Workshop on The Biological Weapons Convention Supporting Global Health: Reducing Biological Risk by Building Capacity in Health Security Oslo, Norway, 18-19 June 2009

Biological Science, Technology and Education in International Cooperative Networks - An Industry Perspective

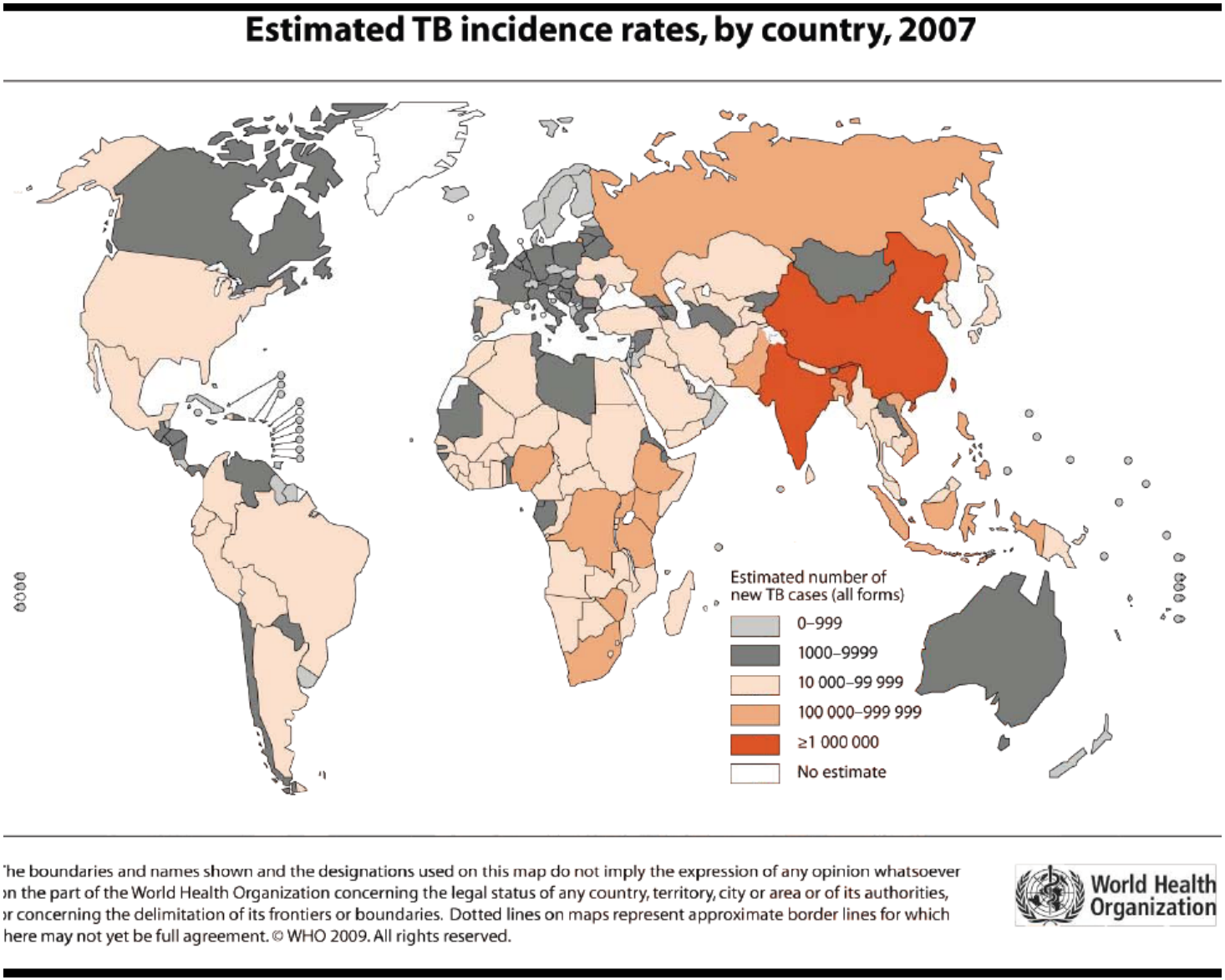
Gary Burns Global Biosafety Manager - AstraZeneca Pharmaceuticals

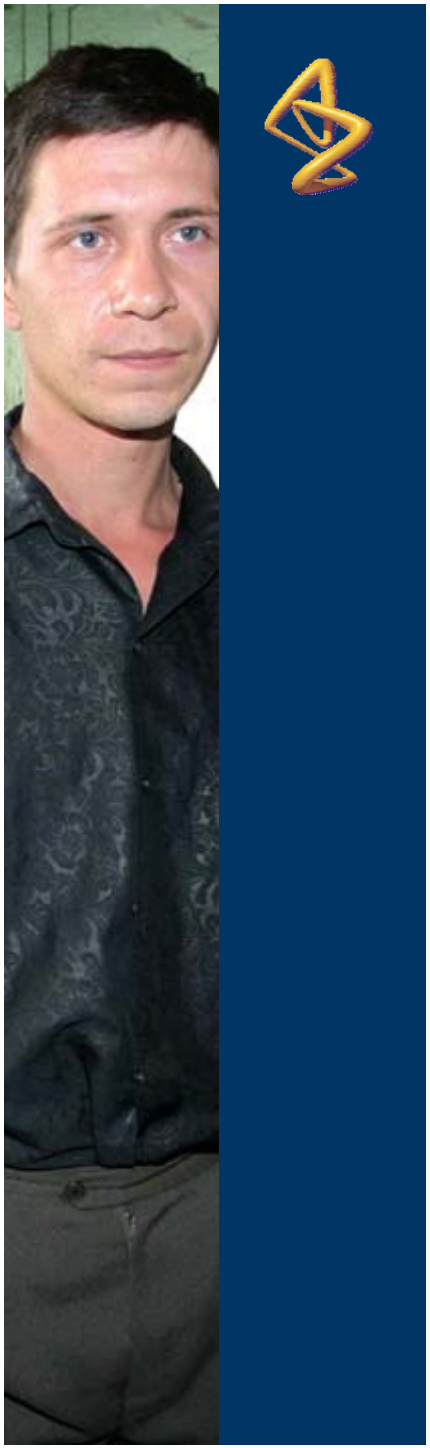
AstraZeneca
life inspiring ideas

Commitment

- AstraZeneca is committed to making a contribution to improving health in the developing world
- Our approach is two-fold:
  - Dedicated research into finding a new treatment for tuberculosis (TB) – a major threat to life in the developing world
  - Helping local communities strengthen their healthcare capabilities
- Integrated into our business strategy – understanding the needs and building important relationships in the markets of the future

Why Tuberculosis?



