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Drug-resistant tuberculosis: challenges, consequences and strategies for control

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building science into policy
at EU level

EASAC

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Drug-Resistant Tuberculosis: Challenges, Consequences and Strategies for Control

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EASAC Secretariat
The Royal Society
6–9 Carlton House Terrace
London SW1Y 5AG
tel: +44 (0)20 7451 2697
fax: +44 (0)20 7925 2620
email: easac@royalsociety.org

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Foreword

Tuberculosis remains a major global public health threat. Despite historical successes in tackling tuberculosis, Europe cannot be considered insulated from the worldwide problem, for several reasons: the high prevalence of tuberculosis in vulnerable groups of the population, the association with HIV co-infection and, of great concern, the continuing emergence of drug resistance.

This report is the latest in a series published by EASAC (European Academies Science Advisory Council) on issues that policy-makers need to consider in the domain of infectious diseases. Our previous publications in this series are the following:

1. 'Infectious diseases – importance of co-ordinated activity in Europe', Report, May 2005.

2. 'Vaccines: innovation and human health', Report, May 2006.

3. 'Tackling antibacterial resistance in Europe', Report, June 2007.

4. 'Impact of migration on infectious diseases in Europe', Statement, August 2007.

5. 'Combating the threat of zoonotic infections', Report, May 2008.

Throughout this work, we have explored priorities for the European Union with regard to the importance of building the evidence base as an integral part of public health infrastructure; strengthening capabilities in fundamental science; supporting innovation for health and wealth creation; creating strategic coherence across different decision-making functions; engaging with the public; and identifying opportunities for European Union partnership and leadership at the global level.

The present report aims to continue that analytical and advisory tradition, to expand on points made previously and to identify new issues. In particular, there is necessary continuity of purpose between this report and the earlier one on 'Tackling antibacterial resistance in Europe', where some of the pervasive themes discussed previously are well illustrated by the growing problem of drug-resistant tuberculosis. We share the concern expressed that policy in Europe has so far failed to respond adequately to the changes experienced in both microbial and human populations. In tackling the threat of tuberculosis, it is vital that Europe makes the most of all its resources. In particular, it must use the strengths of its collective science to develop new insights and generate new options for public health delivery. EASAC recommendations identify a set of tangible actions where impact, from the immediate to the longer-term, can reasonably be expected. We recognise what is already being achieved in this broad area by the European institutions and at Member State level. However, we emphasise that there is considerable scope to do more, even allowing for the many other pressing demands on public funding at this time.

The report was prepared by consultation with a group of experts acting in an individual capacity. It was independently reviewed and approved for publication following procedures established by the Council of EASAC. I thank all my Working Group colleagues for giving their time so generously, and I thank my Council colleagues for their commitment and support. I also thank the Foundation for Innovative New Diagnostics for their financial contribution to the work of EASAC.

I welcome feedback on any of the points raised in our report.

Professor Volker ter Meulen
Chairman of the Working Group and
Chairman of EASAC

Summary

Tuberculosis (TB) is a major public health problem worldwide, with considerable economic impact. Since the discovery of the pathogen, achievements in biomedicine have provided tools for diagnosis, treatment and prevention, and TB had been considered conquered in many European countries. However, it has re-emerged as a significant problem for the European Union (EU). There are a growing number of TB strains resistant to the commonly used antibiotics (first-line drugs), necessitating the use of more complicated, expensive and less well-tolerated treatment schedules with second-line drugs. Moreover, reports since 2006 have documented the worldwide appearance of extensively drug-resistant TB (that is, resistant to first- and second-line drugs), now recorded in 50 countries worldwide, which threatens progress made previously in the control of TB. There are particular problems for TB associated with HIV co-infection and with migration. Drug-resistant TB is an urgent crisis that has been created by poor infection control. Raising awareness and tackling this previously underestimated problem represents an enormous challenge for public health systems and policy-makers.

Incidence rates of TB differ markedly across the EU, but the growing propensity for drug resistance threatens all Member States: the rates of multi-drug-resistant TB (MDR-TB) in the countries of Central and Eastern Europe are among the highest in the world, and most EU countries have reported cases corresponding to the definition of extensively drug-resistant TB. There has been a renewed effort to define and tackle the public health challenges for TB in Europe. The European Commission, with the European Centre for Disease Prevention and Control (ECDC), and successive Council Presidencies have taken a lead to begin to identify what is needed for better funded, better co-ordinated disease management. However, there is much more to be done, both to use the currently available evidence to inform policy-making and develop new healthcare products and services, and to fill the scientific gaps in the current evidence base. This EASAC Report discusses where the EU should focus its efforts and what needs to be taken into account in formulating and monitoring a coherent strategy.

We cover issues for strengthening public health capacity and for increasing the awareness by medical professionals, politicians and the public. Notwithstanding the economic recession, we also urge increased funding of TB research – basic, translational and clinical – alongside better processes to identify and agree research priorities and better application of research advances to the development of new and improved diagnostics, drugs and vaccines. Our specific recommendations require action at the level both of the European institutions and in Member States. It is also vital to understand that TB cannot be isolated from other public health issues and that the policy priorities for the EU cannot be isolated from the global context.

Strengthening tuberculosis data collection and use across the European Union

We recognise that much is already being achieved by the ECDC and the World Health Organization (WHO). However, there is more to be done to collect and analyse data, particularly strengthening capacity in some Central and Eastern European countries, in order to identify the biggest opportunities for tackling TB. The wider scientific community must be involved in advising on those new opportunities that result from scientific progress. Among priority areas for attention are the following:

- Procedures for collating and reporting national surveillance data to the ECDC.
- Standardising methodologies and the practical implementation of those standardised techniques across the EU for drug sensitivity testing and strain typing, with clarification of the minimum data set required for case definition.
- Organisation of Reference Laboratories across the EU and their networking.
- Opportunities for the generation of interactive, user-oriented databases of genotypic and phenotypic information, to improve understanding of the relationship between molecular variation and clinical consequences.

Determining European Union strategy in a global context

The ECDC and its partners must clearly define strategies for control of TB and MDR-TB in all settings in the EU, and disseminate guidance on standards of care consistent with international recommendations. The disease-specific focus on TB must be made an integral part of the broader European development of health systems capacity. The public health objectives for the EU and its immediate neighbourhood should be aligned with global policy needs, and EU countries can play a major role in a strong, internationally co-ordinated effort to combat TB as follows:

- Accepting a responsibility to develop research and laboratory services (infrastructure, training, quality assurance) in neighbouring countries and worldwide.
- Increasing support for the European and Developing Countries Clinical Trial Partnership to fulfil its potential in clinical research and innovation.

- Resolving uncertainties in TB screening principles and procedures for migrants, integrating diagnosis into a strategy that encompasses care and treatment irrespective of the legal status of the individual and promoting research in molecular epidemiology to clarify the geographical and historical origins of drug resistance.
- Contributing to better resourcing and co-ordination of data collection to strengthen the evidence base for the potential impact of air travel and large gatherings at international public events on drug-resistant TB.

Raising awareness of tuberculosis as a public health issue

It is still necessary to increase the visibility of TB as a public health priority for the EU. The scientific community has a responsibility to help communicate the nature of the threat, as follows:

- Better informing of medical professionals in their training and retraining programmes and encouraging the uniform adoption of standards of TB care.
- Supporting public engagement to educate about the risks, to tackle misconceptions and the stigmatisation of affected individuals and groups; sharing best practice in advocacy.
- Stimulating commitment by policy-makers at the national, European and global levels. TB must be included in all high-level discussions of national and international health priorities.

To avoid previous problems of multiple initiatives proceeding without effective co-ordination, there must be still better interaction between the EU, WHO, G8, World Bank, International Monetary Fund and other stakeholders to drive a shared policy agenda. New structures, for example a European Council on Global Health, might help to build the wider alliance. However, whatever the policy framework, the European biomedical research and public health communities have key roles in developing the validated evidence base and in identifying and communicating the best practices that will inform and guide improved healthcare delivery.

Support for new research

New models for TB research support in Europe are required to help identify and agree priorities, build the necessary multidisciplinary functions and direct an increasing level of investment. Efforts in fundamental microbiology and immunology of TB must be increased, and the focus on basic research must be accompanied by renewed endeavours in clinical research to evaluate current practices and inform clinical decision-making, ensuring that the newer Member States are also involved in these collaborative research efforts. Among specific research priorities are the following:

- Characterising the determinants of TB strain resistance and fitness.
- Understanding host-pathogen interactions in pathogenesis, rapid disease progression and protection.
- Identifying new biomarkers to monitor disease activity, based on advances in genomics and post-genomics technologies.
- Evaluating the socio-economic consequences of drug-resistant TB and of the impact of control measures.
- Using mathematical modelling and simulation techniques to explore trends in disease incidence and the impact of control measures.
- Assessing the determinants of the rapid expansion of drug resistance in Eastern Europe and other regions.

Support for innovation

There is a continuing need for the public and private R&D sectors to work in complementary ways, reducing current impediments. This will support the translation of research findings into innovation and enable the practical application of novel products and services in the healthcare sector, even in resource-poor settings. Some examples of this include the following:

- Diagnostics: progress is being made in the identification and development of novel diagnostics and of biomarkers to assess clinical outcomes. More can be done to encourage R&D and to achieve consistent use of testing methodologies between Member States and to progress partnerships for the validation and application of tests. Public–private partnerships for development of TB diagnostics should also capitalise on advances in the application of technology for point-of-care testing, to provide cheap and reliable tests for TB. In addition, recent advances in research are now bringing within range the possibility of novel, non-invasive, diagnostic approaches based on customised sets of biomarkers. It is also important to optimise performance of the older testing methods in parallel with developing new approaches.
- Drug regimens: there is scope to tackle bottlenecks in R&D for both multinational pharmaceutical and smaller biotechnology companies, by rationalising regulatory requirements to encourage innovation without compromise to drug safety and efficacy. In addition, there are some urgent issues with current

TB treatment regimens: to remove inconsistencies in the management of drug supply across the EU; to ensure consistency in quality assurance; to clarify and resolve the problems of drug interaction in HIV-TB combination therapies; and to design better drugs to shorten or simplify the drug regimen and to counter resistance development.

- Vaccines: strengthening of fundamental research to discover novel vaccine candidates for better efficacy and safety. It is also important to improve clinical trial capacity, incorporating the latest understanding of biomarkers as correlates of clinical protection, and to better communicate the value of vaccines in order to promote their appropriate uptake.

There is merit in exploring innovative health financing mechanisms., One example is to extend the Advance Market Commitment to TB drugs, diagnostics and vaccines. We recommend further consideration of the options during the Italian Presidency of G8.

It is important for policy-makers to recognise the concern that Europe has, so far, failed to respond adequately to the global TB threat. Europe has major strengths in the quality of its TB research and innovation. It has a major opportunity to develop co-ordinated and effective public health capabilities. However, increasing awareness, commitment and action across a broad front are needed if the urgent problem of drug-resistant TB is to be resolved.

1 Introduction: the shared global agenda

1.1 Scientific and societal aspects

Tuberculosis (TB) has a long history as a leading cause of death throughout the world. Until the onset of the AIDS epidemic, TB was the largest single contributor to death from infectious disease. TB infection in humans is caused by the bacterium *Mycobacterium tuberculosis*, usually transmitted as an airborne infection from a person with the active pulmonary disease. Only about 5–10% of those initially infected will progress to clinical disease and contagiousness, usually within the first two years after infection. In the remainder, the mycobacteria are sequestered inside granulomatous lesions where they remain controlled for many years. This condition is known as latent or asymptomatic TB. TB primarily affects the lungs (pulmonary TB) but can also affect other organs, including the lymph nodes, central nervous system (causing meningitis), joints, bones, genito-urinary and gastro-intestinal tract. Factors that weaken the immune system, including ageing and iatrogenic (immunosuppressive) interventions, but particularly also co-infection with HIV, increase the probability of conversion from latent infection to active disease. TB has become the major cause of death in HIV-positive subjects in sub-Saharan Africa.

Globally, TB is a highly significant public health challenge, which all countries have a collective responsibility to address. Previously considered conquered in many developed countries, TB has re-emerged in recent decades, including in parts of Europe and the USA. This is partly because of immigration and HIV infection, but also in consequence of the association with poor or vulnerable populations: for example, prisoners, drug-users, the homeless, and residents in care facilities. In developing countries, poverty-related malnutrition and poor housing conditions have an additional impact to increase the susceptibility of the population to TB.

The BCG (Bacille Calmette Guérin) vaccine is effective in limiting severe disease in childhood. However, it has little or no effect on preventing adult pulmonary TB, the main, contagious form of TB and, therefore, has virtually no impact on its transmission. Current standard drug treatment of TB takes at least 6 months and is based on the concomitant administration of the four first-line agents isoniazid, rifampin, pyrazinamide and ethambutol (Table 1), fundamentally unchanged during the past 40 years. Although treatment is effective under optimal conditions, efficacy is often compromised by delayed diagnosis, inadequate treatment regimens, poor compliance because of the lengthy duration of treatment required and side effects. These factors lead to the development of drug resistance.

