Antimicrobial Treatment of Resistant Tuberculosis

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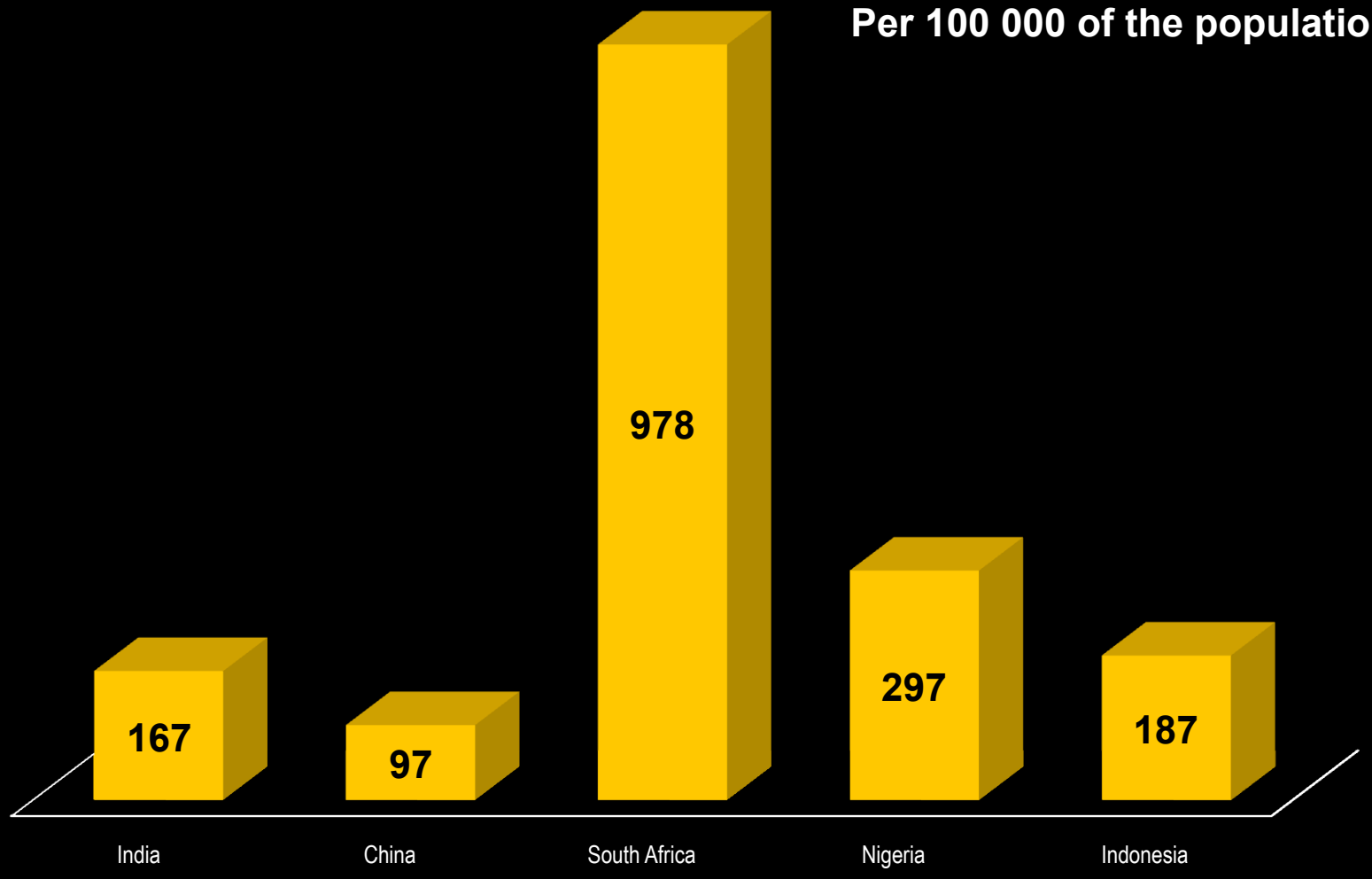
Tuberculosis prevalence per country 2010



WHO Fact sheet N°104, November 2010

World Population Growth

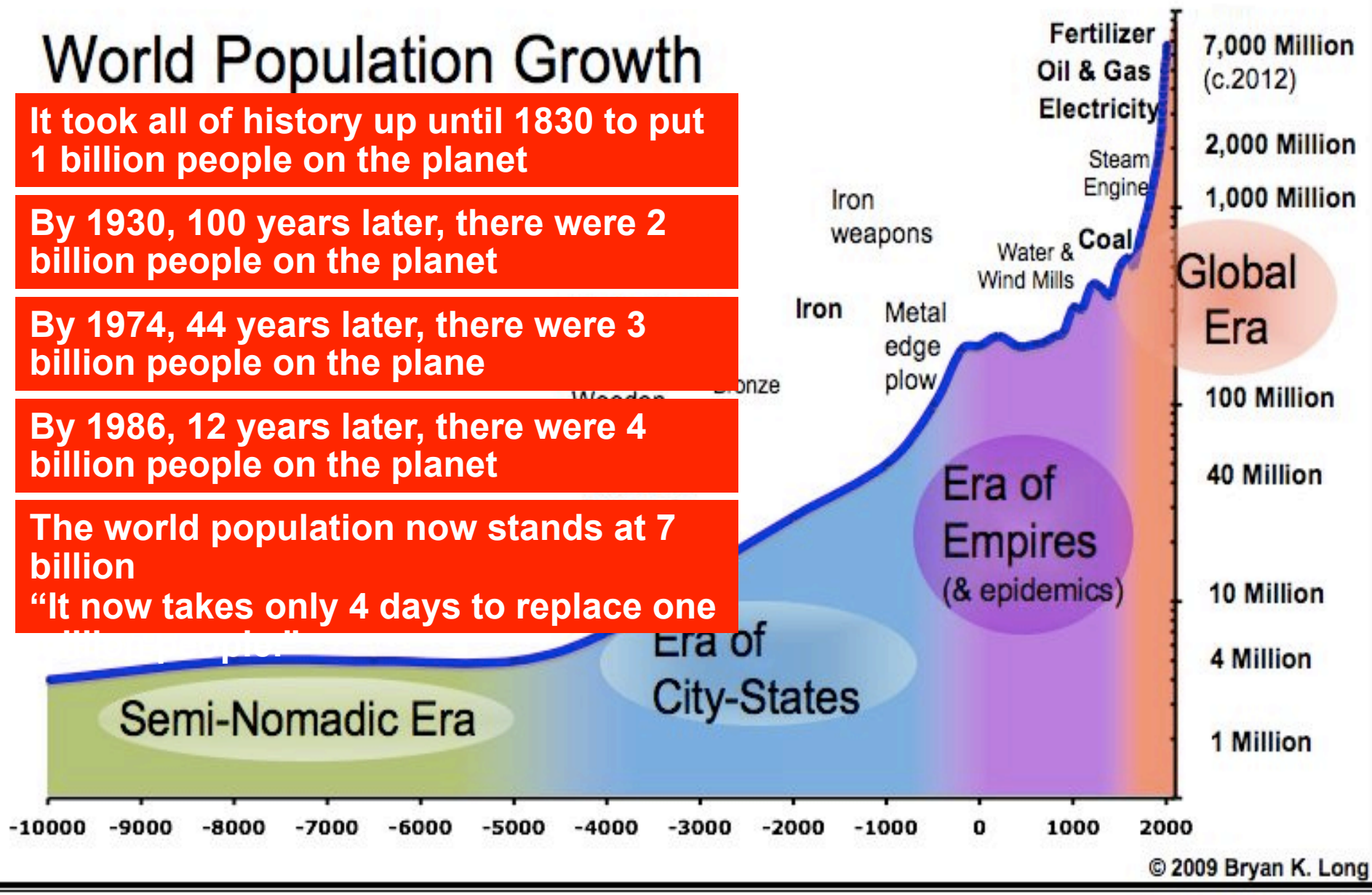
It took all of history up until 1830 to put 1 billion people on the planet

By 1930, 100 years later, there were 2 billion people on the planet

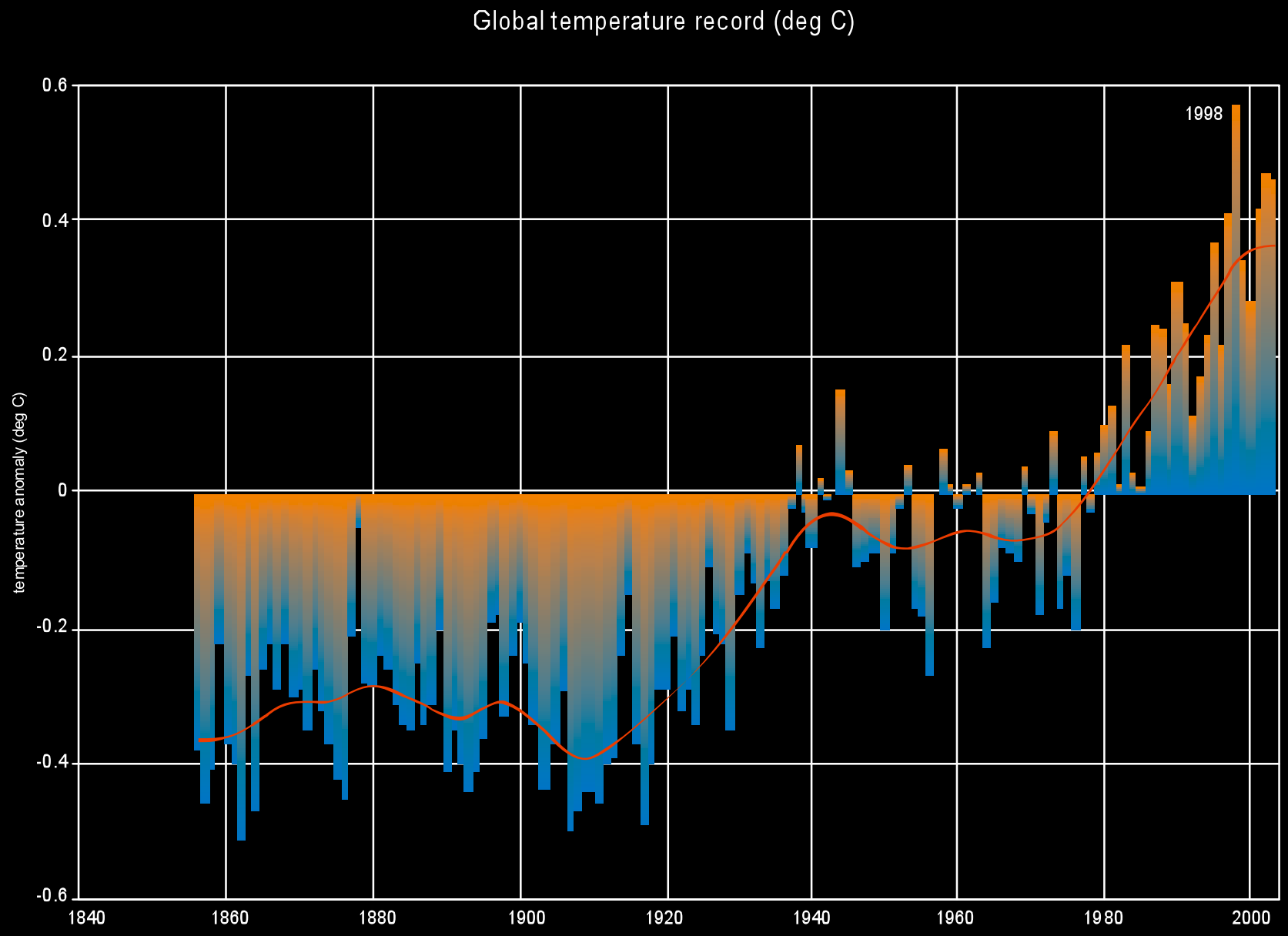
By 1974, 44 years later, there were 3 billion people on the plane

By 1986, 12 years later, there were 4 billion people on the planet

The world population now stands at 7 billion
"It now takes only 4 days to replace one