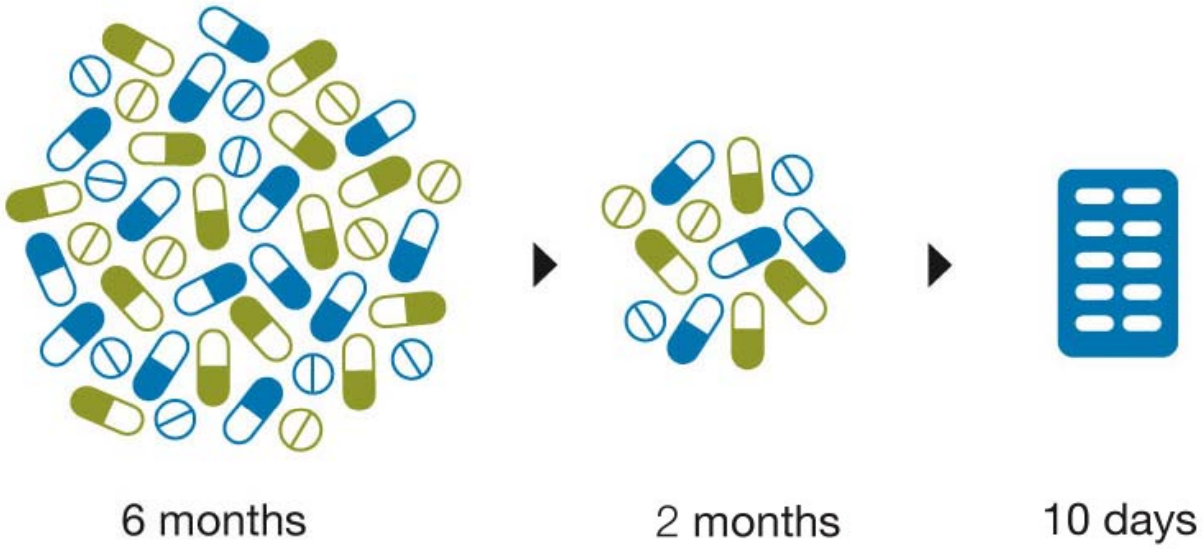


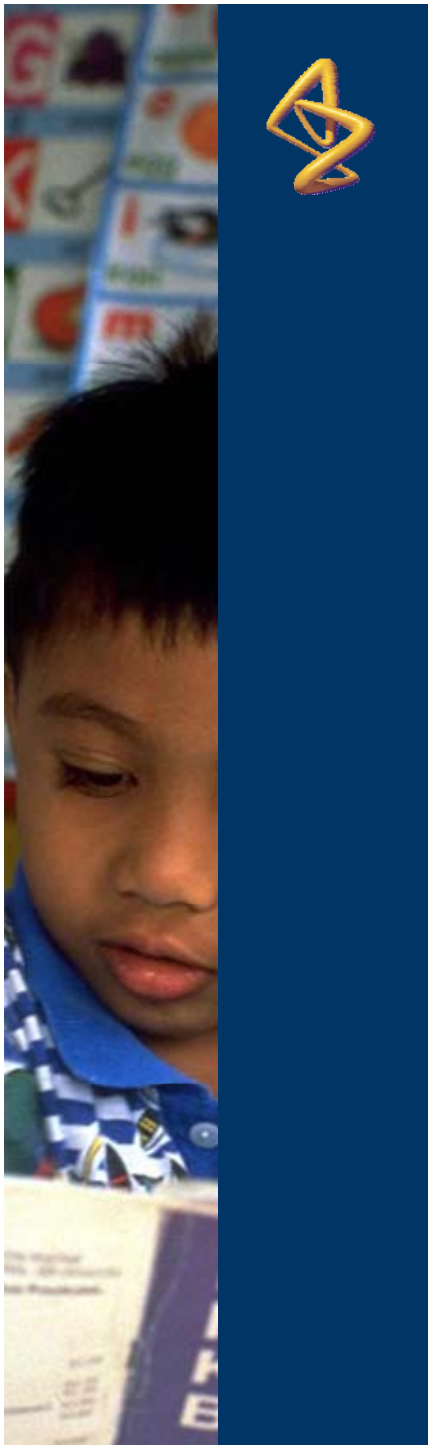
Tuberculosis – current therapy

- Current TB drugs are beginning to fail
  - Drug regimes are complex (up to five different agents) and prolonged (6-8 months)
  - Increasing drug-resistance (MDR/XDR-TB)
- No new drug in the last 40 years
- Novel therapies are desperately needed

Tuberculosis – future therapy

- A shorter TB drug regimen would
  - radically improve treatment and compliance
  - accelerate the reach of Directly Observed Treatment, Short-course (DOTS)
  - allow more patients to be treated cost-effectively





Dedicated research

- We have a dedicated TB research centre in Bangalore, India
- 80+ scientists focused on finding new therapies
- Fully integrated with AstraZeneca's world-wide drug discovery network
- Close collaboration with infection research centre in Boston, US, and with academic leaders in the field

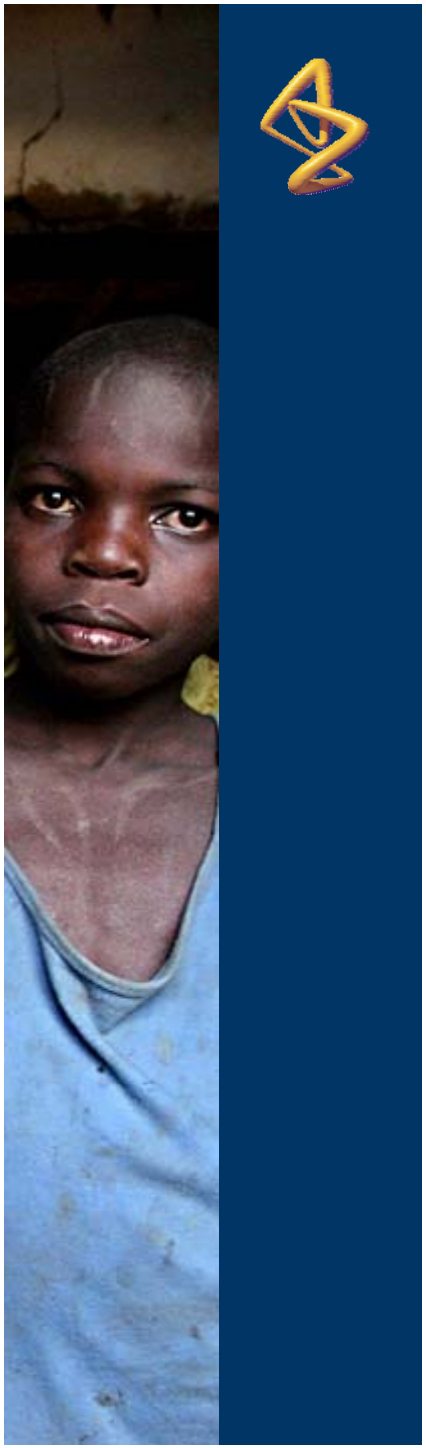
Discovery

- We are focused on finding new therapies that will:
  - Act on drug-resistant strains
  - Shorten the duration of treatment
  - Eradicate disease (including the latent form) to reduce the chances of relapse
  - Be compatible with HIV/AIDS therapies

- Only major pharmaceutical company involved in New Medicines for Tuberculosis (NM4TB) programme
  - Part of the EU Sixth Framework Programme collaboration
  - Enables us to work with Europe's most prominent scientists and researchers on TB

