Doing the Math:
The Dilemma of Drug Resistant Tuberculosis

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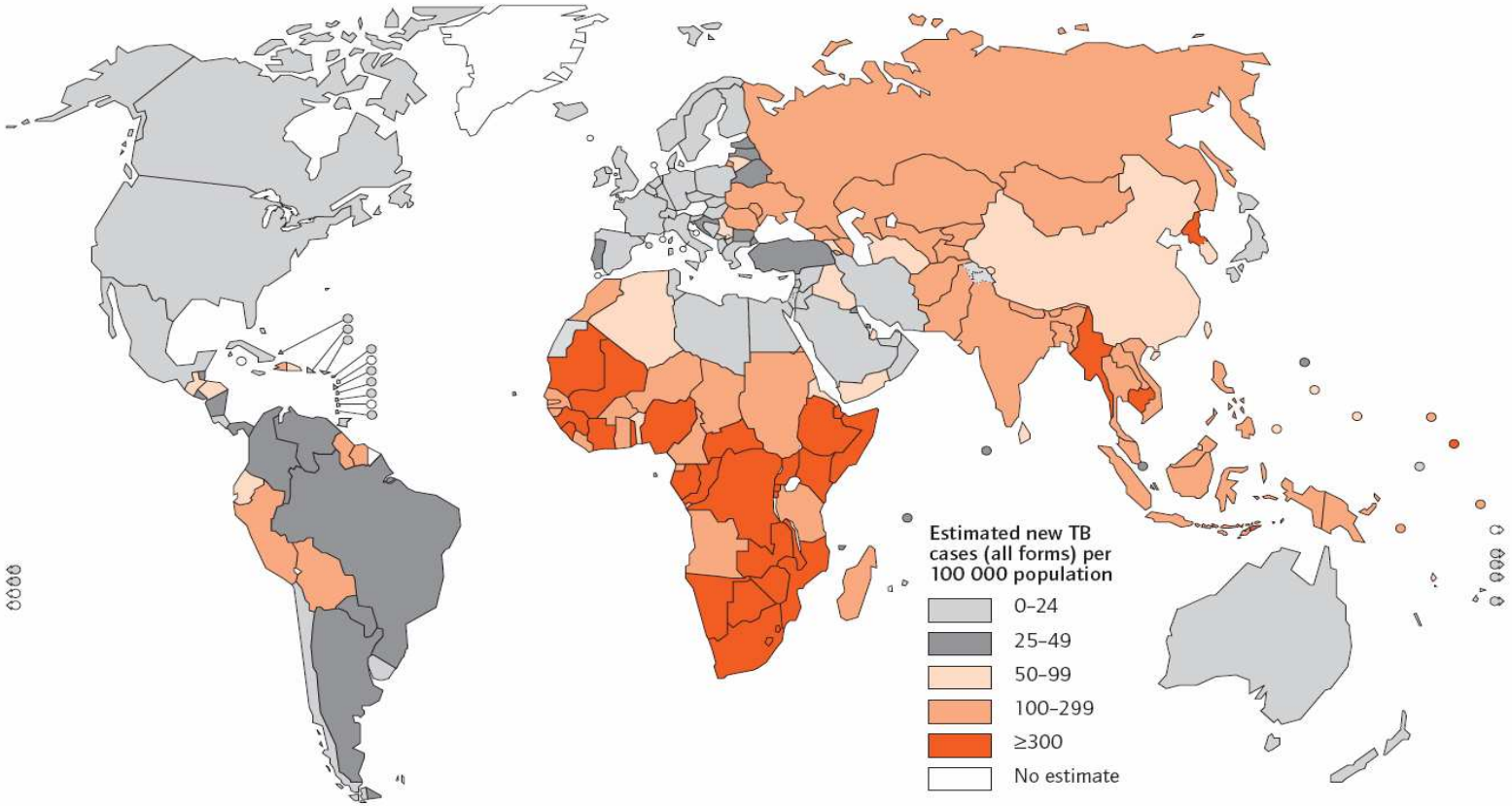
Tuberculosis : A Global Problem

TB by the numbers…

- One third of the world's population is infected with *M. tuberculosis*
- 5-10% will develop active disease
- Almost 2 million persons die annually – almost 5,000 every day
- It is estimated that each case left untreated can infect an average of 10 – 15 persons annually before death

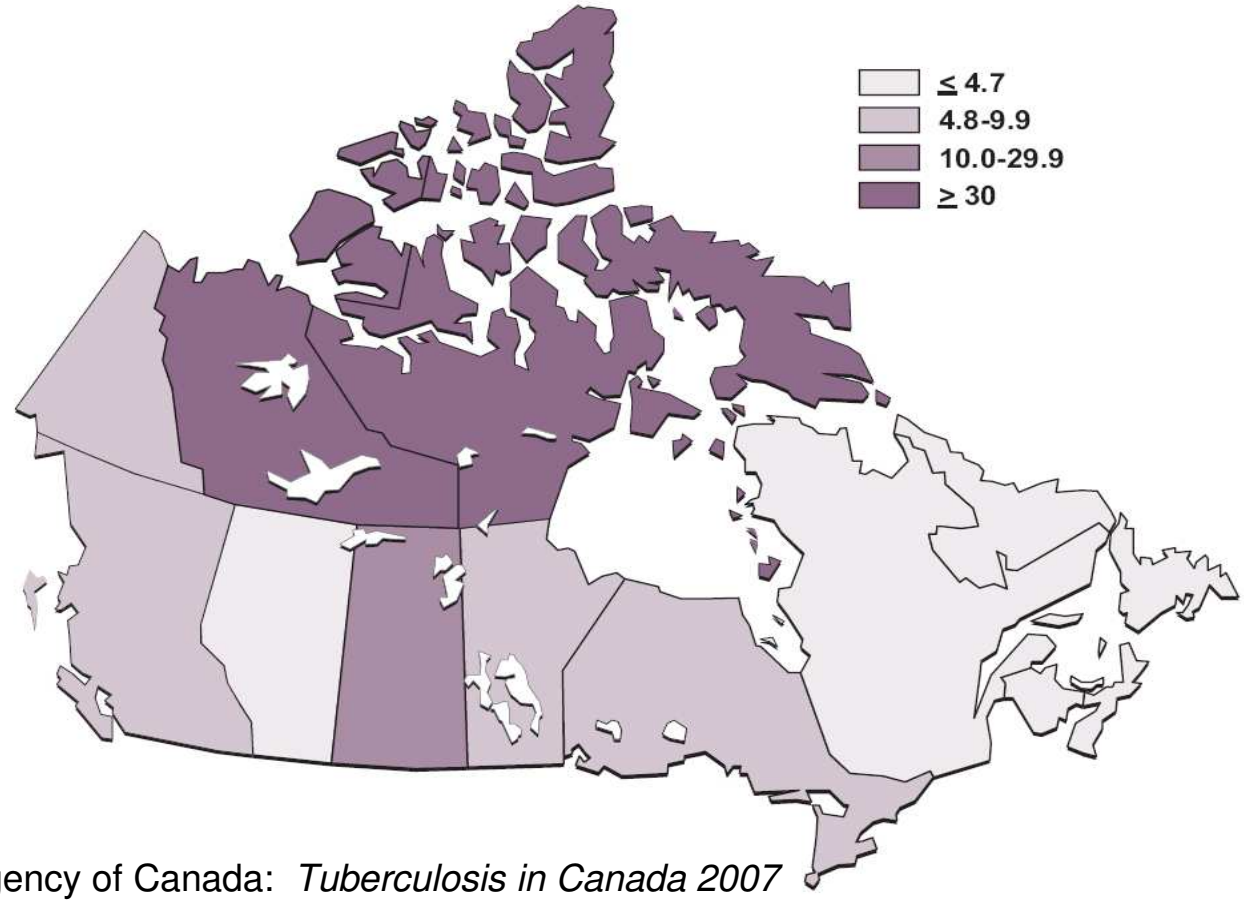
FIGURE 1
Estimated TB incidence rates, 2008