There are a growing number of TB strains emerging, resistant to the commonly used anti-TB drugs and necessitating the use of more complicated treatment schedules comprising second-line drugs, which are more expensive, less effective and more toxic than the first-line drugs. Treatment of drug-resistant TB may require two years of continued heavy medication (Table 1). Reports since 2006 also document the worldwide emergence of

Table 1 Current recommended anti-tuberculosis treatment regimens (after Raviglione and O'Brien 2008)

	Initial phase		Continuation phase	
Indication	**Duration (months)**	**Drugs**	**Duration (months)**	**Drugs**
New smear- or culture-positive cases	2	H, R, Z, E	4	H, R
New culture-negative cases	2	H, R, Z, E	2	H, R
Pregnancy	2	H, R, E	7	H, R
Failure and relapse				
Resistance (or intolerance) to H	Throughout 6		R, Z, E	
Resistance to H+R	Throughout 12–18	Z, E, Q + S (or another injectable agent)		
Resistance to all first-line drugs	Throughout 24	One injectable agent + three of these four: ethionamide, cycloserine, Q, PAS		
Standardised re-treatment (susceptibility testing unavailable)	3	H, R, Z, E, S	5	H, R, E
Drug intolerance to R	Throughout 12	H, Z, E		
Drug intolerance to Z	2	H, R, E	7	H, R

H, isoniazid; R, rifampin/rifampicin; Z, pyrazinamide; E, ethambutol; S, streptomycin; Q, a quinolone antibiotic; PAS, para-aminosalicylic acid, injectable agents (amikacin, kanamycin or capreomycin).

extensively drug-resistant TB (XDR-TB).[1] XDR-TB strains have probably arisen on numerous separate occasions, eliciting the concern that, because of the ease of international travel, such strains will move rapidly from their place of origin. The global threat of XDR-TB has great significance for public health, not least because its very existence is a reflection of weaknesses in TB clinical management, which should minimise the emergence of drug resistance by using well-supported supervised, curative treatment (Raviglione and Smith 2007). It has been judged that the consequences of failing to tackle XDR-TB will be severe (Senior 2007): '*We risk converting the largely treatable TB epidemic into a non-treatable one, as it was before antibiotics … An XDR-TB epidemic would threaten all progress made in TB control in recent years*'.

The present report focuses, in particular, on the issues for TB drug resistance. However, we share the view that the best prevention strategy for drug-resistant TB is the proper management of all TB cases.

1.2 EASAC work on infectious diseases

In a series of reports on infectious disease policy published since 2005, EASAC has examined European Union (EU) priorities for public health and innovation in disease surveillance, health system preparedness, responsiveness and control. EASAC recommendations identified current and future needs for infrastructure, skills, investment in fundamental science and the generation of novel healthcare products and services. Relevant previous EASAC work on cross-cutting themes will be referenced where appropriate in the present report. In particular, some of the specific challenges for Europe posed by drug-resistant TB exemplify the more general challenges for the emergence of drug-resistant pathogens, and the previous EASAC broader perspective for tackling antimicrobial resistance (EASAC 2007a) identified issues that receive further attention in the following chapters.

Following feedback on previous EASAC outputs received from the European Commission, European Parliament, Council of Ministers, industry and specialised scientific societies, EASAC Council agreed to initiate a further study to focus on TB, particularly drug-resistant TB. EASAC goals for this new Working Group (Appendix 1) were to assess how science can inform policy development, to indicate where there are gaps and uncertainties in the evidence base, and to recommend where additional concerted strategic action is warranted in order to tackle the current problems and to provide the flexibility to cope with future developments (both predictable and those as yet unforeseen). The new study was designed to cover EU policy issues associated with surveillance data collection; laboratory services; TB management; public engagement; support for fundamental research and the translation of research into innovation; and other priorities for EU involvement in global dialogue and action. It is not the purpose of the present report to provide a detailed account of the disease biology and its control, but we cite key references for further information.

[1] Multi-drug resistance (MDR) is defined as resistance to at least isoniazid and rifampicin (first-line drugs); XDR is defined as MDR plus resistance to any fluoroquinolone and any of three injectable second-line drugs (amikacin, kanamycin or capreomycin).

2 The magnitude of the global health problem

2.1 The current situation

TB remains a poverty-related disease, most prevalent in developing countries. Discovery of the tubercle bacillus in 1882 opened the way for biomedical achievements providing tools for diagnosis, prevention and therapy that, with improved living conditions, led to a considerable decline of the infection in the industrialised world during the twentieth century. Despite the historical achievements, it is estimated that, worldwide, more than 9 million people develop active TB every year, with 1.7 million dying from the disease (WHO 2008). The annual incidence of TB is about 5–15% in HIV-infected individuals in high-burden communities in both industrialised and developing countries. In total, up to 2 billion people have been infected with *M. tuberculosis*. Moreover, in some countries where TB rates dropped markedly in the last century, a mood of complacency led to dwindling investment in research and public health infrastructure, encouraging sub-optimal clinical practice and a resurgence in TB.

In the EU, the aggregated rate of reported TB (in 2006) was approximately 18 cases per 100,000 of the population (Falzon et al. 2008). Although rates are low by some international standards, the EU is not near to eliminating TB, defined as having fewer than 1 case per million of the population. In the EU-27 countries in 2006, 87,806 cases of TB were reported, slightly fewer than in 2005 (91,578). European surveillance data show that the TB rates differ markedly between countries, ranging from about 4 to more than 120 cases per 100,000. In the EU-15 set of countries, TB rates are generally low, but not always declining. The highest rates tend to be found in the Baltic and Eastern European Member States of the EU, although the evidence from the Baltic States now reveals a decline where the incidence had been highest.

Notwithstanding, the challenges associated with tackling the overall incidence of TB, the growing propensity for drug resistance is a greater cause for alarm in the EU. Cases of MDR-TB have been reported in most of the EU-27 countries, and 17 Member States have reported cases corresponding to the definition of XDR-TB. However, the EU lacks systematic monitoring in these respects, and in 2006 only 18 Member States had nationwide representative drug susceptibility testing data. The rates of MDR-TB in the countries of Central and Eastern Europe and the Commonwealth of Independent States are estimated to be the highest in the world. A recent survey by the World Health Organization (WHO) (WHO/IUATLD 2008) provides further details on the development of drug resistance in European countries in the global context. As of now, XDR-TB has been recorded in 50 countries and it is estimated that there are nearly half a million new cases of MDR-TB a year worldwide. In Baku, Azerbaijan, nearly one quarter of all new TB cases were reported as multidrug-resistant, and the proportion of MDR-TB among new TB cases is in the range 15–20% in regions of the Russian Federation, Moldova and Ukraine. Surveys in China also suggest that MDR-TB is widespread there. It is likely that there are other outbreaks of drug resistance going undetected: only six countries in Africa – the region with the highest rate of TB worldwide – were able to provide drug resistance data to the WHO.

Worldwide, MDR-TB rates are at an all-time high and there are significant failures of control, for example in Russia (WHO/IUATLD 2008). Fortunately, there have also been some notable successes in tackling this problem. For example, in Estonia and Latvia, identified as drug-resistant 'hotspots' in the late 1990s, rates are stabilising because of the substantial political commitment, public health investment and changes in medical practice. These demonstrable achievements in Baltic States have provided the inspiration for proactive public health efforts in other Member States, made before their MDR-TB rates reach such critical levels (for example in the UK; Davies and Cullen 2008).[2]

The ECDC has concluded that three broad epidemiological patterns can be currently discerned for TB in the EU (Box 1).

An increasing rate of MDR-TB in some European countries can become a problem for all of Europe: even a low present prevalence may have significant consequences. Yet this threat receives comparatively little attention by contrast, for example, with the threat from bioterrorism or avian influenza. The TB threat is growing and there is no such place as 'fortress EU'. As the EU expands, its boundaries will include countries with increasingly different TB burdens and challenges. The concept of a wider European region encompassing the EU, Eastern Europe, former republics of the Soviet Union and Central Asia is particularly relevant in defining collaborative international effort.

2.2 Forecasting future trends

Evidence from surveillance studies can determine whether resistance is an issue for a particular pathogen and

[2] The issues for drug-resistant TB from the UK perspective are discussed in detail in written evidence contributed to the EASAC Working Group from the Academy of Medical Sciences and published on www.acmedsci.ac.uk/download.php?file=/images/publication/EASACTB.pdf.

Box 1 EU heterogeneity in tuberculosis epidemiology

1. Mostly Western European countries

Low TB rates and mortality. Disease is increasingly associated with foreign-born individuals, with poverty and with lowered immunity. Drug resistance is currently low but usually higher in the cases of foreign-born individuals.[3] There are particular problems of drug-resistant TB in vulnerable populations in major cities (for example, Berlin, Paris and London). HIV infection rates among TB patients do not exhibit a consistent pattern.

2. Baltic States

High TB rates and mortality that, in some areas, are beginning to decline. Low proportion of patients of foreign origin. High levels of drug resistance and increasing level of HIV infection among TB patients.

3. Central European States (those joining the EU after 2004 or bordering countries of the Former Soviet Union)

Moderate to high TB rates that are declining; new cases of foreign origin. HIV co-infection and drug resistance are, as yet, uncommon.

These data are based on Working Group analysis and the report by ECDC (2008) 'Framework Action Plan to fight Tuberculosis in the European Union'. Longitudinal data (1995–2005) from those Member States with the highest rates (more than 20 cases per 100,000 population per year) are presented in the ECDC Annual Report (2007) 'Microbes without borders: key facts on infectious diseases in Europe' (www.ecdc.europa.eu).

particular antimicrobial agent (EASAC 2007a). When undertaken for a sustained period, surveillance may disclose a pattern of an initial low prevalence of resistance followed by an almost exponential increase that ends in the loss of the clinical indication for that antimicrobial (Drlica et al. (2008), discussing TB treatment with the fluoroquinolone moxifloxacin). The challenge is to identify resistance problems before this increase occurs so that therapy can be adjusted to maintain a low prevalence of resistance. However, the problem posed by XDR-TB is compounded by the time needed to collect data. In the meantime, some insight can be gained from theoretical modelling (Blower and Supervie 2007), which has raised the worrying possibility of exponential progression from MDR to XDR-TB in those circumstances where the currently low success rate in controlling MDR-TB is not improved.

Mathematical modelling is an important research tool with which to augment and evaluate conceptual models and interpret clinical observations in infectious disease transmission. Modelling can be used to explore scientific questions, choose between competing hypotheses, generalise results obtained from trials to different populations (where appropriate), aid decision-making and develop future patterns in disease trends and potential impact of control strategies in conditions where it would not be feasible or ethical to compare interventions in clinical trials. Simulation models of TB prevalence are already helping to forecast the emergence and evolution of MDR strains. One of the first such studies (Dye and Espinal 2001) modelled MDR activity in different scenarios, and subsequent modelling data predicted global 'hot zones' of TB consistent with WHO-reported data (Blower and Chou 2004). Modelling has also been useful in investigating the impact of relative fitness of strains on the emergence of MDR-TB (Cohen and Murray 2004) and the impact of high HIV prevalence on TB (Hughes et al. 2006). However, there appears to be a relative lack of EU-funded activity on modelling TB in Europe, compared with other infectious diseases. This is a research gap that should be filled, while recognising the methodological challenge to capture heterogeneity and uncertainty in data about patients in order to generate meaningful insight.

2.3 Economic impact

Recent analysis of the historical evidence suggests that improvements in national health in Europe have generated very large increases in living standards over the past century, far more than is indicated by conventional economic measures such as national income statistics. One crucial driver of these gains has been the reduction in incidence of infectious disease, particularly TB (Hickson 2008). A study of England and Wales over the period 1900–2000 (that is, before the concern about the possible widespread emergence of drug-resistant strains) estimates that the value of the reduction in TB as a public health problem was in excess of £16 billion, equivalent to an additional 0.5% gross domestic product (GDP) growth per annum over that period (when the compound annual rate of GDP growth was 1.5%). According to this analysis, therefore, health gains from reducing TB in the UK between 1900 and 2000 were about a third as valuable as growth in the economy from all other sources.

Notwithstanding, these historical economic gains in many countries, TB imposes a continuing cost across the EU, which is exacerbated globally. According to the European Lung Foundation,[4] treating TB costs more than €2 billion annually in the EU. Moreover, this figure does not take into account the substantial economic burden associated with lost employment and premature death,

[3] For example, an increasing number of MDR-TB strains have been isolated from migrants in Mediterranean border countries, as recently described in Spain.
[4] www.european-lung-foundation.org/index.php?id=77.

nor the rapidly increasing costs of tackling drug-resistant TB that are likely to create new budgetary pressures for all Member States.

There is a consensus that it is cost-effective to treat TB. Various commentators have noted the additional costs incurred in consequence of earlier cuts in resources for TB, made on the complacent assumption that TB no longer represented a public health problem in developed countries. For example, it was estimated that cutbacks in TB-related resources in the 1970s to 1980s in the USA contributed to a resurgence in TB among predominantly immunocompromised and socially marginalised patients that cost more than $1 billion to control in New York City alone. (These and other US economic impact data are discussed by Gessler et al. (2006).)

The costs of TB fall on both the private and public sectors. A recent survey by the World Economic Forum's Global Health Initiative (World Economic Forum 2008) finds that one-third of companies responding expect TB to impact their business, through effects on their workforce, in the next five years. Firms in sub-Saharan Africa, Asia and Eastern Europe are the most worried about the impact of TB on their business. As the World Economic Forum notes, multinational businesses based in Europe will gain economically by exercising their corporate responsibility to implement TB programmes globally to cover employees, their families and their communities.

