EASAC call for evidence: drug resistant tuberculosis

July 2008

1. The Academy of Medical Sciences welcomes the opportunity to respond to the European Academies Science Advisory Council's *'Call for evidence: drug resistant tuberculosis'* (July 2008).[1] The Academy promotes advances in medical science and campaigns to ensure these are translated into healthcare benefits for society. The Academy's Fellowship includes leading medical scientists from hospitals, academia, industry and the public service, including specialists in infectious disease. The Academy has a specific objective to contribute to developments and improvements in global health and our recent contribution to the United Kingdom House of Lords inquiry *'Acting through intergovernmental organisations to control the spread of communicable diseases'* included discussion on tuberculosis.[2,3]

2. In this response we include material in relation to drug resistant tuberculosis addressing: surveillance; support for fundamental research and its translation; vaccines; academic capacity; patient and public engagement; and threats and opportunities within the European region. We would be pleased to expand on any of the points raised in this submission.

Background

3. The evolution of drug resistance among strains of *Mycobaterium tuberculosis* is an important factor hampering efforts to reduce the global burden of tuberculosis. *M. tuberculosis* can develop resistance to one or more drugs, and a spectrum of strains of varying resistance has now emerged. Amongst these, multi-drug resistant tuberculosis (MDR-TB) is defined as tuberculosis resistant to isoniazid and rifampicin, the two most powerful first line drugs, while extensively drug resistant tuberculosis (XDR-TB) is additionally resistant to fluoroquinolones and one of three second line injectable agents.[4] Drug resistant tuberculosis has become widespread, with strains resistant to at least one drug documented in every country surveyed. [5] Moreover, strains of *M. tuberculosis* resistant to all major anti-tuberculosis drugs have now emerged.[4]

4. Inappropriate, inadequate and incomplete treatment regimes are key contributory factors in the emergence of drug resistant tuberculosis. Thus, as the European Centre for Disease Prevention and Control (ECDC) emphasises, *'the best*

[1] European Academies Science Advisory Council (2008). *Call for evidence: drug resistant tuberculosis.* http://www.easac.org/page.asp?id=28

[2] Academy of Medical Sciences (2006). *Strategic plan 2006-2010.* http://www.acmedsci.ac.uk/p101puid65.html

[3] Academy of Medical Sciences (2008). Consultation response. *House of Lords Ad Hoc Committee on Intergovernmental Organisations inquiry into 'Acting through Intergovernmental Organisations to Control the Spread of Communicable Diseases'.* http://www.acmedsci.ac.uk/p100puid119.html

[4] The World Health Organisation (2008). *Anti-tuberculosis drug resistance in the world. Fourth Global Report*. http://www.who.int/tb/publications/2008/drs_report4_26feb08.pdf
Note that the previous definitions of XDR-TB have varied.

[5] Zignol M *et al.* (2006). *Global incidence of multidrug-resistant tuberculosis*. The Journal of Infectious Diseases **194**, 479-85. Note: Although widespread, MDR-TB is at present relatively infrequent, representing around 4% of tuberculosis cases. However, this percentage is markedly higher in some countries, including former republics of the Soviet Union.

preventative strategy [for the control of drug resistant tuberculosis] is to ensure the proper management of ALL tuberculosis cases'.[6] Treatment options for MDR-TB and XDR-TB are markedly limited. Even best practice treatments are long, toxic, and frequently unsuccessful.[7]

Surveillance

5. The surveillance project conducted by the World Health Organisation (WHO) and International Union Against Tuberculosis and Lung Disease (IUATLD) has gathered the most comprehensive data on *M. tuberculosis* drug resistance in Europe and worldwide.[4] However, the most recent report from this project itself highlights the need for more extensive surveillance to address *'major gaps in the populations covered'*.[4] Within the European region (European Union, Eastern Europe, former Republics of the Soviet Union, Central Asia), there continues to be a lack of adequate routine testing and surveillance for all forms of drug resistant tuberculosis.

