Annex 1a: TB burdens in the expanded European Union (Statistics prepared by Dr W Kaplan, Essential Drugs and Medicines Policy, WHO, Feb 2004)

Total TB Burden (2001)

- Poland
- Spain
- Germany
- France
- United Kingdom
- Italy
- Portugal
- Hungary
- Lithuania
- Latvia
- Netherlands
- Belgium
- Austria
- Czech Republic
- Slovakia
- Estonia
- Greece
- Denmark
- Finland
- Sweden
- Ireland
- Slovenia
- Norway
- Luxembourg
- Malta
Annex 1b: MDR-TB burdens in the expanded European Union
(Surveillance of tuberculosis in Europe. Report on tuberculosis cases notified in 2001; EuroTB (InVS/KNCV); Institut de veille sanitaire, Saint-Maurice, December 2003; p.43)

Table 18. Global drug resistance, all tuberculosis cases, WHO European Region, 2001

<table>
<thead>
<tr>
<th>Geographic area</th>
<th>Country</th>
<th>Cases with DST result</th>
<th>Cases resistant to at least:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Isoniazid (INH)</td>
<td>Rifampicin (RMP)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INH &amp; RMP (MDR)</td>
<td>Ethambutol *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Streptomycin*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A) Culture and DST performed routinely; national data on all notified TB cases / representative sample of TB cases

West
- Austria: 630
- Belgium: 749
- Denmark: 260
- Finland: 410
- Germany: 3,881
- Ireland: 12
- Israel: 104
- Italy: 317
- Luxembourg: 29
- Malta: 10
- Netherlands: 501
- Norway: 214
- Portugal: 436
- Slovenia: 307
- Spain: 3,638

Centre
- Bosnia-Herzegovina: 1,296
- Greece: 801
- Czech Republic: 678
- Poland: 3,741
- Slovakia: 575
- Slovenia: 307

East
- Estonia: 590
- Latvia: 1,090
- Lithuania: 1,452

B) Culture / DST not routinely performed, data on selected cases / areas

West
- France: 1,313
- Italy: 918
- Portugal: 1,163
- Spain: 1,722

Centre
- Albania: 206
- Bulgaria: 293
- Hungary: 369
- Macedonia, FYR: 141
- Romania: 3,058
- Serbia & Montenegro: 389

East
- Armenia: 630
- Azerbaijan: 408
- Georgia: 424
- Kazakhstan: 8,952
- Kyrgyzstan: 699
- Moldova, Rep. of: 1,238

* Data presented if DST results were available for > 90% of cases tested for INH and RMP
† No confirmation that DST results refer only to isolates taken at start of treatment
‡ Only new cases reported for 2001
(Surveillance of TB in Europe, Euro TB: Report on TB cases notified in 2001; KNCV, Institut de veille sanitaire, Saint-Maurice; Dec 2003; p.57)
Annex 2: TB incidence in the expanded European Union (Statistics prepared by Dr W Kaplan, Essential Drugs and Medicines Policy, WHO, Feb 2004)

Austria
Belgium
Czech Republic
Denmark
Estonia
Finland
France
Germany
Greece
Hungary
Ireland
Italy
Latvia
Lithuania
Luxembourg
Malta
Netherlands
Norway
Poland
Portugal
Slovakia
Slovenia
Slovakia
Spain
Sweden
United Kingdom

TB Incidence per 100000

0 10 20 30 40 50 60 70 80 90

Appendices to 6.1-4
Annex 3: Availability of TB culture and drug-sensitivity testing in a sample of developing countries (Statistics provided by Dr Mark Perkins, WHO/TDR and FIND)

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of laboratories performing culture and DST*</th>
<th>DST tests/year*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>76</td>
<td>21,000</td>
</tr>
<tr>
<td>Guatemala</td>
<td>1</td>
<td>?</td>
</tr>
<tr>
<td>Kenya</td>
<td>5</td>
<td>60</td>
</tr>
<tr>
<td>Mexico</td>
<td>3 public (unknown private)</td>
<td>1,426</td>
</tr>
<tr>
<td>Sudan</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Zambia</td>
<td>2</td>
<td>1,000</td>
</tr>
<tr>
<td>Bolivia</td>
<td>1</td>
<td>159</td>
</tr>
<tr>
<td>Turkey</td>
<td>12</td>
<td>395</td>
</tr>
</tbody>
</table>

* Figures for public laboratories come directly from National Reference Laboratories and are highly reliable (in poor countries, the bulk of patients will rely on public sector testing). There may be additional private sector laboratories who are not represented here.
Annex 4: EU-based members of the TB Structural Genomics Consortium