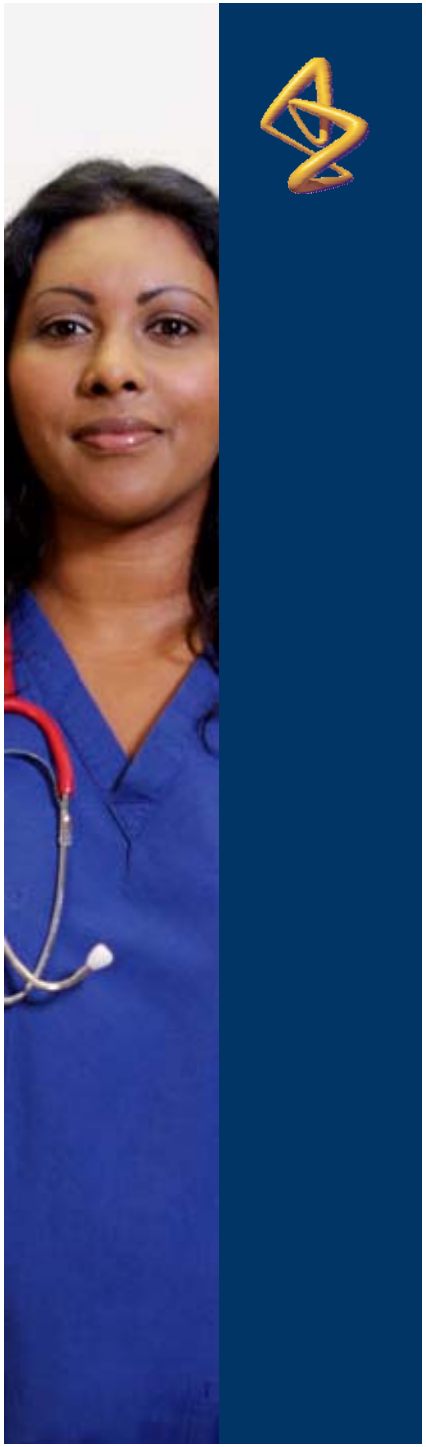
Development

- Potential new medicine delivered by 2010
- Once a CD is identified, we expect development of any compounds discovered by AstraZeneca to:
  - Follow development pathways agreed in discussion with external experts & regulatory authorities
  - Be performed principally in countries with high rates of infection
  - Be performed in collaboration with external groups with relevant expertise
  - Be overseen by AstraZeneca to ensure compliance with global pharmaceutical, ethical and regulatory standards
- We will support industry-wide initiatives to define and simplify optimal development pathways for novel therapies



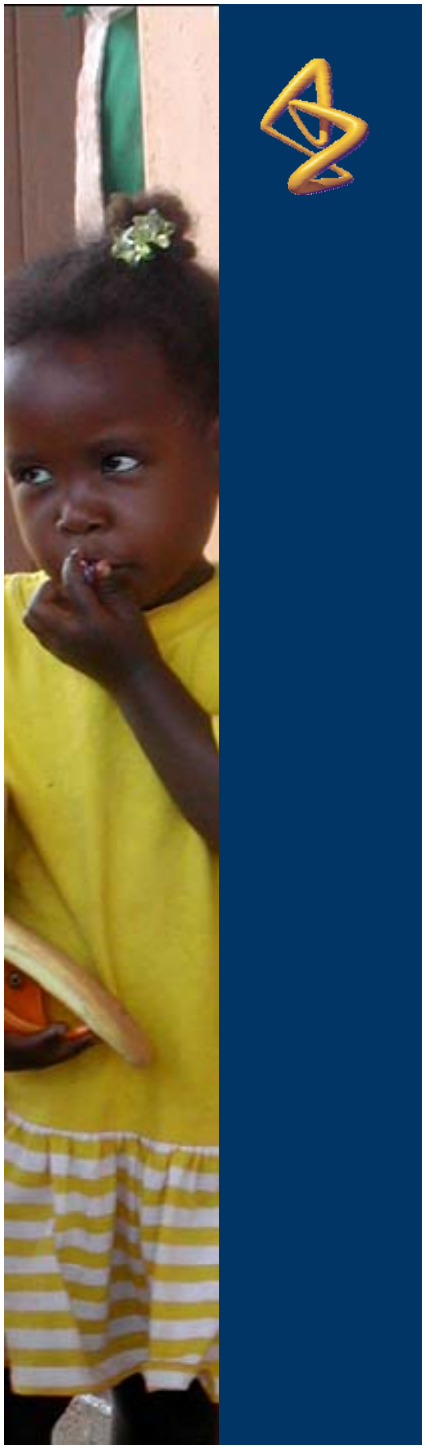
Access

- Access to healthcare and medicines depends on a number of interrelated issues
- We will make any resulting TB therapy widely available in the developing world by use of supply strategies that minimise cost of manufacture and delivery
- We will apply for patent protection in the normal way
- We will seek partnership arrangements with the appropriate global and local organisations to make treatment available at affordable prices to those who need it in the poorest countries.



Beyond research

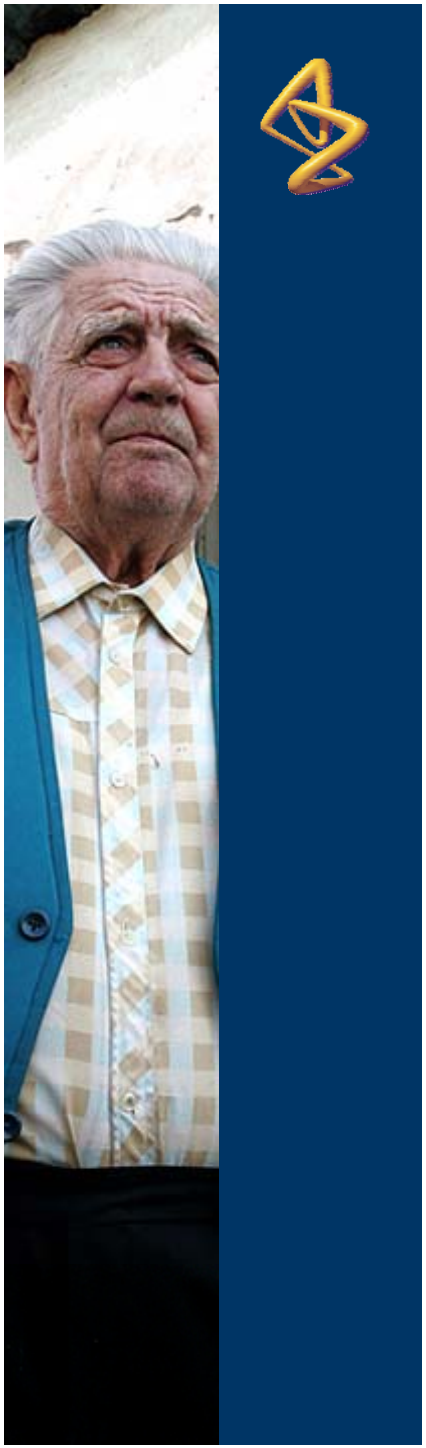
- Alongside our dedicated research we work with NGOs and other partners to help local communities in the developing world to strengthen their healthcare capabilities
- Our partnerships are focused on TB/HIV/malaria and increasingly other diseases that are becoming more prevalent



Community partnerships

BritishRedCross

- Central Asia
  - British Red Cross and the Red Crescent programmes to help local communities combat TB in Kyrgyzstan and Turkmenistan
  - A new programme in Kazakhstan aimed at reducing the incidence of TB/HIV co-infection
  - To date, over 6,000 patients have completed their TB treatment and health education sessions in schools and public places have reached over 750,000 people.
- South Africa and Lesotho
  - Further expansion of the British Red Cross partnership to help local communities combat TB and TB/HIV co-infection



Community partnerships

AXIOS

- Ethiopia
  - A pilot project designed to build local capability in managing breast cancer – second most common cancer
  - Focused on strengthening diagnosis and treatment capabilities in Addis Ababa
  - Started in 2005 and if successful, we hope that it will provide a sustainable model that can be replicated in other countries and disease areas