WHO: Global Tuberculosis Control, 2009 update

Figure 3

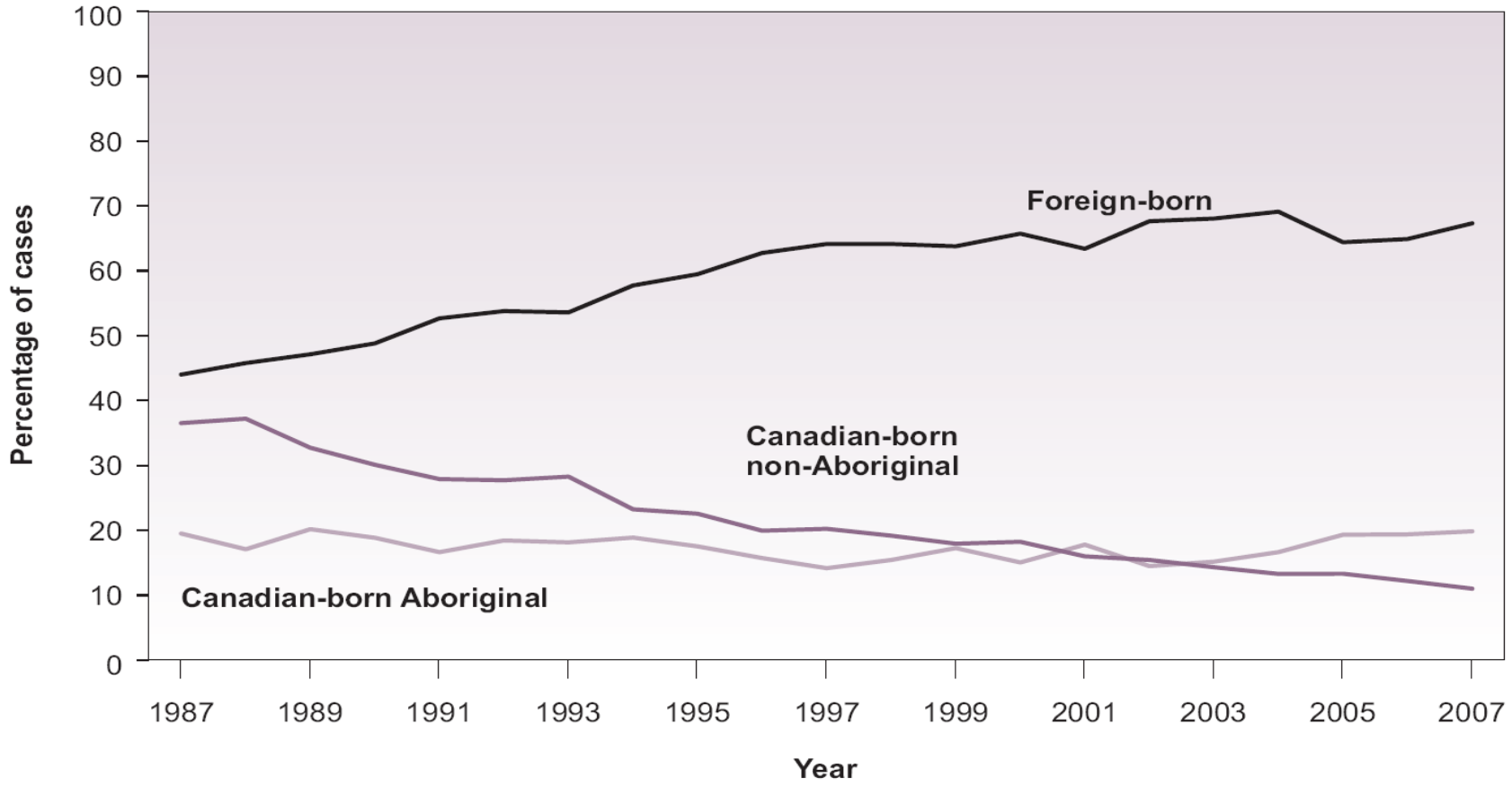
Tuberculosis incidence rate by province/territory as compared with national rate (4.7 per 100,000): 2007