The WHO essential control strategy of DOTS (Directly Observed Therapy Short Course) has now been adopted by many countries. However, further extension of the strategy to TB high-burden countries would bring much additional economic benefit. For example, in the countries of sub-Saharan Africa, the economic costs of TB-related deaths (including HIV co-infection) over the period 2006–2015 are estimated to be US$519 billion (US$239 billion when HIV co-infections are excluded).[5] The economic returns would be even higher in China and India, where income growth projections over these 10 years are higher. The detailed analysis from the World Bank (Laxminarayan et al. 2007) quantified the additional economic benefits that would accrue by extending the DOTS strategy to other high-burden endemic countries as proposed in the Global Plan to Stop TB. This calculated a return on investment in benefits of up to 15 times the costs. Despite this detailed analysis from the World Bank, there is more research to be done to evaluate the current economic impact of TB and the financial gains from its management. Systematic economic evaluation requires both better analysis of the epidemiological impact of treatment and some consensus on the monetary value to be placed on reductions in mortality and morbidity in different circumstances.

[5] 'Aggressive TB control can yield big economic gains, says new study'; December 2007 on www.who.int/mediacentre/news/releases/2007/pr64/en/index.html referring to Laximanarayan et al. (2007).

3 The changing European Union policy landscape: what steps have already been taken to address policy issues for tuberculosis?

3.1 Berlin Declaration on tuberculosis

In October 2007, at the meeting 'All against Tuberculosis' in Berlin co-organised by the German Ministry of Health and WHO Europe, ministerial representatives from 49 countries met on an emergency basis to advance development of a Europe-wide approach to controlling and, eventually, eliminating TB.[6] Participants agreed that it was vital for the EU to work with the Commonwealth of Independent States, the Council of Europe and others to tackle the emerging pan-European threat of drug-resistant TB.

The proposed response is based on that defined by The Stop TB Partnership, a network of national and international organisations with secretariat hosted by the WHO (www.stoptb.org/stop_tb_initiative). The Stop TB Partnership was established in 2000 with a target by 2015 to reduce the global burden of TB (deaths and prevalence) by 50% relative to 1990 levels. The core of the response is the adoption of the Stop TB Strategy (Box 2) in all its components, in particular acting to bridge the funding gap between current resources available and those needed to control TB.

The Stop TB Partnership's Global Plan to Stop TB 2006–2015 (www.stoptb.org/globalplan), when released, was costed at US$56 billion over 10 years, but at that time only about 45% of this cost was thought likely to be available. These figures are currently being updated to reflect the additional resources needed for more aggressively addressing the MDR/XDR-TB epidemic.

Box 2 The Stop TB Strategy

- Specific priorities of the WHO Stop TB Strategy are described in www.stoptb.org/resource_center/assets/documents/The _Stop_TB_Strategy_Final.pdf
- The Stop TB Strategy comprises six key elements:
  (1) Pursue quality DOTS expansion and enhancement.
  (2) Address TB/HIV, MDR-TB and other challenges.
  (3) Contribute to health system strengthening.
  (4) Involve all care providers.
  (5) Engage people with TB and affected communities.
  (6) Enable and promote research.
- In 2007, the Stop TB Partnership and WHO published a two-year plan to *urgently* contain drug-resistant TB (www.who.int/mediacentre/news/releases/2007/pr32/en/index.html).

3.2 Portuguese Presidency priority in public health

Preparatory work for the Berlin Declaration, initiated during the Portuguese Presidency of the EU Council,[7] emphasised that the EU must tackle regional challenges, HIV co-infection and high TB rates in vulnerable populations within a broad framework that takes into account the diverse epidemiological situation across the European Community.

Taken together with the Berlin Declaration and other discussions in Europe (see the next paragraph), the Portuguese Presidency initiative was important symbolically as a political expression of the will to resolve inconsistencies in European strategy. There is increasing political recognition among Member States that, to be successful, coherent EU strategy requires greater interaction between the interested parties, with further attention paid to the clarification and consolidation of national control (disease management) programmes, screening programmes, chemotherapy policies and strengthened interventions to enhance adherence to treatment, supported by effective laboratory and other ancillary diagnostic services.

An OECD High Level Forum[8] on Medicines for Neglected and Emerging Disease, in collaboration with the government of the Netherlands, reviewed some of the issues for accelerating the development and delivery of medicines, vaccines and diagnostics for various infectious diseases, including TB. This Forum called upon governments of OECD and developing countries to demonstrate political leadership and join with industry, product development partnerships, non-governmental organisations (NGOs), intergovernmental organisations

[6] www.euro.who.int/mediacentre/PR/2007/20071019_1
[7] Round Table on Health Strategies in Europe: European Strategy for Multidrug Resistant Tuberculosis, Portugal 2007.
[8] Noordwijk Medicine Agenda 2007, 'Changing the face of innovation' on www.oecd.org.

and others to intensify collaboration and promote coherent policies.

Notwithstanding these initiatives, there is still more to be done to maintain the momentum at the political level (see section 7.4).

3.3 From policy to practice: the role of the European Centre for Disease Prevention and Control

In 2007, the European Commission asked the ECDC to develop an action plan to fight TB in the EU (including, for this purpose, countries belonging to the European Economic Area and European Free Trade Association), building on the political commitment expressed in the Berlin Declaration. This Framework Action Plan (ECDC 2008), published in February 2008, provides direction on what needs to be done at national and Community level.

The ECDC regards this Action Plan as the first step in a process that will progress to the development of a framework for national plans to guide countries that do not yet have a plan in place; to the definition of qualitative targets and specific indicators to monitor progress in improving TB control; to the evaluation of national plans (by collaboration between ECDC, the Commission, Member States and the WHO); and to establishment of the mechanism of collaboration for assessing progress, defining priorities and planning actions. In addition to these primary objectives to support and strengthen Member States' efforts against TB and to support those countries from which imported cases originate, the Action Plan aims to increase political and public awareness of TB as a public health issue in the EU. The Action Plan, in line with the WHO Stop TB Strategy, highlights eight areas for strategic development and planning: TB control and capacity of health systems; surveillance; laboratory services; TB care for all; MDR and XDR-TB; TB/HIV co-infection; new tools for TB control; and partnership.

3.4 Adding value in evidence-based policy-making

In summary, there are signs that the EU policy landscape is changing, as denoted by the renewed effort to discuss the public health challenges for TB in Europe. In particular, the European Commission (with the ECDC) and some EU Council Presidencies have acknowledged the importance of taking a better co-ordinated approach. By contrast with earlier pessimism, there is a new wave of enthusiasm for understanding and managing TB, accompanied by some new allocation of resources worldwide (Kaufmann and Parida 2007; Zumla 2008). Thus, for example, the US President's Emergency Plan for AIDS Relief (PEPFAR) announced in mid-2008 has designated US$4 billion, out of a total budget of US$48 billion over 5 years, for the fight against TB. However, there is now concern that the economic recession could complicate efforts to tackle global public health problems, and it remains to be seen whether the promises of additional funding can all be kept.

To maintain this momentum in recent policy development, it is necessary to augment efforts to raise public and political understanding of the key issues. It is also necessary to explore and explain how advances in science are bringing new opportunities within range for innovation and its translation into improved healthcare. How might EASAC add value to the many activities already underway in this area? EASAC is well placed to provide an independent view on where science can contribute further to inform policy development, drawing on evidence from across the EU and from a broad range of scientific disciplines, alerting policy-makers at both the EU and national levels. There is an important collective role for the Academies to explain to policy-makers 'what is known and must be taken account of', while communicating to the wider scientific community their responsibility to elucidate 'what is not yet known but should be'. The key areas that must be tackled are described in the following chapters of this report in order to clarify where the EU must focus and what needs to be considered in formulating and monitoring policies.

4 Objectives for strengthening public health capacity

4.1 Improving data collection in the European Union

The procedures for collecting basic epidemiological data on TB are relatively robust throughout the EU because of the commitment to develop a comprehensive surveillance system.[9] However, as noted previously (section 2.1), only about half of the EU countries routinely perform drug sensitivity testing linked to notification of TB cases. A lack of quality control, particularly for standardised testing for resistance to second-line drugs, coupled with the potential for case-referral bias, creates uncertainties in the evidence base such that it can only be used with caution to inform policy-making. It is important for all Member States to be aware of the recommended standards for modern TB laboratory services, which represent a level of performance that should be attainable in all European settings (Drobniewski et al. 2006). There is particular need to strengthen data generation and collection in some Central and Eastern European countries.

The ECDC Framework Action Plan (ECDC 2008) outlines the priorities for strengthening data collection, developing laboratory techniques, integrating laboratory, clinical and epidemiological data and creating algorithms for detection of disease clusters. In discussing the current situation in the EU, the EASAC Working Group observed that although there are large differences in the incidence of TB and drug-resistant TB between Member States, with major implications for investment in the national infrastructure for surveillance and case management, there are some common challenges. Most, if not all, countries face the problem that a significant proportion of patients and their contacts are lost to follow-up, that it can sometimes be difficult to ensure compliance in absence of legally mandated treatment and that data on the monitoring of treatment outcomes may be incomplete. Experience in the Working Group shows that there is scope for sharing and disseminating best practice across Member States in facing the diverse challenges. These public health issues share a common feature in that their resolution requires better collection of data to quantify the extent of the problem.

The Working Group emphasised several points for capitalising on the new opportunities for laboratory services and data collection, which are as follows.

1. Methodological and organisational issues for sample typing

The systematic characterisation of TB strains is important in understanding drug responsiveness if genotyping is accompanied by sound epidemiological analysis to understand how lineages spread and how outbreaks originate. The European Commission (DG Research) has usefully funded many typing studies. However, it is time to transpose the activity from the present research focus to the health services and, thereby, also inform public health policy-making. It is vital to ensure that the ECDC collects typing data from across the EU in order to: (a) characterise and understand the changing patterns of drug resistance; (b) define frequency and pattern of mutations and thereby improve on current diagnostic capabilities; and (c) track outbreaks.

Pan-European collection of such data requires agreement on the minimum defined criteria for case definition accompanied, where possible, by more detailed information on strain and comparative drug resistance. This generation and collation of standardised data has implications for the organisation of Reference Laboratories in Member States and their networking. Not every Member State currently has a Reference Laboratory for this public health function; nor is it always mandatory to send a designated sample for typing to a Reference Laboratory, where it exists.

The Working Group recommended further consideration of: (a) whether it would be more cost-effective for the EU to create regional Reference Laboratories to support molecular epidemiology rather than contend with the consequences of an unco-ordinated decision by each Member State;[10] (b) how best to develop the network of European Laboratories with expertise to perform the most advanced analyses; (c) how to standardise the analyses to allow an easy exchange and comparison of data; and (d) how to mandate the submission of samples. These issues need to be resolved before the proposals in the ECDC Framework Action Plan for laboratory services can be translated into practical development and implementation: detailed case study-based analysis of the potential added value of a European TB Reference Laboratory network is discussed elsewhere (Drobniewski et al. 2008).

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[9] EuroTB on www.eurotb.org. Funding by the European Commission for this surveillance network ended in 2007, with the functions subsumed into the ECDC.

[10] A good case can be made for the EU, as elsewhere, that routine surveillance should be strengthened by additional measures such as sentinel surveillance – the collection and analysis of data by designated institutions selected for their geographical location, medical specialty and ability to diagnose and report high-quality data accurately (www.usaid.gov/our_work/global_health/id/surveillance/sentinel.html).

2. Hopes and realities for testing and data curation

New diagnostic procedures are becoming available that may transform the surveillance and management of TB. New molecular line-probe assays (LPAs) allow rapid detection of first-line drug resistance with, potentially, major impact on initial treatment options. LPAs specific to fluoroquinolones and aminoglycosides may also soon be available, allowing rapid detection of XDR-TB. Further into the future, the assay of single nucleotide polymorphisms (SNPs) may revolutionise the assessment of drug susceptibility. Rapid whole-genome sequencing technologies can also be applied to TB strains to help understand the molecular genetic basis for MDR and XDR-TB. To support these advances, the construction of extensive databases[11] of mutations related to phenotypes (antibiotic resistance) and generic whole-genome sequencing facilities with capacity for TB research will help to characterise resistance patterns worldwide and facilitate the more rapid development of tests (see section 6.3) for surveillance and management purposes.

It is timely to create an integrated database resource comprising a comprehensive repository of characterised *M. tuberculosis* isolates together with their genomic, clinical and epidemiological data to explore the relationship between molecular variation and clinical consequences. Comprehensive molecular characterisation would provide a platform of knowledge to inform anti-tuberculosis strategies at many levels: advancing drug susceptibility testing (Drobniewski et al. 2007), surveillance, predicting the future course of the drug-resistant TB epidemic (section 2.2) and developing new therapeutics. Although an initial proposal for an integrated database construes a TB archive in national (US) terms (Gessler et al. 2006), there will be a clear advantage to organising databases on an international level. This requires, again, better collaboration in Europe between Reference Laboratories in the clinical collection of isolates, in association with the ECDC and with ongoing work by the scientific community to develop tools for curation and analysis. It also requires collaboration with the US Centers for Disease Control and Prevention (CDC) and with other genotyping and phenotyping resources worldwide. This should be a priority for ECDC attention. Additional potential utility also resides in more extensive databases to enable clarification of the interplay between the genetic make-up of the bacterial strain and of the patient. Recent research has confirmed a role for host genes in susceptibility to TB, relating to the control of acquired and innate immunity, but studies on larger groups are needed to determine the inter-relationships between *M. tuberculosis* polymorphisms, host polymorphisms and disease characteristics (Kaufmann 2008).

4.2 Strengthening partnership for capacity-building outside the European Union

The EU cannot consider its TB surveillance and management needs in isolation. Even if viewed solely in terms of EU interests, a growing global incidence of MDR and XDR-TB is a threat to the EU. It is important to do better in tracing and tackling these origins of drug resistance in the EU. In addition to these domestic objectives, the EU has a humanitarian responsibility to support international development.