Community partnerships

VSO
Sharing skills
Changing lives

- Centred on skill sharing to strengthen core capabilities in the developing world
- Two key aspects:
  - Financial and strategic support given to VSO's Health Goal
  - Employees can volunteer for placements in developing countries
    - Using their skills to help build professional capabilities in improving infrastructures
    - Also provides key learning for employees as part of their career development.
- During 2006 and 2007, we funded 17 volunteers working across Indonesia, Cambodia and Sri Lanka

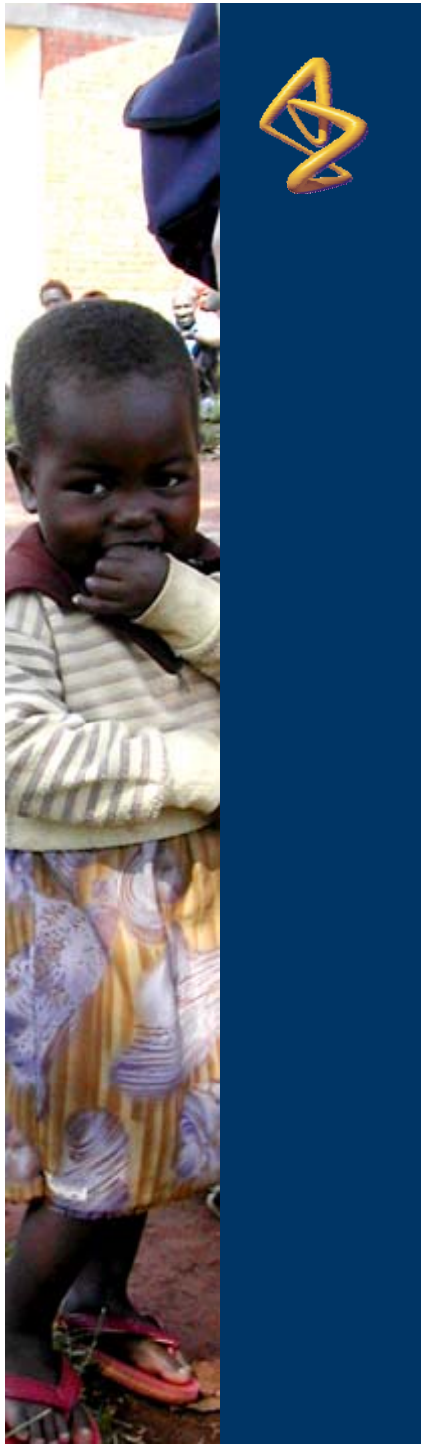
Community partnerships

AMREF
African Medical and Research Foundation

- South Africa
  - TB control and management project to raise community awareness, provide testing, treatment and training for health workers
- Uganda
  - New partnership aimed at strengthening healthcare systems and integrate delivery of TB/HIV/malaria programmes
  - Two programmes are underway to train health workers, improve efficiency and work practices in laboratories and improve health information management systems

Joining forces – international effort

- Organisational partner – support the delivery of Global Plan to Stop TB
- Co-funded Open Forum I - III on TB Drug Development
- Involved in TB drug development working groups and strategy
- Gates Foundation Award for Bangalore



Joining forces – international effort

- Increasing focus on HIV/TB co-infection and role of businesses
- Recognised AstraZeneca as one of top private funders of TB R&D
- Highlights industry initiatives aimed at improving healthcare in the developing world

New Medicines for Tuberculosis - NM4TB

NM4TB

SIXTH FRAMEWORK PROGRAMME

- Introduction
- Participants
- Management
- Scientific Meetings
- Links
- Members' Section

Sixth Framework Programme

New Medicines For Tuberculosis
NM4TB

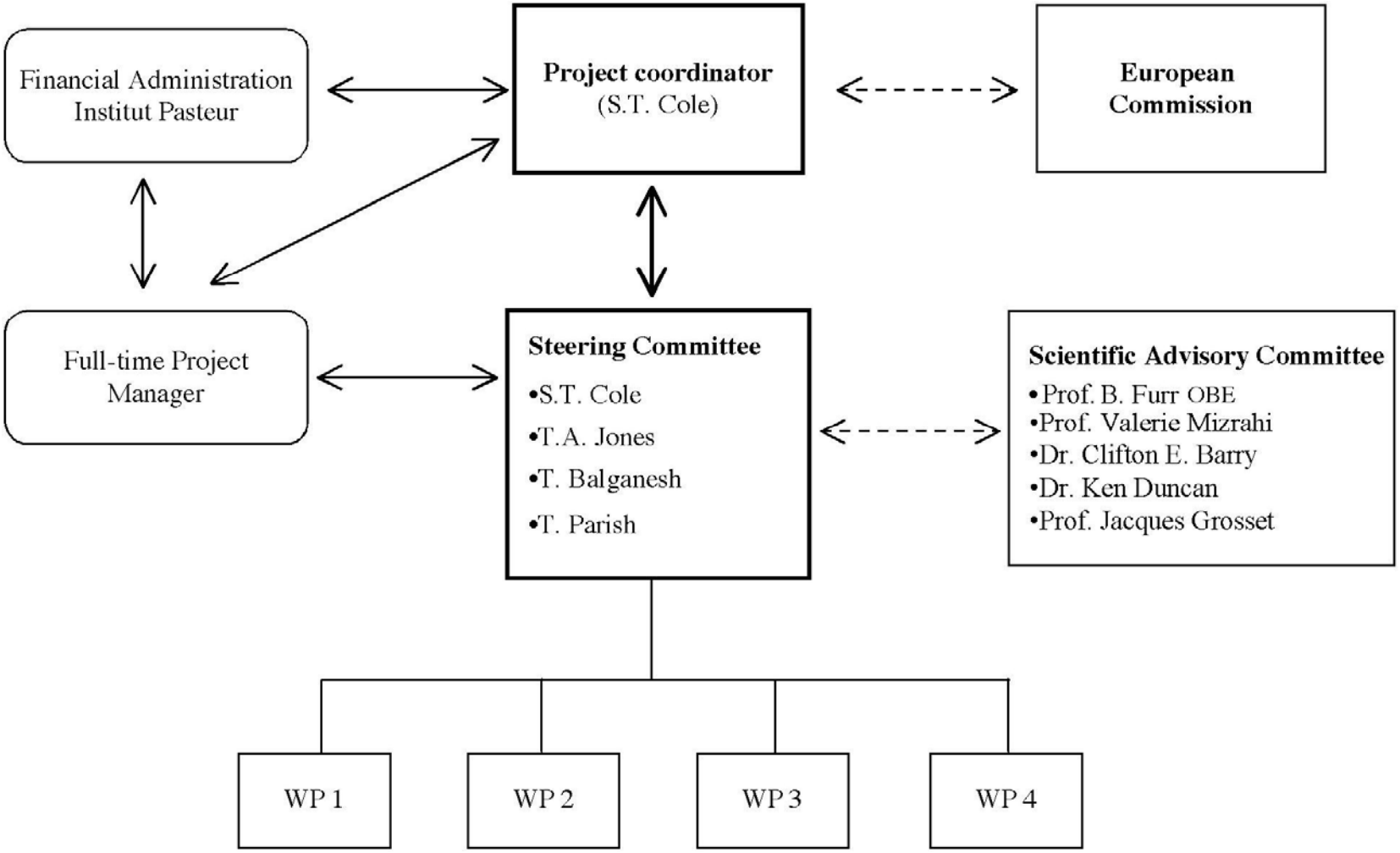
Acronym: NM4TB

Project number: 018923
Requested EC contribution: 10.87 M Euros
Duration: 60 months
Starting date: January, 2006
Type: Integrated project

Summary

New Medicines for Tuberculosis (NM4TB) aims to successfully develop new drugs for the treatment of tuberculosis (TB) through an integrated approach implemented by a team that combines some of Europe's leading academic TB researchers with a major pharmaceutical company and three SMEs, all with a strong commitment to discovering new anti-infective agents. NM4TB has a comprehensive portfolio of potential and validated targets plus several novel, proprietary anti-TB agents in its drug development pipeline. Among the validated targets are several enzymes involved in highly druggable areas such as cell wall biogenesis, nucleic acid synthesis and central metabolic pathways for which assays amenable to high-throughput screening are available. Intensive efforts will focus on rapidly emerging targets that impact upon two as-yet untouched areas of the physiology of *Mycobacterium tuberculosis* signal transduction pathways and persistence.