Public Health Agency of Canada: *Tuberculosis in Canada 2007*

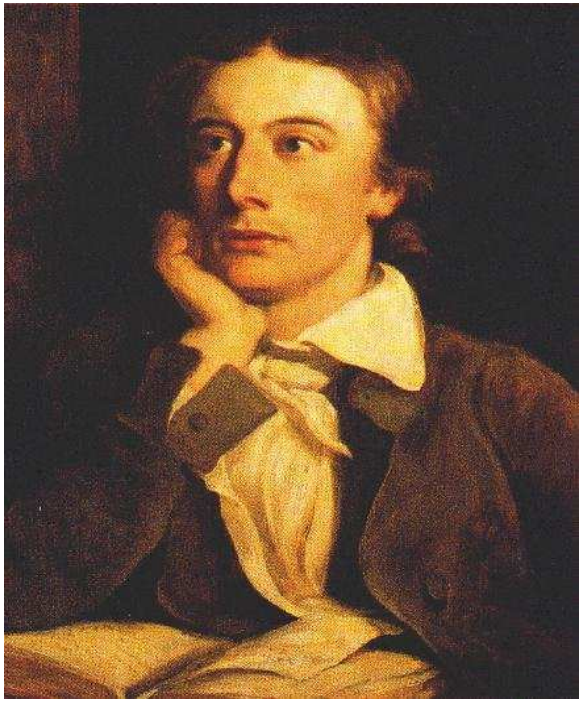
Figure 7

Percentage of tuberculosis cases by origin – Canada: 1987-2007

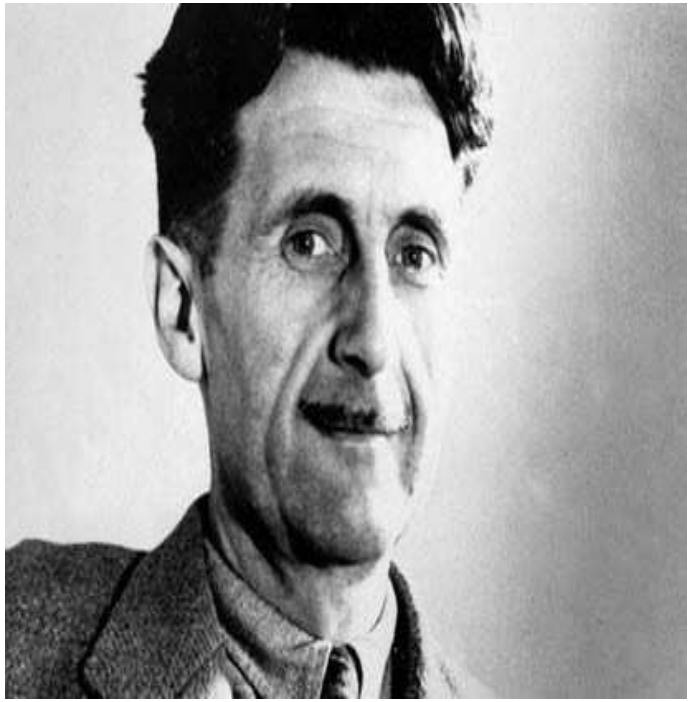


Public Health Agency of Canada: *Tuberculosis in Canada 2007*

No one is spared…



John Keats



George Orwell

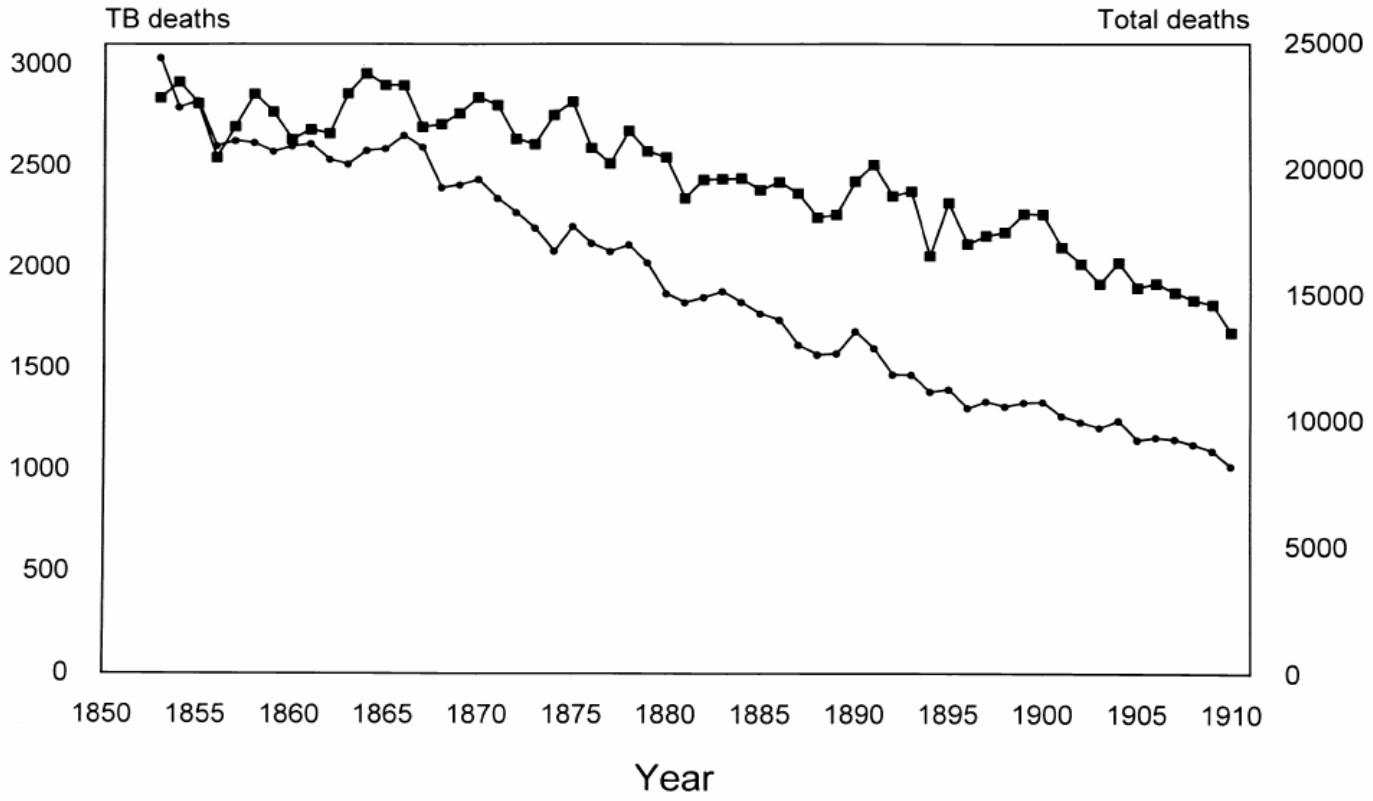
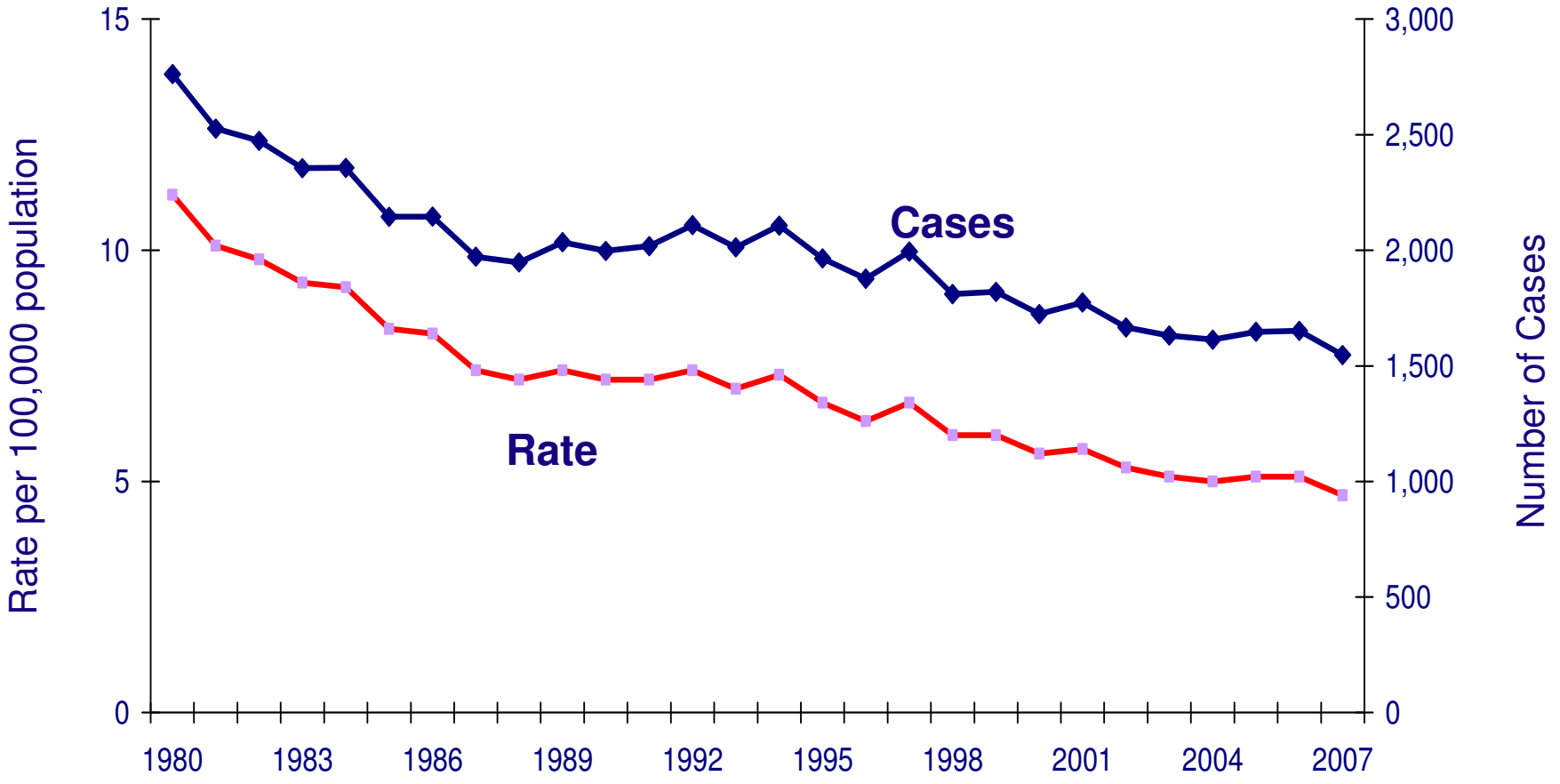


Figure 1 Death rates for tuberculosis per million per annum, left hand scale (●), and all causes per million, right hand scale (■), for England and Wales.

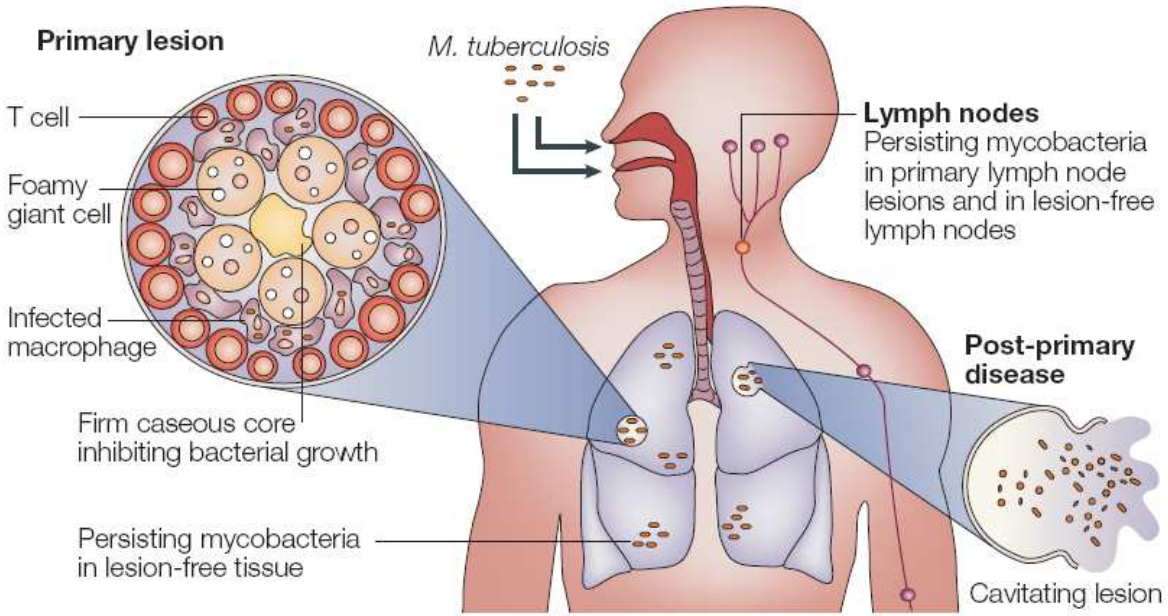
Davies RPO et al, Int J Tuberc Lung Dis 1999;3(12):1051-54