Increase in Global temperature




Emerging and reemerging diseases
Poverty
Famine
War

Probability of Infection

Mathematical model of airborne infections

$$C = S(1 - e^{-Ipt[Q]})$$ Wells-Riley equation

Probability of Infection = s/c

$$S/C = (1 - e^{-Iqpt[q/Q]})$$

C = number of new cases
S = number of susceptible individuals exposed
e = base of natural logarithms
I = number of infectors
p = pulmonary ventilation rate of susceptible individuals (0.6 m^3/h)
t = exposure time (hours)
Q = absolute room ventilation (m^3/h) = [q/Q]
q = number of infectious "quanta" produced per hour by infectors
Q = volume of disinfected air into which quanta are distributed

Particle size and Infection

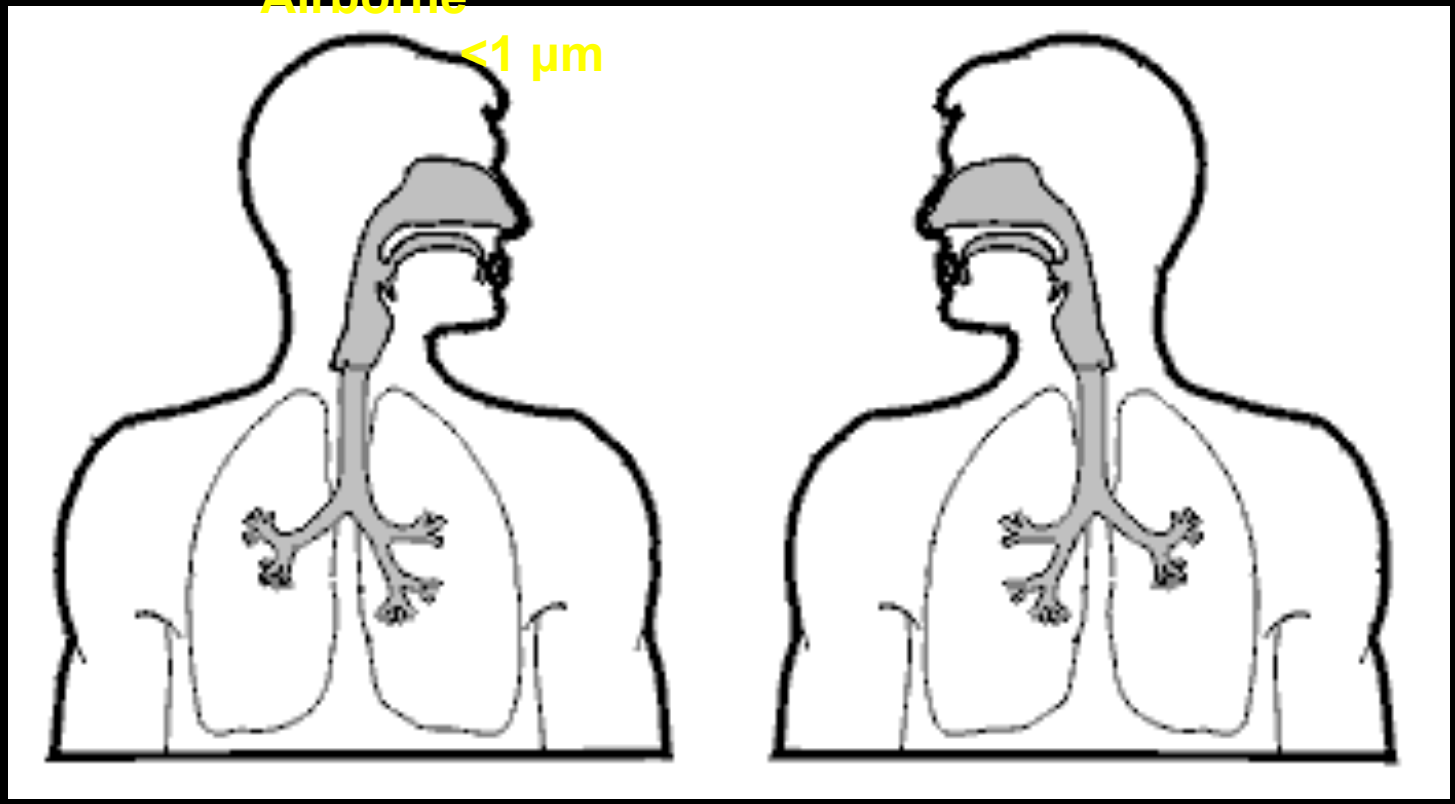
Droplets

>5 µm

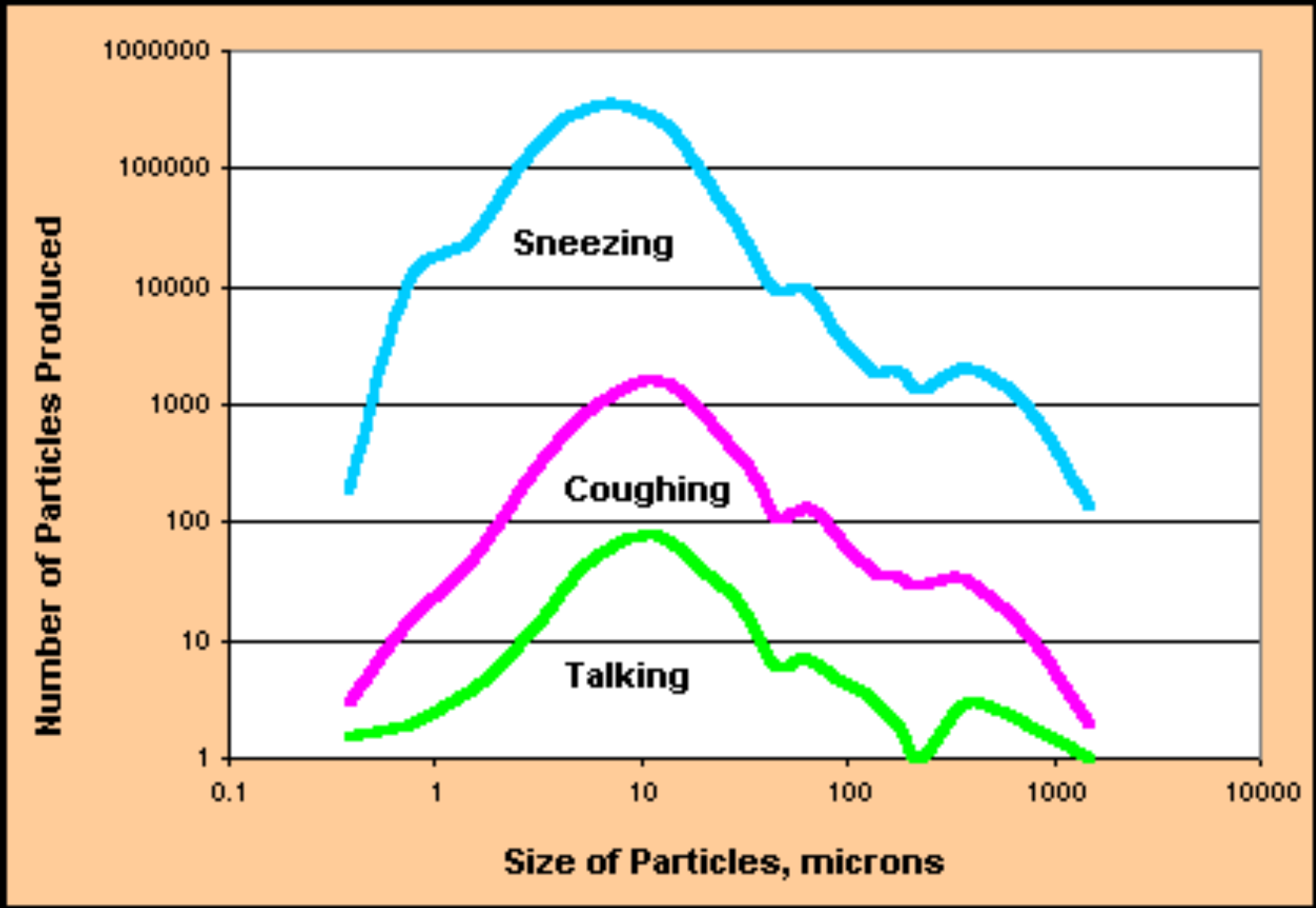
Droplet nuclei **1-5 µm**

Airborne

<1 µm



Airborne tuberculosis

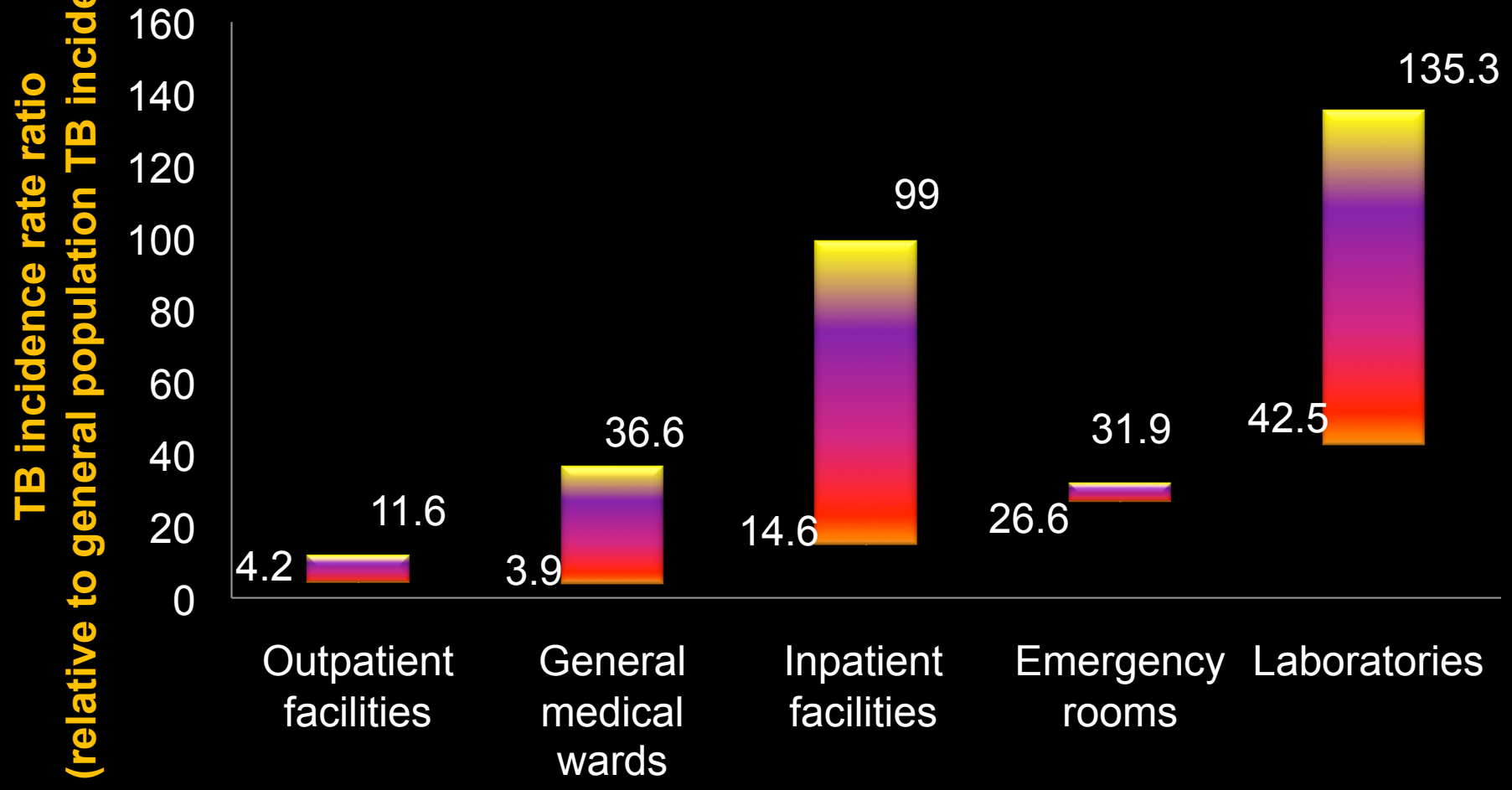


Effect of Particle size

Diameter (μm)	Terminal settling velocity (m/s)	Time to fall 1 meter	Distance to touchdown (m)
1	3.50E-05	7.9 hours	240
5	7.80E-40	21 minutes	11
10	2.90E-03	5.7 minutes	2.9
50	7.50E -02	13 seconds	0.11
100	1.70E-01	5.9 seconds	0.049

