategy for the control of drug-resistant TB is to ensure the proper functioning of European country TB programs and early detection and management of all TB cases. Improved infection control can only succeed if there is action across a broad front for better data collection, more funding to support research and its translation into innovation and application in health services. The academies conclude that the EU has failed so far to respond adequately to the global TB threat but can still draw on considerable strengths in its science. The academies of science, together with other scientists have important continuing roles in advising European governments and the EC on surveillance strategies, in clarifying the research agenda for epidemiology, basic and clinical research, in identifying gaps and uncertainties in the evidence base, and in building partnerships for innovation and communication for moving forward to achieve TB control globally. With the emergence of MDR- and XDR-TB in Eastern Europe, the rest of Europe risks a potentially ominous drug-resistant TB problem which requires a joint strategy to combat this growing threat.

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