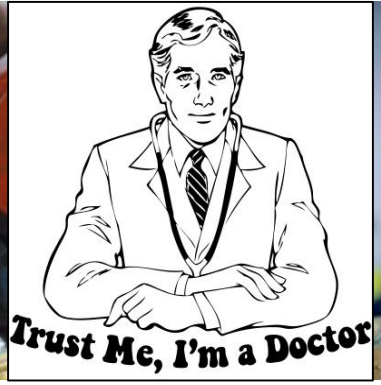





'*Do not go gentle into that good night*'. Lessons learned from our slide into the post-antibiotic era

Marc Mendelson

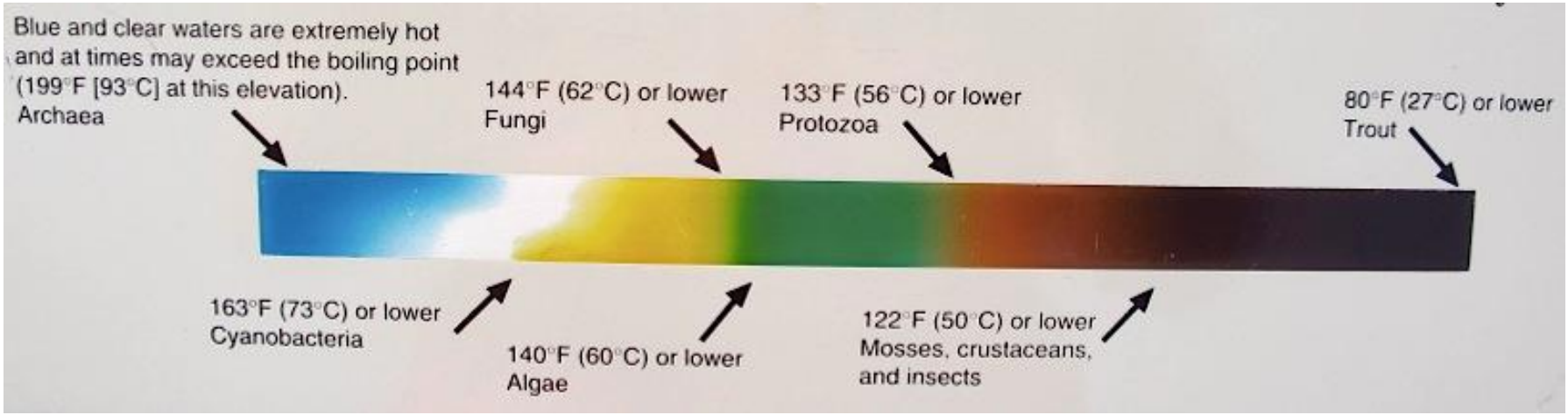
Division of Infectious Diseases & HIV Medicine

University of Cape Town

Antimicrobial Stewardship describes the multi-disciplinary, systematic approach to optimising the appropriate use of antimicrobials to improve patient outcome and limit emergence of resistant pathogens whilst ensuring patient safety.

While drivers of resistance and treatment failure differ between microbes unifying themes exist.

Extremophiles (thermophiles)

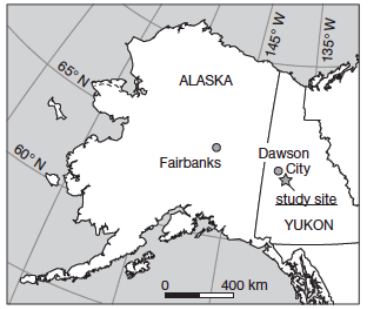


LETTER

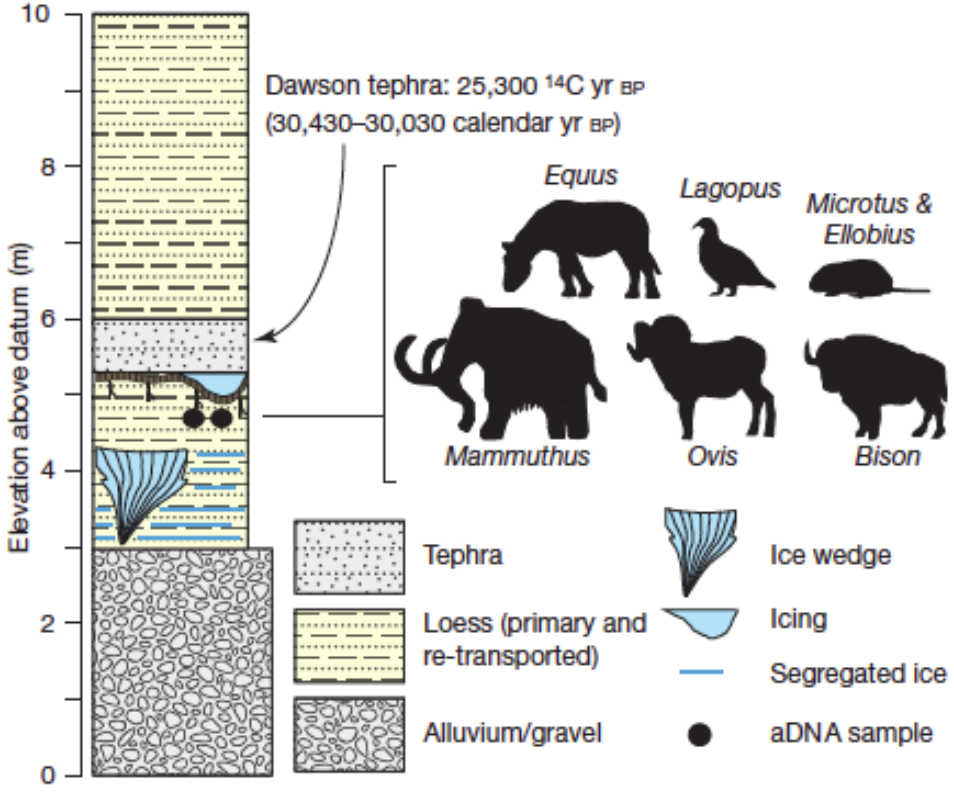
doi:10.1038/nature10388

Antibiotic resistance is ancient

Vanessa M. D'Costa[1,2]*, Christine E. King[3,4]*, Lindsay Kalan[1,2], Mariya Morar[1,2], Wilson W. L. Sung[4], Carsten Schwarz[3], Duane Froese[5], Grant Zazula[6], Fabrice Calmels[5], Regis Debruyne[7], G. Brian Golding[4], Hendrik N. Poinar[1,3,4] & Gerard D. Wright[1,2]