6. Routine surveillance programmes should be strengthened by additional measures such as sentinel surveillance[8], and targeted epidemiological studies. There is a particular need for data from high-risk populations, including those with previous exposure to tuberculosis, human immunodeficiency virus (HIV) co-infection, prisoners, injecting drug-users, those with malnutrition and those in conditions of poverty. For example, the link between tuberculosis and HIV infection is well recognised, but sufficiently robust surveillance data to study this association are currently only available from two regions: Latvia and the Donetsk Oblast in the Ukraine, where significant associations between MDR-TB and HIV infection are reported. There is also a need to understand how biological as well as environmental factors, such as the concentration of disease in certain social settings, underpin the association between drug resistant tuberculosis and other conditions.[9]

7. Recent technological advances in the genetic analysis of mycobacterial genomes hold particular value for future tuberculosis surveillance programmes. Strain-specific genetic information (e.g. variable number tandem repeats and single nucleotide polymorphisms) can now be determined, and data can be readily transferred between laboratories though web-based systems. This technology enables the rapid tracking of the spread of individual drug resistant tuberculosis strains, and therefore has great potential in expediting strain identification and prevalence studies. Moreover, readily available tests for specific drug resistance markers will facilitate the use of drug treatment customised to individual patients. The United Kingdom has played a lead role in developing this technology through the work of the Pathogen Genomics Unit at the Wellcome Trust Sanger Institute.[10]

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[6] European Centre for Disease Prevention and Control (2008). *Framework action plan to fight tuberculosis in the European Union.* http://ecdc.europa.eu/pdf/080317_TB_Action_plan.pdf

[7] Stop TB Partnership (2008). *Research agenda on drug resistant tuberculosis with a focus on scaling-up programmes.* Priority Area 2: Treatment strategies of drug-resistant tuberculosis. http://www.stoptb.org/wg/dots_plus/assets/documents/Revised%20DR-TB%20Research%20Agenda.pdf

[8] Sentinel surveillance is the collection and analysis of data by designated institutions selected for their geographic location, medical specialty, and ability to accurately diagnose and report high quality data. http://www.usaid.gov/our_work/global_health/id/surveillance/sentinel.html

[9] The National Institute of Allergy and Infectious Diseases (2007). *NIAID research agenda multidrug-resistant and extensively drug resistant tuberculosis.* http://www3.niaid.nih.gov/topics/tuberculosis/Research/PDF/MDRXDRTBresearchAgenda06-06-07.pdf

[10] The Wellcome Trust Sanger Institute. http://www.sanger.ac.uk/Projects/Pathogens/

We believe that such methods would be of greatest benefit applied at a pan-European, rather than national level. Moreover, the Academy is aware that this approach has already been implemented in America under the co-ordination of the Centres for Disease Control and Prevention (CDC), and would support a globally integrated scheme.

8. The contributions of both national tuberculosis programmes and the network of supra-national reference laboratories in the surveillance of drug-resistant tuberculosis should be recognised and supported by appropriate resource. A lack of laboratory capacity for mycobaterium culture and drug-sensitivity testing remains a key obstacle.[11] This is particularly significant in countries with the highest burden of tuberculosis, where the ability to determine and anticipate trends is most acute, yet demands on resources are highest. In these countries novel rapid methods for bacterium culture (e.g. polymerase chain reaction-based methods rather than the traditional culture approach) should be implemented as soon as possible.

9. The WHO and the ECDC both have an important role in promoting the use of standard testing methods and procedures for use in tuberculosis drug-sensitivity testing. The work of these bodies in co-ordinating national efforts requires continued support by the governments of European Union countries and others.

Support for fundamental research, and its translation

10. The Academy has previously asserted the value of genomic medicine in contributing to advances in many aspects of public health.[12] In relation to drug resistant tuberculosis, we consider that current understanding of the ecology and evolution of drug resistance in human populations is restricted by a lack of high-quality epidemiological data at a molecular level. The newly available DNA-sequencing technologies are ideal for identifying putative drug resistance-conferring mutations within pathogen genomes. Comprehensive molecular characterisation of circulating *M. tuberculosis* strains would provide a platform of knowledge to inform anti-tuberculosis strategies at many levels. This would include advances in the methods for drug susceptibility testing[13], in surveillance (see paragraph 7 above), in predicting the future course of the drug resistant tuberculosis epidemic and in the development of new therapeutics. The following paragraphs (11-13) indicate some specific research questions that need to be addressed.