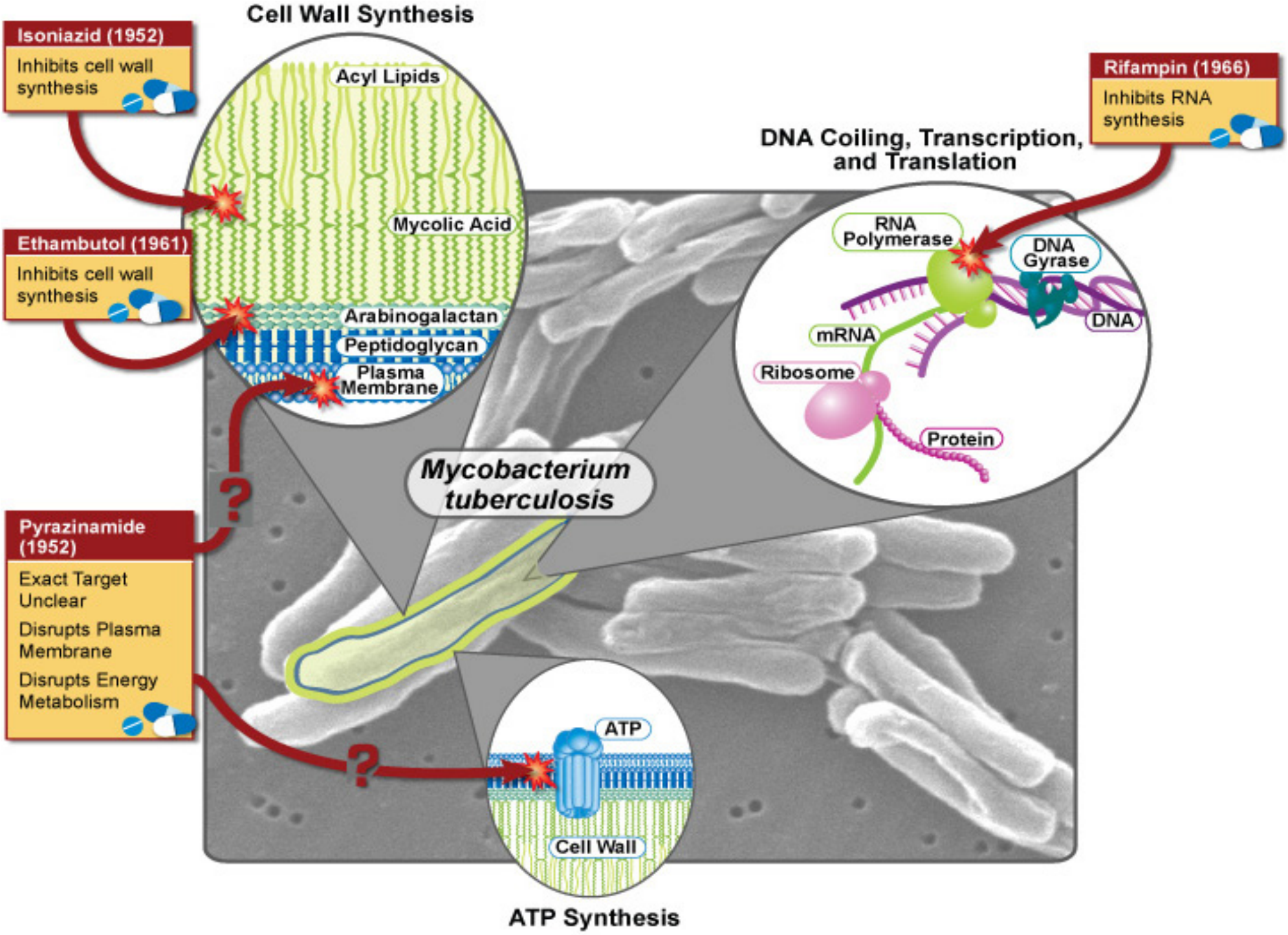
Data by Paul Jensen, CDC

Excess Occupational Risk



Joshi R, Reingold AL, Menzies D, Pai M [2006]. Tuberculosis among health-care workers in low- and middle-income countries: a systematic review. *PLoS Med* 3(12): e494.

Menzies D, Joshi R, Pai M [2007]. Risk of tuberculosis infection and disease associated with work in health care settings. *Int J Tuberc Lung Dis* 11(6): 593-605.


Cell Wall Synthesis
Isoniazid (1952)
Inhibits cell wall synthesis
Acyl Lipids
Mycolic Acid
Ethambutol (1961)
Inhibits cell wall synthesis
Arabinogalactan
Peptidoglycan
Plasma Membrane
Rifampin (1966)
Inhibits RNA synthesis
DNA Coiling, Transcription, and Translation
RNA Polymerase
DNA Gyrase
DNA
mRNA
Ribosome
Protein
Mycobacterium tuberculosis
Pyrazinamide (1952)
Exact Target Unclear
Disrupts Plasma Membrane
Disrupts Energy Metabolism
?
?
ATP
Cell Wall
ATP Synthesis

Types of DR-TB

Mono-resistance

- TB strains that are resistant to at least one anti-TB first-line drug (R or H or Z or E)

Poly-resistance

- TB strains that are resistant to at least two anti-TB first-line drugs (R or H or Z or E) but not R and H together

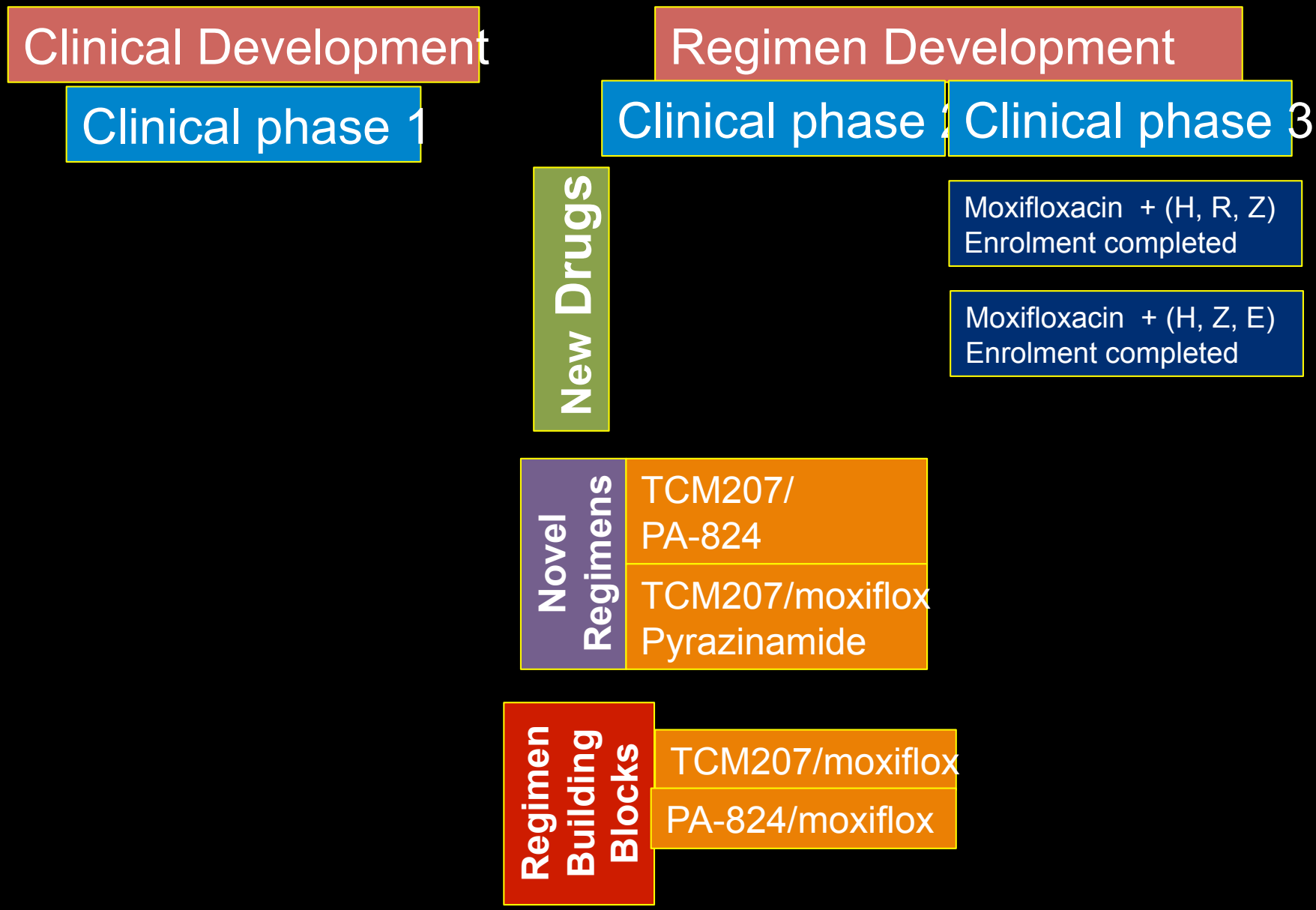
MDR-TB

- TB strains resistant to rifampicin and isoniazid with or without resistance to other first-line TB drugs

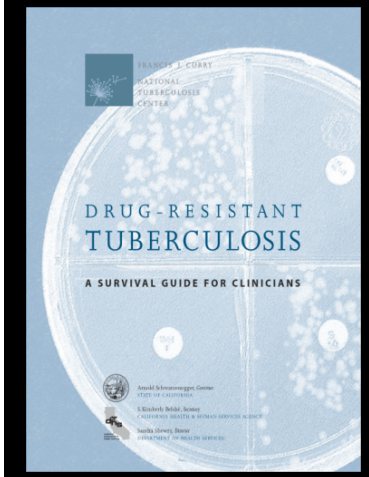
XDR-TB

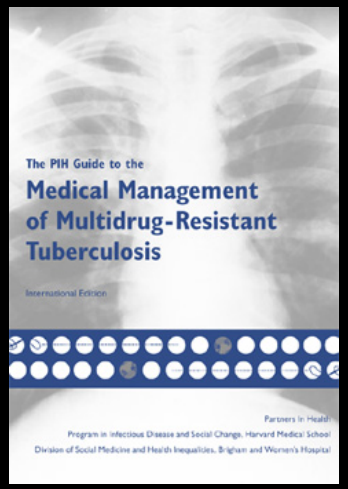
- TB strains resistant to rifampicin, isoniazid, any second line injectables (Am, Km or Cm) and to any fluoroquinolone