The Working Group recommended that EU countries assist in improving the TB diagnostic situation in neighbouring countries. In Russia, for example, there is evidence to show that the overall effectiveness of TB chemotherapy has declined over the period 2000–2005, probably because of emerging MDR-TB. Because drug susceptibility testing is not necessarily performed outside the major centres in Russia, the initial assumption that new cases will be susceptible to first-line drugs is made too often. In addition, even though the measured incidence of TB in Russia is relatively high (Falzon et al. 2008), there is concern about under-diagnosis in some regions.

In focusing on neighbouring regions, the Working Group recommends that the EU do more, through capacity-building, to develop laboratory services for TB testing (as part of a co-ordinated approach that includes other threats, particularly HIV). This improved laboratory capacity must include the capabilities for typing and drug sensitivity testing. The physical infrastructure must be accompanied by provision of external expertise in quality control and by training programmes in testing, including the use of newer diagnostics. This is an opportunity for the EU to provide training fellowships that will help to develop the body of public health leadership in neighbouring countries. It is also an opportunity for the scientific community to work together with the ECDC to provide professional expertise in the clinical microbiology needed to implement new tests outside the EU. The partnership between the American Society for Microbiology and the CDC provides one model for this through their International Laboratory Capacity Building Program.[12] Although training

[11] The Institut Pasteur has provided a TB genome browser for over 10 years (http://genolist.pasteur.fr/TubercuList) and the Max Planck Institute for Infection Biology has produced a TB proteome database (www.mpib-berlin.mpg.de/2D-PAGE/). With support from the Bill and Melinda Gates Foundation, a global TB database is currently being built (www.who.int/globalatlas/dataQuery/default.asp; www.tbdb.org).

[12] www.asm.org/International/index.asp?bid=55614.

fellowships could usefully be supported by the current research funders at European and national level, we suggest that new sources of such funding should also be explored. In this regard, those involved in developing and implementing European Neighbourhood Policy (DG External Relations) and DG Europe Aid should be made aware of the importance of health issues associated with communicable diseases in neighbouring countries.

In addition to offering training in microbiology and public health, there is also a need for the EU to help with training in the social sciences in neighbouring countries so as to progress understanding of the determinants of micro-epidemics, for example as a consequence of overcrowding in prisons, hospitals and other care facilities.[13] Both within and outside the EU, there is significant scope to develop infectious disease modelling and simulation methodologies to inform the design and management of new public facilities.

Of equal importance, and looking beyond the neighbouring countries, the European Commission and some Member States are already active in building partnerships for TB data collection and management with developing countries (see section 6.6 for a discussion of current and future opportunities for the European and Developing Countries Clinical Trial Partnership (EDCTP)). However, in the experience of Working Group members, there are some difficult realities to face, especially in sub-Saharan Africa. The core facilities to assess drug-resistant TB may be weak or completely absent, and the management of XDR-TB particularly challenging. Where there are problems of political instability, European partners may also need to provide project management training. African NGOs may be more appropriate partners than governments for EU initiatives aiming at the operational delivery of improved health services, but it is also necessary to involve governments to facilitate sustainability of efforts.

4.3 The significance of HIV co-infection

About 15 million people are already co-infected with TB and HIV worldwide, with more than 700,000 new cases and a quarter of a million deaths each year. TB is the main cause of deaths in patients with HIV. Both infections are concentrated in high-risk groups, and the interaction between TB and HIV tends to worsen both. However, information on HIV sero-status of patients with TB varies widely in the EU because of disparities in testing policy and data collection (ECDC 2008).[14]

1. Is there a fitness cost to drug-resistant TB clones?

There has been speculation previously that XDR-TB could only thrive in immunocompromised patients, because of the potentially reduced fitness of such strains. Although the association between XDR-TB and HIV is well-documented in the Kwa Zulu-Natal outbreak (Raviglione and Smith 2007), it is now clear from elsewhere in South Africa (Shean et al. 2008) that XDR-TB can also be found in HIV-negative patients. Moreover, most European cases of XDR-TB (and MDR-TB) are among HIV-negative individuals (see Migliori et al. (2007) for characterisation of XDR-TB in Italy and Germany). In aggregate, the evidence suggests that XDR-TB originates from poor medical practice creating drug resistance regardless of HIV status, even though HIV co-infection may facilitate its more rapid spreading into an epidemic. The need for further research to investigate the determinants and consequences of differences in strain fitness is discussed in section 6.1.

2. TB and AIDS should not be treated as separate diseases in co-infected patients

HIV and TB are typically treated as separate diseases in the same patient (see Kaufmann 2007). However, there are issues for drug interaction between the TB first-line drug rifampicin and anti-retroviral drugs (Ribera et al. 2007), and shared drug toxicity, that may lead to treatment failure and problems of compliance. There is a particular need to develop anti-retrovirals that are more compatible with rifampicin or to find a drug to replace rifampicin.

The Working Group agreed with the proposals in the ECDC Framework Action Plan to strengthen collaboration between TB and HIV/AIDS control programmes, noting that collaboration must systematically encompass screening, intervention and follow-up. In addition, the Working Group advised that it is a priority (a) to conduct comprehensive population studies of clinical practice in this area to inform clinical decision-making and improve current diagnostic and treatment algorithms, and (b) to find novel combination therapies to avoid the side effects currently complicating the decision to treat TB and AIDS as single entities.

4.4 Infection control

MDR-TB and XDR-TB result from poor infection control; if public health systems are not working properly then the consequences will become increasingly

[13] A recent publication on modelling the impact of TB control strategies in overcrowded prisons in Brazil exemplifies the useful insight that can be obtained from such research (Legrand et al. 2008).
[14] Moreover, a report from the US CDC showed that one-third of American patients with TB did not know their HIV status despite the official policy that routine testing be performed on everyone with TB (Anon 2007).

severe. The strategic approaches for control of TB, and MDR-TB specifically, must be clearly defined to guide EU countries in setting their national response plans. The ECDC and its partners must, therefore, make every effort to disseminate and monitor standards of medical care consistent with the recommendations of the WHO and the international standards of TB care (Hopewell et al. 2006), targeting all providers – private as well as public (Box 2) – involved in healthcare provision. In addition, we emphasise the need for optimal infection control strategies, including contact tracing, to be applied in all settings – healthcare, social care and other (including homeless shelters and prisons) – in order to prevent highly damaging outbreaks.

Implementation of consistent infection control in the EU may also have implications for the research agenda, to provide further insight on what infection control measures should be put into place as part of agreed EU guidelines. Furthermore, the disease-specific focus on TB must be made an integral part of the broader European development of the capacity of health systems, ensuring that health systems have the accountability to collect, understand and use data.

5 Implications for an increasingly mobile population

5.1 Migration

The European Commission's new health strategy[15] includes the objective to focus on challenges that have not yet been fully addressed, with one such challenge noted to be the spread of infectious disease by the global increase in human migration. In evidence reviewed at a conference organised during the Portuguese Presidency of the EU Council,[16] the International Centre for Migration and Health (www.icmh.ch) illustrated the scale of this challenge by the significant increase in the proportion of TB cases attributed to migrants in the wealthier European countries. For example, 60% of the new cases of TB in the Netherlands and Denmark and 43% in Germany are associated with migrants. However, there is little evidence from molecular epidemiology to indicate TB transmission from migrants to the general population.

The literature on TB associated with migration to EU Member States has been reviewed in detail by Carballo (2007) as background briefing to the Portuguese Presidency meeting. Although TB is an emerging epidemic in many other large European cities (for example in Spain, Greece, Italy and the UK) associated with migration from Asia, Africa and Latin America, many of the migrants may only be infected after arrival in the host country, in consequence of their impoverished socio-economic status, such that screening at entry is likely to be of only very limited effectiveness. Drug-resistant TB is becoming a problem for these migrant communities (Carballo 2007; Falzon et al. 2008; Kruijshaar et al. 2008). However, the Working Group observed that many migrants may be carrying the latent infection on arrival so that new stress, for example an impoverished socio-economic status, then stimulates progression to the active disease. There are gaps in the evidence base here and more studies are needed on the molecular epidemiology of strains.

At the time of the Portuguese Presidency of EU Council, EASAC published a statement (EASAC 2007b) on the impact of migration on infectious disease more generally, identifying some of the challenges for research and for healthcare systems. The EASAC conclusions (Box 3), that better data are needed and that migrants should be offered the same access to healthcare services as the rest of the population, were subsequently reinforced by recommendations in a report of the European Economic and Social Committee (2007) and are broadly applicable to the management of TB.

Box 3 Impact of migration on infectious diseases in Europe: recommendations from EASAC (2007b)

Priorities for filling gaps in the evidence base:

- Quantifying the burden of infectious disease in migrants and pattern of health inequalities compared to other population groups.
- Assessing degree of public health risk attributable to migration, including modelling of disease transmission to assess impact.
- Comparing efficacy of screening options.
- Clarifying barriers in access to treatment and follow-up.

Developing coherence in screening, surveillance and treatment strategies:

- Sharing examples of good practice from Member States for initial presentation of migrant to healthcare system.
- Devising standardised protocols for testing and healthcare provision.
- Building key role for ECDC in collection of statistics and evaluation of options.

Global co-ordination:

- Implementing EU leadership role in strengthening public health capacity in newer Member States and in developing countries and reducing the global burden of communicable diseases.

These previous EASAC conclusions are all applicable to the particular challenge of TB. The Working Group emphasised the following:

- Surveillance and screening are a priority in the management of public health, but must be accompanied by efforts to raise awareness of TB in high-risk groups and by the provision of care and treatment irrespective of the legal status of the subject.
- There is a growing need for genotyping samples, including samples archived in the countries of

[15] Together for Health: A Strategic Approach for the EU 2008–2013.
[16] Health and migration in the EU, conference in Lisbon, September 2007.

origin, to understand the epidemiology of drug resistance.[17]

- The issues for TB screening policy for migrants must be resolved to provide EU coherence. Screening practices vary between Member States (Carballo 2007), which creates uncertainty if migrants move between countries: should Member States then re-screen or assume initial assessment at port of entry? There is need for better harmonisation of the criteria for developing screening approaches.
- There is weakness in current screening procedures, which usually rely on skin testing or X-ray assessment, that are often not accurate.
- While there is a need to diagnose active TB decisively and to focus on high-risk groups, it is also necessary to develop the capability to search for latent infections and provide preventive care.

The Working Group concluded that better plans must be conceived and implemented to deal with the results from screening and answer some critical questions. For example, should all those with a positive skin test receive X-ray assessment? What prophylactic measures should be taken, with whom and when? Clear algorithms for screening, management and treatment need to be put into place to avoid confusion and inconsistent practice by the sometimes inadequately trained local services.

The EASAC statement in 2007 (Box 3) further advised that the EU must not succumb to a parochial approach in tackling the public health problems associated with migration but must work in partnership to reduce the burden of disease in the countries of origin. The essential complementarity of action at the European and global levels has been highlighted by Currey et al. (2007) in commenting on the Berlin Ministerial Forum: the control of TB should encompass improvement of the health of vulnerable populations rather than concentrating only on the ways in which those vulnerable populations negatively affect health in Europe. This implies a bold commitment by all donor governments and NGOs to support efforts in TB control in countries neighbouring the EU and worldwide.

5.2 Air travel

Exposure to serious communicable diseases during air travel is a potential concern for passengers, aircrew and public health officials. Although one recent example of a traveller believed to be infected with XDR-TB was very well-publicised by the media, the ECDC risk assessment[18] concluded that the contagiousness of the patient was very low.

According to the latest edition of the WHO Air travel and Tuberculosis Guidelines,[19] no case of clinical or bacteriologically confirmed TB disease associated with exposure during air travel has yet been identified, although skin-test conversion has been reported and future consequences of latent infection cannot be excluded. The WHO guidelines provide full advice for all involved in air travel, and it is important not to provoke unwarranted media-induced anxiety about the potential transmission of XDR-TB. Nonetheless, the available evidence on the risk of transmission of TB during air travel and on subsequent outcomes is limited and, as the WHO advises: '*In order to strengthen the evidence base for operational decision-making and policy development, a co-ordinated international approach to research, data collection, analysis and dissemination is needed*'.

In the view of the Working Group, better resourced and co-ordinated activity along these lines is imperative not only to aid public health decision-making but also to provide better information to politicians and the community-at-large (see chapter 7); international co-ordination for contact tracing may represent a particular challenge (Chemardin et al. 2007).

[17] For example, to clarify the contribution made by the Beijing family of the East Asian lineage, notorious for causing MDR-TB and spreading globally (Kaufmann 2008).
[18] May 2007, www.ecdc.eu.int/Health_topics/Tuberculosis/XDR/risk_assessment.html. Subsequent analysis in the USA by the CDC (July 2007) ascertained that this subject had MDR-TB rather than XDR-TB (www.cdc.gov/media/transcripts/2007/t070703.htm). Clarification of the complexities in testing for XDR-TB and MDR-TB was subsequently published by the CDC (www.cdc.gov.news/2007/07/tuberculosis.html).
[19] May 2008, TB and air travel guidelines for prevention and control, third edition on www.who.int/tb/publications/2008/WHO_HTM_TB_2008.399_eng.pdf

6 The case for increased investment in R&D: what are the priorities?

The continuing public health challenges for TB necessitate research across a continuum from fundamental science, translational medicine, new product and service development and operational research. The Stop TB Strategy global plan (Box 2) provides a detailed account of some of these research priorities. In the following sections, we focus on some of the specific opportunities to progress basic and translational research as the resource for health services innovation, building on general points made previously by EASAC (EASAC 2007a). Recent funding initiatives, in particular by the Bill and Melinda Gates Foundation, are welcome and there is reason to be more optimistic than previously about achieving critical mass in TB research (Kaufmann and Parida 2007; Zumla 2008). However, in the opinion of the Working Group there is much more to be done to build investment, particularly by EU stakeholders.