11. While the molecular mechanisms involved in resistance to first-line antibiotics in *M. tuberculosis* are well characterised, many additional resistance determinants remain unknown, particularly those involved in resistance to second-line drugs. Increased understanding of the mechanisms of resistance would facilitate the development of novel diagnostics and therapeutics.

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[11] Stop TB Partnership (2008). *Research agenda on drug resistant tuberculosis with a focus on drug resistant tuberculosis.* Priority Area 1: Laboratory aspects. http://www.stoptb.org/wg/dots_plus/assets/documents/Revised%20DR-TB%20Research%20Agenda.pdf

[12] The Academy of Medical Sciences (2008). Consultation Response. *House of Lords Science & Technology Committee inquiry into genomic medicine.* http://www.acmedsci.ac.uk/p100puid125.html

[13] Drobniewski *et al.* (2007). *Report of the Subcommittee On Antimicrobial Susceptibility Testing of Mycobacterium tuberculosis of the European Committee For Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID).* http://www.escmid.org/Files/CMI%20review%20j%201469-0691%202007%2001813.pdf

12. There is increasing evidence of variability in the physiological impact of specific drug resistant *M. tuberculosis* strains; some drug resistant strains are able to transmit between individuals as effectively as drug sensitive strains, while other drug resistant strains have impaired transmission. Such differences in 'strain fitness' are determined by particular resistance-conferring mutations in combination with the genetic background of the specific strain. Elucidation of these factors is critical to the understanding of the spread of drug resistant tuberculosis among populations.

13. The micro-evolution of resistance among *M. tuberculosis* is a further aspect requiring investigation. It is currently unknown how drug resistant strains of *M. tuberculosis* evolve upon acquiring drug resistance determinants, and how the emergence of compensatory mechanisms might affect the spread of drug resistant strains. For example, the recent outbreak of XDR-TB in Kwazulu Natal, South Africa has largely affected HIV-coinfected individuals.[14] The XDR-TB strains involved appear to have a reduced potential to transmit and cause disease to immune-competent individuals. However, it is conceivable that compensatory mutations might accumulate in such strains over time, making them more transmissible and enabling infection of immune-competent individuals.

Vaccines

14. In our 2001 report *'Vaccines: current status and future needs'*, the Academy noted the pressing global need for a more effective anti-tuberculosis vaccine.[15] The Bacille Calmette-Guérin vaccine (BCG vaccine) remains the only anti-tuberculosis vaccine in use to date, and though effective in protecting children against severe tuberculosis, BCG provides minimal and inconsistent protection against tuberculosis in adults.[16] Novel vaccines would be greatly beneficial both in prevention strategies, and used in combination with chemotherapeutic regimes to shorten treatment duration (immunotherapy). It is encouraging that 'first' and 'next generation' tuberculosis vaccine candidates have been identified and entered into phase I and II clinical trials.[17]

15. The Academy is aware of European tuberculosis vaccine development initiatives including TB-VAC[16] and MUVAPRED[18], as well as tuberculosis-specific programmes within global programmes including the Initiative for Vaccine Research within the WHO. Consideration of drug resistant tuberculosis should be integral to such programmes, and new vaccines should be evaluated for efficacy against MDR-TB and XDR-TB alongside drug sensitive strains. Further investigation of the optimal use of vaccines (both the existing BCG and novel candidates) in drug resistant tuberculosis outbreak situations is also warranted.