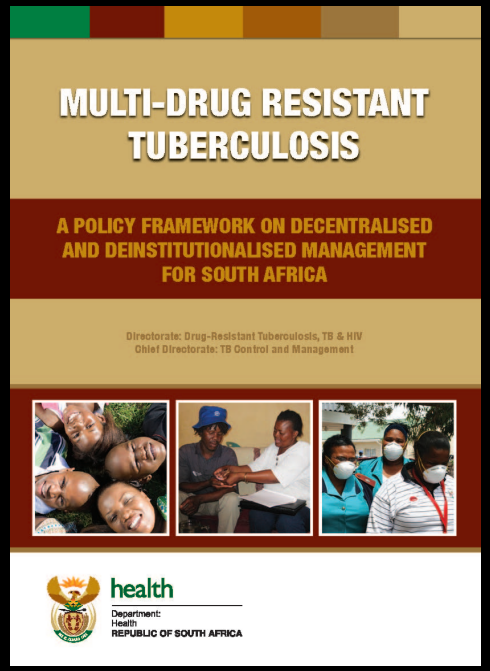
Tuberculosis treatment pipeline 2012

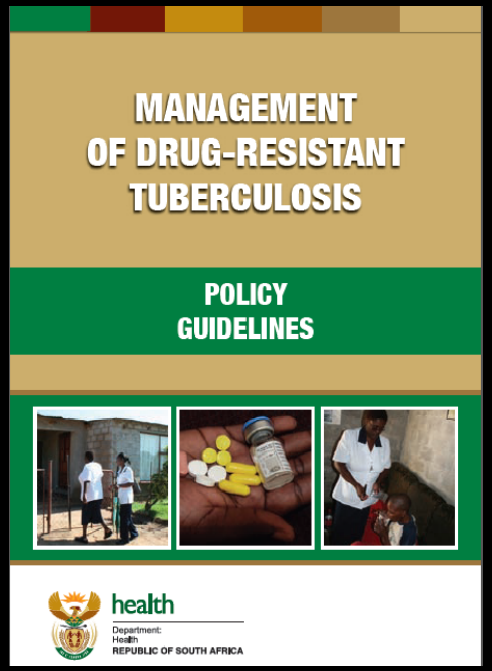


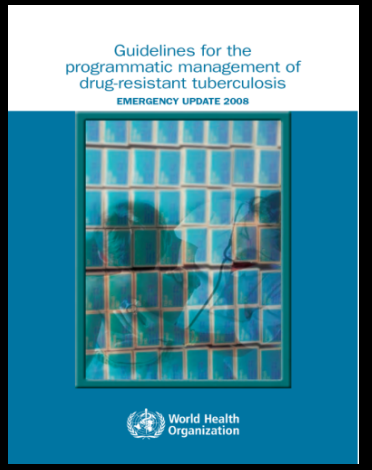
MDR-TB Treatment Strategies

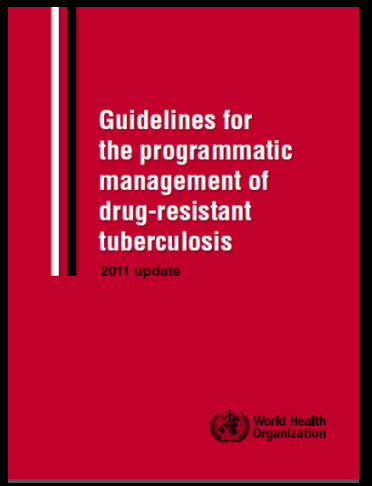








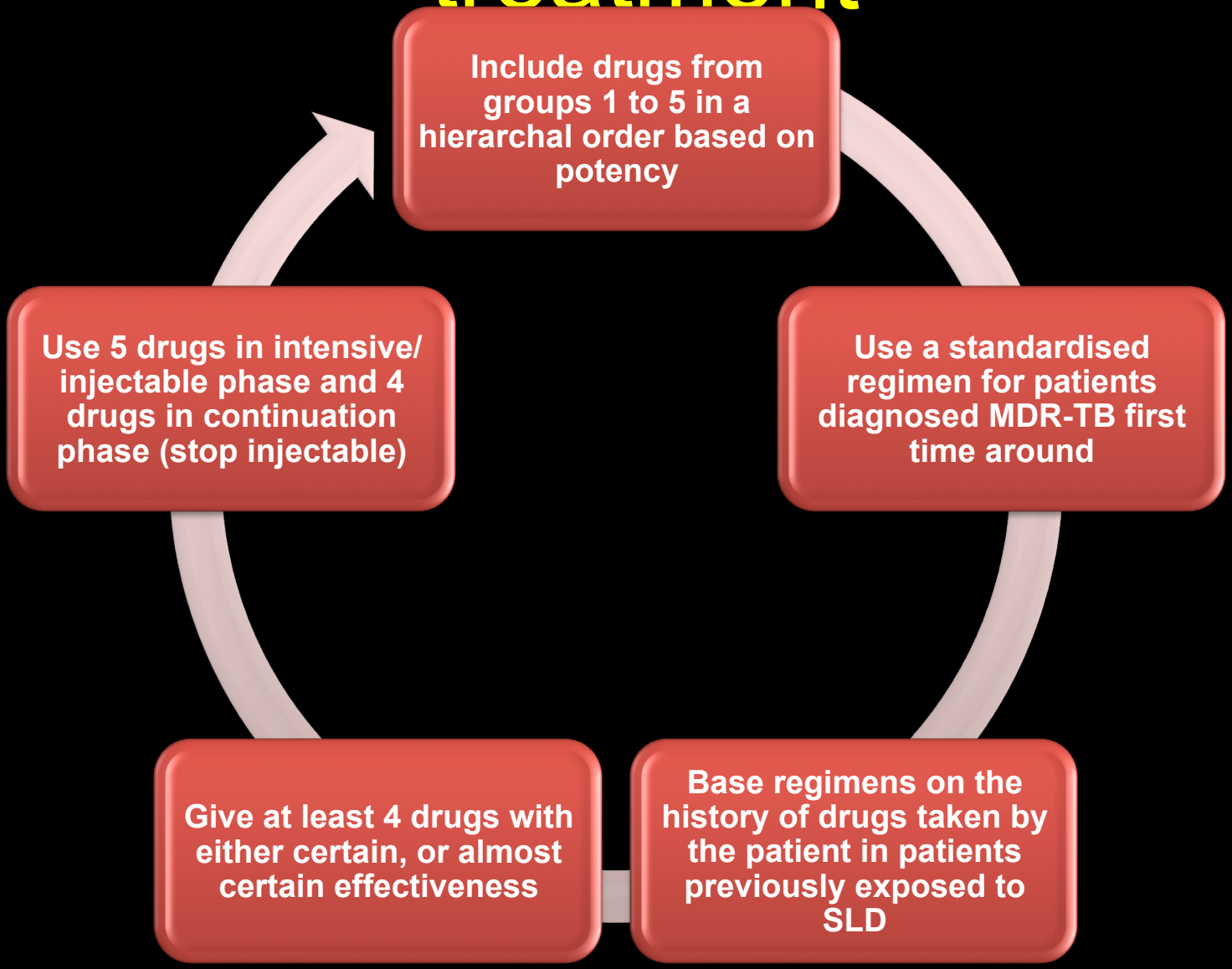




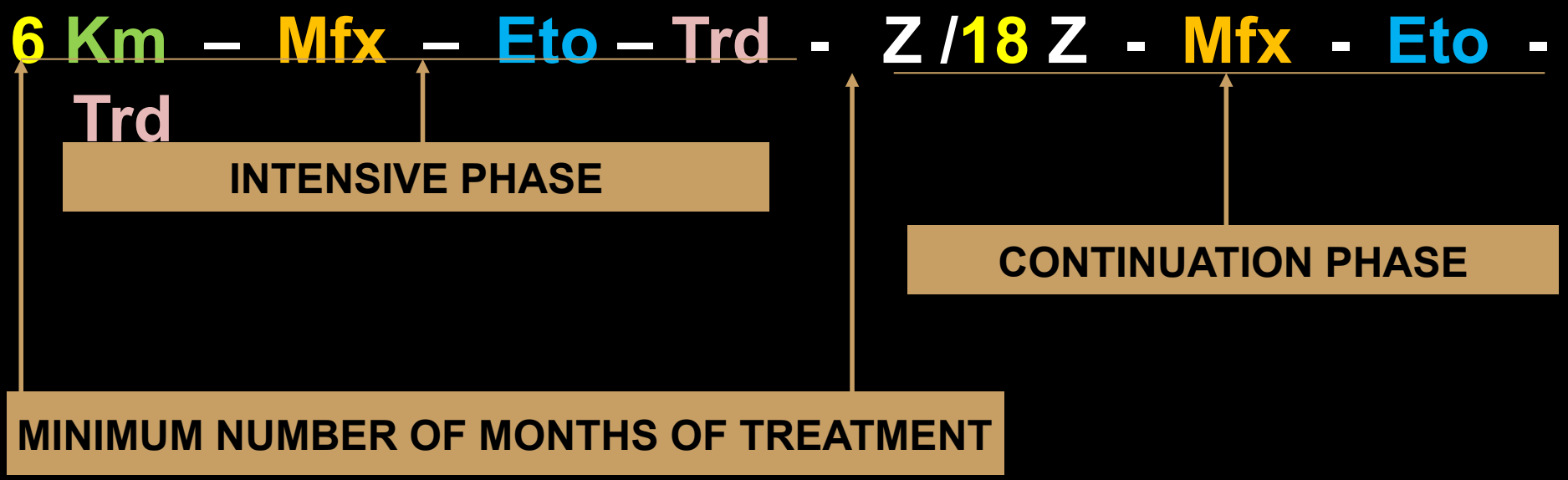
TB Drugs Grouping

Group	Anti-TB agents	Drugs
1	First-line oral	Isoniazid (H), Rifampicin (R), Ethambutol (E)and Pyrazinamide (Z)
2	Injectables	Streptomycin (S), Kanamycin (Km), Amikacin (Am), Capreomycin (Cm) and Viomycin (Vi)
3	Fluoroquinolones	Ofloxacin (Ofx), Levofloxacin (Lfx), Moxifloxacin (Mfx) and Gatifloxacin (Gfx)
4	Second-line oral bacteriostatic	Ethionamide (Eto), Protionamide (Pto), Cycloserine (Cs), Terizidone (T) p-aminosalicylic acid (PAS)
5	Anti-TB agents with unclear efficacy	Clofazimine (Cfz), Amoxicillin/Clavulanate (Amx/Clv), **Thioacetazone, Imipenem, High-dose INH** Clarithromycin (Clr), Linezolid (Lzd)

General Principles MDR treatment



MDR-TB Regimen (Adults &Children > 8 years)



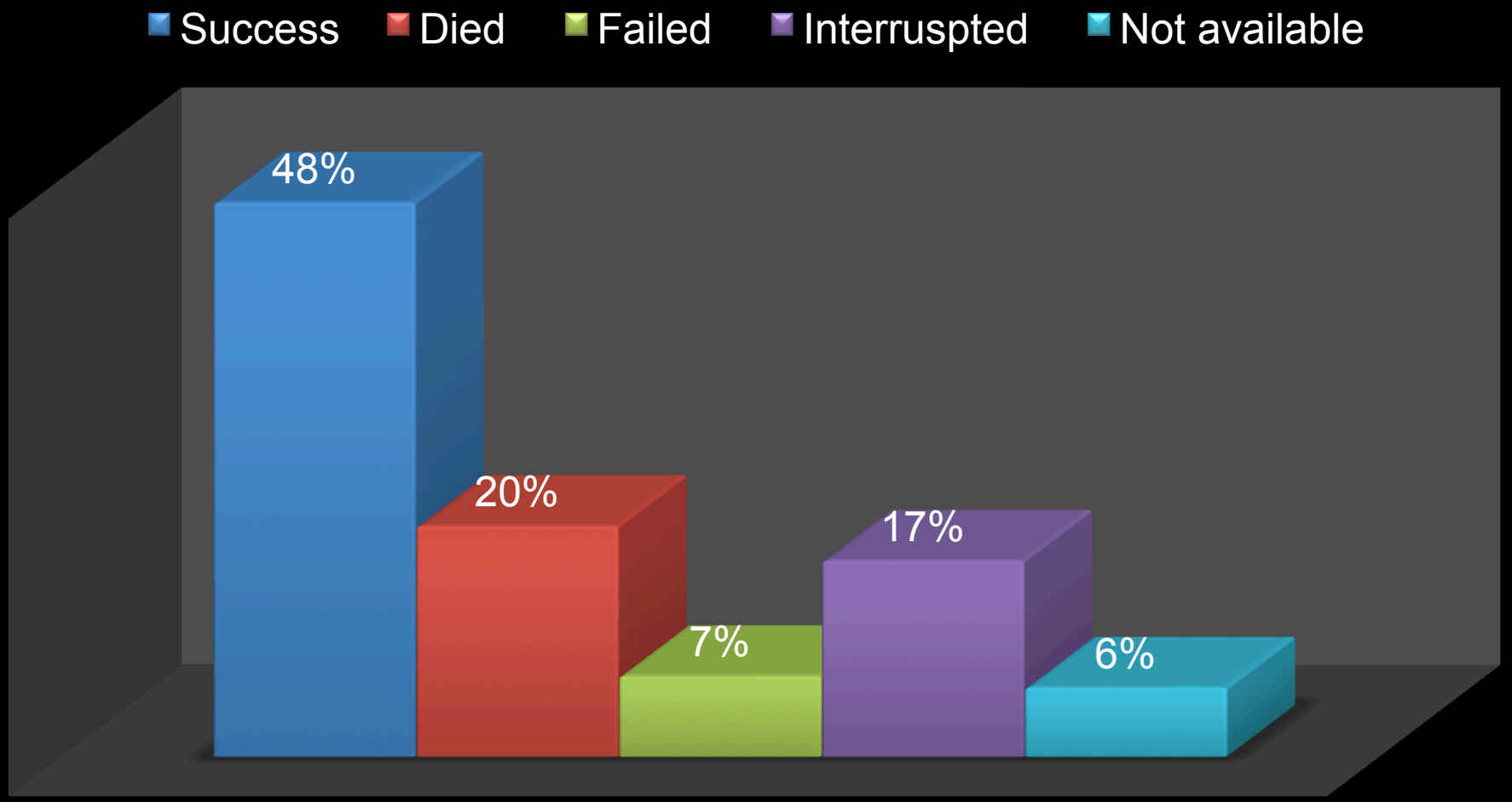
Source: RSA MDR-TB Guidelines,2011

Medical cost of treating MDR-TB patient > 50 kg [Tender HP01-2011TB, HP01-2011TB/01 & HP01-2011TB/01 (supplementary contract)]