Management


Financial Administration
Institut Pasteur
Project coordinator
(S.T. Cole)
European
Commission
Full-time Project
Manager
Steering Committee
•S.T. Cole
•T.A. Jones
•T. Balganesh
•T. Parish
Scientific Advisory Committee
•Prof. B. Furr OBE
•Prof. Valerie Mizrahi
•Dr. Clifton E. Barry
•Dr. Ken Duncan
•Prof. Jacques Grosset
WP 1
WP 2
WP 3
WP 4

Partnership

ACADEMIA

IP, CNRS, France
Cambridge, Manchester, QMC,
SGHMS, London, UK
Comenius University, Slovakia
HKI, Jena, Germany
SSI Denmark
Uppsala Sweden
Pavia, Padua, Milano Italy
EPFL, UZ Switzerland
SCRA, Moscow, Russia

BIG PHARMA

AstraZeneca India

SME

NeED Pharma Italy
Vichem Hungary

ENDEMIC COUNTRIES

CSIR South Africa
Bakh Institute, Russia

And collaborators in South Korea and the US

TB Drug Development

- High potency to reduce treatment duration
- Activity against persistent bacilli
- Inhibition of new target classes
- Activity against multidrug-resistant TB
- Specificity for *Mycobacterium tuberculosis*

Twin-Track Approach

- **Compound based**
  - Azoles,
  - Dithiocarbamates,
  - Dibenzofurans.
- **Target based**
  - Category 1: nucleic acid metabolism, Intermed. & general metabolism,
  - Category 2: Cell wall biosynthesis.
  - Category 3. Signal transduction, Persistence e.g. serine-threonine protein kinase pknB

Progress

1. Under development	2. Validated &/or structure /assay available	3. Validated, structure and assay available
>20	11	6

Science
AAAS

Benzothiazinones Kill Mycobacterium tuberculosis by Blocking Arabinan Synthesis
Vadim Makarov, *et al.*
Science **324**, 801 (2009);
DOI: 10.1126/science.1171583

Benzothiazinones Kill *Mycobacterium tuberculosis* by Blocking Arabinan Synthesis

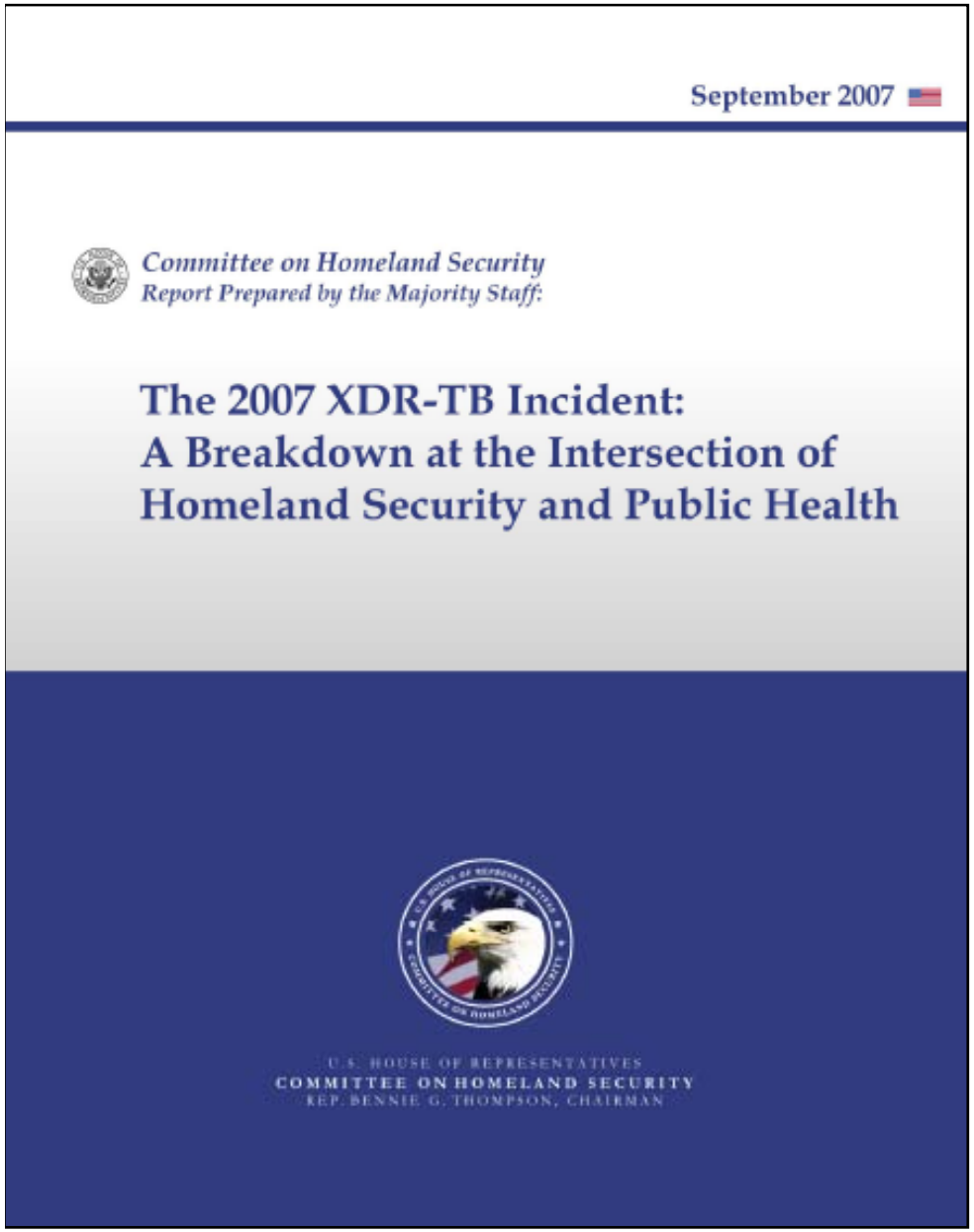
Vadim Makarov,[1,2]* Giulia Manina,[1,3]* Katarina Mikusova,[1,4]* Ute Möllmann,[1,5]* Olga Ryabova,[1,2] Brigitte Saint-Joanis,[1,6] Neeraj Dhar,[7] Maria Rosalia Pasca,[1,3] Silvia Buroni,[1,3] Anna Paola Lucarelli,[1,3] Anna Milano,[1,3] Edda De Rossi,[1,3] Martina Belanova,[1,4] Adela Bobovska,[1,4] Petronela Dianiskova,[1,4] Jana Kordulakova,[1,4] Claudia Sala,[1,7] Elizabeth Fullam,[1,7] Patricia Schneider,[1,7] John D. McKinney,[7] Priscille Brodin,[8] Thierry Christophe,[8] Simon Waddell,[1,9] Philip Butcher,[1,9] Jakob Albrethsen,[1,10] Ida Rosenkrands,[1,10] Roland Brosch,[1,6] Vrinda Nandi,[1,11] Sowmya Bharath,[1,11] Sheshagiri Gaonkar,[1,11] Radha K. Shandil,[1,11] Venkataraman Balasubramanian,[1,11] Tanjore Balganesh,[1,11] Sandeep Tyagi,[12] Jacques Grosset,[12] Giovanna Riccardi,[1,3] Stewart T. Cole[1,7]†