Tuberculosis incidence rate and counts Canada: 1980-2007



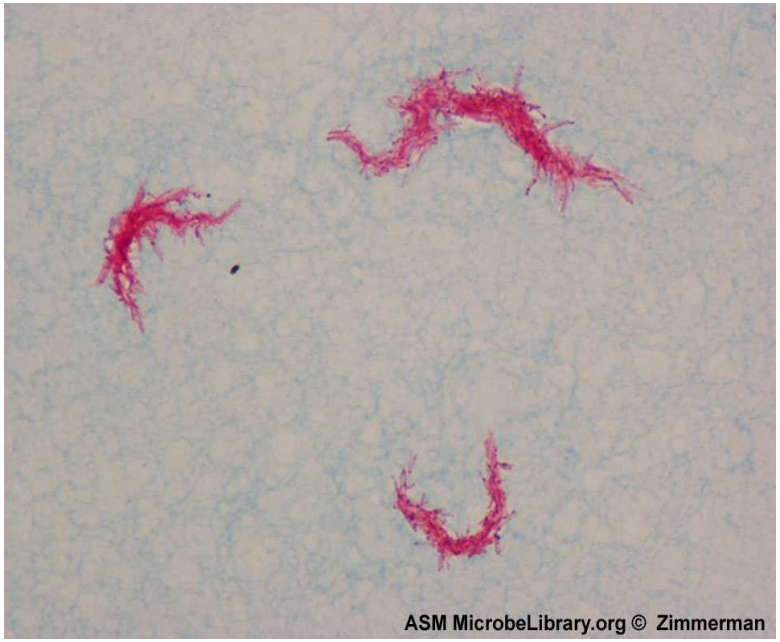
Public Health Agency of Canada

Pathogenesis of Tuberculosis



Stuart GR et al, Nature Rev Microbiol 2003;1:97-100

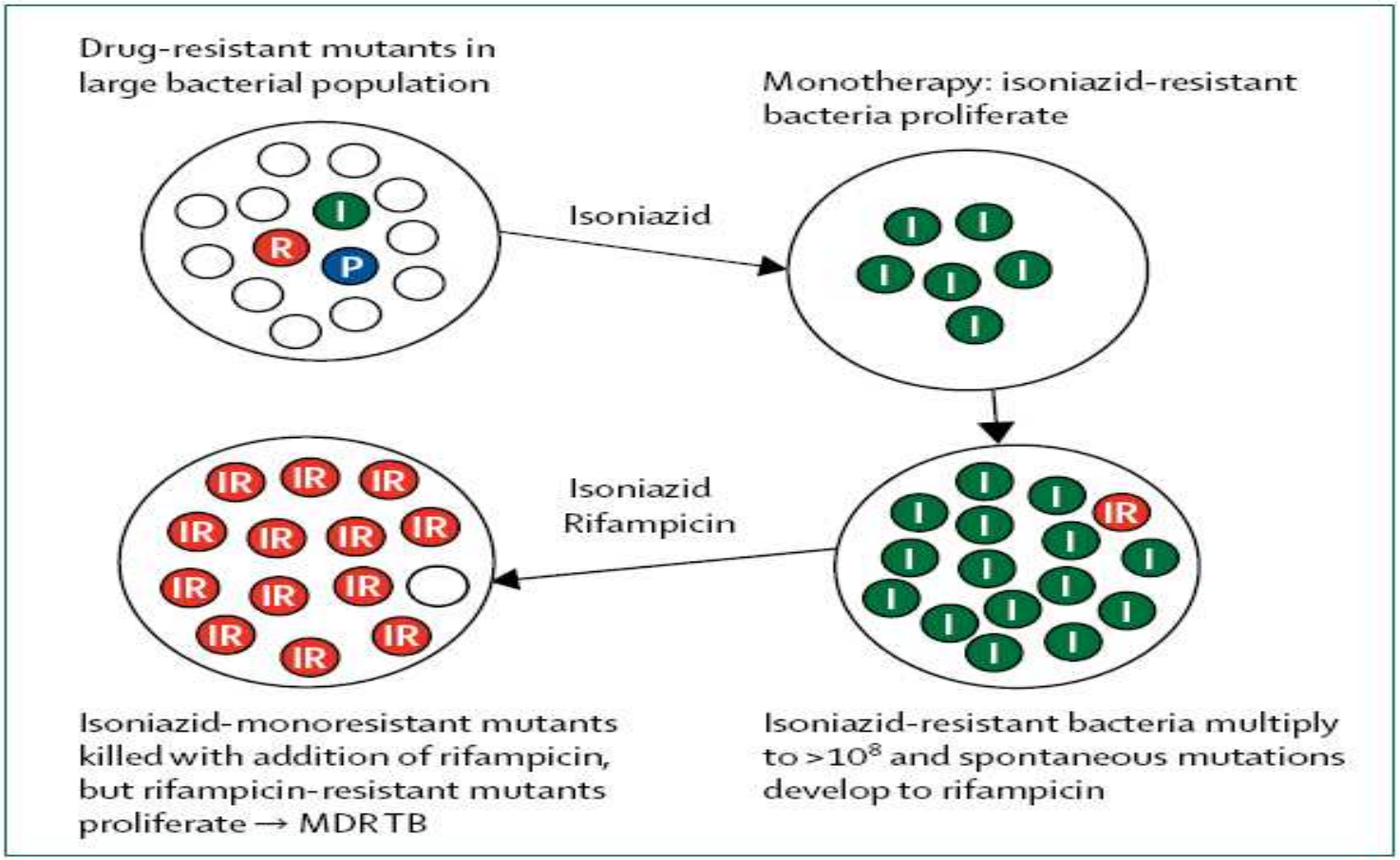
Biology of *M. tuberculosis*



- Very long generation time – approx. 18 – 20 hours
- Can remain dormant in cells (inactive, low metabolic activity)
- Cavitary lesions form with large numbers of organisms

M. tuberculosis isn't like other bacteria…

- *M. tuberculosis* (Mtb) infection usually acquired early in life; organisms enter "latency" (metabolically inactive)
- Mtb organisms do not interact and exchange genetic information (unlike other bacteria, e.g. *S. aureus* colonizing the nasopharynx)
- Resistance can only occur through chromosomal mutation
- Mutation rate for individual genes varies between and within genes



Ghandi NR et al, Lancet 2010; May 19 ePub

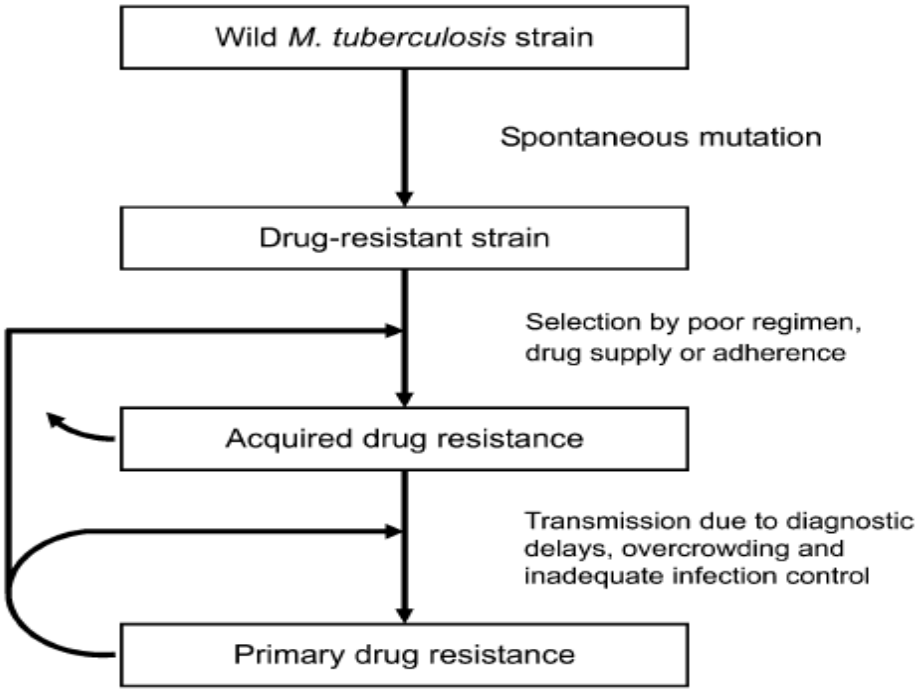


Figure Concepts in the development of drug-resistant TB.

Zhang Y et al, Int J Tuberc Lung Dis 2009;13(11):1320-30

Doing the Math: The Development of Drug Resistance in *M. tuberculosis*

Risk of drug resistant mutants emerging in a patient depends on the product of the risks of mutation for each agent and the size of the bacterial population within compartments (e.g. lung cavities):

$$P = 1 - (1 - r)^n$$

where P = probability of drug resistance emerging; r is the mutation rate, and n is the number of bacilli in a lesion (usually estimated at 10^8)

Gillespie SH, Antimicrob Agents and Chemotherapy, 2002

Doing the Math…risk of drug resistance

Single drug therapy with a risk of mutation of 10^{-6}:

Probability = 100%

Two drug therapy with combined risks of mutation of 10^{-12}:

Probability = 0.01%

Above two drug therapy with a bacterial population in a lesion of 10^{10}:

Probability = 1.0%

Spontaneous mutation rates for first-line TB drug therapy

Rifampin:	3.32×10^{-9}
Isoniazid:	2.56×10^{-8}
Ethambutol:	1.0×10^{-7}
[Streptomycin:	2.29×10^{-8}]