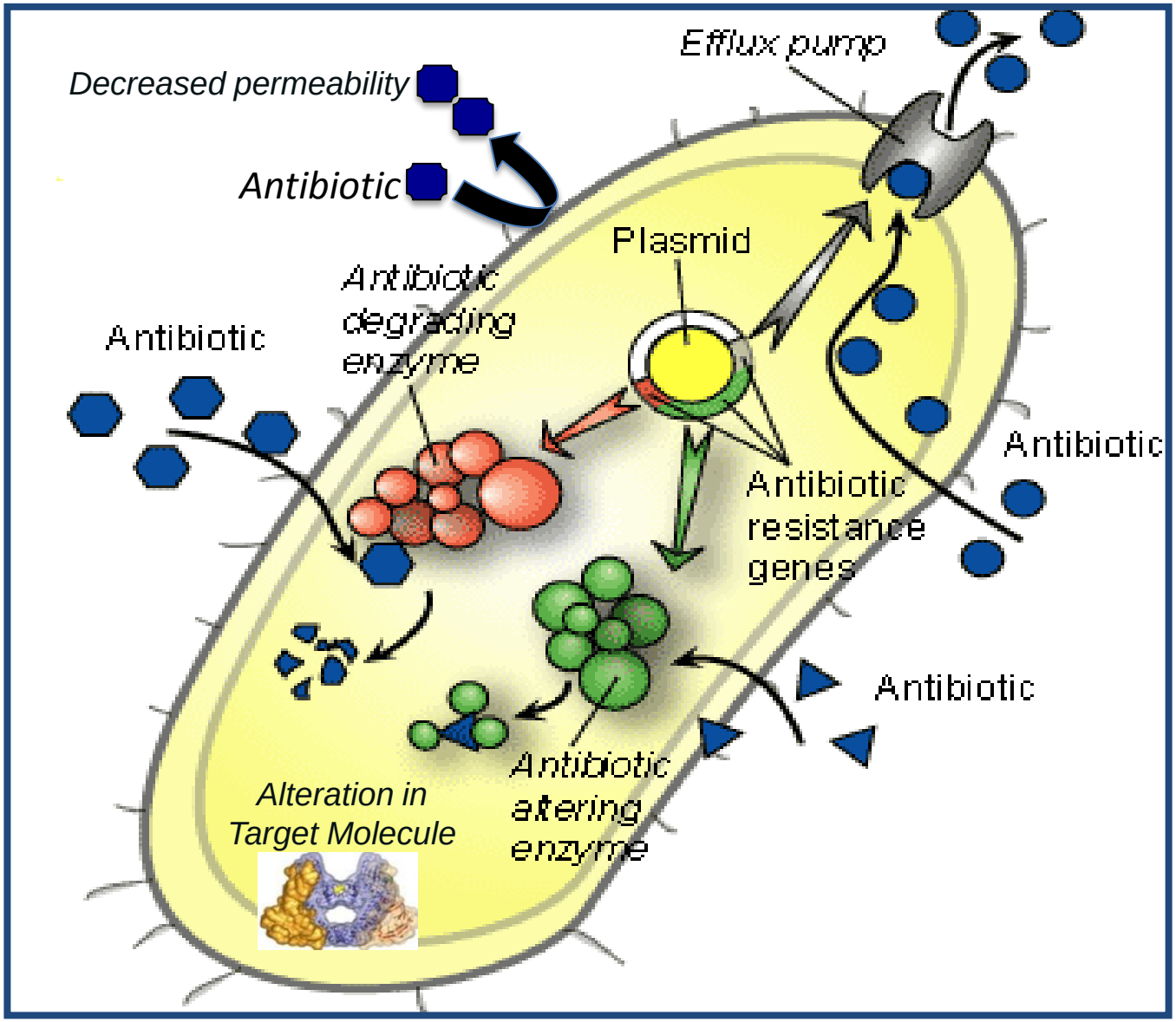


Metagenomic analysis of 30,000 year old permafrost samples

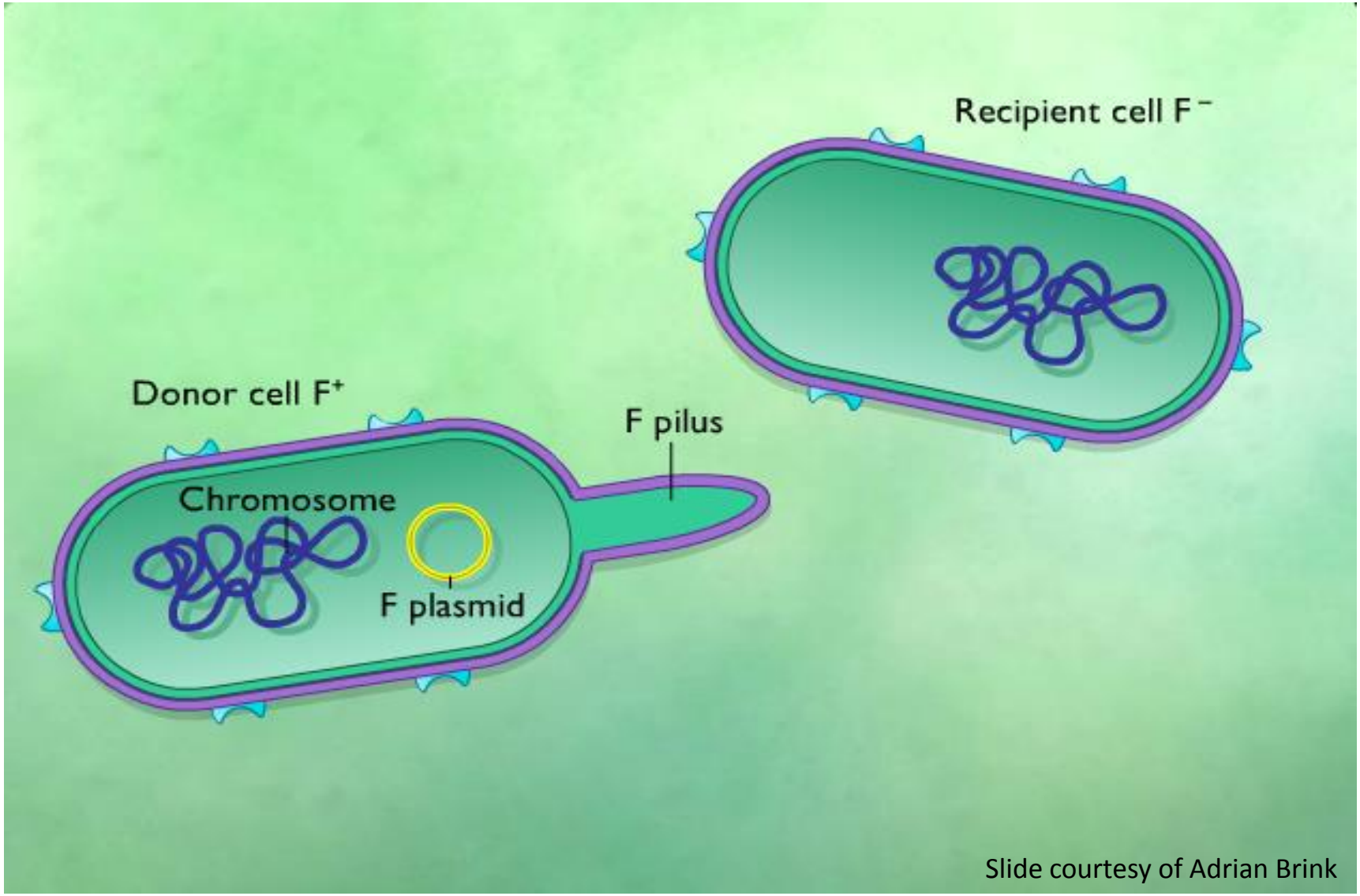


- β-Lactam resistance - bla_{TEM}
- Tetracycline resistance - *TetM*
- Vancomycin resistance - *VanX*
- Aminoglycoside-antibiotic-modifying acetyltransferase *AAC(3) ribosome methyltransferase*
- Macrolide, lincosamide and type B streptogramin antibiotic resistance – *Erm*