6.1 Supporting fundamental research

More than ever, it is necessary to support research into the fundamental microbiology of the agent of TB, its interaction with the human host, and the occurrence and transmission of drug resistance, as the basis for developing new and improved healthcare interventions. Although the molecular mechanisms involved in resistance to first-line antibiotics are well characterised, many additional determinants of resistance remain unknown, particularly those to second-line drugs. Elucidation of the determinants of 'strain fitness' (influencing transmission between individuals) is also important to understand the spread of drug-resistant TB in populations. Among the attributes of strain fitness to be clarified by further research are the following: (1) the capacity of bacteria to infect the host; (2) differences in growth rate and growth characteristics that may determine if the host develops primary infection, latent infection or clears the infection; and (3) altered ability to be aerosolised and transmitted to a new individual.

Current advances in understanding the genomics of *M. tuberculosis*, building on pioneering work from Europe, will fuel multiple applications in improved surveillance, detection of virulence, elucidation of antibiotic resistance, as well as new therapeutic approaches. Draft analysis by a South African–US research collaboration[20] of the genome of a XDR-TB strain has detected only a relatively small number of mutations distinguishing it from less drug-resistant strains. Potentially, clarifying the molecular basis of XDR-TB may not be as difficult as some had expected. More broadly, the current advances in genomics, transcriptomics, proteomics and metabolomics will inform the development of new markers for disease activity – for diagnosis and monitoring treatment progress, cure and relapse.

Despite the promise of new scientific advances, according to an analysis of funding trends (Feuer 2007, for the Treatment Action Group), investment in basic TB research declined by about 8% in 2006 compared with 2005. Nearly 60% of the global funding for this basic science was provided by the US National Institute of Allergy and Infectious Diseases, which recently identified its priority objectives for TB biology and epidemiology (Fauci and the NIAID Tuberculosis Working Group 2008). There is no equivalent, unifying agenda for European research. Moreover, European Commission funding contributed only about 3% to the global total for TB basic research in 2006,[21] although translational research is funded in addition. This low spending on basic research by the European Commission is not unexpected, because the Framework Programmes were not designed to focus on it. Nonetheless, the Working Group expressed concern at the relative underfunding of basic research for TB in Europe, a weakness that is compounded by a relative lack of attention in EU Framework Programmes to measuring the impact of the research that is funded. The Working Group congratulated the European Commission for acknowledging in principle the research needs of poverty-associated diseases and for its recent recognition that TB research is currently underfunded. EASAC recommends that the total spend on TB research should be increased by the European Commission (see sections 6.2 and 6.3) and even more so by many Member States, whose individual programmes would also gain by better co-ordination across Europe.

Notwithstanding the comparatively modest investment, an ambitious portfolio of projects has been selected under Framework Programme 6[22] with the aim of validating novel approaches to support the development

[20] www.broad.mit.edu/cgi-bin/news/display_news.cgi?id=4142

[21] In addition to the money provided by the European Commission through Framework Programmes, individual Member States also fund basic TB research although their record is very variable. In 2006, the UK was the largest country of origin, attributable to the Wellcome Trust and, to a lesser extent, the Medical Research Council (who spent significantly less than in 2005). More recently, the UK Government Department for International Development has identified research on TB drug resistance as one priority for its five-year (£1 billion) research strategy (www.dfid.gov.uk/research).

[22] http://ec.europa.eu/research/health/poverty-diseases/projects/l_tb_en.htm

of new vaccines, drugs and diagnostic tools. For example, researchers recently identified a transcriptional regulator gene that determines whether the TB pathogen remains dormant in the host or develops into the active disease (Seok Lee et al. 2008). Several new candidate TB vaccines have entered their first clinical trials under this project.

One other key issue was raised in the evidence contributed by the Academy of Medical Sciences (see footnote 2). The Academy's 2006 report, 'The use of non-human primates in research',[23] found that non-human primates were of particular value for research into TB, because these species develop pathology closely analogous to that of human TB, including hypoxic lesions and latent infection. Non-human primates may also have a key role in identifying candidate vaccines to be taken forward into human clinical trials (see section 6.5). It is important, therefore, that the current revision of Directive 86/609/EC on the protection of animals used for experimental and other scientific procedures does not inadvertently constrain the opportunities to make new discoveries (discussed in further detail in EASAC (2008)). In the opinion of the Working Group, there is continuing need to undertake and validate studies to identify suitable animal models to use in basic research, vaccine testing and drug development.

6.2 A new funding model?

Funding for TB in Framework Programme 7 continues with similar innovation objectives to those of Framework Programme 6, while also covering health services delivery policy. However, the Working Group again expressed concern about the perceived inadequacy of the forecasted funding that is expected to respond to a broad agenda proposed by a large and diverse research community.

In the opinion of the Working Group, it is now time for DG Research to examine alternative models for targeting TB research priorities. TB research may be a relatively special case to be addressed in strategic terms because of its multidisciplinarity and arduous nature, requiring high biosecurity in laboratory and animal facilities for extended periods (Kaufmann and Parida 2007). Rather than continuing with the current funding system based on competition between individual research groups, it is suggested that the European Commission should delegate to an advisory expert group the identification of goals and specific research priorities and then encourage the leading researchers to combine to bid for funding. This is characterised as a research 'pull' rather than 'push' mechanism.[24] This is particularly relevant because many excellent researchers of TB are based in EU Member States. Furthermore, such funding needs to be allocated for a much longer period, to support research sustainability and flexibility (perhaps 5 + 5 years with interim assessment), than has been customary in Framework Programmes. It is appreciated that a radical proposal of this nature cannot be decided by DG Research alone. A decision to increase grants to this extent requires political input from Member States. Moreover, a new focus on sustaining continuity in good established collective research programmes will need to be accompanied by a mechanism to initiate smaller projects to encourage new researchers and new ideas.

This is an appropriate time to debate how Europe's research system can and must change. A recent commentary from the Chairman of the European Research Area Rationales Expert Group (Georghiou 2008) makes the general case for partly replacing future 'classical' Framework Programmes by target-oriented, fully integrated large research projects and greater co-ordination between national research funding budgets. According to this funding model, a new combination of top-down and bottom-up phases would agree priorities, encouraging stakeholders to form platforms to define what research is possible, in response to the top-down expression of political priorities. From the perspective of EASAC, TB is seen as an excellent example of one priority fulfilling all the criteria for an EU 'Grand Challenge': agreed societal need, feasible goals, an excellent base of research and industrial capability with viable prospects for implementation of research advances. There is a good case to be made for funding models that encourage the development of infectious disease research centres, to take an integrative view of the greatest public health challenges. Such centres would incorporate research competencies spanning microbiology, immunology, clinical infectious disease epidemiology, field experience, social sciences, mathematical modelling, genomics, bioinformatics and drug discovery.

The necessary focus on basic research must be accompanied by more clinical and translational research in Europe. There is need for large-scale population studies to delineate the risk factors for contracting and transmitting TB and for developing drug resistance as well as studies on the optimisation of healthcare services, evaluation of clinical management and treatment. This spectrum of research requires multidisciplinary teams of European scientists in collaboration with the research

[23] Weatherall (2006) The use of non-human primates in research. Available at www.acmedsci.ac.uk/p48prid6.html.
[24] An analogy might also be drawn with the proposal (for HIV/AIDS) by the EU consortium 'European action on global life sciences' (www.efb-central.org/eagles) for a research programme jointly funded by the European Commission and Member States, responsible for awarding large grants for fundamental or applied research, based on scientific excellence and with potential to form new public–private partnerships. To an extent, such initiatives are already being modelled in the current generation of European Technology Platforms/Joint Technology Initiatives.

communities in other countries. To highlight one key area: there is a need for research by the EU together with the WHO to understand the full range of determinants in the rapid emergence of drug resistance in Eastern Europe (and elsewhere) to establish if, for example, a circulation of counterfeit TB treatments has compounded the effect of the social problems and the challenge of sub-optimal infection control.

6.3 Addressing the shortcomings in innovation

As noted previously, diagnosis of TB is benefiting from the use of molecular probes to identify TB bacilli and resistance more rapidly. However, the main current diagnostic test for TB in developing countries remains sputum smear microscopy, which is more than 100 years old. There has not been a new marketed drug specifically developed to treat TB in nearly 40 years; and there has been no new vaccine for nearly 90 years. The early achievements in innovation have turned out to be insufficient (Kaufmann and Parida 2007), and the emergence of increasingly drug-resistant strains of TB brings new urgency to the search for better diagnostics, drugs and vaccines.

The analysis by the Treatment Action Group (Feuer 2007) calculates a total R&D investment for TB (covering basic, applied and operational research) in 2006 of $413 million ($393 million in 2005). However, it estimates, startlingly, that this sum would need to increase fivefold (to $2 billion per year) to meet the ambitious goals set by the Global Plan to Stop TB. Within the current total, philanthropies, primarily the Gates Foundation[25], have substantially increased their contribution but, alarmingly, some government spending has declined. The Treatment Action Group[26] recently published an interim analysis of latest funding trends (up to 2007), indicating that the reported trend in R&D investment appears to be decelerating. Aside from lack of investment, the respondents in the funder survey identified the top barrier to accelerating and improving R&D into TB as attributable to the lack of knowledge surrounding TB pathogenesis and appropriate biomarkers. This weakness highlights the importance of focusing on the basic science of TB as well as the application of that science.

In addition to proposing substantially increased funding, the Treatment Action Group recommends that a comprehensive, global R&D agenda for TB must be developed to provide the framework for better co-ordination, nationally as well as globally, and for the more accurate, more transparent, tracking of investments. The Treatment Action Group notes particular problems in Europe in these respects: '*Europe's research funding situation is a jigsaw puzzle of complexity, lack of transparency, lack of co-ordination, and lack of clear priorities. With few exceptions most of the rich EU countries were not in a position to either report or increase their investment in TB research. A few exceptions were the UK's DFID, Irish Aid, and the Netherlands Foreign Ministry.*' The contribution by the European Commission in 2006 (Framework Programme 6) to the total funding of R&D into TB was relatively small in global terms (ranking number 8) compared with the US National Institutes of Health (ranking number 1), a disparity that reinforces the difference in performance in funding basic research (section 6.1).

This point is emphasised by a recent report from Médecins Sans Frontieres (2008), which concluded that the European Commission and Member States together spend only one-third as much on R&D into TB as the US public sector, despite European GDP being at least 20% higher than that of the USA and despite the current situation where Europe is on the frontline of the TB epidemic. According to Médecins Sans Frontieres, the European shortfall in R&D funding into TB is more than 80% if an equitable contribution were to be made to the objectives in the Global Plan to Stop TB (see section 3.1).

The Working Group endorsed the call for renewed effort by funding agencies across Europe to provide more funds in a more co-ordinated way, to support both fundamental research and its translation into innovation. One format for collaboration between Member States and the European Commission to progress R&D into TB that merits further attention is the European and Developing Countries Clinical Trials Partnership (see section 6.5). It is noteworthy that the leading funders in this area (the Gates Foundation, NIAID, the Wellcome Trust), in common with the European Commission, have converged on a model of applied research comprising consortia of academic institutions and industry (Kaufmann and Parida 2007).

6.4 Developing novel diagnostics and optimising existing tools

Poor diagnosis of TB carries high costs. These costs are borne by the patient (inappropriate treatment, chronic ill health and premature death, loss of economic activities), by the clinician (increasing patient load, ineffective prescription practices), by laboratory staff (poor use of

[25] The Gates Foundation has supported (among others) the formation of the Global Alliance for TB Drug Development (TB Alliance), the Foundation for Innovative New Diagnostics (FIND) and the Aeras Foundation for research into TB vaccines. Subsequent to publication of the Treatment Action Group analysis, The Gates Foundation announced an additional $280 million grant for R&D into TB relating to development of diagnostics, vaccines and drugs (www.gatesfoundation.org, September 2007).
[26] Treatment Action Group, October 2008 'Funding trends in TB research and development: 2005–2007' on www.treatmentactiongroup.org/publication.aspx?id=2486.

resources) and by the health system (increasing number of contagious patients, wastage of scarce resources). It has been calculated (Nantulya 2008) that the world spends US$1 billion globally on the diagnosis of TB, yet fewer than 25% of the estimated 9 million new cases of TB each year are diagnosed by sputum smear microscopy. The current drug-sensitivity testing methods are laborious and time-consuming; these inadequacies delay case management and can lead to increased development of resistance and poorer treatment outcomes. In addition, for the second-line drugs, these methodological weaknesses are compounded by lack of standardisation.

Objectives for improved tests include quick, specific and sensitive diagnosis, preferably at the point-of-care, ability to distinguish latent TB from active disease, and in the presence of HIV, and rapid determination of the drug resistance profile (both first-line and second-line drugs). Achieving these priorities requires investment in new diagnostic tools, their quality assurance and regulatory authorisation, and in the application of these tools in TB control programmes.