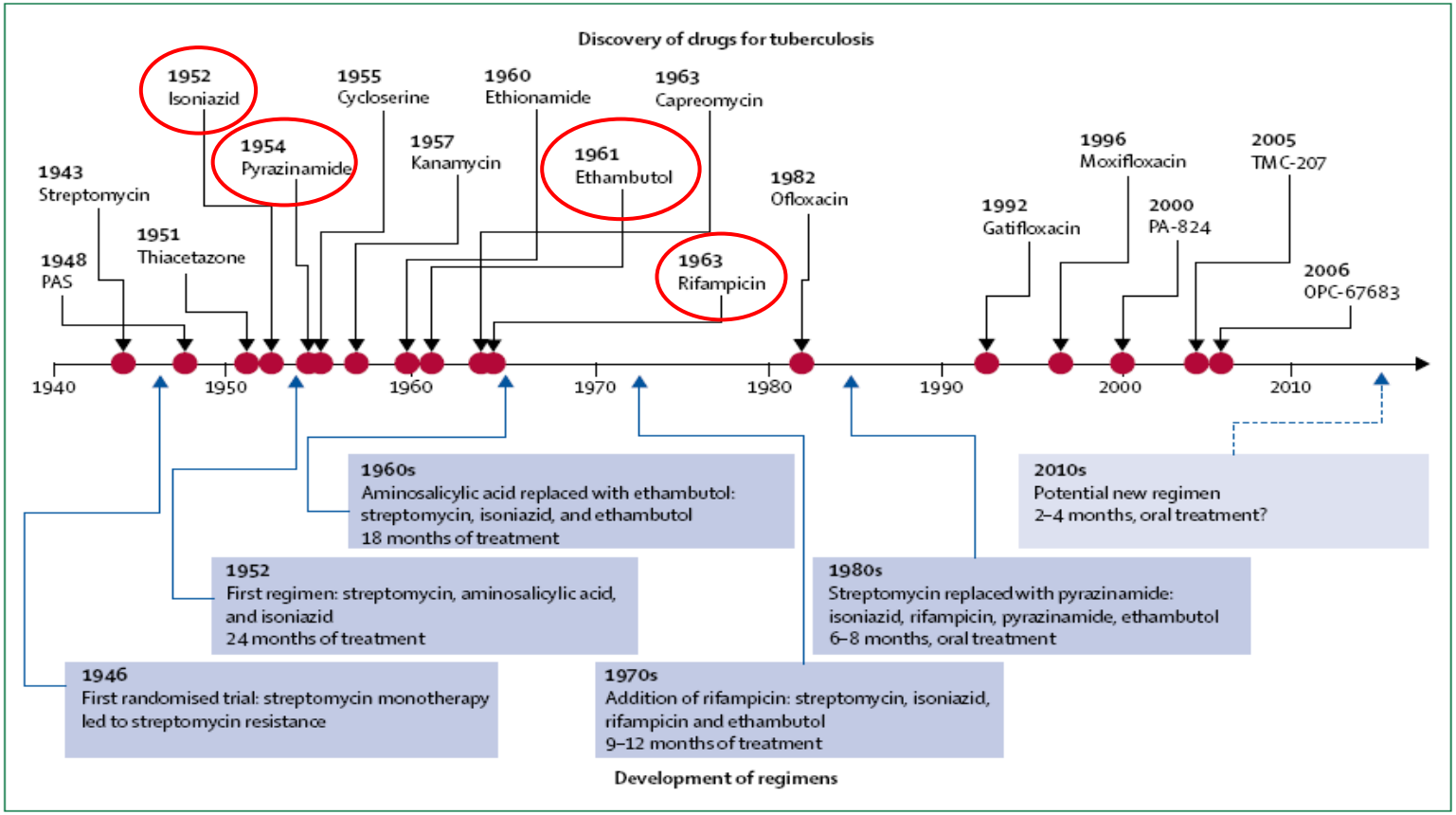


Figure 2: **History of drug discovery and development of treatment regimens for tuberculosis**
Compounds that are in the early-stage of development, but for which there are no human proof-of-concept data, are not shown. Arrow with dashed line represents future regimen. Red dots represent when the drugs were first reported.

Ma Z et al, Lancet; May 19 2010 epub

What is a "First-line" drug?

Table 1
Activity of First-Line Anti-TB Drugs

		Bactericidal Effect		
Drug	Resistance Effect*	Rapid Replication Rate	Slow Replication Rate	Sterilizing Effect
INH	++	++	+	++
RMP	++	++	+	+++
EMB	+/-	+/-	+/-	0
PZA	0	0	++	+++

**The effect in preventing resistance is similar to the bactericidal effect in rapidly replicating organisms; 0 = no effect, 3+ = greatest effect, +/- little or no effect.*

Canadian Tuberculosis Standards, 6th Edition, 2007

Drug Resistant Tuberculosis: Definitions*

Multi-drug Resistant Tuberculosis: MDRTB

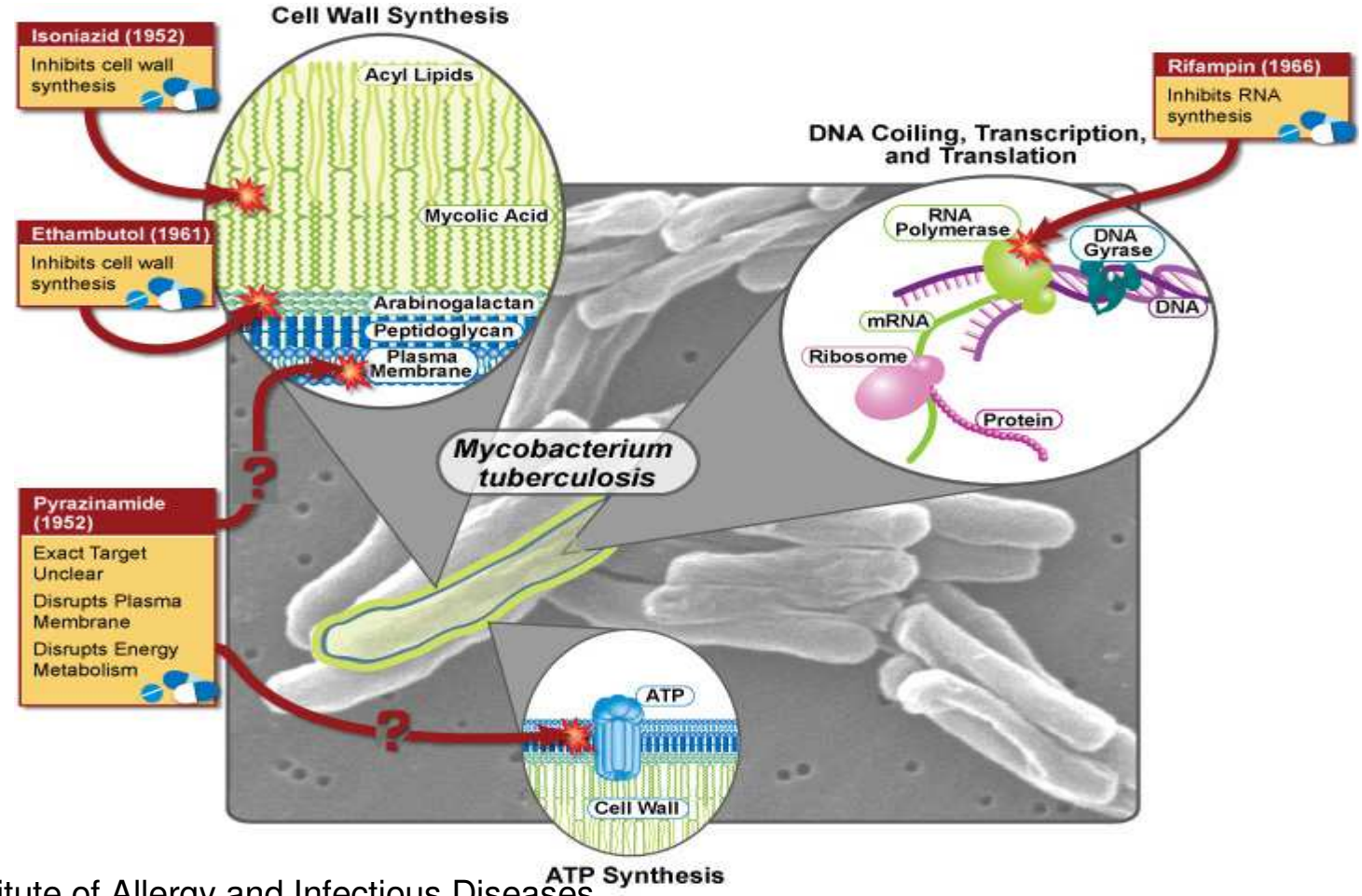
-resistant to isoniazid (INH) and rifampin (RMP)

Extensively-drug Resistant Tuberculosis: XDRTB

-resistant to INH, RMP, any of the fluoroquinolones (e.g levofloxacin, moxifloxacin or gatifloxacin) and at least one of the 3 injectable drugs (capreomycin, kanamycin, amikacin)