Bacterial resistance mechanisms

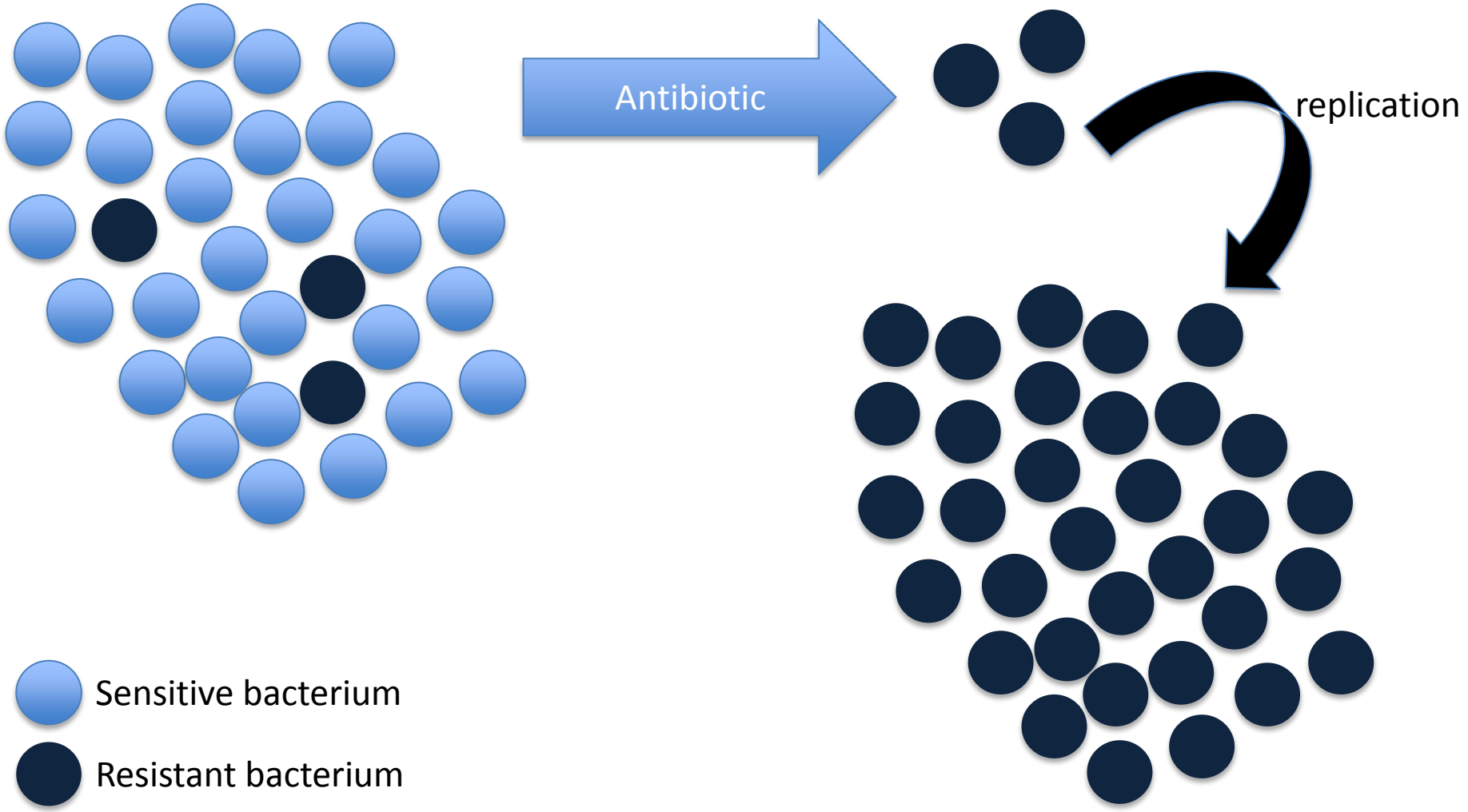


Antibiotic resistance is transferable

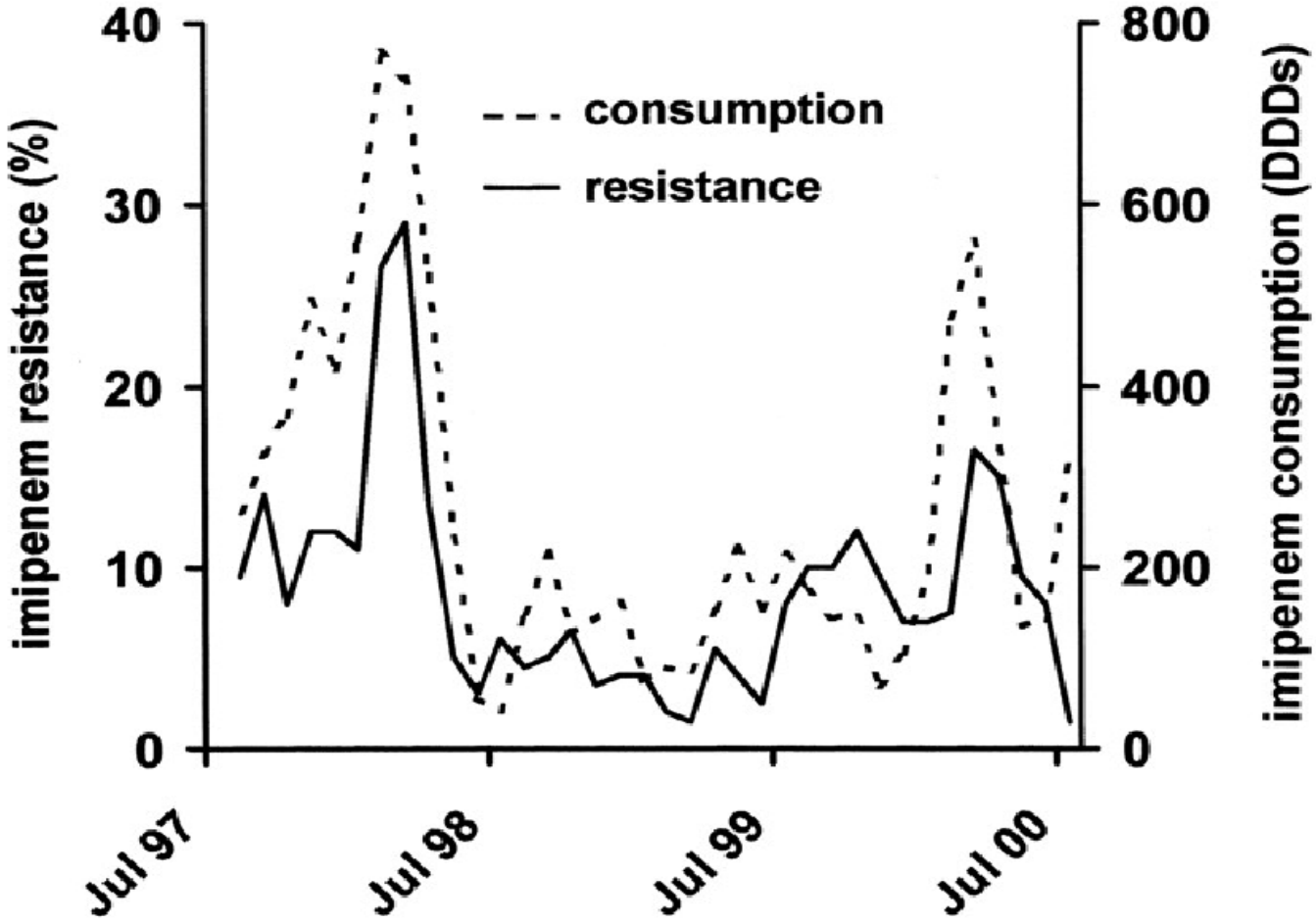


Slide courtesy of Adrian Brink

Selection of antibiotic resistant bacteria

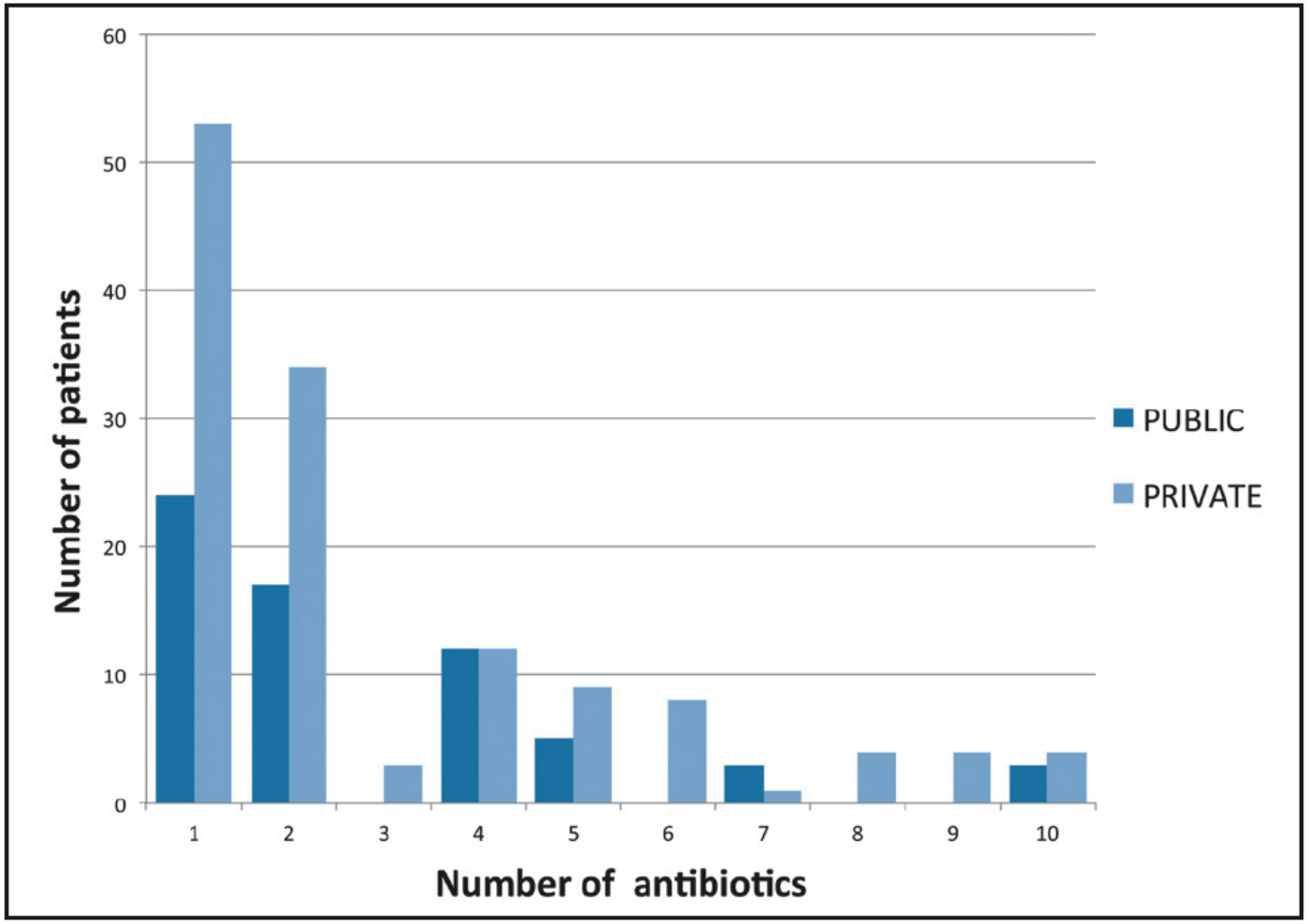


Antimicrobial use drives the emergence of antimicrobial resistance



Lepper PM et al. Antimicrob Agents Chemother 2002;46:2920-5.

Simultaneous prescription of antibiotics in South African ICUs



Example: 1 patient simultaneously received:

Cloxacillin

Teicoplanin

Metronidazole

Amikacin

Ceftazadime

Meropenem

Levofloxacin

Erythromycin

Co-trimoxazole

Fluconazole

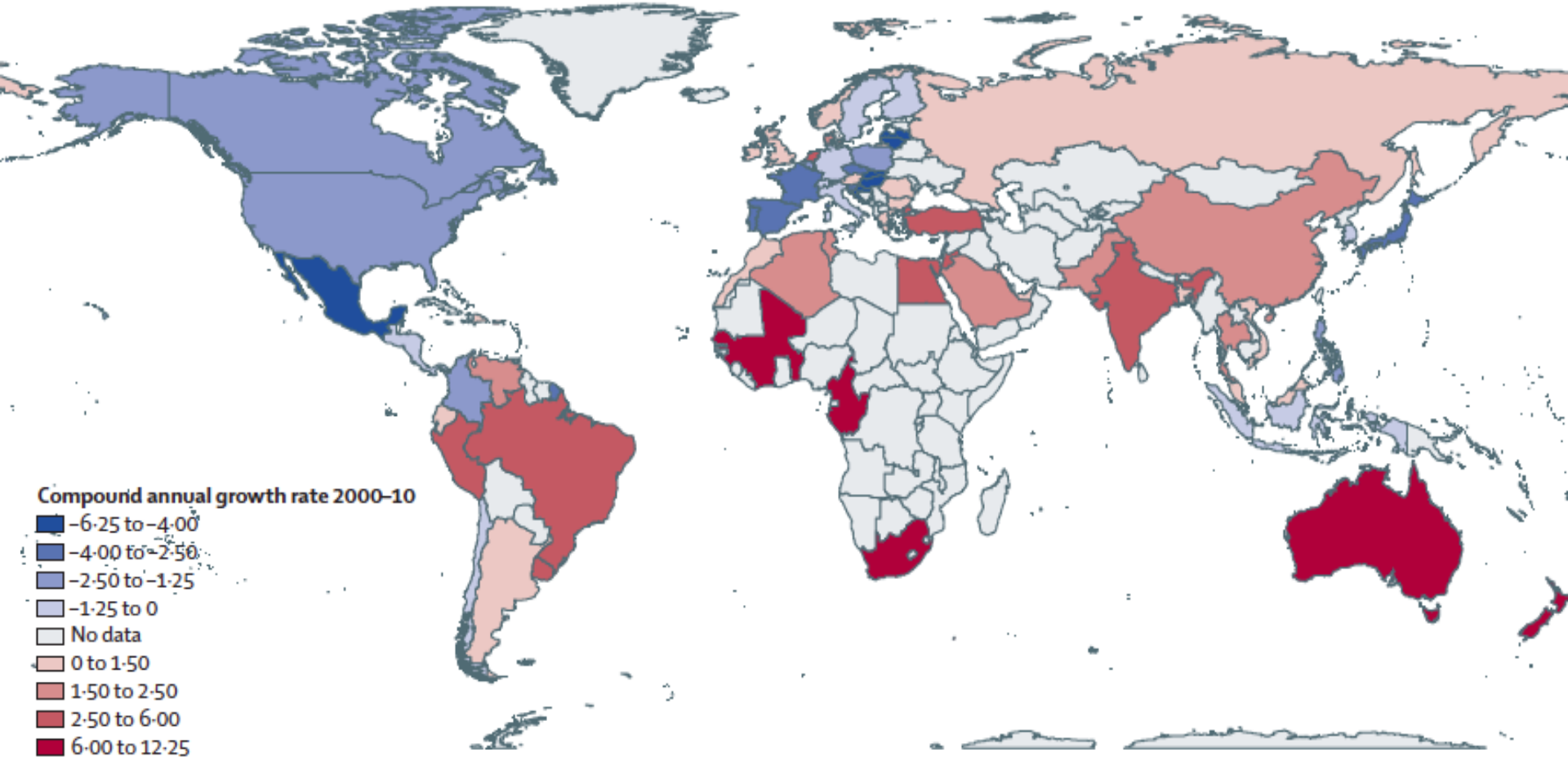
Paruk et al. SAMJ 2012; 102(7): 613-6

Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data

Thomas P Van Boeckel, Sumanth Gandra, Ashvin Ashok, Quentin Caudron, Bryan T Grenfell, Simon A Levin, Ramanan Laxminarayan

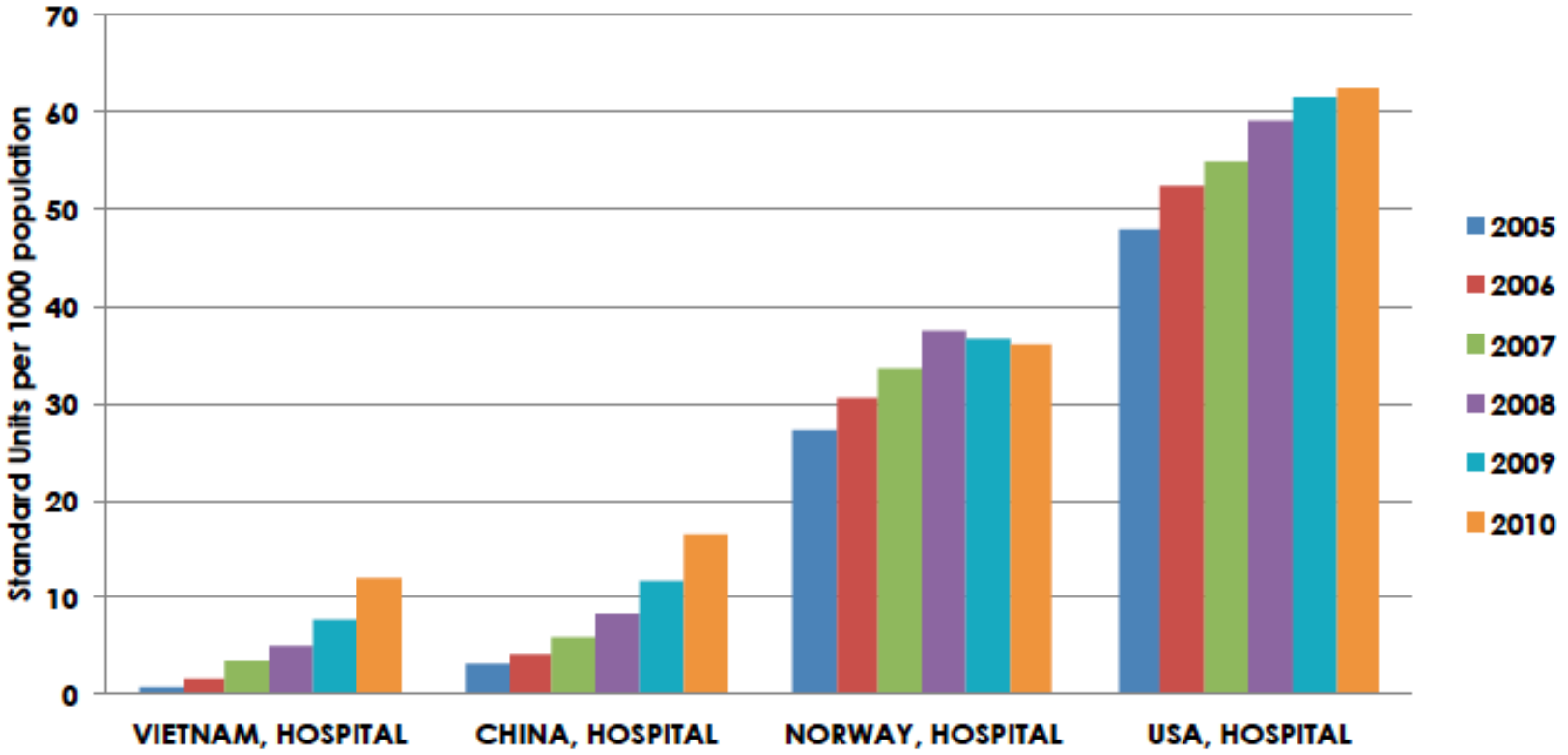
36% increase in global antibiotic consumption between 2000 – 2010