As remarked by NIAID (Fauci 2008), pursuing these goals requires a change in the way partnerships between academia and industry are structured to ensure that new platform technologies are applied and that promising new diagnostics are progressed into clinical development and the marketplace without delay and at reasonable cost. The Foundation for Innovative New Diagnostics (FIND) initiative (www.finddiagnostics.org) is of particular importance; the Working Group also emphasised the importance of increasing effort to translate the application of novel diagnostics into field conditions as part of the operational research agenda. The recent endorsement by the WHO and planned introduction of the first new molecular technique, LPA,[27] which is able to identify MDR-TB quickly and cheaply in resource-poor settings, is an important achievement. In this context of improved detection technologies, it is now important for public–private partnerships to capitalise on the recent broader advances made in Europe in applying technology to develop cheap and reliable point-of-care testing.

It is also important, however, at the same time to invest in methodological improvements to the existing diagnostic tests, especially microscopy, to improve their detection success rate. These efforts should not be mutually exclusive: new tests can be developed in parallel with optimising the older methods.

The Working Group made several additional points, as follows:

- An increasingly enlightened attitude within WHO and the Stop TB partnership to embrace modern technology, in particular the quicker diagnostic tests, is very welcome (see section 7.4).

- There is a problem in Europe where many hospitals engage in diagnostic research, typically using a variety of culture methods, but there is no co-ordination on methodology and no consensus on which laboratories should be involved. An integrated process is required to monitor and provide quality control across the EU, a role for the ECDC.

- There are several new diagnostic tests in the pipeline[28] including the culture-based tests to identify *M. tuberculosis* and determine drug resistance and molecular assays to detect antigens or DNA from the TB pathogen and the patient's immune response. However, there is a concomitant need to ensure that new tests can be used in resource-poor settings where there may be lack of technical expertise and equipment and greater potential for false positives.

- For the future, there are also promising non-invasive approaches, in particular: (1) the molecular assay of *M. tuberculosis* DNA fragments in urine; and (2) the measurement of volatile biomarkers of TB in the breath (volatile organic compounds generated by mycobacteria or the oxidative stress resulting from infection, for example, as documented by Syhre and Chambers (2008)).

- Biomarkers of TB should also be exploited in due course for development of: (1) a diagnostic test which differentiates between latently infected healthy individuals and patients with active TB; (2) a prognostic test which allows prediction of the risk of TB outbreak in latently infected individuals; and (3) a diagnostic test serving as surrogate endpoint of disease for monitoring drug and vaccine trials in TB. The basis for these novel diagnostic measures will be biomics, comprising metabolomic, proteomic and transcriptomic profiles in a custom-made biosignature (Kaufmann and Parida 2008).

6.5 Developing novel vaccines

The attenuated live BCG vaccine does not provide adequate protection against pulmonary TB, particularly in adults. Therefore it has limited use in controlling the transmission of TB. The current state of vaccination policy

[27] July 2008, output from a research collaboration between FIND and South Africa's National Health Service and Medical Research Council (www.scidev.net/en/news/powerful-new-tool-to-diagnose-drug-resistant-tb.html). Further details on the background to the development of this novel diagnostic are provided by Nantulya (2008). A recently announced collaboration between FIND and the American Society for Microbiology, capitalising on the latter's International Capacity Building Program (footnote 11) will help with training and technical assistance to progress diagnosis and service integration in resource-poor settings.
[28] www.bvgh.org/resources/landscape/default.asp

for TB varies across the EU. Member States take differing views on whether BCG should be used as a universal vaccine in the newborn. Some countries now focus instead on high-risk populations (for example, migrants).

The Working Group advised that the priority is not to focus only on the protective effect of novel vaccine candidates but also on their delivery route, formulation (to enable appropriate storage, shelf-life and global distribution) and use for HIV-infected individuals, particularly children. Several products, most originating in Europe, are now in the vaccines pipeline after a long period of relative neglect in R&D. The furthest advanced is MVA-85A in phase II of clinical development, offering a prime-boost strategy with BCG. Three other products are currently in phase I (72f, Hybrid 1, Aeras 402),[29] each representing R&D collaboration between the public and private sectors.

Several other candidates are at the pre-clinical phase of evaluation, including ones from the Framework Programme 6 projects TB-VAC (New Vaccines against TB) and Muvapred (Mucosal vaccines for poverty-related diseases), where some valuable progress has been achieved. For example, mutation of virulence genes produced a TB strain potentially conferring greater protection with fewer side effects than BCG (Martin et al. 2006). There is the encouraging prospect of an improved, recombinant, BCG vaccine with higher efficacy and better safety profile (Grode et al. 2005), currently in a phase I clinical trial[30].

Current vaccine candidates are aimed for administration pre-exposure with *M. tuberculosis.* However, with one-third of the world's population already infected, there is an urgent need for a post-exposure vaccine to prevent re-activation. Moreover, current vaccines can delay TB outbreak but do not achieve sterile eradication. There is, therefore, continuing need for a vaccination strategy that achieves sterile eradication or prevention of infection.

Increasing optimism for a new generation of vaccines can only be sustained if policy-makers act to tackle the barriers to development in a concerted way. Many of these barriers are not specific to TB. Table 2 presents conclusions from previous EASAC work on vaccine policy more generally. Recommendations for action by the European Institutions must be accompanied in many cases by action in the Member States.

A detailed global perspective on the regulatory issues for new TB vaccines has been published by Brennan et al. (2007), which provides recommendations to redress the current absence of a clear global regulatory pathway. Global mechanisms are needed for sharing both product and clinical review. There is also an increasing role for the European Medicines Agency (EMEA) (with the US Food and Drug Administration (FDA)) to share its broad experience in vaccine development to provide global leadership in strengthening regulatory science skills and regulatory authority capacity in developing countries.

It is worth noting that many of the routes to tackling the obstacles in vaccine R&D are also applicable in principle to tackling the obstacles in therapeutic drug R&D (see section 6.6). We suggest that the previous interest

Table 2 Addressing market failure: options for promoting innovation for novel vaccines and drugs

Proposed action (European institution)	**Vaccines (EASAC 2006)**	**Therapeutics (EASAC 2007a)**
Legislative (Parliament, Commission, Council of Ministers)	Promoting patent and liability protection; new incentives for vaccine manufacturers, SMEs	Promoting patent and liability protection; guaranteed market commitments; SME support
Regulatory (European Medicines Agency)	Streamlining processes, including fast-tracking; building regulatory authority research role	Simplification of requirements; priority review status; encouraging innovative clinical trial design and partnership
Funding agency (Commission)	New research on immunity, correlates of protection, molecular epidemiology, modelling; augmenting research infrastructure and collaboration with developing countries	New basic and translational research; new funding models for public-private partnership; quantifying economic and public health burden of disease
Surveillance (ECDC)	Collecting standardised statistics; taking longer-term perspective; building interface between human and animal infection policy	Strengthening epidemiology evidence base; support for standardised methodology; increased horizon scanning to prepare for future needs
Training and skills (Commission)	Providing next generation of researchers and public health scientists	Rebuilding expertise in medical microbiology
Public engagement (Parliament, Commission)	Articulating value of vaccines to counter anti-vaccine lobbies and promote vaccine uptake	Using social sciences to understand public attitudes, expectations, behaviour

[29] Status May 2008 as assessed by BioVentures for Global Health (www.bvgh.org/resources/landscape/default.asp). Further information on current programmes, their goals, rationale and evaluation, is provided by Hoft (2008).
[30] www.vakzine-manager.de/Tuberculosis_vaccine.169.0.html?&L=1

expressed by global funders in the Advance Market Commitment[31] for vaccines might be extended as an innovative health financing mechanism for TB – new diagnostics and drugs as well as vaccines. We recommend that the G8 countries should consider strategic options for expanding the Advance Market Commitment during the Italian Presidency of G8.

In considering the general applicability of the vaccine recommendations made previously in EASAC reports (Table 2) to TB, the Working Group also noted:

- It is vitally important to evaluate clinical efficacy faster. To achieve this, it is necessary to: (1) do better in identifying and using highly predictive biomarkers as surrogate markers of infection and correlates of immune protection; (2) establish additional clinical trial sites; and (3) grow public support for incentives to attract industry investment.

- There is need to develop the full spectrum of tools and interventions, rapid diagnostics, vaccines and drugs, requiring sustained commitment from both the public and private sectors. It is essential to use all means to tackle the current problem of TB.

6.6 Developing novel drugs

A review by the Global Alliance for TB Drug Development (2007)[32] brought together information on all approved drugs used to treat TB plus other drugs in clinical development and other approved drugs investigated for potential use in TB (for example, thioridazine). The Global Alliance (2008) also reviewed current purchasing, procurement and distribution mechanisms for first- and second-line treatments in representative countries to try to understand the determinants of the future global market. It is predicted that the TB drug market will grow as a consequence of the use of improved diagnostics, increasing case finding, as well as the intended expansion of TB control programmes. However, the dynamics of the TB drug market are complex and the market is fragmented. In particular, in the EU, there is need to do better to ensure uniform regulations and registrations in drug supply such that all second-line drugs used to manage MDR-TB are made available. This is not yet the case, even in some EU-15 countries; without this consistency, it is impossible to implement the lessons learnt elsewhere in best clinical practice.

Given the risk associated with the use of poor quality and counterfeit second-line drugs in circumstances when the standard preparations may be difficult to procure, the European Commission and Member States' regulatory authorities must promote the strictest possible criteria for quality assurance control. The EU should also contribute to global quality assurance mechanisms, for example supporting pre-qualification work, to ensure that the second-line drugs available are of high quality. However, the problem of counterfeit drugs does not concern only the drug licensing authorities but also customs and excise, for example. The European Commission may need better policy co-ordination in this area across the Directorates-General, including closer working between DG Sanco and DG Enterprise and Industry.

There are increasing numbers of drug candidates in the discovery and pre-clinical phases.[33] Desired objectives for new drugs can be summarised as follows: rapidly acting and potent; able to be used in shorter treatment regimens; effective against MDR-TB; safer than existing treatments; able to be co-administered with anti-retrovirals; and easily used in the field. It is also essential to use new drugs appropriately (for example, not to add to failing treatment regimens) in order to avoid the rapid development of resistance to new agents. As the failure of currently available drugs to act on latent *M. tuberculosis* is considered a major factor for the long treatment time of six to nine months, efforts are also being made to develop drugs that act on the latent as well as the metabolically active forms.

Where large pharmaceutical companies are involved in TB research, their activity is concentrated in R&D centres for diseases in the developing world[34] and is often undertaken as part of product development partnerships. For example, GlaxoSmithKline and the TB Alliance renewed their joint TB drug discovery programme (initiated 2004) in 2008.[35] So far, this collaboration has nearly doubled the number of drug discovery projects

[31] www.vaccinesamc.org, based on the new funding model of International Finance Facility for Immunisation, www.iff-immunisation.org.
[32] The Global Alliance for TB Drug Development (TB Alliance) is a not-for-profit product development partnership funded by the Gates Foundation (see footnote 25), other philanthropies and public funding agencies from the UK, USA, Ireland and the Netherlands (www.tballiance.org).
[33] Listed by BioVentures for Global Health (www.bvgh.org/resources/landscape/default.asp), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA 2007) and the TB Alliance (www.tballiance.org/new/portfolio/html-portfolio.php) with further analysis of the TB drug pipeline in www.accessmed-msf.org/fileadmin/user_upload/diseases/tuberculosis/TBPipeline.pdf.
[34] GlaxoSmithKline in Tres Cantos, Spain (started 2002), Novartis in Singapore (started 2002), AstraZeneca in Bangalore, India (started 2003) and Eli Lilly in Seattle, USA (started 2007) (www.ifpma.org/Health/health_tub.aspx).
[35] www.gsk.com/ControllerServlet?appId=4&pageId=402&newsid=1177.

in the TB Alliance pipeline. The EU has also been highly active, and the New Medicines for TB Consortium[36] is confident of delivering at least one new drug candidate by 2010.

One other potential therapeutic option proposed by the Working Group is immunotherapy, designed to up-regulate the patient's own immune responses (Hoft 2008), as part of the efforts to shorten the duration of TB chemotherapy and prevent TB recurrence (WHO 2007). As none of the currently available immunotherapeutic agents has proof of efficacy in TB, further evaluation is required to develop this approach as an adjunct to chemotherapy. Such research would also be facilitated by the use of validated biomarkers: the need to tackle the current bottleneck in the availability of biomarkers is a pervasive theme in progressing novel anti-TB agents (Perrin et al. 2007; Kaufmann and Parida 2008; www.biomarkers-for-tb.net).

Although the resurgence in the TB drug pipeline is promising, and the commitment for joint working between public and private sectors is most welcome, the magnitude of the challenge must not be underestimated. One model used to assess the aggregated probability of new TB drugs forecasts rather low success in the near term (Glickman et al. 2006). It was estimated that the TB Alliance might need 30 compounds entering phase I in order to be confident of generating at least one successful drug. Clearly there is a continuing need to grow the product development partnerships with concomitant attention to building clinical trial infrastructure. As noted previously (Table 2), the range of possible actions that public policy-makers could take to reduce the obstacles in new drug R&D is equivalent in many respects to the actions needed to address the vaccine shortfall.

There is an additional problem: a growing concern that onerous clinical governance procedures for multi-site clinical trials are hindering progress in developing new therapies for TB. The International Consortium for Trials of Chemotherapeutic Agents in TB (INTERTB) recently expressed anxiety about the proliferation of clinical research governance authorities: better co-ordination among local, national and international authorities could reduce the delay in starting clinical trials (Senior 2008). The European Commission is well placed to take a lead in promoting co-ordination to streamline the regulatory and governance environment, in consequence of its sponsorship of the EDCTP. The EDCTP harnesses the efforts of European national programmes in the development of new interventions against TB, investing in clinical trials and supporting human and institutional capacity-building in Africa. Although the EDCTP had been criticised for its slow start, a useful programme of clinical research has now started and more is in prospect (Box 4), including a commitment to help develop the regulatory and ethical framework.