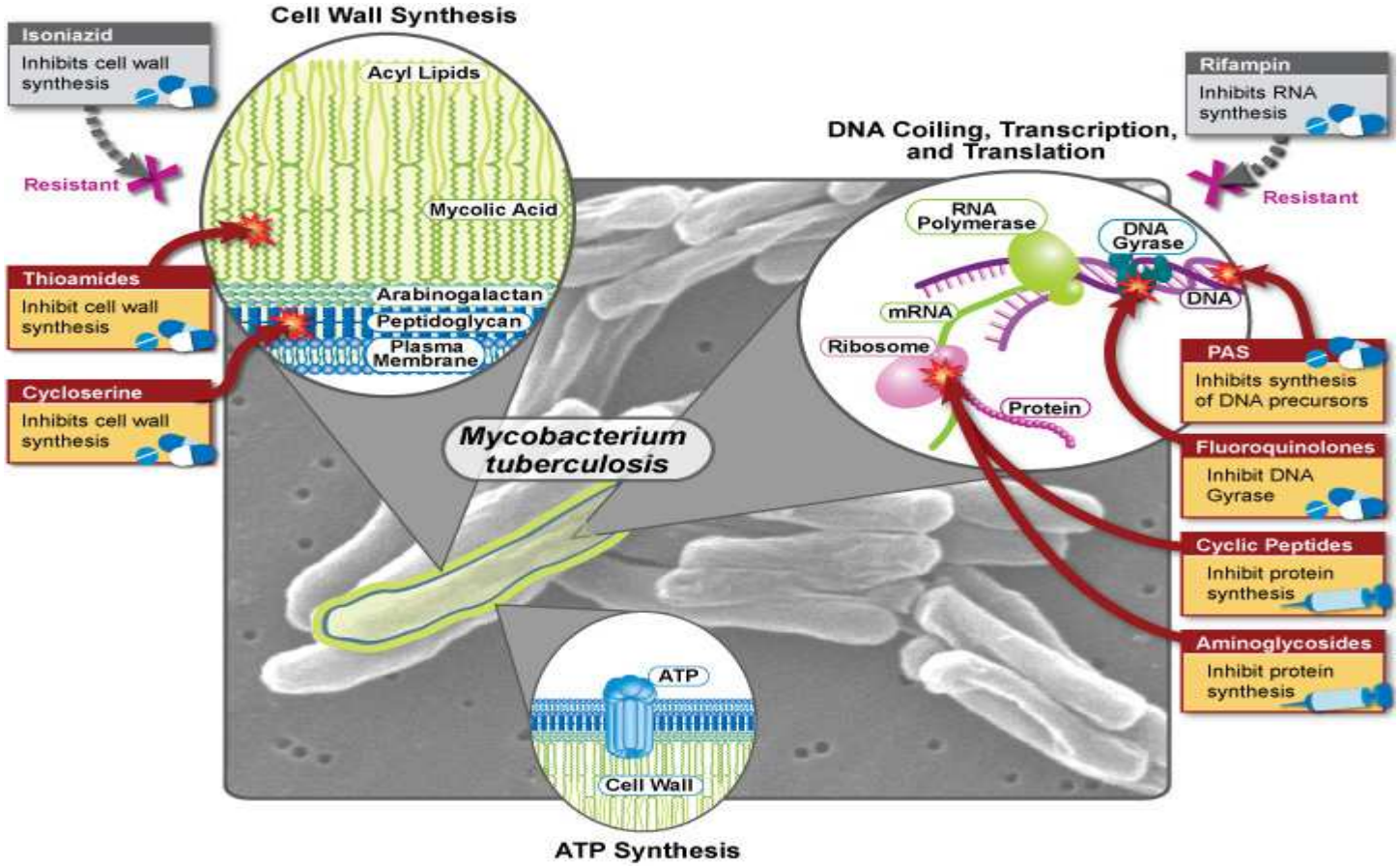
*MMWR November 3rd,2006

First-line drug therapy for fully-susceptible TB



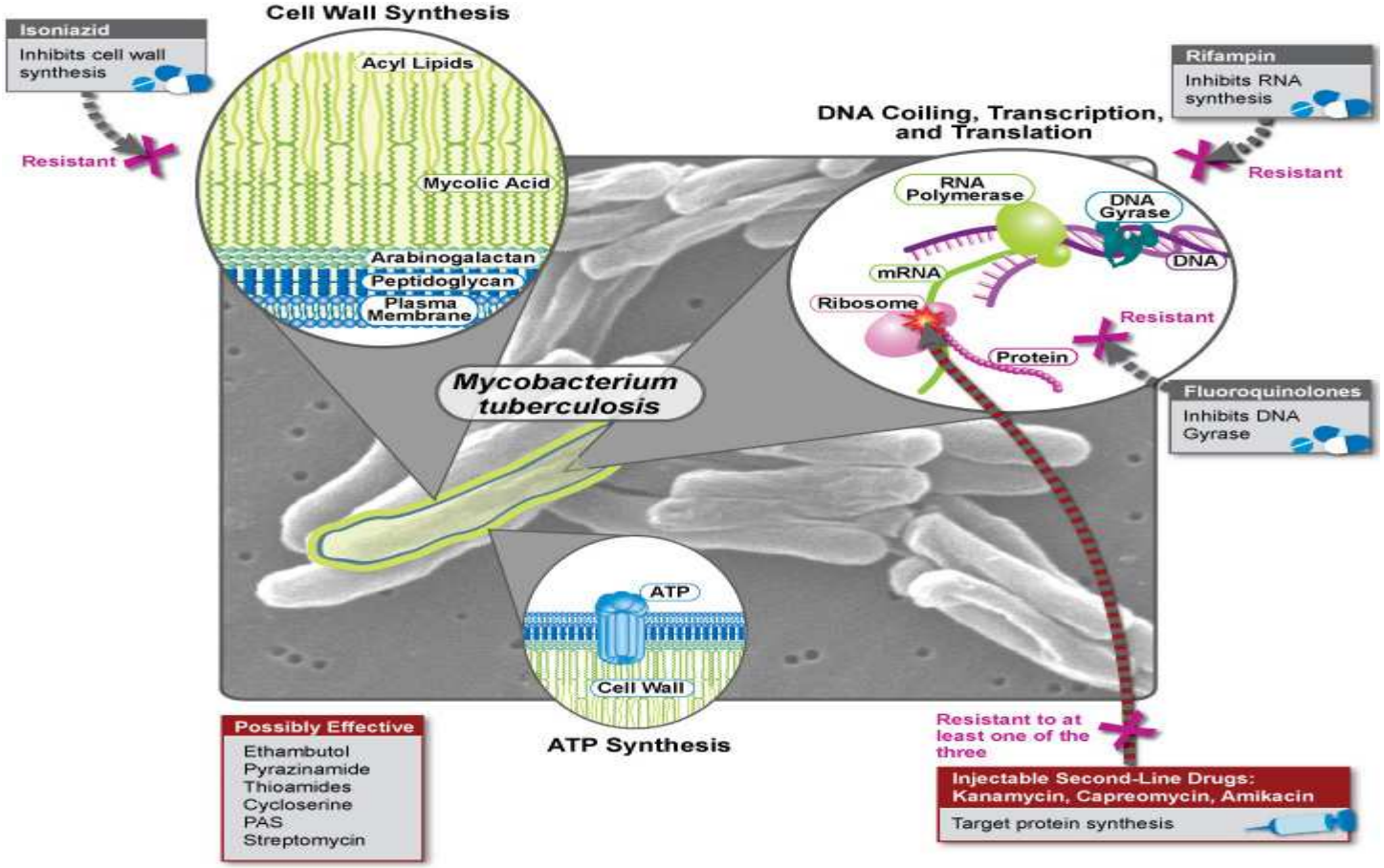
National Institute of Allergy and Infectious Diseases