75% of that increase occurred in BRICS countries



Lancet Infect Dis 2014;14: 742–50

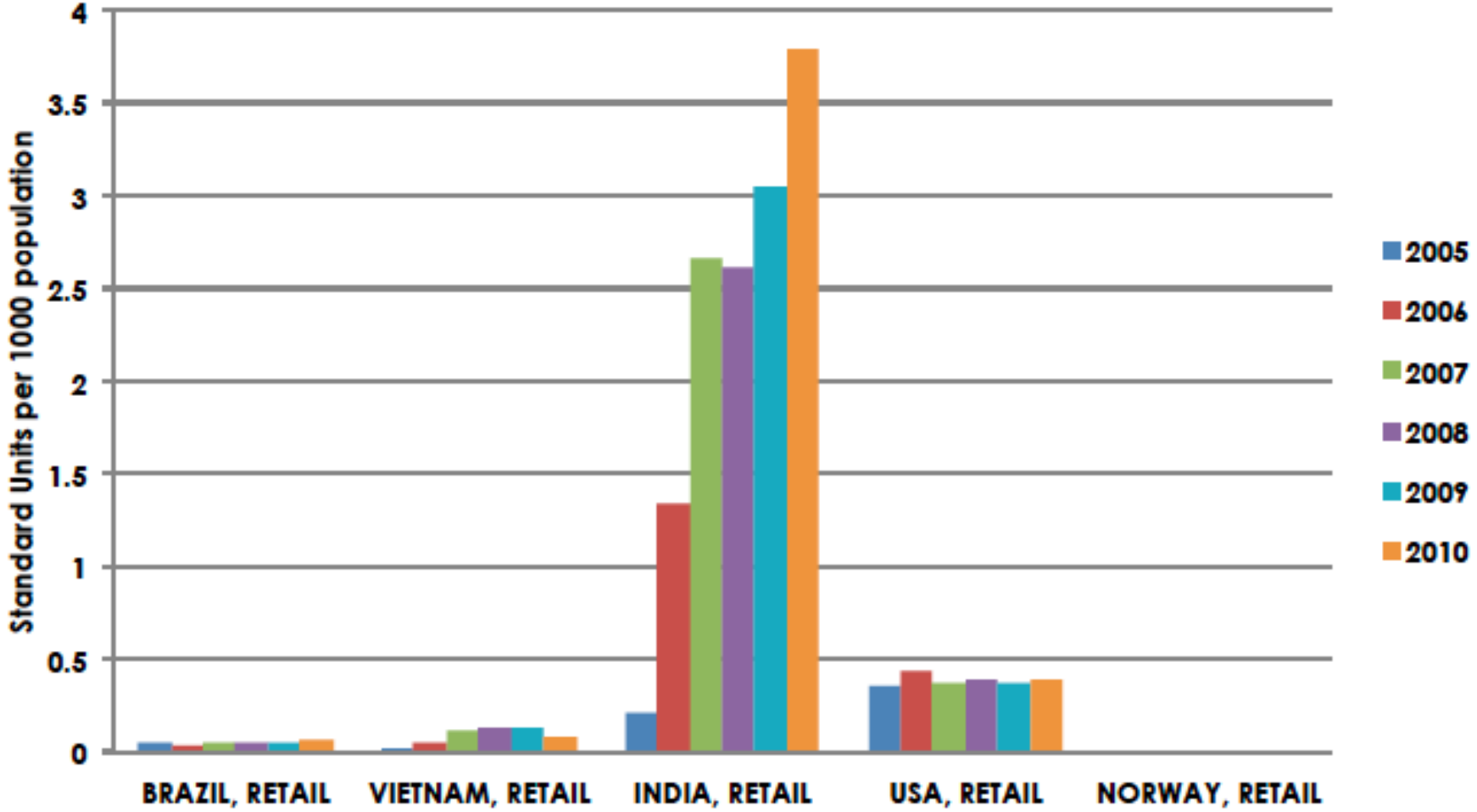
Increasing hospital sector use of carbapenems 2005-2010



CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy WASHINGTON DC • NEW DELHI

PUBLIC HEALTH FOUNDATION OF INDIA

Per capita total carbapenem use; retail sector 2005 - 2010



Source: Based on data obtained under license from IMS Health MIDAS ™ (January 2005-December 2010); IMS Health Incorporated. All Rights Reserved.

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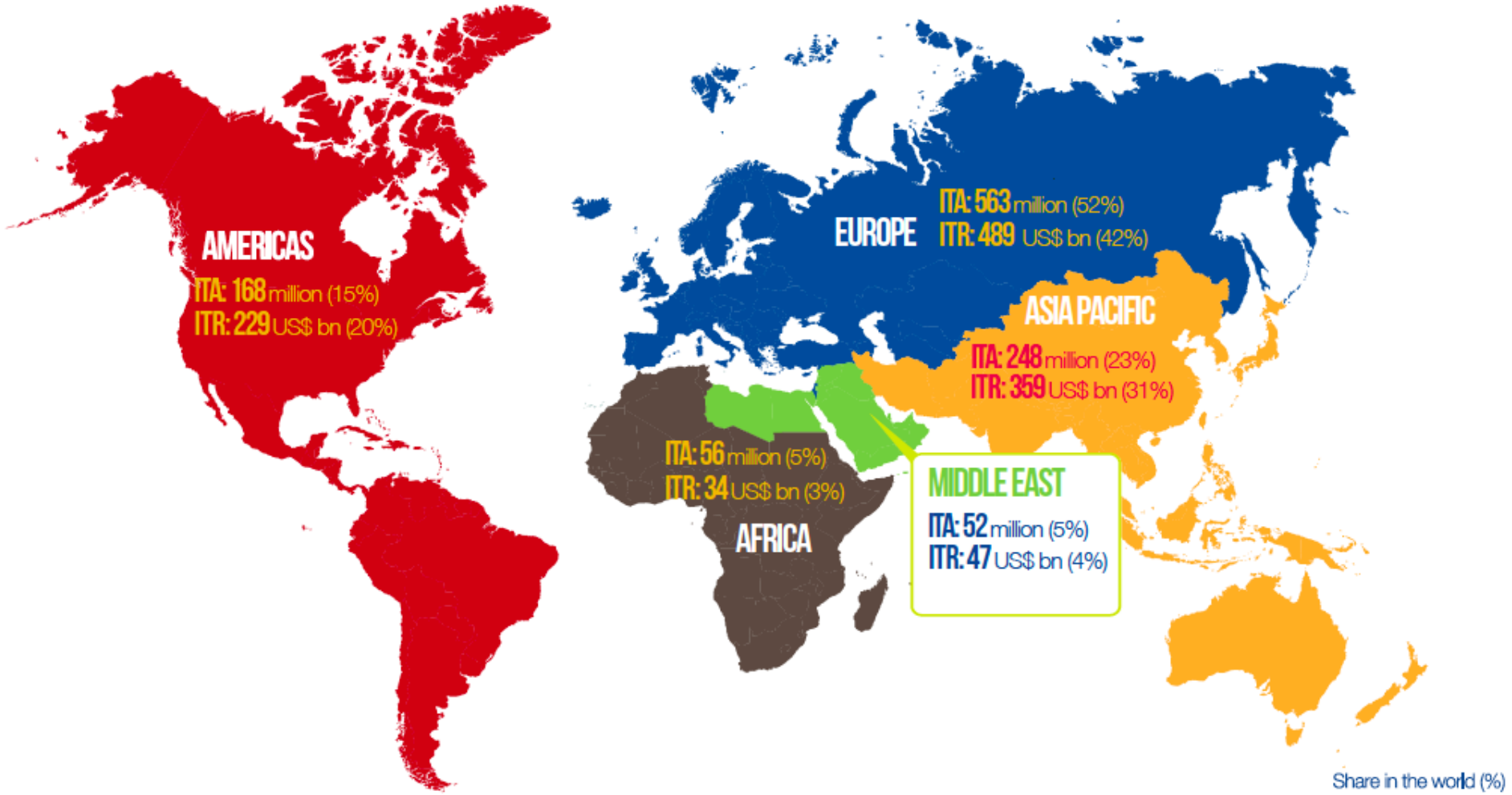
PUBLIC HEALTH FOUNDATION OF INDIA