New drugs are required to counter the tuberculosis (TB) pandemic. Here, we describe the synthesis and characterization of 1,3-benzothiazin-4-ones (BTZs), a new class of antimycobacterial agents that kill *Mycobacterium tuberculosis* in vitro, ex vivo, and in mouse models of TB. Using genetics and biochemistry, we identified the enzyme decaprenylphosphoryl-β-D-ribose 2′-epimerase as a major BTZ target. Inhibition of this enzymatic activity abolishes the formation of

antifungal activity (*12*, *13*). Among their derivatives, compounds belonging to the nitrobenzothiazinone (BTZ) class showed particular promise in terms of their potency and specificity for mycobacteria. One of them, 2-[2-methyl-1,4-dioxa-8-azaspiro[4.5]dec-8-yl]-8-nitro-6-(trifluoromethyl)-4*H*-1,3-benzothiazin-4-one (BTZ038), was selected for further studies. This compound (series number 10526038; $C_{17}H_{16}F_3N_3O_5S$, with a molecular weight of 431.4; log*P* = 2.84) (Fig. 1A) was synthesized in seven steps with a yield of 36%. Structure activity relationship work showed that the sulfur atom and the nitro group at positions 1 and 8, respectively, were critical for activity. BTZ038 has a single chiral center, and both enantiomers, BTZ043 (*S*) and BTZ044 (*R*), were found to be equipotent in vitro. Because early metabolic studies with bacteria or mice indicated that the nitro group could be reduced to an amino group, and because many TB drugs are prodrugs that require activation by *M. tuberculosis* (*14*), the *S* and *R* enantiomers of the amino derivatives and the likely hydroxylamine intermediate were synthesized and tested for antimycobacterial

What's needed?

- More research funding
- More chemists
- Access to chemical libraries
- Access to natural product libraries
- Access to screening centres
- More cooperation/communication
- Access to knowledge e.g. failure database



"The twin spectres of diseases that are increasingly resistant or completely without current treatments and antimicrobials, and the ability of diseases to spread more quickly than ever before due to rapid transit and other enablers, place **public health concerns squarely on the homeland, national, and trans-national security agendas**."

Biosafety and Biosecurity…..

BIOSAFETY BREACHES

Accidents Spur a Closer Look at Risks at Biodefense Labs

Failure to report a *Brucella* infection and other problems at a Tex microbiologists searching for ways to ensure safety and public trus

and bring out the fire trucks is counter-productive," says virologist Clarence J. Peters of the University of Texas Medical Branch (UTMB) in Galveston. But there is room for improvement, he adds: "One of the biggest problems is transparency. I think we're all

Some Recent Exposures in U.S. Biodefense Labs

nature news

News

Nature **433**, 344 (27 January 2005)

Infection scare in network

Rex Dalton, San Diego

Accidental cases of tul

The accidental infection University researchers w bacteria is raising questi expansion of biodefence

Massachusetts-based Bc been chosen by the Nati Health to host one of tw containment centres for

Published online 20 May 2009 | *Nature* **459**, 31

News in Brief

Canadian charged with Ebola

The arrest at a US border of a researche non-infectious Ebola DNA in from Canada high-containment lab security.

But officials on both sides of the border the samples were removed from the Can Laboratory in Winnipeg, or about the sus Michel Yao, who was a fellow at the labo

On 5 May, Yao was discovered to have vectors as he tried to drive into North D three days later with smuggling biologica statements to authorities. The incident

NEWS OF THE WEEK

BIOSECURITY

Reports Blame Animal Health Lab In Foot-and-Mouth Whodunit

Neglected leaky pipes and England's record-setting wet summer likely combined to cause the country's recent outbreak of foot-and-mouth disease (FMD), according to two reports issued last week. The virus responsible probably escaped from a company, Merial, that grew vast amounts of it for vaccine production, the studies say. Yet the reports assign most of the blame for the outbreak to the Institute for Animal Health (IAH), a government lab at the same site in Pirbright that owned the aging network of underground wastewater pipes and was aware that it needed maintenance. IAH reached biosecurity in other ways as well, the reports found.

The findings are ablow to the reputation of IAH, a world-renowned FMD research center, says Andrew Mathieson, an environmental health expert at the University of the West of England in Bristol. But they should also serve as a more general warning. "My worry is: What about the many other research establishments of the same age?" he says.

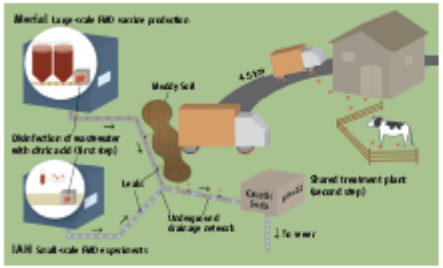
Rapid government action helped contain the FMD outbreak, first confirmed on 3 August, to just two farms in Surrey (*Science*, 10 August, p. 732). Still, the National Farmers' Union puts the accident's economic impact at more than $100 million, and some politicians have called for resignations at the Department for Environment, Food and Rural Affairs (Defra), which oversees biosafety at IAH and also funds some 65% of its work.

Genomic comparisons of the outbreak virus to strains from Merial and IAH can't pinpoint from which of the two labs the virus escaped, according to the reports, one led by the U.K.'s Health and Safety Executive (HSE), a government agency, and the other by molecular epidemiologist Brian Spratt of Imperial College London. Still, the panels say, it's much more likely that the virus came from Merial, which grew it in two 6000-liter vats shortly before the accident, producing a million times more virus than IAH used in its small-scale experiments.

But how did it escape? The reports conclude that air leaks, contamination from solid waste, and foul play by terrorists or disgruntled employees are unlikely. Instead, both focus their suspicions on the site's wastewater system.

A two-step chemical strategy is used at Pirbright to prevent FMD from escaping in liquid waste. Both Merial and IAH first treat wastewater at their own buildings with a disinfectant such as citric acid. Then, a complex system of pipes takes the water to a shared effluent treatment plant, managed by IAH, where caustic soda is used to raise the pH to 12 and kill off any remaining virus during a 12-hour holding period. Finally, the liquid is released into the sewer.

Although the first treatment step proba-



Recipe for an outbreak. The escaped foot-and-mouth disease virus (red) probably originated at vaccine manufacturer Merial, two reports say, but the Institute for Animal Health owns the leaky drainage system that presumably let the virus seep into the soil. Trucks may have then carried it close to a farm.

bly killed off almost any leftover virus at IAH, it likely didn't inactivate the larger amounts in Merial's wastewater. The second treatment step would normally take care of that, but the network of pipes, pumps, and manholes leading to it suffered from leaks due to cracks, tree roots, and other problems. The reports hypothesize that live virus seeped into the soil as a result, especially because July's excessive rainfall may have caused the drains to overflow.