MDRTB and possible effective treatments



National Institute of Allergy and Infectious Diseases

XDRTB and diminishing options for therapy



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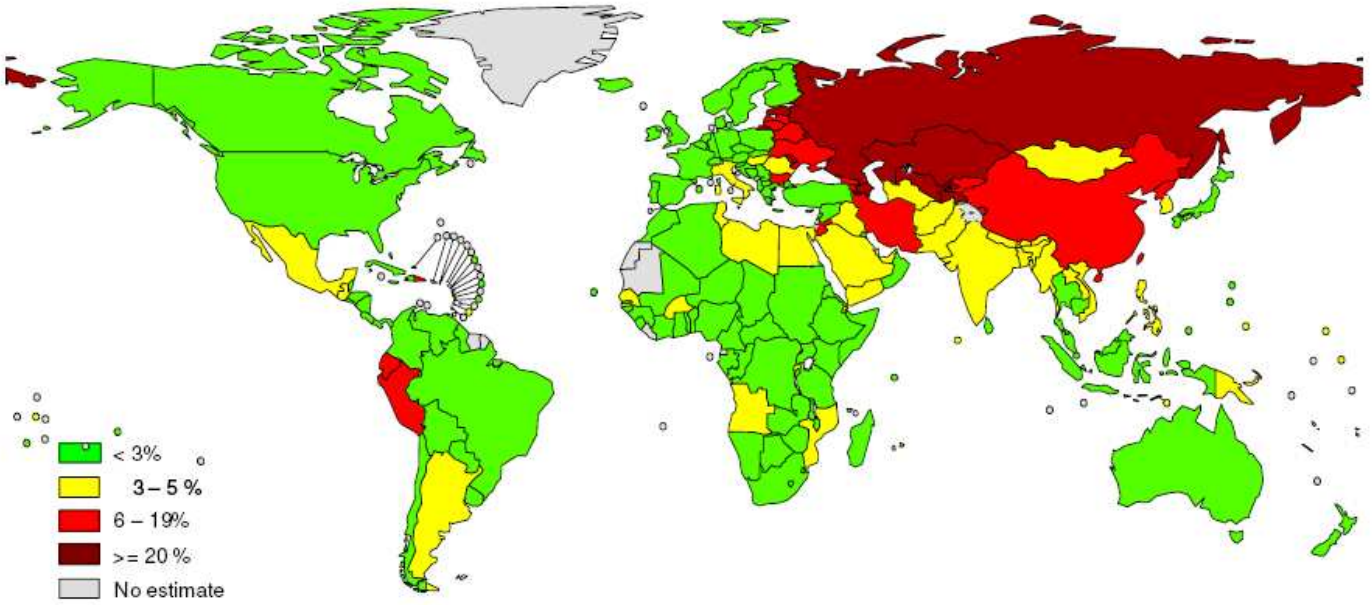
Tuberculosis : A Global Problem

MDRTB among new and re-treated cases, 2007

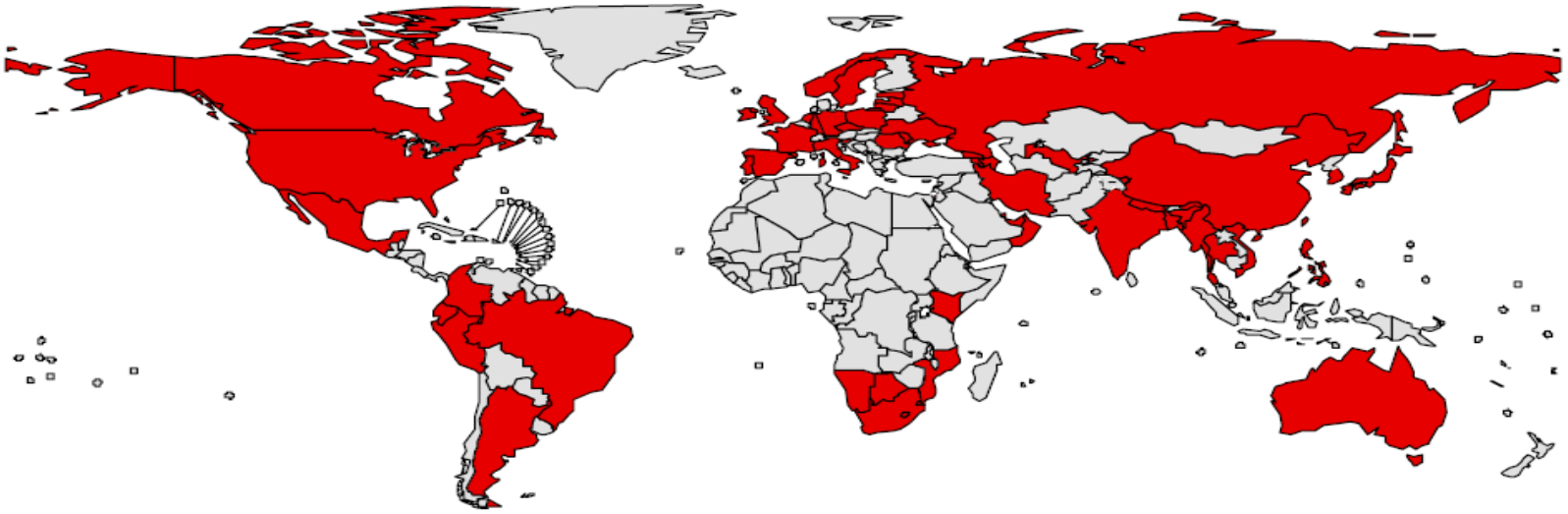


WHO 2009 Antituberculosis Drug Resistance in the World

Countries that had reported at least one XDR-TB case by end April 2009

World Health Organization

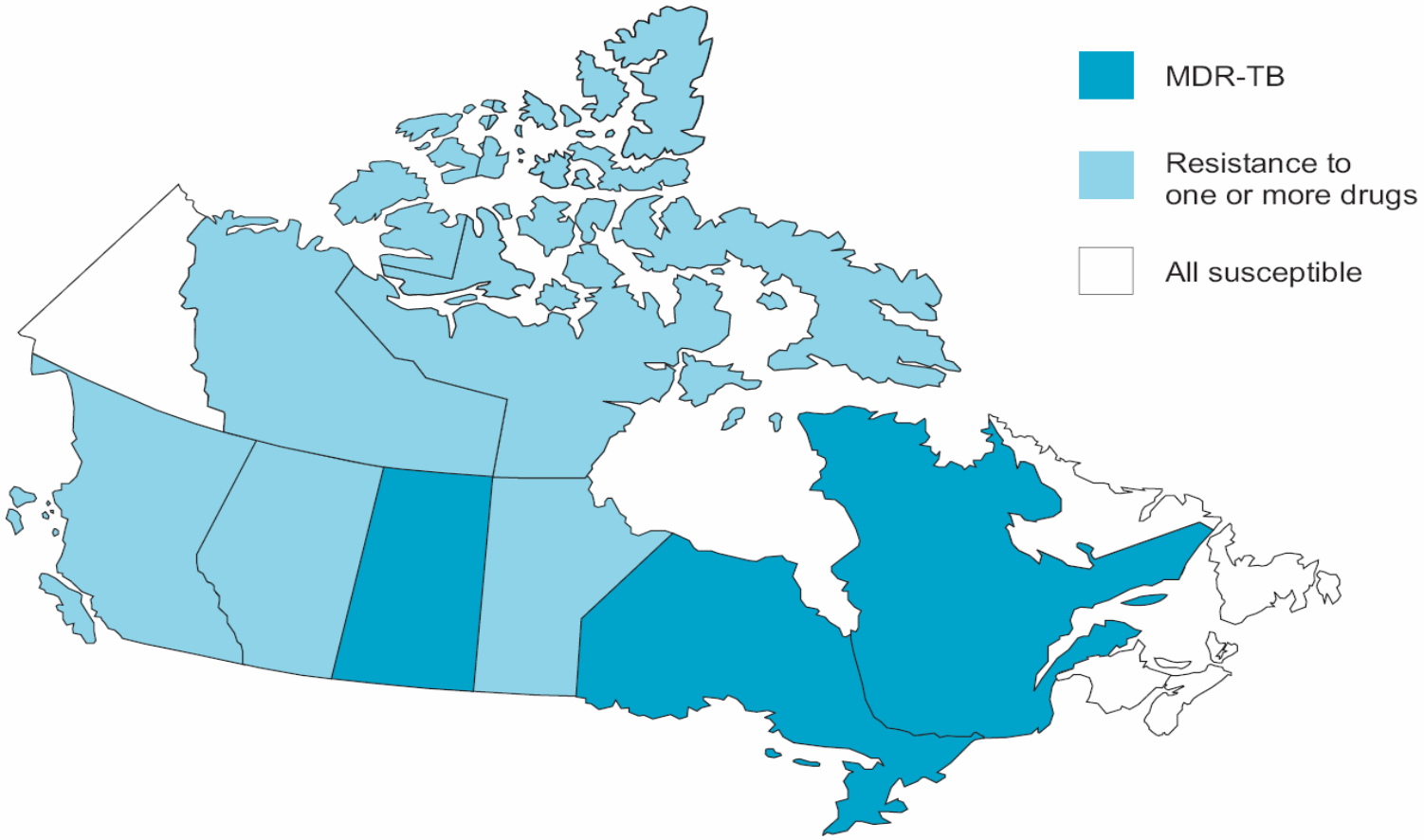
THE STOP TB DEPARTMENT



Argentina	Canada	Georgia	Japan	Myanmar	Philippines	Russian Federation	Ukraine
Armenia	China	Germany	Kenya	Namibia	Poland	Slovenia	United Arab Emirates
Australia	Colombia	India	Latvia	Nepal	Portugal	South Africa	United Kingdom
Azerbaijan	Czech Republic	Iran (Islamic Republic of)	Lesotho	Netherlands	Qatar	Spain	United States of America
Bangladesh	Ecuador	Ireland	Lithuania	Norway	Republic of Korea	Swaziland	Uzbekistan
Botswana	Estonia	Israel	Mexico	Oman	Republic of Moldova	Sweden	Viet Nam
Brazil	France	Italy	Mozambique	Peru	Romania	Thailand	