The increasing momentum now being developed by the EDCTP, in funding research to identify simpler, shorter drug regimens, to promote capacity development and to translate research into global policy, is welcome. There is room for a bigger future role for the EDCTP if EU national TB research programmes can be better co-ordinated (see section 6.3) and if all Member States, including the newer ones, become part of the EDCTP. Although it may not be appropriate at this time to consider expansion of the remit of the EDCTP beyond Africa, the Working Group noted that there is also need to find mechanisms to stimulate collaborative research between the EU (including the newer Member States) and other Eastern European countries where the MDR-TB problem is greatest.

Box 4 The EDCTP and TB research: a new coalition for effective action?

So far, TB clinical trials have been funded in nine African countries.

- Trials have included: use of biomarkers to predict outcome of therapy; evaluation of moxifloxacin and comparison with rifapentine; determining optimal doses of anti-retroviral and anti-TB medications used in combination and examining drug-drug interactions.
- Site preparedness and capacity-building is underway for TB vaccine trials for neonates, adolescents and high-risk populations.
- Between 2008 and 2010, the EDCTP expects to spend €9 million on phase II-III vaccine trials and €14 million on improved, shorter TB therapies plus further funding of infrastructure, training and development of a regulatory and ethical framework.

EDCTP Fact Sheet 'EDCTP joins the world in stopping TB', March 2008 (www.edctp.org)

[36] www.nm4tb.org.

7 Raising awareness, building global effort

7.1 The opportunity for shaping knowledge

If the public health challenges of TB are to be tackled effectively then, in the opinion of the Working Group, it is imperative to raise the visibility of TB as a priority for Europe. This requires action to communicate to medical professionals, politicians and the public. Although the specific actions needed to serve these audiences will vary, what they have in common is the opportunity for the scientific community to be more proactive in describing the current threat posed by TB, its causes, and the potential future impact if drug resistance is not managed effectively.

New effort in communication and advocacy, marshalling the evidence base to quantify the threat in tangible ways, requires the professional scientific associations (in particular those involved with infectious or respiratory diseases) to work with medical groups and other professionals such as social workers involved with TB patients and communities, to build awareness and disseminate information. One issue that concerns some Member States is 'treatment tourism', whereby TB patients travel across borders for diagnosis and treatment. This can be tackled by ensuring adoption of the consistent standards of care throughout the EU (section 4.4) and support as appropriate to other countries (section 4.2).

7.2 Training medical professionals

Where the incidence of TB is currently low in Member States, medical practitioners are often unaware of it as a modern threat, both in terms of recognising the symptoms and in knowing which are the high-risk countries of origin for drug resistance. This lack of awareness must be remedied.

One weakness in many Member States is the medical curriculum. TB is often taught as a disease of previous centuries, not as a modern threat. There are several levels to the necessary reform to ensure that all health practitioners do the right things in TB care. First, teaching in medical schools and other education provision, in public health and nursing for example, should adopt a uniform, common set of teaching standards for TB, ranging from basic science to clinical and disease management. Secondly, relevant retraining programmes for graduate workers should always cover TB. Thirdly, all medical and nursing societies should formally adopt the International Standards for TB Care (Hopewell et al. 2006) and promote them among their members (see section 4.4).

The recent initiative by the World Medical Association[37] to expand training courses for physicians on MDR-TB to refresh the basic knowledge on standard TB management is a welcome new tool. However, it is important to be clear that training may be just as necessary for physicians in the EU as in developing countries.

7.3 Engaging with the public

The European public is not sufficiently informed about the danger of TB and its drug-resistance. This lack of awareness has implications, for example, for international travel. Tourists and other travellers are usually warned about the risks of malaria, typhoid and some other diseases when visiting certain countries, but not about the risks of drug-resistant TB although, arguably, that may represent a greater threat in some destinations or during travel (section 5.2).

One of the impediments to raising the public profile is that TB has a 'poor image': it is perceived as a disease of developing countries, or is associated with stigmatised groups in the population, and as a chronic disease where immediate action is not important by contrast, for example, with HIV and SARS. Apart from this issue of stigmatisation, in many countries there is often lack of public awareness of the significance of the principal symptoms of TB and of the freely accessible healthcare available. It is imperative that the scientific community does more to correct misconceptions about TB.

Notwithstanding some excellent advocacy achieved by the International Union against TB and by patients' groups at the national level[38], lessons in better articulating the threat of TB can be learnt from the experience of other patients' interest groups: for example, the power of celebrity endorsement. In this context, the support of the celebrity Portuguese footballer Luís Figo in the Stop TB Partnership[39] is valuable, perhaps particularly so because an interest in international football involves extensive travel by supporters that may expose them to unexpected risks of drug-resistant TB. Generally, the definition and quantification of risk of communicable disease associated with attendance at large-scale events

[37] www.wma.net/e/press/2008_5.htm
[38] For example, the charity TB Alert in the UK (www.tbalert.org), started a decade ago in response to the resurgent threat of TB.
[39] www.stoptb.org/figo.

warrants further study so that the community-at-large can be appropriately informed[40].

7.4 Supporting informed political leadership and collaboration

Advocacy activities in communicating to society-at-large are also relevant to raise awareness of policy-makers in the European and national parliaments and in other European institutions. At the global level, the excellent work done in high-level advocacy by former Portuguese President Jorge Sampaio, the UN Secretary-General's Special envoy to Stop TB (Sampaio 2007), has contributed to political awareness. Archbishop Desmond Tutu has also been a powerful advocate[41].

However, it is noteworthy that despite the considerable efforts made to generate and publicise the Berlin Ministerial agreement (section 3.1), the Declaration did not actually attract much attention and little appears to have transpired in Europe in consequence. The potential for impact of Ministerial Declarations might be augmented by incorporating the experience and motivation of TB community groups. The recent 'Offer of Partnership from Civil Society to Ministers of the European Region'[42] could represent a significant advance in developing critical mass for communicating key messages. The All-Party Parliamentary Group on TB in the UK[43] also represents a useful model for the scientific community, with other stakeholders, to inform political awareness. Such efforts might usefully be emulated in other national parliaments and the European Parliament.

TB remains underfunded and the problem of low visibility has been compounded, until recently, by poor political commitment. However, this situation is changing for the better. The re-invigorated WHO approach mediated through the Stop TB strategy deserves additional support, not just to increase funding – although Stop TB has inadequate resources – but to accelerate the momentum in thinking about the use of new technology (see section 6.3) and to provide the champions to inform society about TB.

As discussed previously, the EU should not see the issues for TB control only in terms of its own borders. TB must be recognised as an issue in EU strategies for social cohesion and poverty reduction developed for the European Neighbourhood Policy (ENP).[44] In the opinion of the Working Group, it is now necessary to move forward from initial recognition of the public health capacity issues within ENP (ECDC 2008) to concrete action.

A recent analysis demonstrating the perverse outcome of International Monetary Fund (IMF) economic programmes, associated with increased TB incidence, prevalence and mortality rates in post-communist countries (Stuckler et al. 2008), challenges the general proposition that all forms of economic development necessarily improve public health. It is important, therefore, for national and international decision-makers to take into account possible direct and indirect impacts on the management of disease when developing their policies across a broad spectrum, particularly if seeking efficiency gains in government expenditure, in order to avoid unintended consequences on public health.

The goal for increasing global coherence must also take account of the need to establish linkage with other disease programmes, especially HIV, within integrated health systems. To achieve the new policy coherence and avoid the previous problem of multiple initiatives proceeding without effective co-ordination, there must be still better interaction between the EU, WHO, G8, World Bank, IMF, Gates Foundation, UNAIDS,[45] the Global Fund to fight AIDS, TB and malaria,[46] and other stakeholders to drive the shared agenda. The recently formed H8 International Health Partnership[47] may help to increase the momentum for action. A recently proposed European Council on Global Health (Kickbusch and Matlin 2008) might form one basis for the wider international alliance. The European biomedical research and public health communities have key roles to play in developing the validated evidence base and best practice that will inform and guide the policy development.

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[40] For example, some interesting information has been collected to show that respiratory infections (including TB) are the commonest illnesses encountered at the Hajj pilgrimage, an event that has been used to study the potential of pandemic spread of disease during mass migration (Rashid et al. 2008). *M. tuberculosis* was found to be the most common pathogen identified in community-acquired pneumonia during the Hajj, and a study of Singaporean pilgrims revealed that 10% of the group had a substantial rise in TB antigen after the Hajj. This threat of TB is compounded by the finding that the prevalence of drug-resistant TB is up to three times greater in Mecca and Medina than the Saudi national average (these results are discussed in detail in a review by Ahmed et al. (2006)).

[41] www.stoptb.org/events/world_tb_day/2001/News-2001EN.html

[42] www.tbnetwork.eu

[43] www.appg-tb.org.uk

[44] German Presidency Progress Report 'Strengthening European Neighbourhood Policy', General Affairs and External Relations Council, June 2007 (www.eu2007.de/en/News/download_docs/Juni/0628ENP/ENP_en07.pdf).

[45] www.unaids.org

[46] www.theglobalfund.org

[47] www.internationalhealthpartnership.net

8 Building momentum in science and policy

8.1 Clarifying the strategic framework

Adequate TB care requires robust health systems in terms of the infrastructure for proper surveillance, laboratory analysis and access to primary care for all, including vulnerable groups. As described previously in this report, there is need to accumulate better evidence, to inform policy to develop health systems, across a broad front including the introduction of new diagnostics and the management of the challenges presented by an increasingly mobile population. We concur with one of the key points made in the recent independent assessment of the Stop TB Partnership (Anon 2008): that there is more to be done to collect and analyse data in order to identify the biggest opportunities for progress. It is also vital that policy-makers do not isolate TB policy from other public health issues in Europe, not least because other public health threats may also serve as risk factors for TB: for example non-communicable diseases such as diabetes, smoking and alcohol abuse as well as communicable diseases such as HIV/AIDS.

The assessment of the impact of the Stop TB Partnership (Anon 2008) judged that success has been achieved in terms of the funding that has enabled the progression of a new generation of candidate drugs, vaccines and diagnostics and in terms of the increasing international political focus on TB such that it is now a routine agenda item on G8 Summits. European TB policy issues cannot be isolated from the global context, and the EU must be part of a strong, internationally co-ordinated effort to combat the global impact of TB. In finding ways to build the momentum to secure the prioritisation of TB in global health policy, it may be useful to apply the recent analysis by Stuckler and McKee (2008) that interprets health policy as metaphors. Adapting this approach to TB policy reveals a broad range of interested parties, according to the metaphor:

- Global health as foreign policy (covering trade issues, alliances and the exertion of political influence) – a priority for Member State governments, the European Commission and Parliament.
- Global health as security (protecting the European population) – a priority for ECDC.
- Global health as charity – a priority for the philanthropies.
- Global health as investment – a priority for the World Bank, IMF and the private sector.
- Global health as public health – a priority for WHO and the NGOs.

The Working Group also emphasised the overarching objective of 'Global health as a human right', established by the Alma-Ata Declaration[48] in 1978.

Policy proposals that do not take account of each of the metaphors risk being marginalised by public policy-makers. As Stuckler and McKee observed, '*Now the challenge is to build a coalition that embraces the principal metaphors being used, explicitly aligning the pursuit of public health with foreign policy, security, charity and investment and when contradictions emerge, exposing and dealing with them.*'

A pervasive theme of the EASAC recommendations is that the EU contribution to coherent global policy objectives must be indissolubly linked with the public health objectives for the EU population and its immediate neighbourhood. In seeking to add value to what is already being achieved by other expert groups, the EASAC recommendations focus both on tractable opportunities for early action and on areas where the evidence base needs strengthening in order to inform subsequent policy development. In both cases, we aim to identify where activity at a national level will complement and augment activity at the European and global levels. We believe that the issues we cover in our recommendations in the present report (and, where indicated in this report from the previous work (EASAC 2006, 2007a, 2007b, 2008)) are important to a wide range of interested parties (Table 3).

Table 3 Targeting EASAC recommendations

Objectives	Who is responsible at the institutional level?
Data collection	Member States, ECDC, WHO, DG Sanco, DG Research
EU strategy in a global context	European Commission,[49] ECDC, WHO, EDCTP, Council of Ministers, European Parliament
Raising awareness	DG Research, DG Sanco, Council of Ministers, European Parliament, European Economic and Social Committee, NGOs, WHO and Stop TB Partnership
Investing in research	Member States, DG Research, Philanthropies, Private sector companies
Promoting innovation – diagnostics, drugs and vaccines	DG Research, DG Sanco, DG Enterprise, EMEA, EDCTP, Philanthropies, Private sector companies, WHO, FIND, Aeras, Global Alliance for TB Drug Development

[48] 'Health for All' on www.who.int/hpr/NPH/docs/declaration_almaata.pdf.
[49] DG Research, DG Sanco, DG Development and Humanitarian Aid, DG Justice, Freedom and Security, DG External Relations and European Neighbourhood Policy.

8.2 EASAC recommendations

Strengthening TB data collection across the EU

(1) EASAC welcomes the continuing commitment by ECDC and the WHO to build comprehensive strategies to tackle drug-resistant TB and to develop an increasingly effective working relationship; it is also important to continue to find ways to involve the wider scientific community in advising on the new opportunities coming into range in consequence of scientific progress.