Drug-susceptible TB: R 257		
Intensive phase (4 tabs RHZE dly)	R 50/month	R 100 for 2 months
Continuation phase (2 tabs RH 300/150 dly)	R 40/month	R 157 for 4 months
MDR-TB: R 23,755.44 per patient		
Injectable phase	R 1,248.56/month	R 7,491.36 for 6 months
Kanamycin 1g IM daily	R 345 (30 vials)	R 2,070
Moxifloxacin 400 mg po daily	R 108.30 (30 tablets)	R 649.8
Ethionamide 250 mg x 3 po dly	R 122.09 (84 tablets)	R 732.54
Terizidone 250 mg x 3 po daily	R 641.82 (100 capsules)	R 3,850.92
Pza 500 mg x 3 po dly	R 31.35 (84 tablets)	R 188.1
Continuation phase	R 903.56/month	R 16,264.08 for 18 months

The cost of treating 1 MDR-TB patient is equivalent to treating 100 drug-susceptible patients

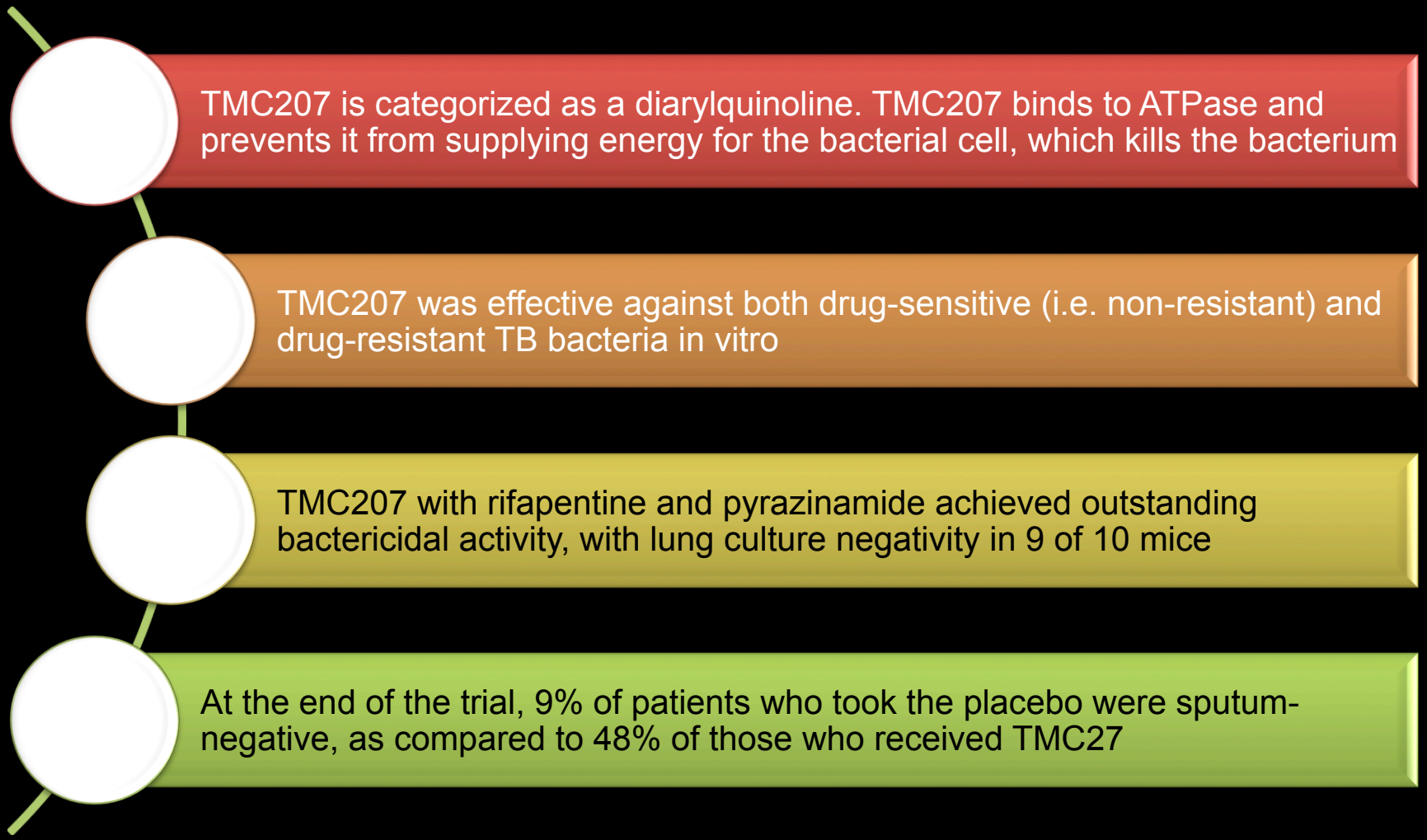
Treatment Outcomes of MDR-TB cases, South Africa: 2007-08



Dr Norbert Ndjeka


New Drugs

TMC207 (diarylquinoline)

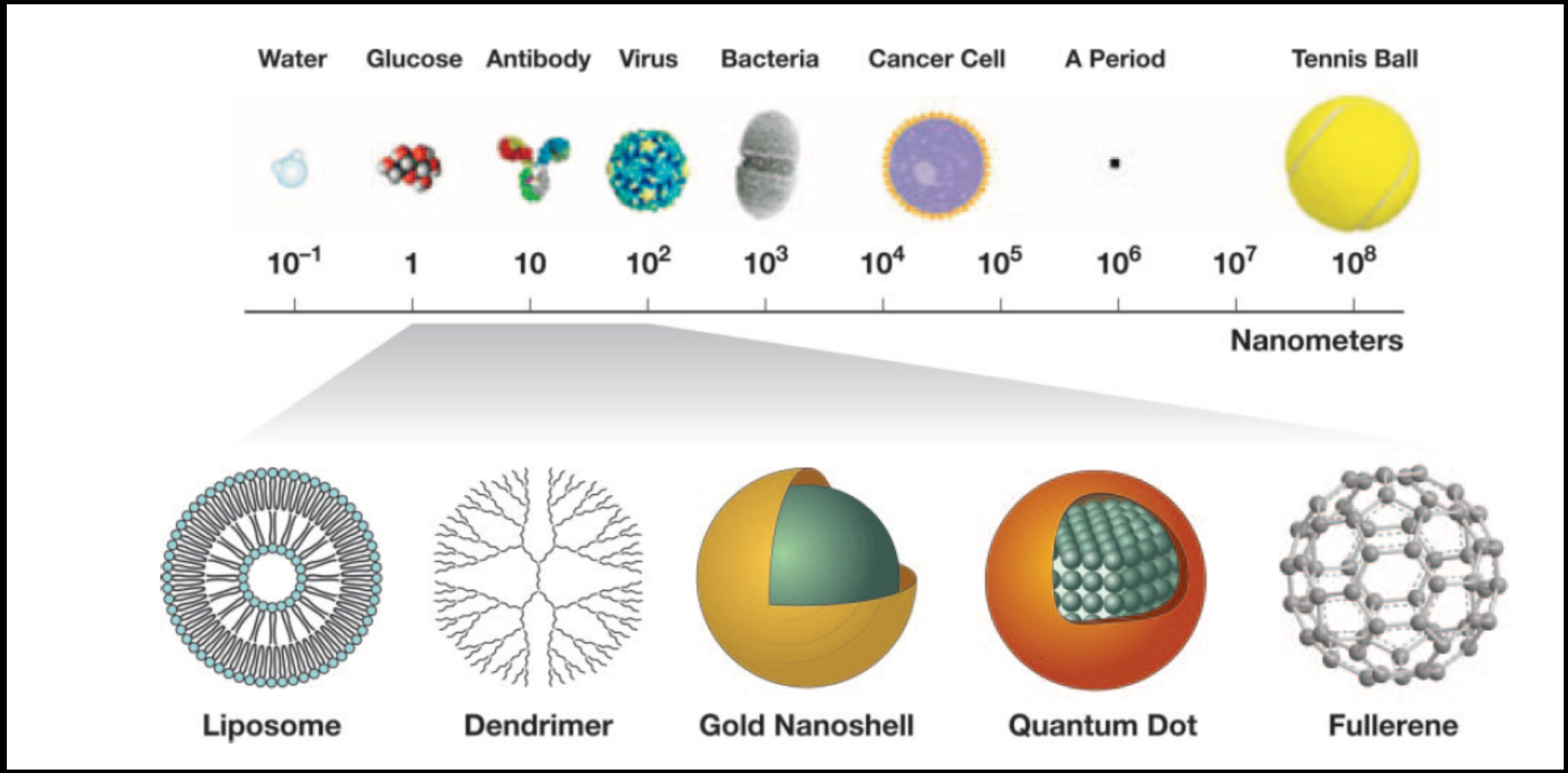


K Andries et al. A Diarylquinoline Drug Active on the ATP Synthase of Mycobacterium tuberculosis. Science. 2005 Jan 14; 307(5707): 223-7


New Developments

Nanomedicine

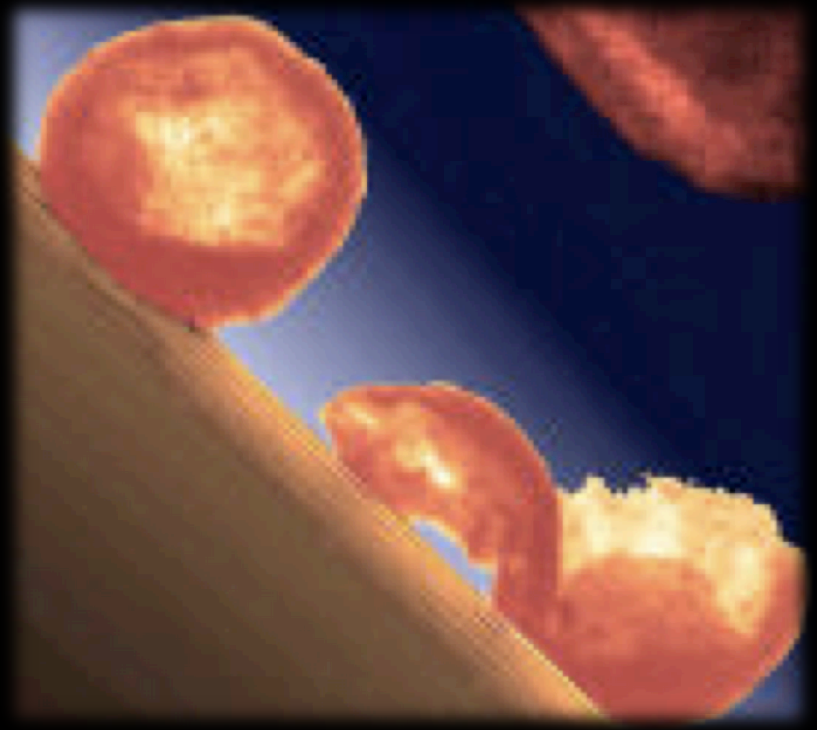
- Application of nanotechnology in health
- Nanosized drug delivery systems for treatment