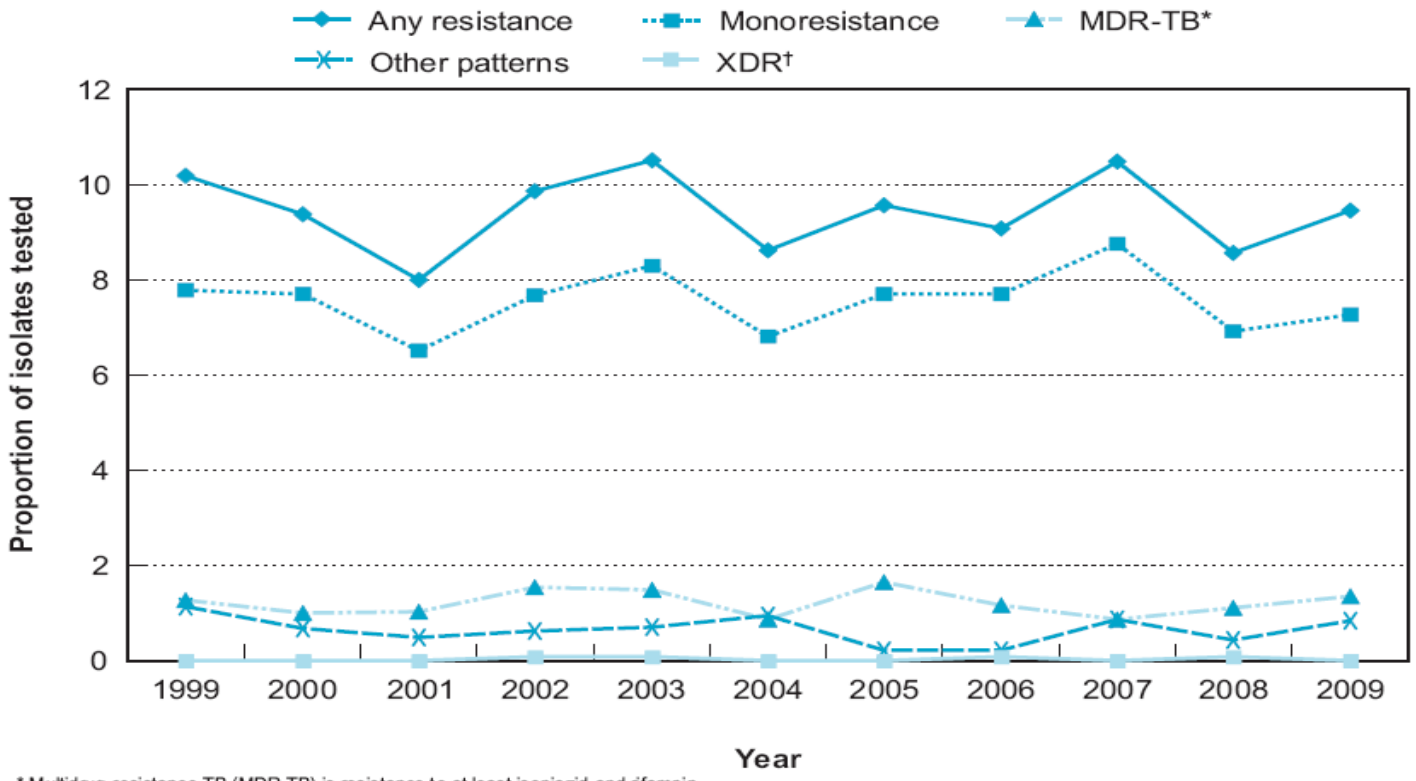
WHO 2009 Antituberculosis Drug Resistance in the World

Figure 1
Reported TB drug resistance in Canada by province/territory – 2009



Public Health Agency of Canada: *Tuberculosis: Drug Resistance in Canada - 2009*

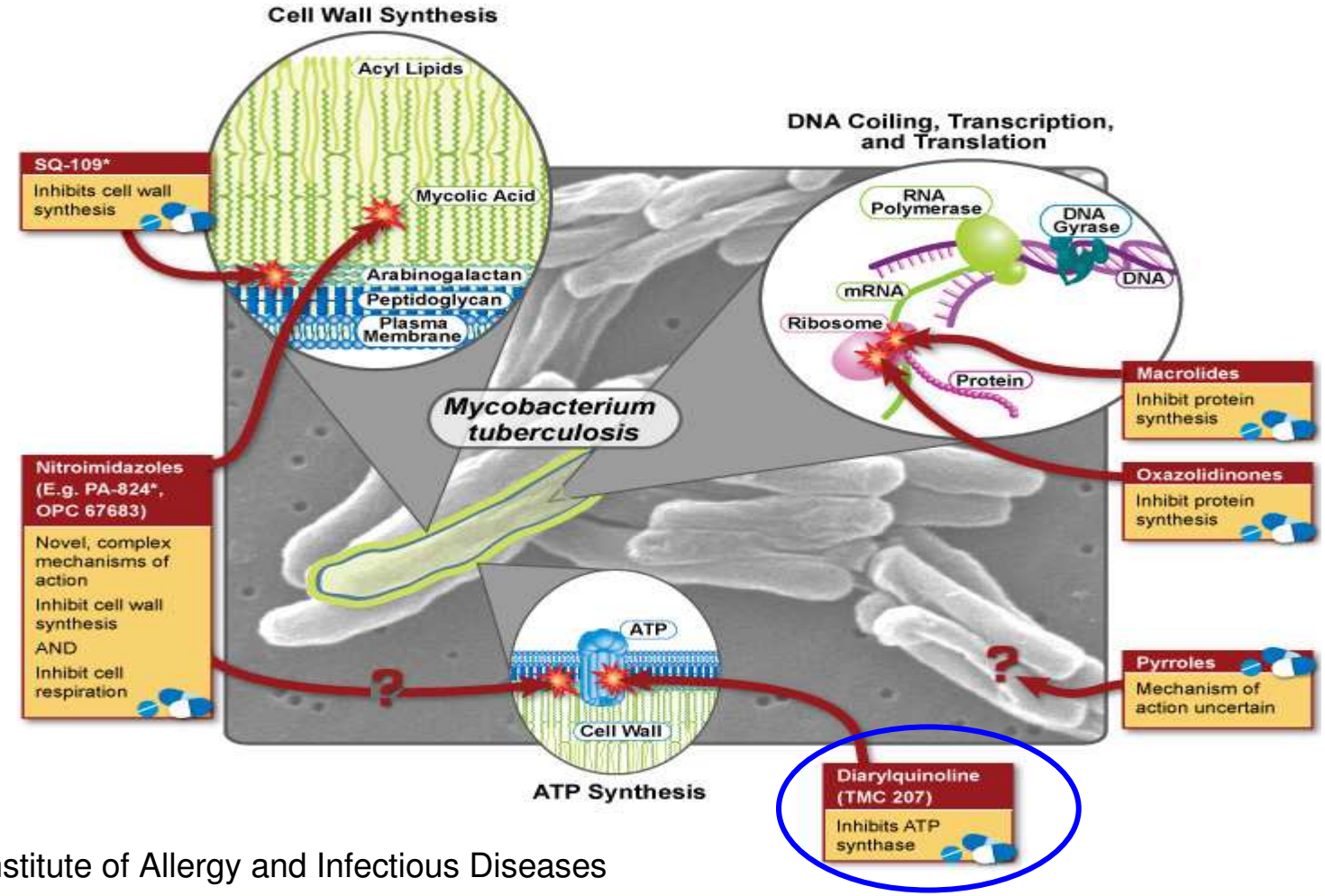
Figure 6
Overall pattern of reported TB drug resistance as a percentage of isolates tested – 1999-2009



* Multidrug-resistance TB (MDR-TB) is resistance to at least isoniazid and rifampin.
† Extensively drug-resistant TB (XDR-TB) is MDR-TB plus resistance to any fluoroquinolone and at least 1 of 3 injectable second-line drugs: amikacin, capreomycin, and kanamycin.

Public Health Agency of Canada: *Tuberculosis: Drug Resistance in Canada - 2009*

New drug therapies on the horizon…



National Institute of Allergy and Infectious Diseases

Thank-you!