As it happened, construction crews were digging holes around the leaks at the time, and heavy trucks—without proper IAH oversight—drove through the presumably virus-laden mud. Some of these vehicles later took a road that went very close to the first infected farm. From there, the farmer may have carried the virus to his herd.

IAH, a part of the U.K. Biotechnology and Biological Sciences Research Council (BBSRC), owns the antiquated drainage system, the HSE report says. It was also aware of some of the network's problems. In fact, IAH, Defra, BBSRC, and Merial had debated an upgrade since 2003; the problem was money.

As to Merial's discharge of virus into its wastewater, HSE says this wasn't a breach of biosecurity, because Defra had approved the procedure used in the first disinfection step. But in a statement, IAH pointed its finger at Merial, suggesting that the company should have taken better care to inactivate any virus. Strangely, the Spratt report says, IAH didn't seem to know that Merial might release active virus into the system; biosafety officers from the lab and the company hardly ever talked.

Both panels question the wisdom of chemically inactivating wastewater altogether. Indeed, most modern labs use thermal inactivation—that is, pressure-cooking at 121°C—to destroy any pathogens, says Lee Thompson, a biosafety officer at the University of Texas Medical Branch in Galveston. Still, the second step, using caustic soda, "is very effective against FMD," Thompson says—but underground pipes that cannot be inspected "are a big problem."

Defra says it will adopt a range of recommendations to fix problems at Pirbright, such as keeping better track of visitors and making sure biosafety officers communicate. Merial has agreed not to grow live virus until U.K. authorities give it the green light. IAH, which was constructed in 1924, is due to be almost completely rebuilt by 2012, although some funding issues remain. Defra has also asked Health and Safety Commission chair Bill Callaghan to review the regulatory framework for animal pathogens. He is due to report by December. —MARTIN ENSERINK

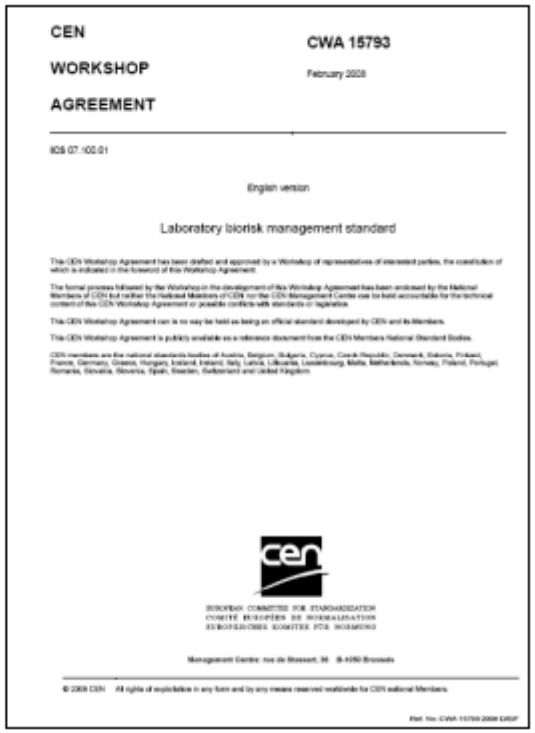
1486 14 SEPTEMBER 2007 VOL 317 SCIENCE www.sciencemag.org

Slide 3

Reducing risks….

European Biosafety Society • American Biological Safety Association • Det Norske Veritas

International Biosafety and Biosecurity Laboratory Standard Development Initiative



CEN

WORKSHOP

AGREEMENT

CWA 15793

February 2008

ICS 07.100.01

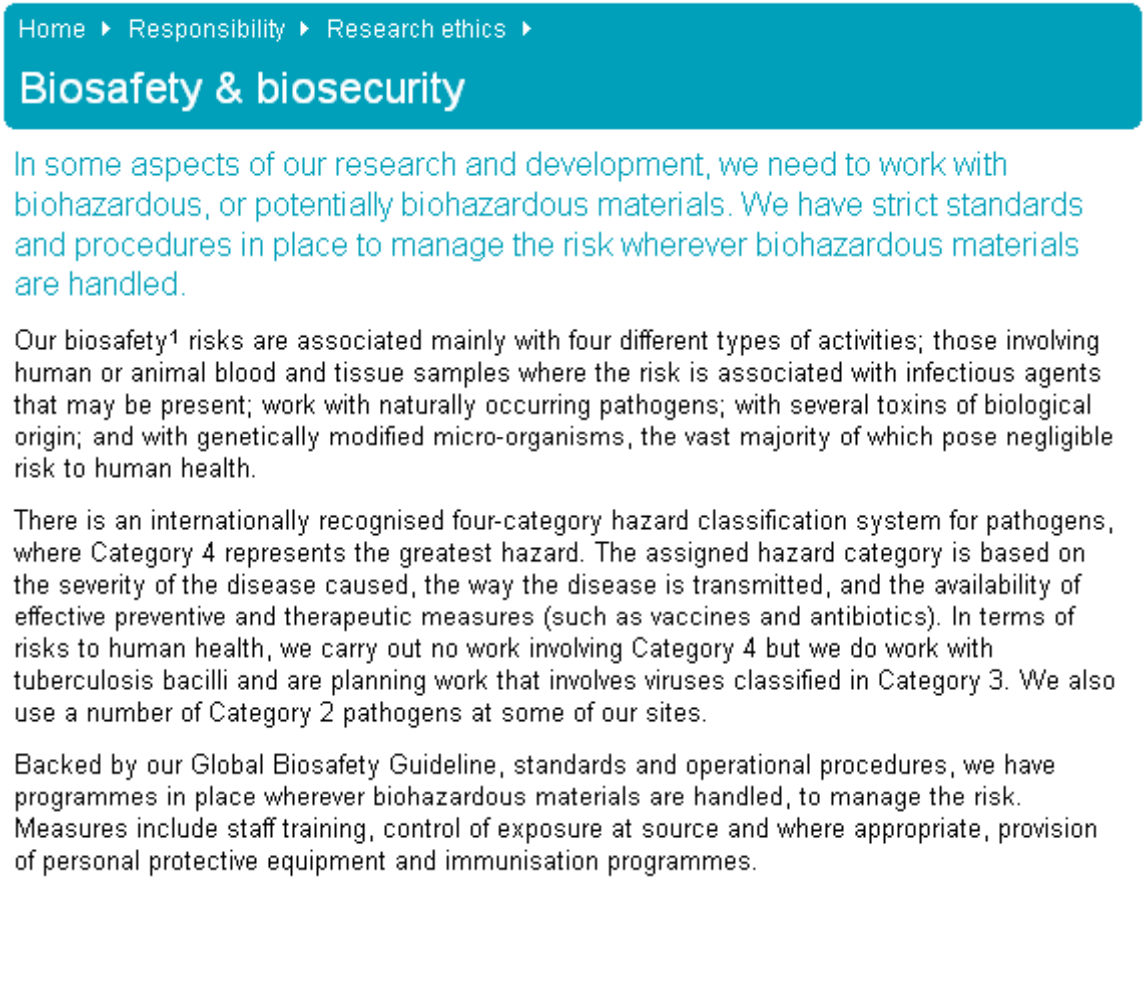
English version

Laboratory biorisk management standard

biorisk@icid.com • www.biorisk.eu

AZ Biosafety and Biosecurity

- Global Biosafety Network
- Global Biosafety and Biosecurity Standards and Guidelines



Home ▸ Responsibility ▸ Research ethics ▸

Biosafety & biosecurity

In some aspects of our research and development, we need to work with biohazardous, or potentially biohazardous materials. We have strict standards and procedures in place to manage the risk wherever biohazardous materials are handled.