Journal of Leukocyte Biology Volume 78, September 2005

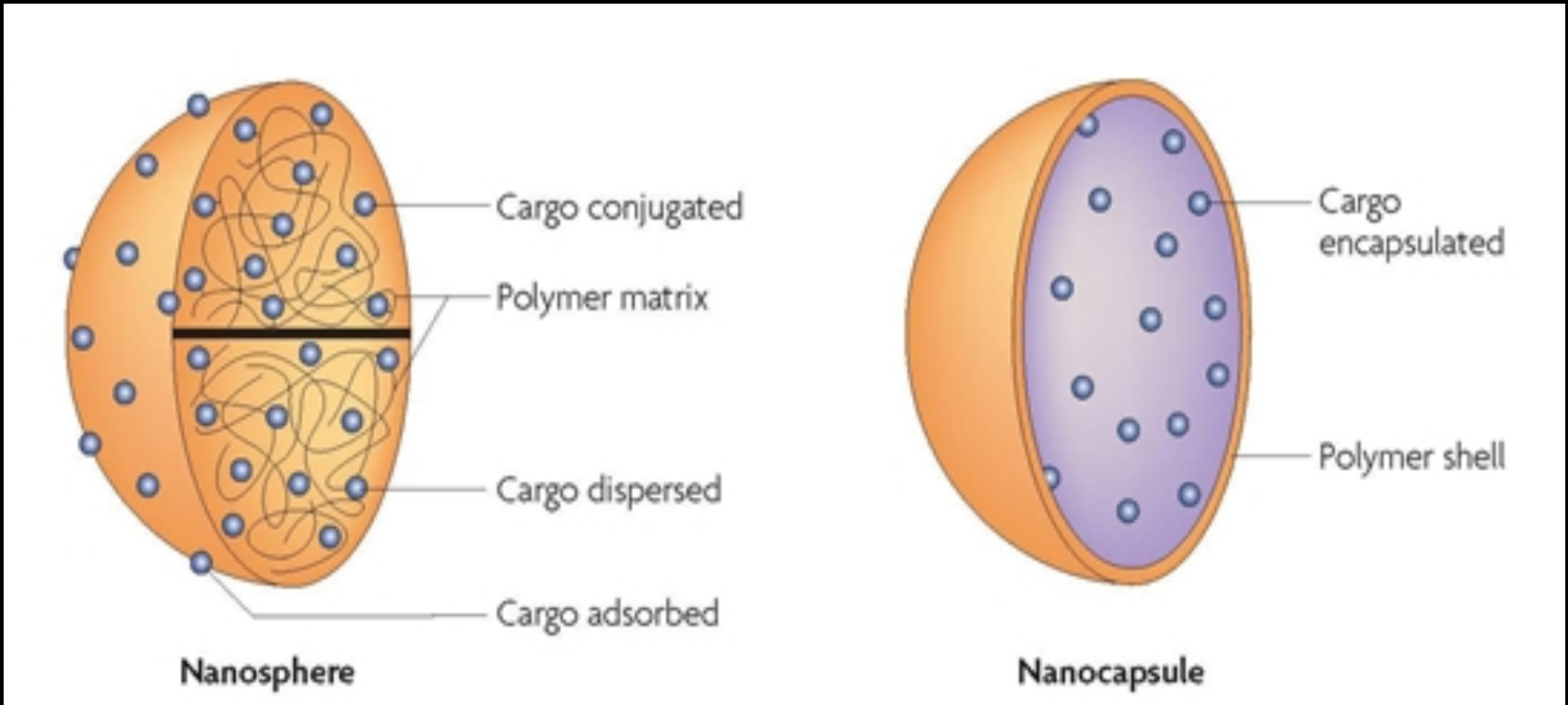
Pharmacokinetic advantages of nanomedicine

- Enhanced drug stability
- High carrying capacity
- Enhance absorption and bioavailability
- Reduce clearance
  - minimised first pass metabolism
- Selective uptake by tissues (passive targeting)



Lemmer Y , et al. CSIR.

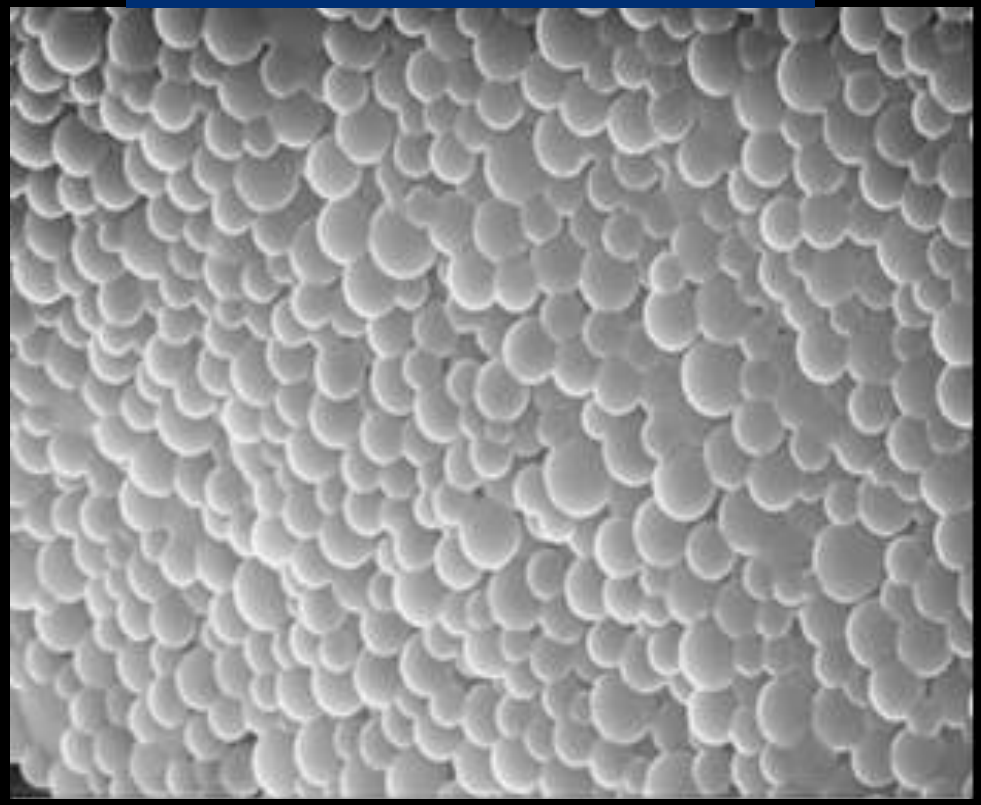
Nanotechnology



Nature Reviews Microbiology. Nov2010, Vol. 8 Issue 11, p827-834

Nanoparticles encapsulating anti-TB drugs (Nanodrug)

250 nm average size

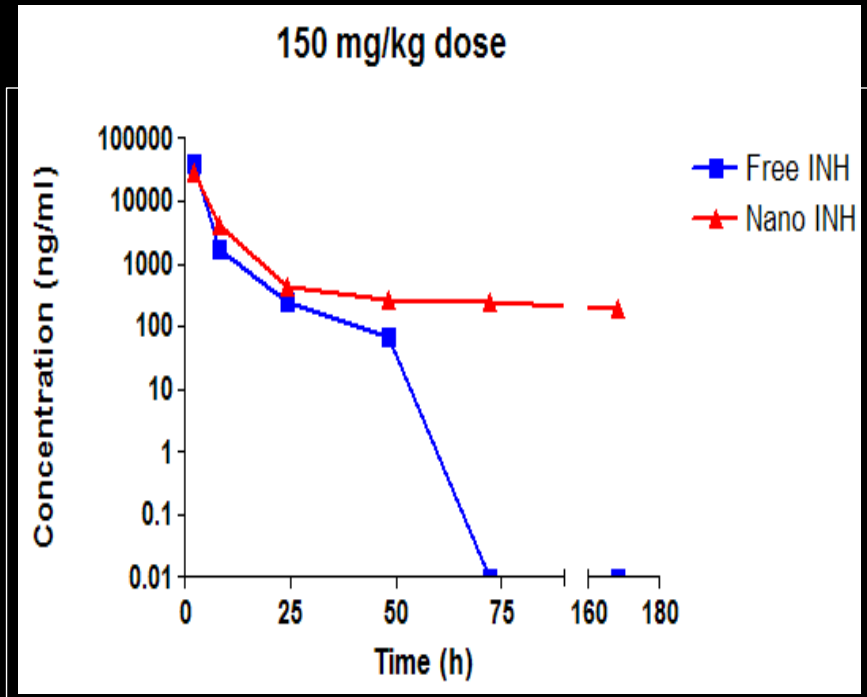


Poly (lactide-co-glycolide) (PLGA) polymer

- Successfully nano encapsulated 4 of the first line anti-TB drugs
  - Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA) and Ethambutol (ETB)
  - Double emulsion solvent evaporation - spray drying technique

Lemmer Y , et al. CSIR.

Pharmacokinetics of nano-encapsulated rifampicin



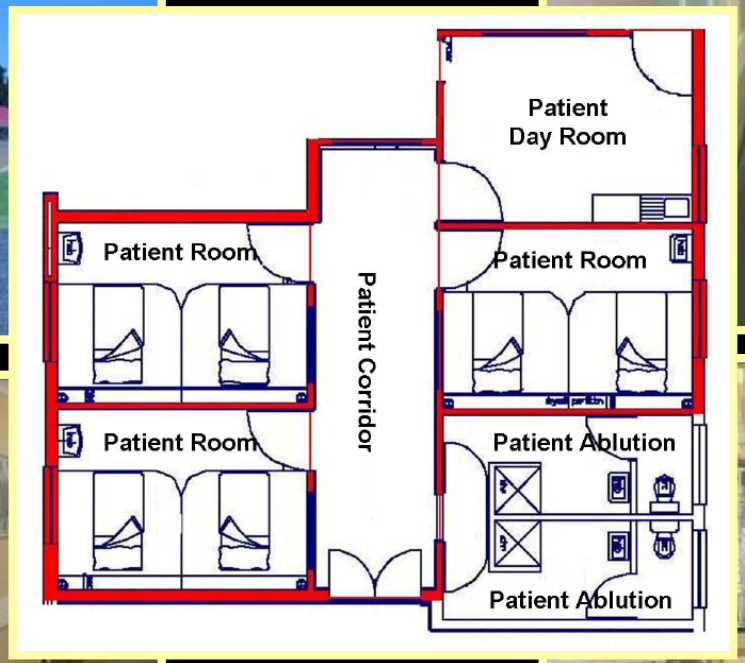
- **Sustained release of RIF and INH from PLGA nanoparticles**
- **Increase in drug half-life**
- **Potential for dose frequency reduction**

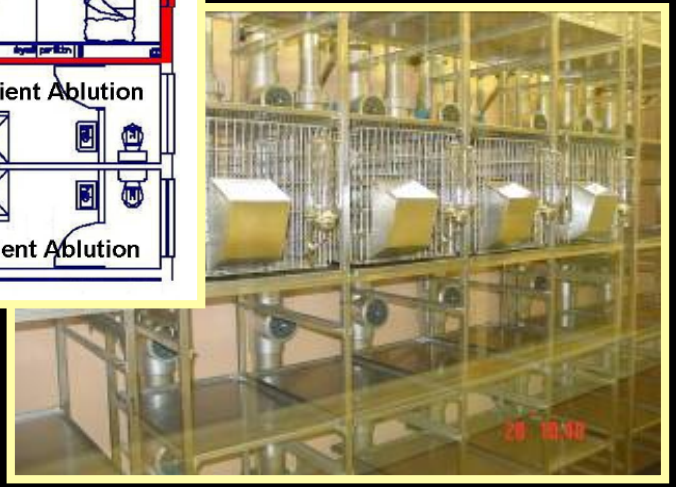
Once weekly dose nano TB drug equal to daily dosing

Lemmer Y , et al. CSIR.