ITALY
University of Pavia – Italy

SWEDEN
Lund University

UNITED KINGDOM
Liverpool JMU
de Montfort University
Daresbury Laboratory
Birkbeck College
University of Leicester
University of St. Andrews
University of Sherbrooke
University of Warwick
University of London
Royal Veterinary College
University of Dundee
St. Jude Children's Research Hospital
University College London
St. George's Hospital Medical School
Manchester University
Imperial College

**BELGIUM**
- Institut Pasteur du Brabant
- IPBS-CNRS
- Institut Pasteur de Bruxelles
- SmithKline Beecham Biologicals

**DENMARK**
- Staten Serum Institut

**FRANCE**
- Institut Pasteur de Lille
- Centre National de la Recherche Scientifique
- Pasteur Serums et Vaccins
- Institut de Pharmacologie et de Biologie Structurale
- Institut Pasteur
- INSERM

**GERMANY**
- Universitat Erlange-Nurnberg
- GBF
- Max-Planck-Institut for Infection Biology
- Med.Hochschule Hannover

**ITALY**
- Institute for Infectious Diseases

**THE NETHERLANDS**
- Biomedical Primate Research Centre
- TNO Prevention and health
- University Hospital Leiden

**NORWAY**
- University of Bergen

**SPAIN**
- Universitat Autonoma de Barcelona
- Universidad de Zaragoza

**SWEDEN**
- Swedish Institute for Infectious Disease Control

**UNITED KINGDOM**
- University of Surrey
- DANI
- BIBSC
- London School of Hygiene and Tropical Medicine
- St. Mary’s Hospital Medical School
- VLA Weybridge
- CAMR
- National Institute Medical Research
- Oxford University
Annex 6: EU-based groups working in TB diagnostics R&D (Information provided by Dr Mark Perkins, WHO/TDR and FIND)

BIOTECH COMPANIES (28, as of 2003)

BELGIUM
Cypress Diagnostics
Innogenetics, N.V.

FRANCE
Ivagen
Anda Biologicals
Amtech
BioMerieux
Vedalab
Sanofi Diagnostics Pasteur

GERMANY
Biotest AG
Lionex Diagnostics
Hain Diagnostika
Behring Diagnostics
Humana Diagnostica

IRELAND
BioResearch
Cambridge Diagnostics

NETHERLANDS
KreaTech

NORWAY
NorChip AS

SPAIN
BioKit

SWEDEN
Pyrosequencing, Inc

UNITED KINGDOM
BioTec Diagnostics, Ltd
Cortecs Diagnostics
Oxford Immunotec
Zetatrionics Ltd
ABP Diagnostics
Quest Biomedical
Rapid Biosensor Systems Ltd.
Omega Diagnostics
Appendices to Chapter: Tuberculosis

NOT FOR DISTRIBUTION OR ATTRIBUTION

Newmarket Laboratories
SmartSensor telemed Ltd
Kherion Limited

ACADEMIC GROUPS

There are many more unlisted groups involved in TB diagnostic discovery research, as opposed to those working in test development, as below:

UNITED KINGDOM
Advanced Computing Research Center, University of Bristol
Cranfield University
Oxford University
University of Leicester
St George's Medical School

PUBLIC INSTITUTIONS

NETHERLANDS
The Royal Tropical Institute (KIT)

FRANCE
Pasteur Institut

IRELAND
National Diagnostics Centre

DENMARK
Staten Serum Institut
Annex 7: EU-based groups participating in TB drug development
(Information collected from the TB Alliance, Stop TB Working Group on New Drugs, and by the author of this paper)

Multinational pharmaceutical companies
Astra-Zeneca (UK)
GlaxoSmithKline (UK)*

Academic institutions
St Jude Childrens Hospital (UK)
St George’s Hospital Medical School (UK): *

Biotech companies and Contract Research Organisations
NIL

Public health institutions (including those supporting clinical trials)
WHO/TDR
International Union Against TB and Lung Disease
European and Developing Countries Clinical Trials Partnership

* These groups are also members of TB Alliance expert committees
Annex 8: Fact Sheet on EU-funded TB research

European Research Area Fact Sheet
EU-funded research in the fight against Tuberculosis
24 March is World Tuberculosis day

The EU has channelled €28 million into TB drug and vaccine research in the last four years, during the course of the Fifth Framework Programme for research and development (FP5), and will be committing significantly more during the course of the current framework programme (FP6). World Tuberculosis day reminds us that this disease is still killing millions of people, mostly in the developing world but also gaining strength in the developed world. We must now combine the knowledge and expertise available in Europe and beyond to eliminate this suffering.