Our biosafety[1] risks are associated mainly with four different types of activities; those involving human or animal blood and tissue samples where the risk is associated with infectious agents that may be present; work with naturally occurring pathogens; with several toxins of biological origin; and with genetically modified micro-organisms, the vast majority of which pose negligible risk to human health.

There is an internationally recognised four-category hazard classification system for pathogens, where Category 4 represents the greatest hazard. The assigned hazard category is based on the severity of the disease caused, the way the disease is transmitted, and the availability of effective preventive and therapeutic measures (such as vaccines and antibiotics). In terms of risks to human health, we carry out no work involving Category 4 but we do work with tuberculosis bacilli and are planning work that involves viruses classified in Category 3. We also use a number of Category 2 pathogens at some of our sites.

Backed by our Global Biosafety Guideline, standards and operational procedures, we have programmes in place wherever biohazardous materials are handled, to manage the risk. Measures include staff training, control of exposure at source and where appropriate, provision of personal protective equipment and immunisation programmes.

International Biosafety Working Group

Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction. (Русский)

Geneva, August 18-22, 2008

The IBWG was honoured to take up the invitation of the Chairman of the Meeting, Ambassador Georgi Avramchec, to be a guest at the Meeting of Experts in Geneva, August 18-22, 2008. In addition we were afforded the most excellent platform to host a side meeting with our members (EBSA, ABSA, ABSA Canada, Industry group) in attendance to present the activities not only to the main hall but in this meeting chaired by Heather Sheeley, Co-chair of IBWG. The side meeting was well attended by approximately 50 persons including Ambassadors, representatives and NGOs for a lively discussion.

Key points from this meeting were:

a. to ensure that our compendium included references to non-proliferation convention
b. to ensure in the educational material that the ethical and obligations of the BTWC were included.

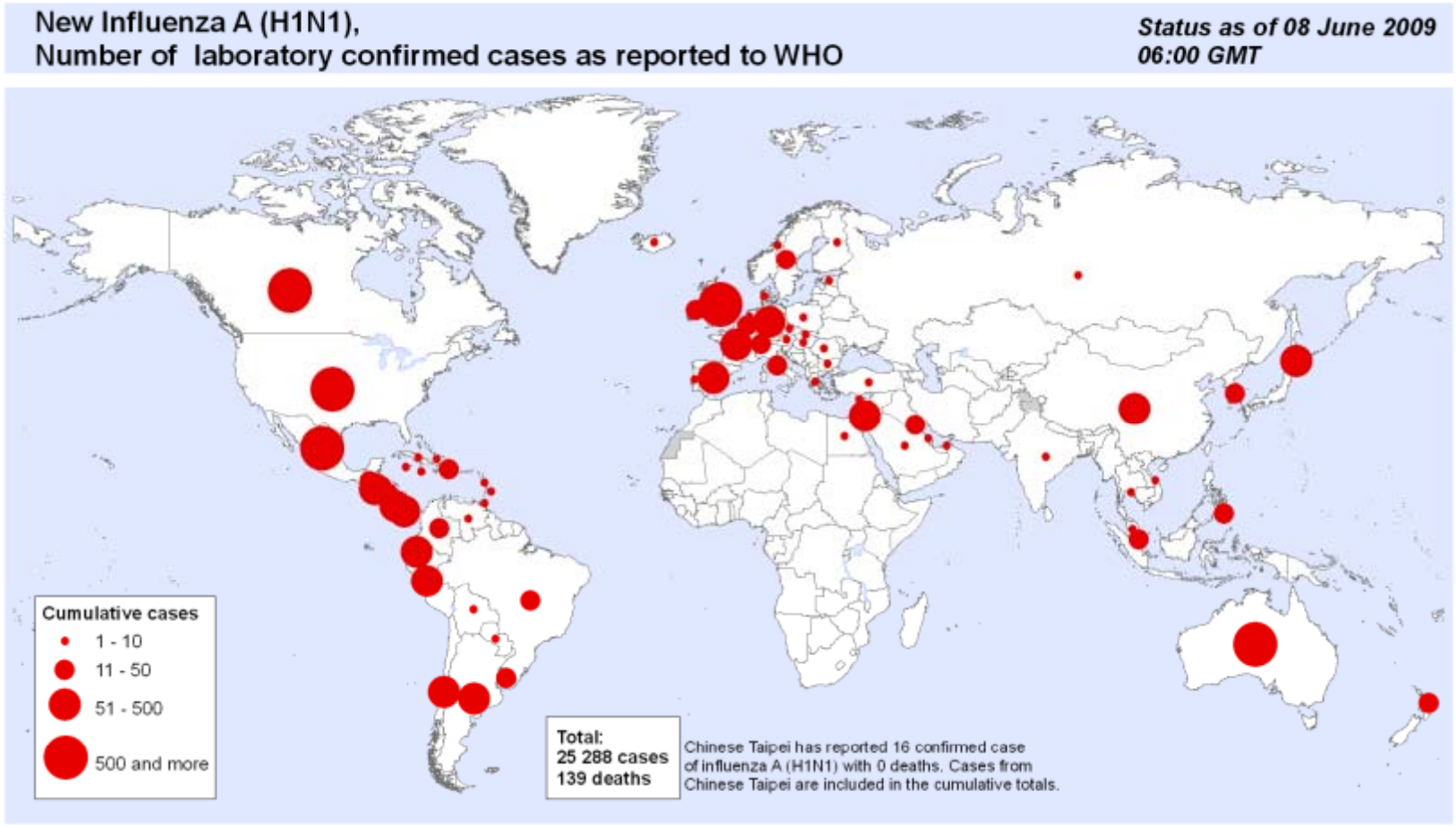
The role of the Biosafety associations was well received and left a strong impression that there was a body of knowledge and responsibility in promoting biosafety practices.

We also took the new poster which received great interest and the following countries came to have a discussion: China, US, Canada, Japan, Russia, Germany, Ireland, the Netherlands, Norway, Morocco, Singapore, Swiss, Mexico, Venezuela, Indonesia, Tajekestan, Sudan, Ukraine, Brazil, Argentina, Pakistan, Zimbabwe and ICLS, WHO, OIE and the Chair of the Meeting.

MEMBER GROUPS

- European Biological Safety Association (EBSA)
- Asia Pacific Biosafety Association (APBA)
- American Biological Safety Association (ABSA)
- ABSA Canada
- Associacao Nacional de Biossegurance, Brasil (ANBio)
- Japanese Biosafety Association
- International Level-4 Users Group
- International Veterinary Biosafety Working Group (IVBWG)
- Pharmaceutical Biosafety Group
- CDC
- OLS/PHAC
- GPP (FAC)
- International Society for Biosafety Research

Pandemic Flu – MedImmune Vaccine Development



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Map produced: 08 June 2009 06:30 GMT

Conclusions

- Great potential for fighting serious infectious disease through international collaborations between industry and academic and other research organisations, charitable organisations, NGOs etc
- Potential concerns around safety and security associated with such work
- Adoption of high internal standards supported by national and international standards will help to ensure these concerns don’t hinder progress