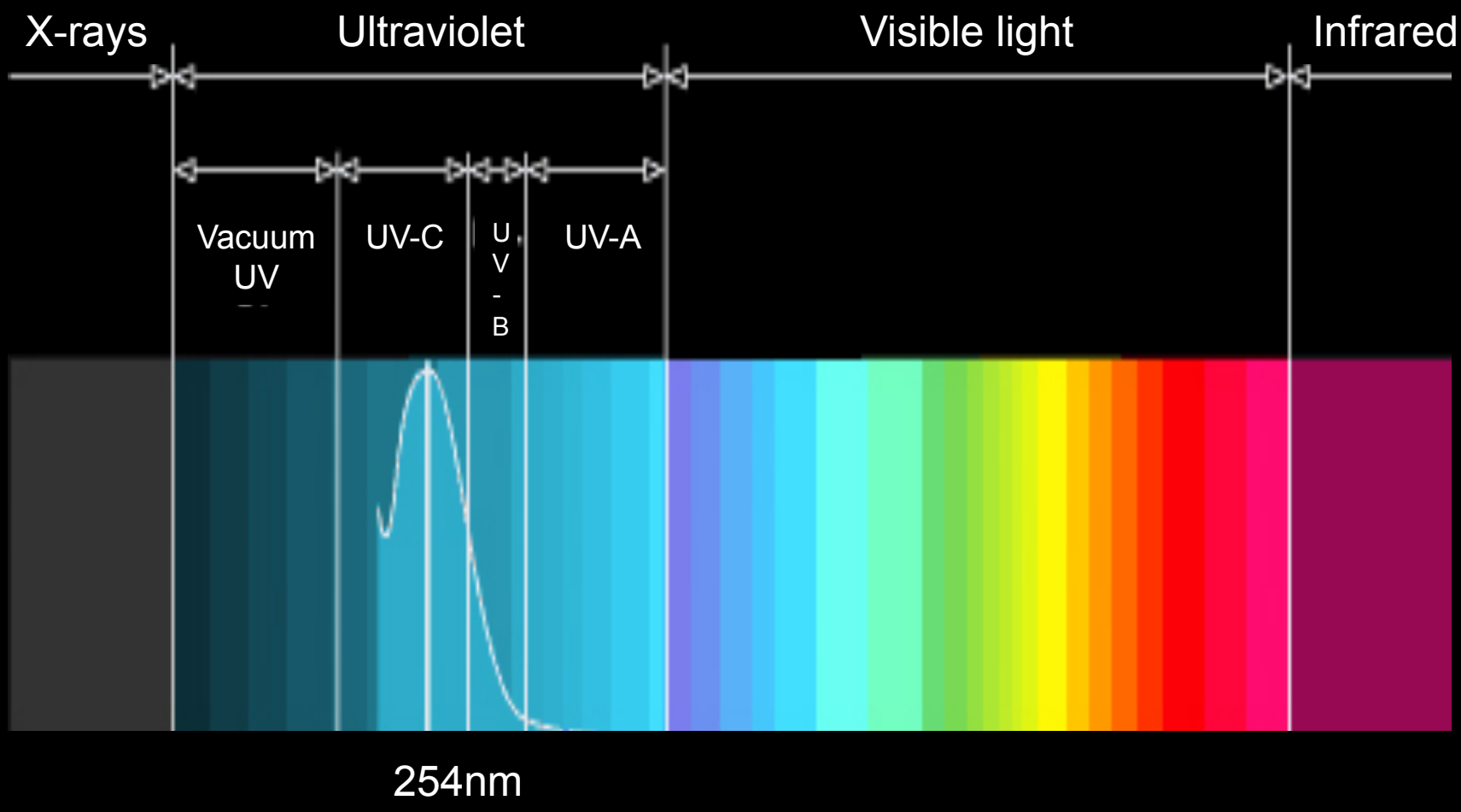
The AIR Facility

Witbank, Mpumalanga Provence, RSA



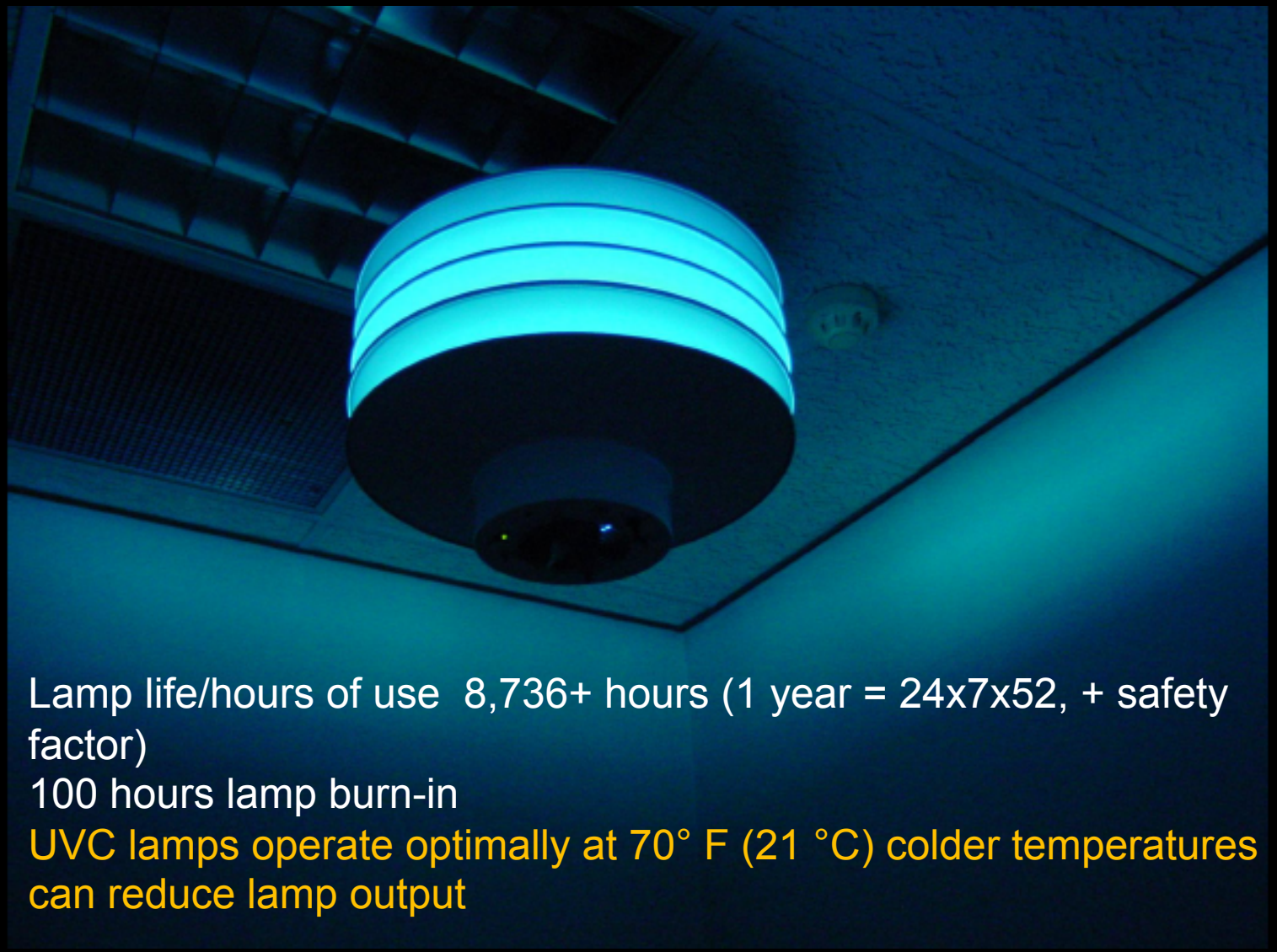


Engineering controls - UVGI



UVA (380–315 nm), also called Long Wave or "blacklight"
UVB (315–280 nm), also called Medium Wave
UVC (< 280 nm), also called Short Wave or "germicidal"

South Africa designed UVGI



Lamp life/hours of use 8,736+ hours (1 year = 24x7x52, + safety factor)

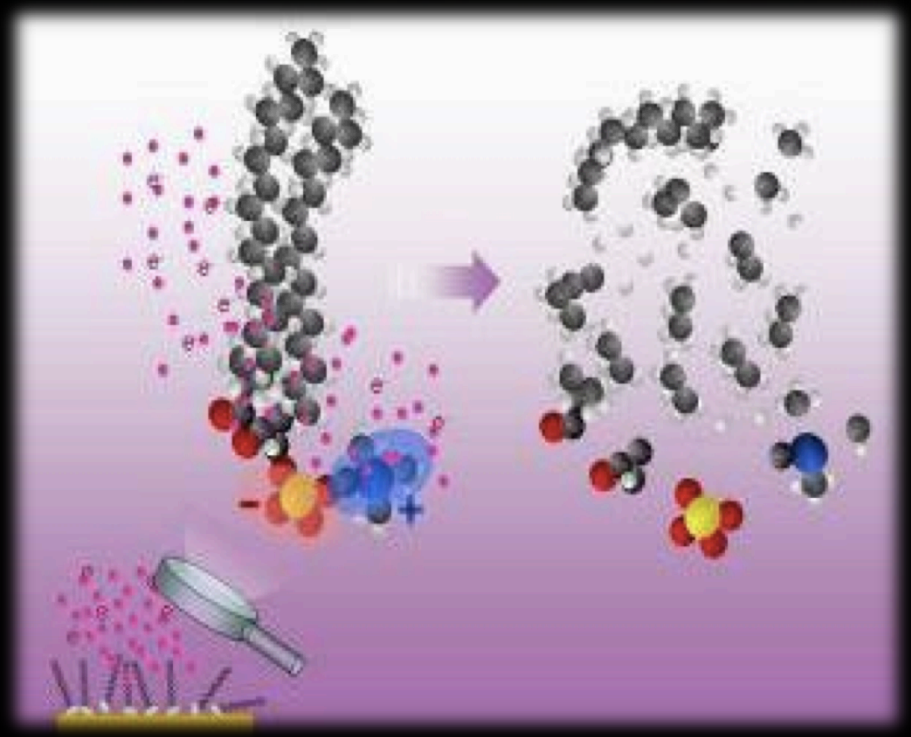
100 hours lamp burn-in

UVC lamps operate optimally at 70° F (21 °C) colder temperatures can reduce lamp output