(2) The procedures for collating and reporting of national surveillance data to the ECDC warrant strengthening, although this may raise broader issues relating to the degree of responsibility allowed to Community governance in public health. What can immediately be capitalised on is the opportunity to use standardised methodologies for more consistent generation and sharing of drug sensitivity testing and typing data within the public health sector, informed by agreement on the minimum data set needed for case definition. There are implications for the organisation of Reference Laboratories across the EU and the networking between centres of excellence: one option is to create regional Reference Laboratories with the expertise in molecular epidemiology to facilitate standardisation of analysis and exchange of data.

(3) It is also now opportune to determine how best to build international databases of genotypic and phenotypic information to improve understanding of the relationship between molecular variation and clinical consequences, including exploration of the historical and geographical origins of outbreaks. The objective is for database systems to have interactive and user-oriented interfaces to make full use of the information in the database. For this utility to be achieved efficiently, it is essential to develop and adopt diagnostic methods that are consistent, reproducible and comparable between laboratories. Such efforts must take advantage of advances in sequencing technology and bioinformatics to build powerful, integrated systems. Sequence-based diagnostic tools provide an excellent example of how a rapid diagnostic method is combined with precise data output in the form of mutation profiles that can directly and automatically be contributed to network databases, which are accessible for both country-level and Europe-wide surveillance as well as by the individual clinician treating a patient.

EU strategy in a global context

(1) The ECDC and its partners must clearly define strategies for control of TB and MDR-TB in all settings, and disseminate guidance on standards of care consistent with international recommendations (Box 2). The disease-specific focus on TB must be made an integral part of the broader European development of the capacity of health systems.

(2) There is a responsibility to help develop TB laboratory services in neighbouring countries: investing in physical infrastructure and training and in the provision of continuing assistance to maintain quality control. The scientific community in the EU should consider the options (for example, as pioneered by the American Society for Microbiology in partnership with the CDC and FIND) for providing their services as laboratory and research personnel to neighbouring countries, and globally. A shared focus on improved diagnosis could usefully be accompanied by investment in research to improve understanding of the determinants of micro-epidemics and provide new routes to their control, for example by improved physical design of care facilities.

(3) The EU must continue its commitment to partnerships for data collection and TB management in developing countries: this may require the contribution of training in project management as well as in health research methodologies. The EDCTP should be encouraged to fulfil its potential to support innovation, as part of an improved co-ordination between the funding agencies of Member States.

(4) When considering the public health impact of migration to the EU, it is important to resolve uncertainties in current TB screening procedures. Policy-makers need to understand that diagnosis can only be part of an integrated strategy that includes care and treatment, irrespective of legal status of the individual. Research on TB epidemiology in Member States will benefit from genotyping of archived samples in the migrant countries of origin, to clarify the history of drug resistance. Public health in the Member States will benefit from efforts to improve the health of vulnerable populations worldwide.

(5) To understand the potential impact of air travel on drug-resistant TB transmission, there needs to be better resourced and better co-ordinated data collection to strengthen the evidence base and support decision-making in public health and to better inform politicians and the community-at-large.

Raising awareness of TB as a public health issue

Many medical practitioners in the EU lack awareness about TB. It is important to inform them better at all levels: in their initial training, in retraining programmes, and in supporting the uniform adoption of standards for TB care. The scientific community has important roles to inform the healthcare workforce and to support concerted, informed advocacy among the community-at-large and with politicians. There are already opportunities for the scientific community to

exercise these roles through the Stop TB Partnership (Box 2) and the ECDC Framework Action Plan (ECDC 2008). We suggest that DG Research should further consider the options for encouraging scientists in these communication efforts.

Support for new research

(1) New models for TB research support in Europe are required to identify and agree priorities and direct an increasing level of investment. More funding by some Member States and more co-ordination of that funding within the EU is essential: we suggest that these are issues to consider within the broader development of the European Research Area. More must also be done to identify new models for European Commission R&D subvention – to allow sustained funding targeted to societal priorities ('Grand Challenges') and to provide the means for collaboration between the R&D funding sectors – within the timescale of preparing for the next Framework Programme. Funding options to encourage the development of multidisciplinary infectious disease research centres should be considered further.

(2) Although it is not the purpose of the present report to specify TB research priorities, it is clear that there is both the research opportunity and the societal need to do more in fundamental microbiology and in several key areas relating to TB transmission and public health impact, as follows:

- Characterising the determinants of TB strain resistance and fitness, including infectivity, growth and transmissibility.
- Exploring host-pathogen interactions in order to understand why only a small proportion of infections progress to clinical disease.
- Understanding the biological mechanisms of pathogenesis and protection as a basis for design of novel vaccines, and characterisation of biomarkers from the systems biology perspective.
- Identifying biomarkers of disease activity, drawing on advances in genomics, transcriptomics, proteomics and metabolomics.
- Evaluating the socio-economic consequences of emerging drug resistance and of public health control measures, including immunisation strategies. This requires both continuing research to assess the epidemiological impact of treatment and the further exploration of the range of monetary values to be assigned to reduction in morbidity and mortality in Member States.
- Improving mathematical modelling, forecasting and simulation techniques to compare future scenarios for disease trends and the impact of control strategies.
- Instituting population studies with other clinical and translational research to evaluate current practice and inform better clinical decision-making, ensuring the inclusion of newer Member States in this collaborative research.
- Assessing the determinants of the rapid emergence of drug resistance.

Support for innovation

(1) *Novel diagnostics and biomarkers of protection*
Significant progress has been made as a consequence of the activities of the Stop TB Partnership and the new funding streams described previously. It is important to maintain the momentum, as follows:

- By encouraging R&D, applying recent advances in generic detection technologies to develop cheaper point-of-care testing and by better co-ordination in the development and use of testing methodologies between Member State public sector laboratories.
- By continuing to grow public–private partnerships for development of novel diagnostic agents and their application in TB control programmes. There is a continuing challenge to face in translating the outputs from R&D into clinical practice at the local level and it is vital that the scientific community persists in encouraging the efforts of WHO to embrace new technology, when it becomes available in validated form.
- By capitalising on new scientific discovery to ascertain the promise of novel, non-invasive, diagnostic approaches.
- By optimising the performance of the older testing methods in parallel with the development of novel diagnostics.

(2) *Novel drug regimens and immunotherapy*
The recommendations in the EASAC report on 'Tackling antibacterial resistance in Europe' (EASAC 2007a) provide the broad context for addressing issues both for the optimisation of current treatment regimens and for the discovery of novel approaches to the treatment of TB. It remains hugely important to minimise the current impediments to innovation for both large pharmaceutical companies and smaller biotechnology companies, by facilitating public–private partnerships and by rationalising regulatory requirements to encourage development without compromise to drug safety or efficacy.

In addition to attending to the array of measures listed in EASAC (2007a) and to clinical governance issues associated with a proliferation of regulatory authorities (see section 6.6), there are specific issues relating to

current TB treatment regimens that require urgent solution, as follows:

- Resolving inconsistencies in the regulation of TB drug supply and quality assurance across Europe that impede the availability of second-line drugs.

- Clarifying and tackling problems of drug interaction in HIV–TB combination therapies.

- Using the growing knowledge about drug resistance to design better future drugs, for shorter and simpler treatment regimens that may be able to counteract resistance development. It is important to consider new approaches to public-private partnership to ensure the optimal interaction between public sector and private sector researchers in communicating and capitalising on new research findings.

(3) *Novel vaccines*
The recommendations in the EASAC report on 'Vaccines: innovation and human health' (EASAC 2006) provide the broad context for the current use of BCG vaccine and for the pursuit of novel approaches. In addition to the necessary strengthening of fundamental research to discover pre-clinical candidate vaccines and progress them to clinical evaluation, it is vitally important to improve clinical trial capacity (and incorporate new biomarkers and endpoints), to provide incentives to the private sector to develop and manufacture vaccines, and to better communicate the value of vaccines so as to promote uptake.

There is merit in further exploring innovative health financing mechanisms, for example by expanding the Advance Market Commitment to cover TB drugs, diagnostics and vaccines. We recommend that the G8 countries consider the options for this during the Italian Presidency of G8.

In conclusion, TB presents a major challenge for public health. However, there are also great opportunities to build on the current approaches to tackling the challenge. As the ECDC has emphasised (ECDC 2008), the best prevention strategy for the control of drug-resistant TB is to ensure the proper management of all TB cases: inappropriate, inadequate and incomplete treatment regimens are key contributory factors in the emergence of drug-resistant TB. Better data collection is needed, with more funding to support research, innovation and implementation, to provide the evidence base, tools and standardised procedures to ensure infection control. For the funding to be used increasingly effectively, and notwithstanding the economic recession, there must be good strategic co-ordination at the global level by building the partnerships for research, healthcare delivery and policy development.

We welcome the growing global political commitment exemplified by forthcoming meetings of ministers and other decision-makers[50]. EASAC and the member academies recognise our responsibilities to catalyse ongoing discussion with all interested parties, both on the nature of the scientific evidence and the scope of the policy agenda.

[50] (1) WHO-organised Ministerial Meeting on TB Care and Control: Addressing MDR-TB and XDR-TB, Beijing, April 2009; (2) Pacific Health Summit on MDR-TB, Managing Global Resistance, Seattle, June 2009.

List of abbreviations

AIDS	Acquired immune deficiency syndrome
BCG	Bacillus Calmette-Guerin vaccine
CDC	Centers for Disease Control and Prevention (USA)
DG Sanco	Directorate-General for Health and Consumer Protection
DOTS	Directly observed therapy short course
EASAC	European Academies Science Advisory Council
ECDC	European Centre for Disease Prevention and Control
EDCTP	European and Developing Countries Clinical Trial Partnership
EFTA	European Free Trade Association
EMEA	European Medicines Agency
ENP	European Neighbourhood Policy
EU	European Union
ESCMID	European Society of Clinical Microbiology and Infectious Disease
FDA	Food and Drug Administration (USA)
FIND	Foundation for Innovative New Diagnostics
GDP	Gross domestic product
HIV	Human immunodeficiency virus
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IMF	International Monetary Fund
IRIS	Immune reactivation inflammatory syndrome
IUATLD	International Union Against Tuberculosis and Lung Disease
LPA	Line-probe assay
MDR-TB	Multi-drug-resistant tuberculosis
NGOs	Non-governmental organisations
NIAID	National Institute of Allergy and Infectious Diseases (USA)
PEPFAR	President's Emergency Plan for AIDS Relief (USA)
SARS	Severe acute respiratory syndrome
SNP	Single nucleotide polymorphism
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

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Appendix 1: Working Group remit and composition

This report was prepared by consultation with a group of experts acting in an individual capacity and was reviewed and approved by EASAC Council.

The Working Group met three times during the period May–December 2008, and a call for external evidence was published in June 2008. The remit of the Working Group was to address EU policy issues associated with drug-resistant TB, including the following: testing procedures; surveillance; public health delivery; support for fundamental research; translation of research into innovation for diagnostics, therapeutics and vaccines; priorities for EU co-ordination and for involvement in global discussion and action. As in previous EASAC work, the goals of the report are to review the relevant science, to clarify the strengths, weaknesses, opportunities and threats in the current situation and potential developments, to indicate where there are gaps and uncertainties in the evidence base and to recommend where EU policy development is needed.

Members of the Working Group

Volker ter Meulen (Chairman)	President of the German Academy of Sciences Leopoldina
Alan Altraja	Department of Pulmonary Medicine, University of Tartu, Estonia
Roland Brosch	Institut Pasteur, UP Integrated Mycobacterial Pathogenomics, Paris, France
Stewart Cole	Global Health Institute, Ecole Polytechnique Federale de Lausanne, Switzerland
Wouter Arrazola de Onate[51]	Belgian Lung and Tuberculosis Association, Brussels, Belgium
Brigitte Gicquel[52]	Institut Pasteur, Mycobacterial Genetics Unit, Paris, France
Alexander Indra	AGES-Institute for Medical Microbiology and Hygiene, Vienna, Austria
Stefan H E Kaufmann	Department of Immunology, Max Planck Institute for Infection Biology, Berlin, Germany
Maria Korzeniewska	National TB and Lung Diseases Institute, Warsaw, Poland
George Kosmiadi	Department of Immunology, Central Institute for TB, Moscow, Russia
Carlos Martin	Department of Microbiology, University of Zaragoza, Spain
Staffan Normark	Department of Medical Microbiology, Karolinska Institute, Sweden
Tom H M Ottenhoff	Department of Infectious Diseases, Leiden University Medical Center, the Netherlands
Pascal Van Bleyenbergh	Department of Pulmonary Medicine, University of Leuven, Belgium
Dick van Soolingen	National Institute of Public Health and the Environment, Bilthoven, the Netherlands
Tuula Vasankari	Department of Respiratory Diseases, Turku University Hospital, Finland
Ali Zumla	Centre for Infectious Diseases and International Health, University College London, UK
Mario Raviglione (Observer)	Stop TB Department, WHO, Geneva, Switzerland
Robin Fears (Secretariat)	EASAC, UK

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[51] Veronique Van de Ghucht represented the Belgian Lung and Tuberculosis Association at the first Working Group meeting.
[52] Brigitte Gicquel was represented at the first Working Group meeting by Catherine Pierre-Audigier.

For further information:

EASAC Secretariat
The Royal Society
6–9 Carlton House Terrace
London SWIY 5AG
tel +44 (0)20 7451 2697
fax +44 (0)20 7925 2620
email easac@royalsociety.org

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