16. Respondents to the Academy's 2006 working-group study '*Use of non-human primates in research*' emphasised the importance of animal models in advancing

[14] Koenig R (2008). *News focus drug resistant tuberculosis: in South Africa, XDR-TB and HIV prove a deadly combination.* Science **319** (5865) 894.
[15] Academy of Medical Sciences (2001)*. Vaccines: current status and future needs. http://www.acmedsci.ac.uk/p99puid49.html*
[16] TBVAC.ORG (2008) *State of the art.* http://www.tb-vac.org/state.htm
[17] Brennan M *et al.* (2007) *Development of new tuberculosis vaccines: a global perspective on regulatory issues,* PLoS Medicine **4**, 8. http://medicine.plosjournals.org/perlserv/?request=cite–builder&doi=10.1371/journal.pmed.0040252
[18] MUcosal VAccines for Poverty RElated Diseases (MUVAPRED). http://www.mucosalimmunity.org/muvapred/

research into tuberculosis. [19] Non-human primates were considered to be of particular value, since these species develop pathology closely analogous to that of human tuberculosis, including hypoxic lesions and latent infection. More specifically, the working group noted significant constraints on vaccine trials in humans (e.g. high cost, long duration) and indicated the importance of studies in non-human primates in identifying candidate vaccines to be taken forward into human phase III trials. The working group concluded that, in addition to extensive work in rodents, exposure of novel vaccines to a limited number of non-human primates would continue to be essential to vaccine development programmes in the near future.

17. There is a need for a clearer global regulatory pathway for the development of tuberculosis vaccines.[17] Established regulatory agencies, including the European Agency for the Evaluation of Medicinal Products (EMEA), have a valuable role in leading a globally co-ordinated approach. International co-operation is essential as countries with a high prevalence of tuberculosis, (i.e. the patient populations neccessary for clinical studies), may be relatively inexperienced and may lack the regulatory resources necessary to bring new vaccines to market.

Academic Capacity

18. The Academy's 2001 report *'Academic medical bacteriology in the 21st century'* indicated that, despite some notable exceptions, academic medical (and veterinary) bacteriology was in an overall 'state of torpor' and decline within the UK.[20] The Academy expressed the need for academic bacteriology in the UK to be developed as a research discipline, and for departments of medical microbiology to be encouraged to address the exciting challenges within the field. A wider analysis of the research portfolios of major UK health-related research funders was conducted by the UK Clinical Research Collaboration (UKCRC) in 2006. [21] This work highlighted ongoing concerns about the status of microbiology research and capacity, and called for greater co-ordination between funding bodies and researchers.

19. These findings, alongside the views of further stakeholders, prompted the foundation of the UKCRC Strategic Planning Group on Microbiology and Infectious Disease (MIDR), and the launch in June 2007 of the UKCRC Translational Infection Research Initiative.[22] This jointly funded programme is intended to provide direct support for internationally leading MIDR research through various mechanisms (e.g. the establishment of consortia, the award of Strategy Development Grants and Challenge Workshop). The Academy welcomes this initiative and is supportive of its objectives.

Patient and Public Engagement

20. Data from the Health Protection Agency (HPA) and others indicate that, within the UK, a significant proprtion of burden of tuberculosis falls within some non-UK born

[19] Academy of Medical Sciences (2007). *Use of non-human primates in research. http://www.acmedsci.ac.uk/p48prid6.html*
[20] The Academy of Medical Sciences (2001). *Academic bacteriology in the 21st Century.* http://www.acmedsci.ac.uk/p99puid27.html
[21] UK Clinical Research Collaboration (2006). *UK health research analysis.* http://www.ukcrc.org/activities/coordinatingresearchfunding/ukhealthresearchanalysis.aspx
[22] UKCRC Translational Infection Research Initiative (2007). http://www.ukcrc.org/activities/coordinatingresearchfunding/infectionresearch/infectioninitiative.aspx

population groups. [23] Tuberculosis and drug resistance are also concentrated among hard to reach populations including the homeless, drug and alcohol users and prisoners.[24] Priorities for public engagement must therefore include targeted activities to access the relevant groups, and patient/public awareness programmes which are culturally and language appropriate. TB Alert, the UK's National and International Tuberculosis charity, is a leading voice in tuberculosis awareness, advocacy, information and education. [25]

21. The National Knowledge Service TB Pilot is a collaborative project, co-ordinated by the HPA, working with the NHS and various voluntary organizations. This project aims to ensure that sources of information and knowledge on tuberculosis are brought together for healthcare professionals and patients. [26]

22. We are also aware of the success of the Mobile X-Ray unit (MXU) Programme in working with marginalised groups as part of a public health response to controlling tuberculosis in London.[27] This service, offering a rapid chest x-ray and direct referrals, reached over 25,000 people during its two-year pilot phase. Through engagement with a range of agencies and provision of information resources (e.g. posters, question and answer sessions for staff, residents and prisoners) this initiative directly contributes to raising awareness of tuberculosis.