DHHS (NIOSH) Publication 2009-1

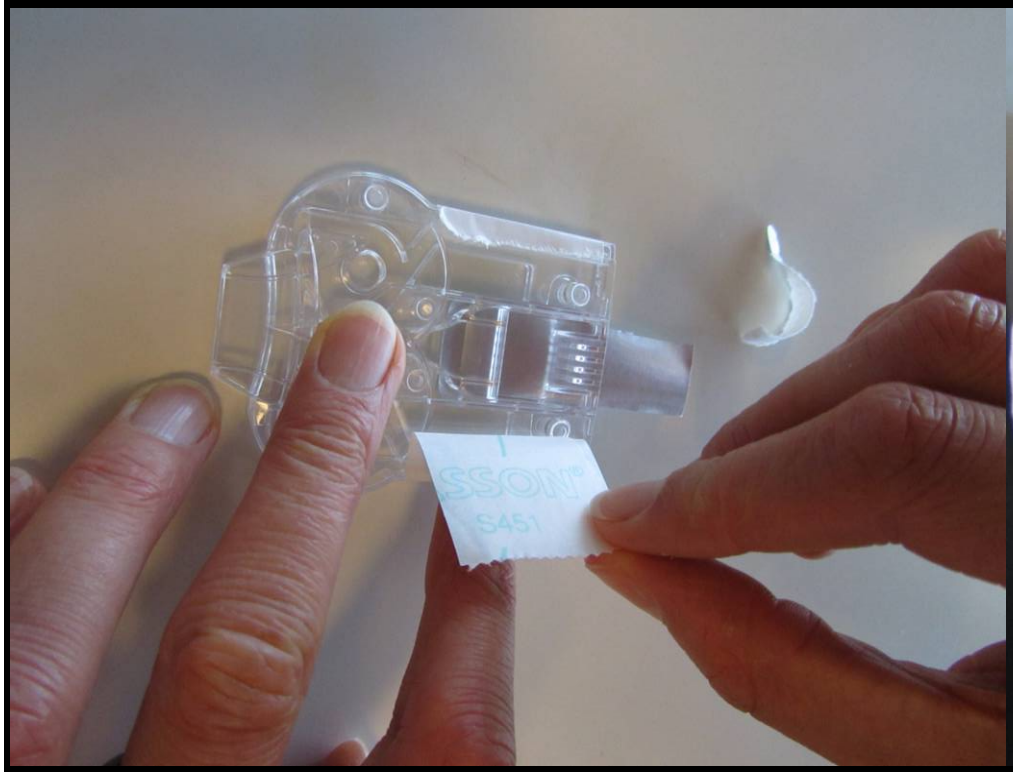
Decrease TB infection by 83%

Colistin and membranes



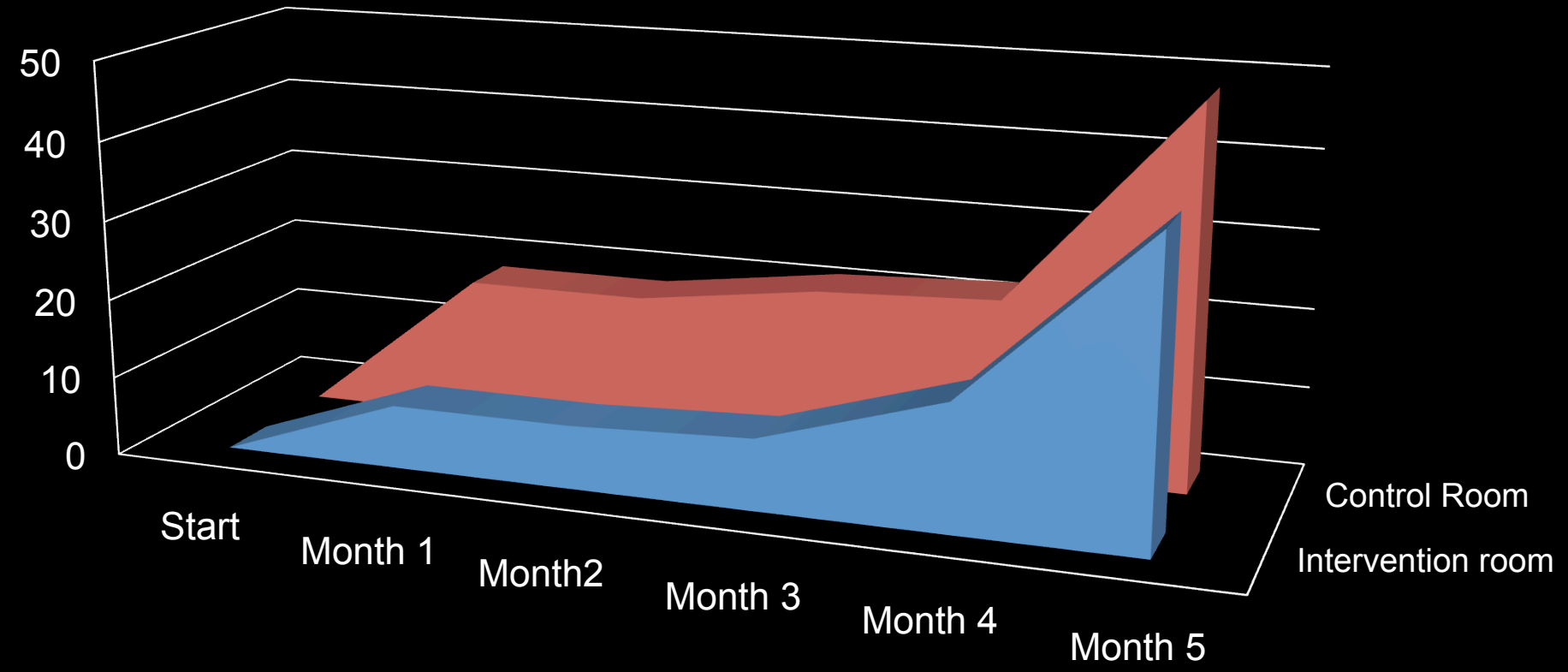
Colistin displaces divalent cations on lipid membranes

Dry powder Colistin via Twincer™ device



Stoltz A C, et al. unpublished data

ICARUS study



	Start	Month 1	Month2	Month 3	Month 4	Month 5
Intervention room	0	8	8	9	16	38
Control Room	0	18	18	21	22	48

Stoltz A C, et al. unpublished data

TB scanning electron microscope

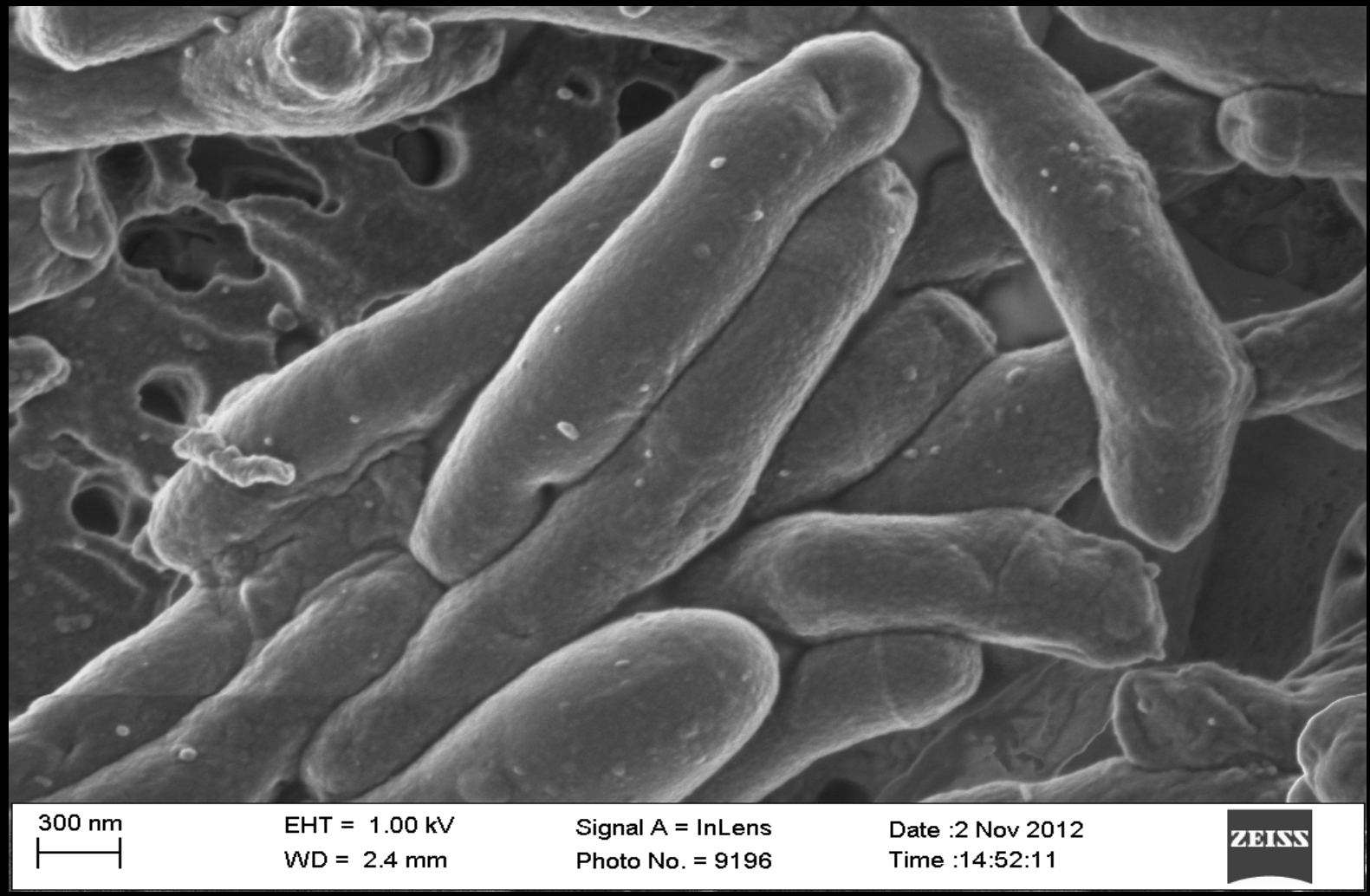


Figure : SEM image of XDR control sample. No membrane damage. Rods are intact. Has a coliflower appreance.

Stoltz A C, et al. unpublished data

TB + colistin scanning - electron microscope

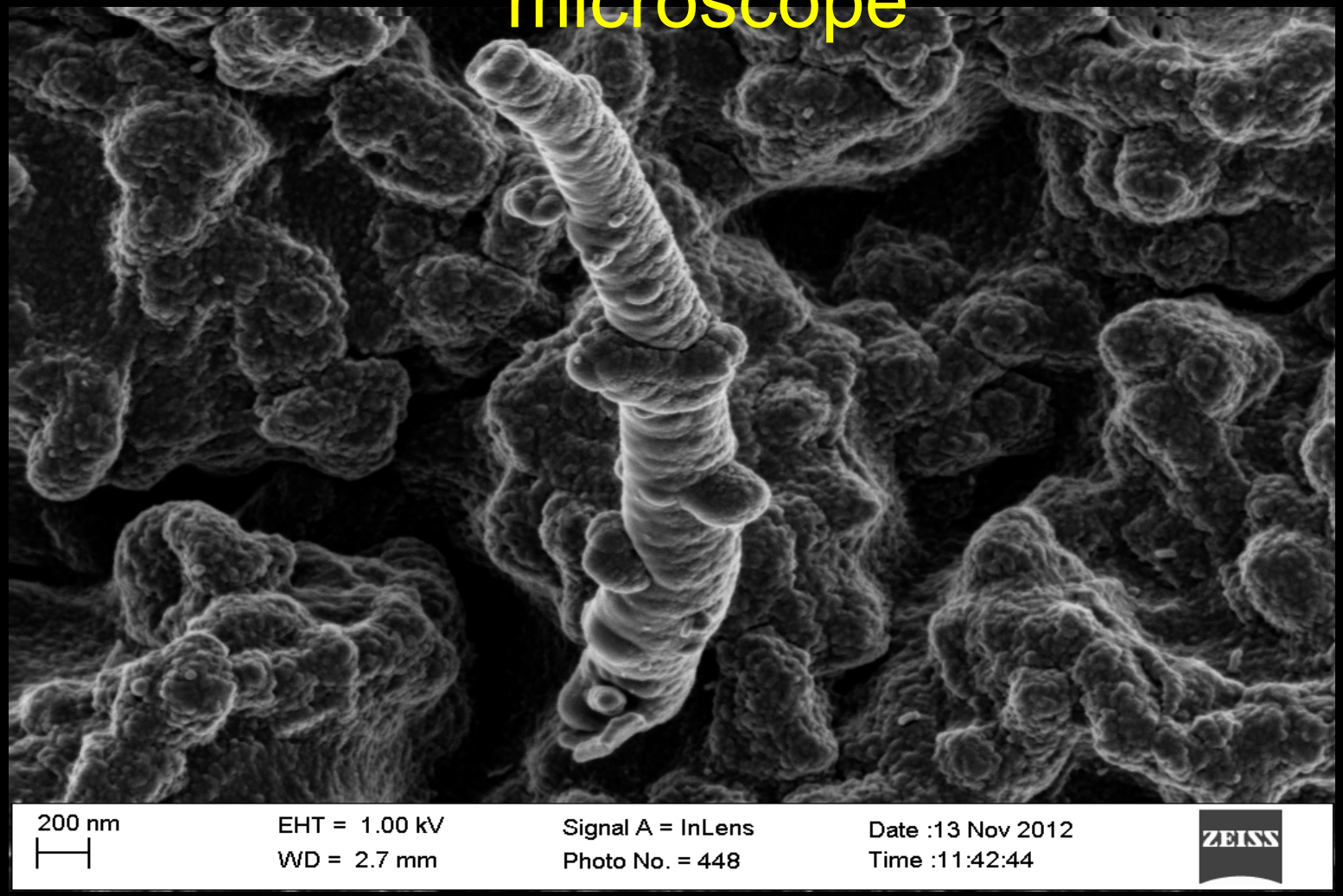


Figure : SEM image of XDR sample 12.5 ug/ml CMS. Evidence of cell wall damage, deformation and bulging. INH samples show cavitation.

Tuberculosis anywhere is Tuberculosis everywhere