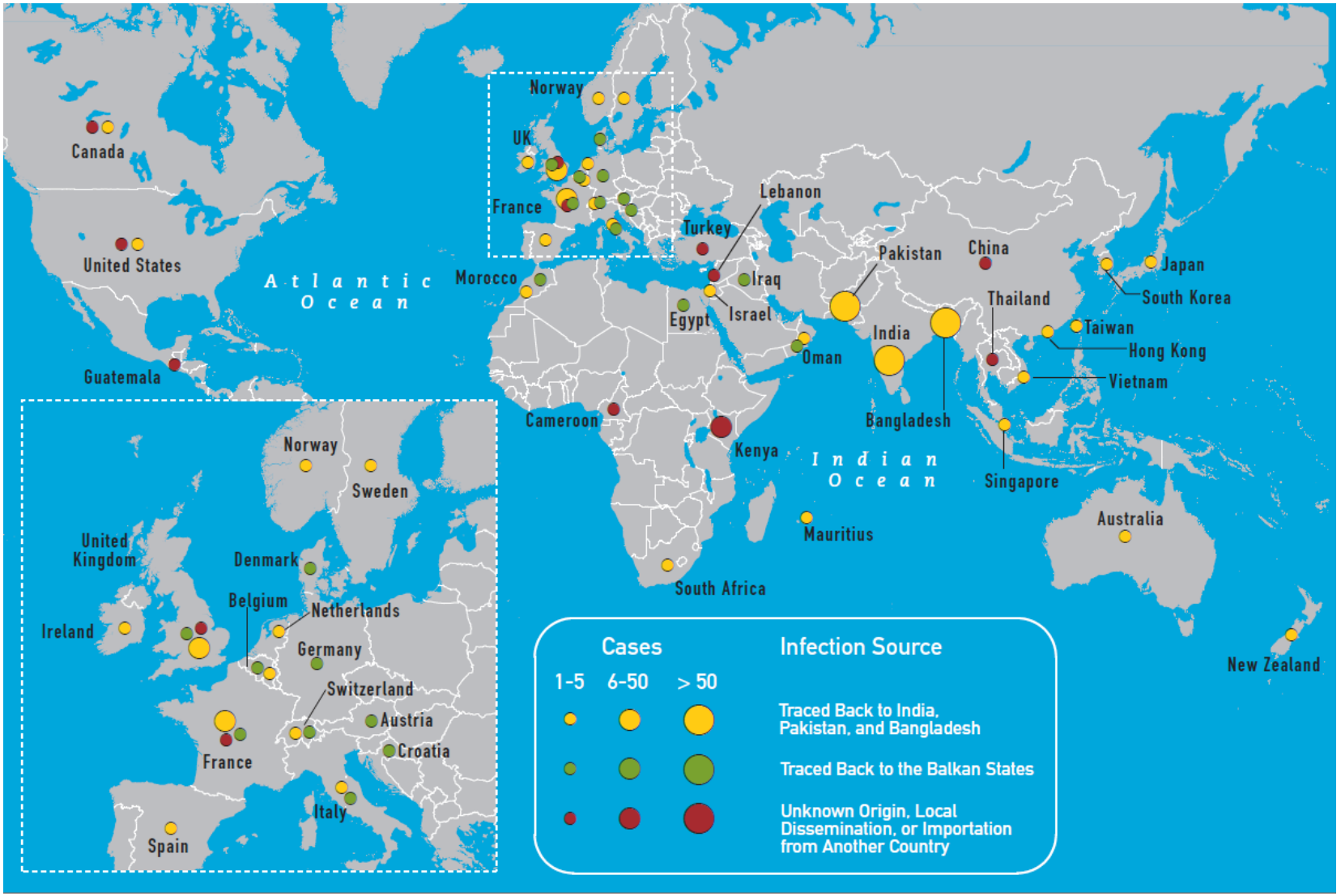
INTERNATIONAL TOURISM 2013

International tourist arrivals (ITA): 1087 million
International tourism receipts (ITR): US$ 1159 billion



