Tuberculosis
Why do we care and what can we do?

Actions for Life
Towards a World Free of Tuberculosis

Reach
Commit
Act
Treat
Achieve
Advocate
Invest
Hope
Innovate
Collaborate

Make an “Action for Life” on World TB Day 2006
These 10 actions are at the heart of the Global Plan to Stop TB 2006-2015 and are key to achievement of the Partnership’s 2015 targets.

World Health Organisation
Stop TB Partnership
www.stoptb.org
While tuberculosis is mostly a memory in the Western countries it remains a grim reality for the majority of the world's population.

- Every year 8–10 million people catch the disease and 2 million will die from it.
- About a third of the world's population carry the TB bacteria but most never develop the active disease.
- Around 10% of people infected with TB actually develop the disease in their lifetimes, but this proportion is increasing in the face of the HIV epidemic.

- TB infection is currently spreading at the rate of **one person per second**.

- It kills more young people and adults than any other infectious disease.

- It is the infectious disease that kills more women than any other.
Tuberculosis: under control?
Tuberculosis is always with us
What makes tuberculosis so pervasive?

2 billion

90%

8 million/year

10%

Vaccine*

Drugs active against non-replicating bacteria

Public health surveillance and treatment

Understanding of bacterial physiology

Understanding of what constitutes a protective immune response

Understanding of factors that affect transmission
Tuberculosis is always with us
XDR = Multidrug-resistant TB (MDR-TB) plus resistance to (i) any fluoroquinolone, and (ii) at least 1 of 3 injectable second-line drugs capreomycin, kanamycin, amikacin (new definition agreed October 2006)

MDR-TB = resistance to at least isoniazid and rifampicin, the two most powerful first-line anti-TB drugs

Of 17,690 isolates from 49 countries during 2000-2004, 20% were MDR-TB and 2% were XDR-TB

XDR-TB found in:
USA: 4% of MDR-TB
Latvia: 19% of MDR-TB
S Korea: 15% of MDR-TB
Figure 2  Countries with confirmed XDR-TB cases thus far (pink). From the World Health Organization, http://www.who.int/tb/xdr/xdr_jan.pdf (accessed 22 January 2007).
FIGURE. Number of reported cases of extensively drug-resistant tuberculosis (XDR TB)* — United States, 1993–2006

* XDR TB defined as resistance to at least isoniazid, rifampin, any fluoroquinolone, and at least one second-line injectable drug (kanamycin, amikacin, or capreomycin).

† Excludes New York City.
XDR-TB in Southern Africa
August 2006

Church of Scotland Hospital, Tugela Ferry, KwaZulu-Natal Province, South Africa

- 53 of 544 patients defined as XDR-TB cases
- 52 of the 53 patients died on average within 25 days, including those on antiretroviral therapy
- Further investigations being carried out
- XDR-TB likely in bordering African countries

Given the underlying HIV epidemic in Africa, drug-resistant TB could have a major impact on mortality and requires urgent action on care and prevention
The fresh air cure 2010

What is it about good food, resting outdoors and no longer being shunned by that makes you feel better when you have TB

Vitamin D
Vitamin A
Stress hormones
How do we work out how to vaccinate?

Have a hypothesis as to what is protective
Test the hypothesis in an experimental model
Interpret results and determine what the outcome is
Publish results allowing investigators who study human disease to integrate the information into their data sets
Mice can be infected with a cloud of droplets similar to those released by cough or sneeze. The cellular and pathological response can be analyzed and definitive results obtained.
What does this mean for the mouse?
We can investigate the function of specific cell types.
We can determine what specific cells do

- CD4 T cells divide
- CD4 T cells produce molecules to activate macrophages

Expression of CD44, a marker of T cell activation
White blood cells accumulate in the lung. The inflammation is controlled by feedback mechanisms.

A  C57BL/6  Intact
B  B6-GKO  Deficient
C  B6-NOS2KO  Deficient
Animal experiments have allowed us to identify what parts of the immune response control tuberculosis.

- **Innate immunity**
- **Acquired antigen-specific immunity**

**Early**
- IL-12p40 KO
- IL-12p35 KO
- TNF-α KO
- IFN-γ KO
- CD4/MHC II KO
- SCID

**Late**
- CD8 KO
- C57Bl/6 BALB/c B Cell KO

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**Graph**
- Y-axis: Bacterial number in lung
- X-axis: Time in days post low dose aerosol exposure
- 20-30 days
- 100 days
Using animal models at Trudeau, we have developed this working model:

- TB bacteria gain entry to the alveoli of the lung via small droplets.
- Dendritic cells take TB bacteria/antigen to the lymph node.
- CD4 T cells migrate back to the lung.
- CD4 T cells that recognize TB bacteria are activated and expanded.
- Dendritic cells take TB bacteria/antigen to the lymph node.
- Macrophages are activated to control TB growth by interferon-γ.
Animal experiments allow us to understand important aspects of disease development.
How can we improve this?