23. The 'Find & Treat' project is a further London-wide health and social care programme, established following findings that a significant proportion of tuberculosis patients are 'lost' between initial MXU screening and referral to local services for follow up.[28] 'Find & Treat' provides support to local services, for example by locating and re-engaging patients, and co-ordinating different service providers. This scheme includes significant stakeholder engagement initiatives, including care conferences and workshops, peer educator programmes and interfacing with policy makers.

Threats and Opportunities within the European region

24. The WHO/IUATLD surveillance project (see paragraph 5 above) indicates that tuberculosis resistance rates in the former republics of the Soviet Union (e.g. Azerbaijan, Uzbekistan, Georgia) are among the highest in the world. These countries are a focus of MDR-TB, which jeopardizes efforts to control tuberculosis in these countries as well as in neighbouring Western and Central Europe. The high rates of MDR-TB within the former republics of the Soviet Union are almost certainly part of the reason why incidence rates of tuberculosis in those regions are not yet on the decline.

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[23] Health Protection Agency (2006) *Migrant health. Infectious diseases in non-UK born populations in England, Wales and Northern Ireland.* http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1201767921328

[24] Kruijshaar M *et al.* (2008). *Increasing antituberculosis drug resistance in the United Kingdom: analysis of national surveillance data.* BMJ Online First. http://bmj.bmjjournals.com/cgi/content/full/bmj.39546.573067.25v1

[25] TB Alert. http://www.tbalert.org/about/what.php

[26] Health Protection Agency, National Knowledge Service - TB Pilot. http://www.hpa.org.uk/web/HPAweb&Page&HPAwebAutoListName/Page/1200055718370

[27] University College London Hospitals (UCLH) NHS Foundation Trust. Mobile X-Ray unit (MXU) Programme. http://www.uclh.nhs.uk/GPs+healthcare+professionals/Clinical+services/Infectious+diseases+%28Hospital+for+Tropical+Diseases%29/Infectious+diseases+-+Mobile+x-ray+unit/

[28] Health Protection Agency (2008). *Tuberculosis Update.* March. http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1207035533566

25. An incentive for continued efforts, however, is the demonstrable success in controlling MDR-TB in the Baltic states (especially Estonia). The high incidence of tuberculosis, including a high rate of drug resistant tuberculosis, has been recognised as a serious public health problem since Estonia gained independence. Measures introduced as part of the Governmental Tuberculosis Control Programme included an extensive reorganisation of the tuberculosis treatment strategy in 1997, including implementation of the DOTS-plus[29] methodology targeting the treatment of MDR-TB, in 2001. Tuberculosis incidence rates in Estonia decreased remarkably in the period 2002-2007. The implication is that this success could be repeated much more widely, notably in Russia, if best practice is observed.

26. In accordance with the Stop TB Partnership, we emphasise that the control of (drug sensitive) tuberculosis can only be achieved through collaborative, international effort. [11] The concept of a wider 'European Region', encompassing the European Union, Eastern Europe, former Republics of the Soviet Union and Central Asia is particularly relevant in this respect. As the European Union expands, its boundaries will include countries with increasingly different tuberculosis burdens and challenges. Moreover, migration and travel will continue to be key factors in the transmission of tuberculosis. [23] We suggest that great care must be exercised to ensure that political sensitivities around migration, nationality and cultural belief do not obstruct the provision of integrated solutions to the global problem of tuberculosis.

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The Academy of Medical Sciences

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[29] Based upon DOTS (the Directly Observed Treatment Short course), DOTS-Plus focuses on specific issues (such as the use of second-line anti-TB drugs) that need to be addressed in areas of high MDR-TB prevalence. http://www.who.int/tb/dots/dotsplus/management_old/en/