UN World Tourism Organization 2014 Report

Global spread of NDM-1-producing-*Klebsiella pneumoniae*, as of June 2012

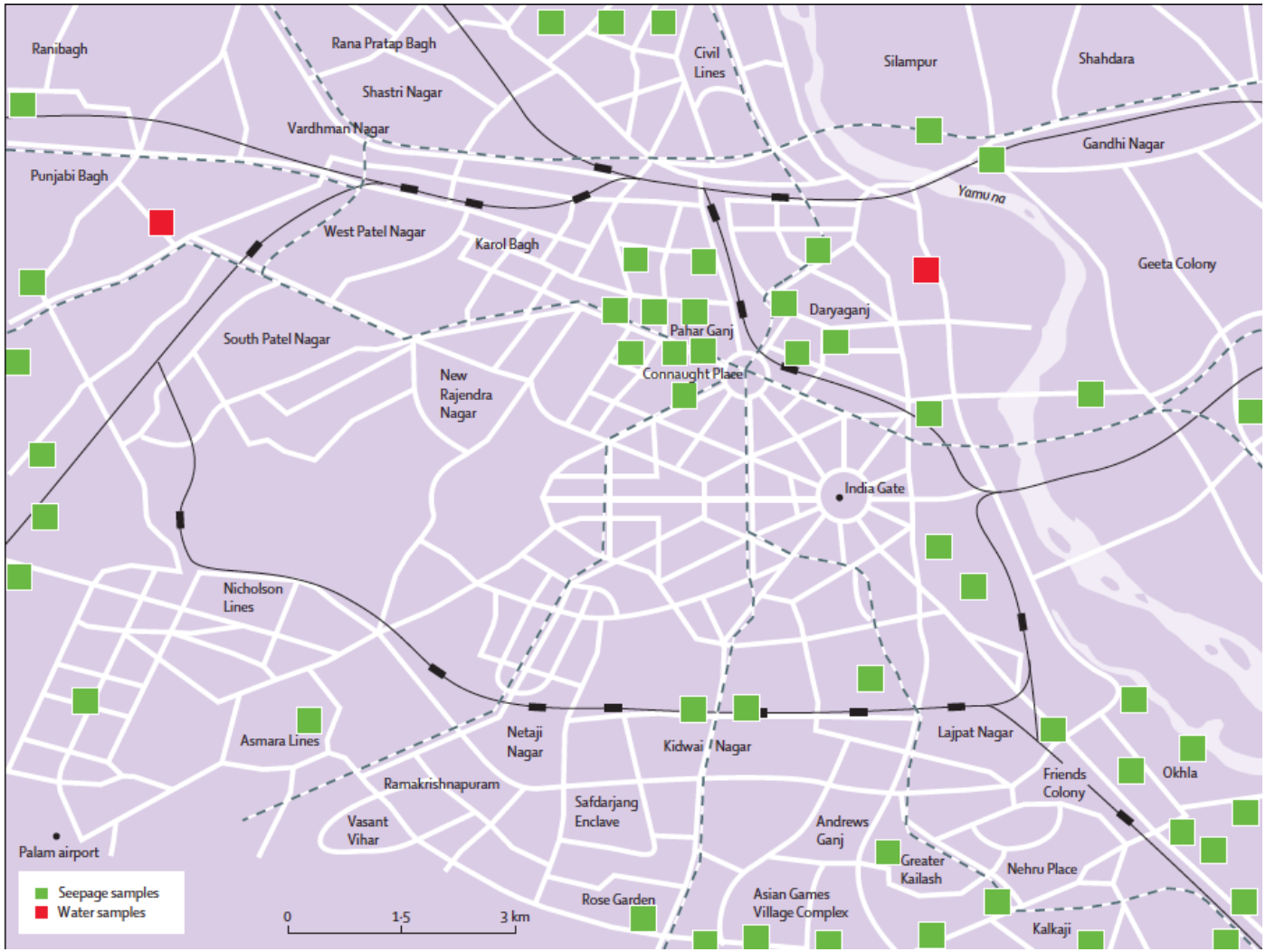


http://dx.doi.org/10.3201/eid1710.110655

Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study

Timothy R Walsh, Janis Weeks, David M Livermore, Mark A Toleman

Lancet Infect Dis 2011;11: 355–62



E. coli

K. pneumoniae

P. aeruginosa

P. putida

P. pseudoalcaligenes

P. aryzihabitans

S. boydii

S. indologenes

A. caviae

S. maltophilia

V. cholerae

C. freundii

Achromobacter spp

Kingella dentricans

THE COMPLETE IDIOT'S GUIDE® TO

Get the most affordable medical care in the world without sacrificing quality

Medical Tourism

Patrick W. Marsek and
Frances Sharpe

Surgery Cost Chart

(Medical Tourism Association 2010 Survey)

Surgery	US	India	Thailand	Malaysia	Mexico
Heart bypass	$144,000	$5,200	$15,121	$11,430	$27,000
Heart valve replacement	170,000	5,500	21,212	10,580	18,000
Hip replacement	50,000	7,000	7,879	7,500	13,000
Dental implant	2,800	1,000	3,636	354	1,800
Face lift	15,000	4,000	3,697	3,440	4,900
IVF treatments	14,500	3,250	9,091	3,819	3,950
Kidney transplant (bring donor)		8,000	21,212		45,000

Slide courtesy of Mary Wilson

High rate of hospital-acquired infections in developing countries

- Meta-analysis: developing-country adult ICUs had infection rates 3x higher than those in the United States
- Surgical site infections higher (5.6 vs. 1.6-2.9 per 100 surgical procedures)
- Rates of device-associated infections high

Allegranzi et al. Lancet 2011;377:228-41.
Rosenthal et al. Infect Control Hospital Epidemiol 2013;52:1657-66.

Rapidly Growing Nontuberculous *Mycobacterium* Wound Infections Among Medical Tourists Undergoing Cosmetic Surgeries in the Dominican Republic — Multiple States, March 2013–February 2014

Centers for Disease Control and Prevention
MMWR
Weekly / Vol. 63 / No. 9 March 7, 2014

- 19 cases from 5 states
- All female 18-59 years
- 12 underwent surgery at same clinic, 7 at others
- Liposuction (74%), abdominoplasty (58%), breast implants (32%)
- 14 hospitalized in US – multiple surgeries & Abx
- M. abscessus (16), M. fortuitum (2)

Inter-relationship of AMR

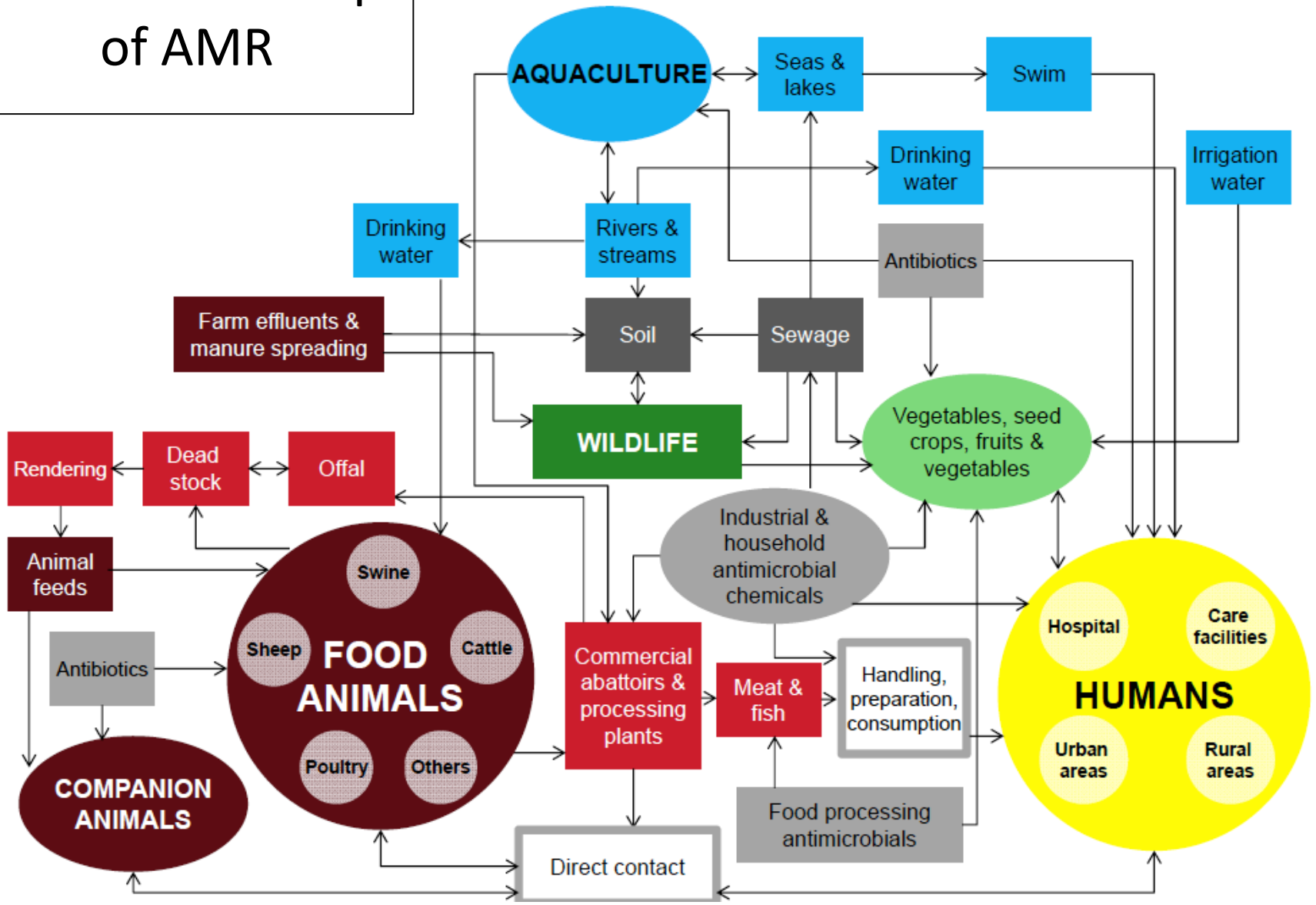
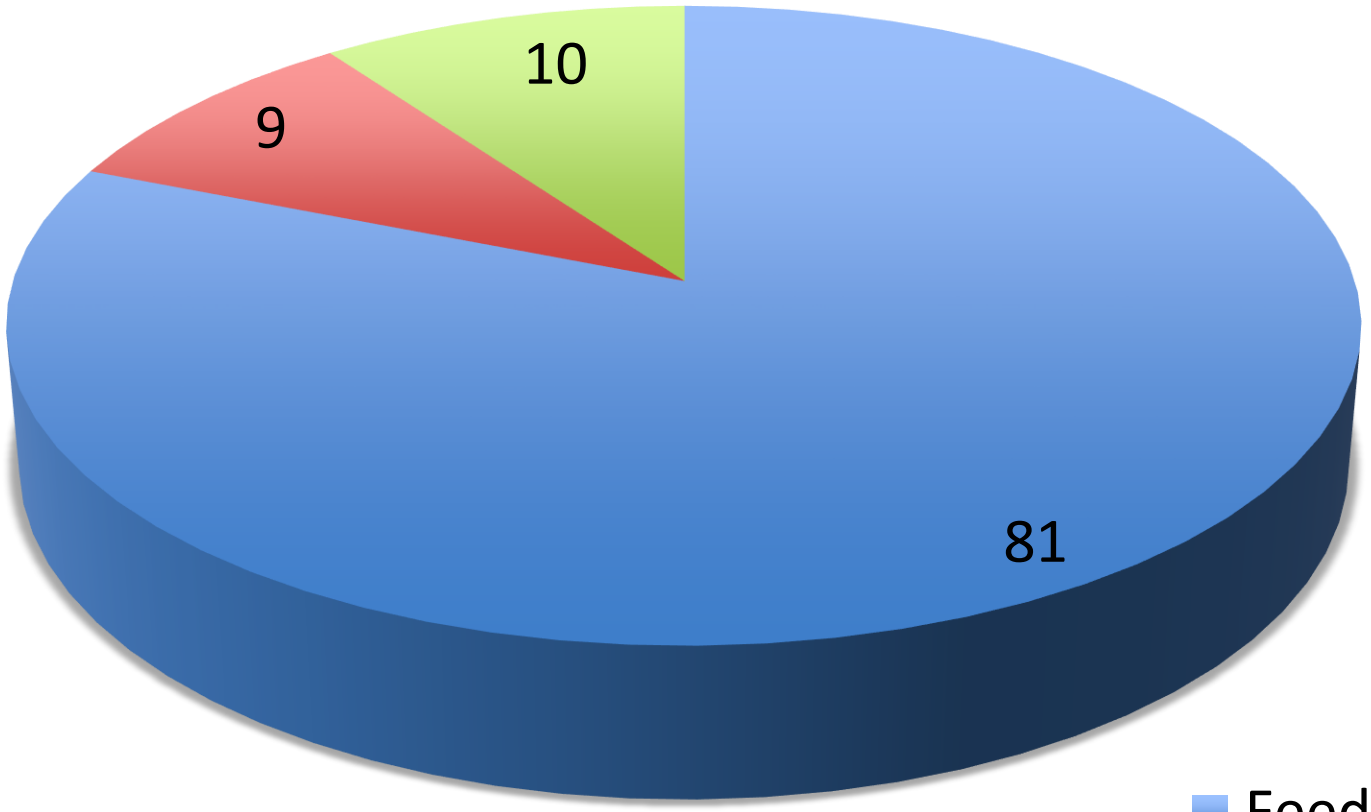