Tuberculosis is a leading infectious killer in the world, causing about 2 million deaths a year, about 98% in developing countries. With the rise in drug-resistant strains of the disease, TB could also, once again, become a major threat to Europe. In the face of this growing epidemic, currently available drugs and the vaccine (BCG) that was developed 70 years ago are proving less and less adequate. New drugs and a more effective vaccine are urgently needed, and the availability of the complete genome sequence of *Mycobacterium tuberculosis* offers new opportunities for developing them. It is in this context that the European Commission has joined battle to beat the disease.

**Vaccine research**

In the Fifth Framework programme (1998-2002) the EC allocated €15 million to vaccine research. The largest single project is the TB Vaccine Cluster (TBVac) that has brought together major public and private research organisations striving to develop new vaccines. With complementary expertise in genomics, genetics, immunology, structural biology and vaccinology, TBVac has successfully established a joint academic-industrial consortium capable of taking tuberculosis vaccine candidates from the laboratory bench to phase I clinical trials. The cluster project is coordinated from the Institute Pasteur in Paris, and involves 38 leading European research groups from 12 different countries, including 2 major pharmaceutical companies (Aventis-Pasteur and GlaxoSmithKline). Within this European framework, a variety of new vaccine candidates have been produced and tested in preclinical studies, with several achieving levels of protection superior to BCG.

In addition to this cluster project, the EU has been supporting complementary TB vaccine projects. Two EU-funded projects are exploring the possibilities of intranasal or oral vaccination as an alternative to intradermal injection. A further two projects are conducting studies in Africa, where TB is endemic. These prepare the ground for future clinical trials, and one will conduct a phase I trial of the first new candidate TB vaccines to enter clinical trials anywhere in the world.
Appendices to Chapter: Tuberculosis

Several more promising candidates should follow. Clinical trials are costly and time-consuming but essential, and the EU has made a strong commitment to supporting them through the sixth framework programme, in particular through the EDCTP initiative. With the aim of continuing the effort to integrate European efforts in developing a TB vaccine, research proposals have been invited for projects to develop TB vaccines up to and including the early clinical trial phase. Subsequent clinical development (phase II and III clinical trials) will be eligible for support through the EDCTP, and there will be an increased emphasis on collaborating with countries where the vaccine is most needed.

Development of new drugs

In the Fifth Framework Programme, the EC awarded €13 million to TB drug research. Several projects are laying the foundations for rational and novel drug design by employing structural and functional genomics, One project already has a "lead compound", an antibiotic that inhibits an enzyme found in TB, and is working on modifying this to produce drugs that more effectively cross the mycobacterial cell wall. In addition, funding has been awarded to projects studying the development of drug resistance, the molecular epidemiology of MDR strains in Europe, and projects to develop faster and more reliable methods of detecting TB infection and the presence of drug-resistant strains. In this latter area, promising advances have been made towards the development of a low-cost marketable kit, and two new methods for the rapid, low-cost detection of drug resistant strains have been developed and published, based on studies in Latin America.

As with the vaccine work, the EC plans to follow-up these past and ongoing efforts with calls for FP6 project proposals, and for bringing the most promising drugs and diagnostics through to clinical application in the places where they are most needed.

Poverty-related diseases in the Sixth Framework programme

Approximately €400m has been allocated to combat TB, malaria, and HIV/AIDS during the course of the Sixth Framework Programme (2002-2006). This is a significant increase compared to FP5, reflecting the positive prospect of being able to help bring the results of promising preclinical studies through clinical trials.

The Sixth FP on poverty-related diseases is focused on two components:

1/ to develop vaccines, drugs and microbicides for HIV/AIDS, malaria and tuberculosis through basic science up to pre-clinical and early human testing (phase I clinical trials) using the two new instruments (network of excellence and integrated projects) which allow a better integration of research efforts across Europe.

2/ to develop new clinical interventions against HIV/AIDS, malaria and TB through a long-term partnership between Europe and developing countries. One of the main goals of the "European and Developing Countries Clinical Trials Partnership" (EDCTP), based on art.169, is to support phase II and phase III clinical trials of promising products in, with and for developing countries. Such large-scale trials have to be conducted in the diseases-endemic countries under local clinical and social conditions, in order to obtain relevant results for the benefit of the population.
Appendices to Chapter: Tuberculosis

The EDCTP is a response to better co-ordinate and increase the impact and efficacy of national research programmes in this area.