Diagram based on Linton (1977), as adapted by Rebecca Irwin, Health Canada (Prescott 2000) and IFT

Antimicrobial Consumption in the USA



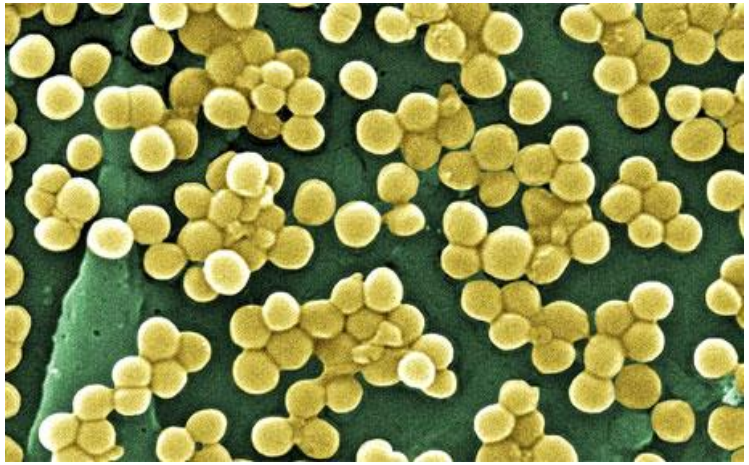
15.75 million
kilograms used per annum

Residential Proximity to Large Numbers of Swine in Feeding Operations Is Associated with Increased Risk of Methicillin-Resistant *Staphylococcus aureus* Colonization at Time of Hospital Admission in Rural Iowa Veterans

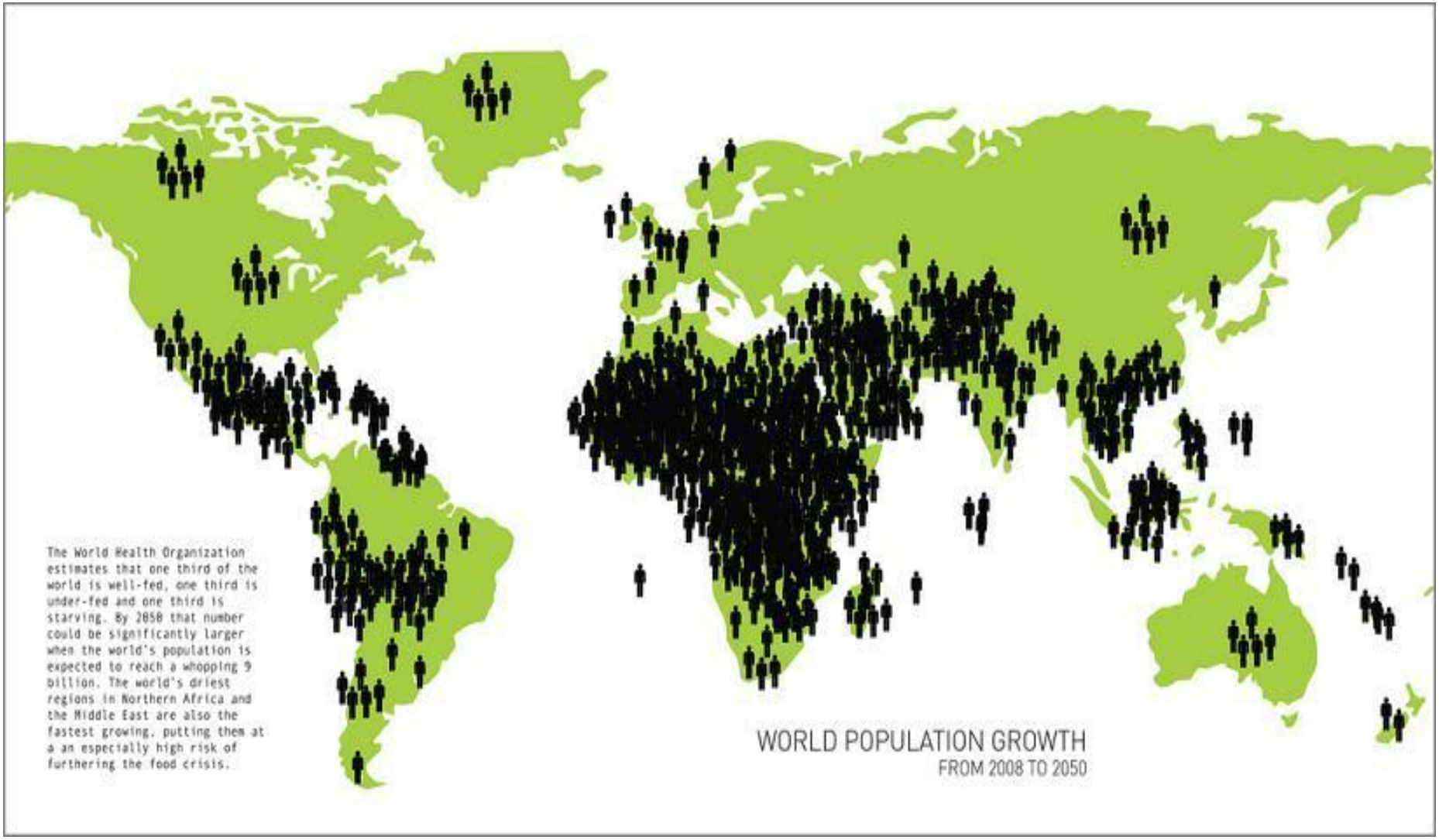
Margaret Carrel, PhD;[1] Marin L. Schweizer, PhD;[2,3] Mary Vaughan Sarrazin, PhD;[2,3] Tara C. Smith, PhD;[4] Eli N. Perencevich, MD, MS[2,3]

Among 1,036 patients, residential proximity within 1 mile of large swine facilities was associated with nearly double the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization at admission (relative risk, 1.8786 [95% confidence interval, 1.0928–3.2289]; $P = .0239$) and, after controlling for multiple admissions and age, was associated with nearly triple the odds of MRSA colonization (odds ratio, 2.76 [95% confidence interval, 1.2728–5.9875]; $P = .0101$).

Infect Control Hosp Epidemiol 2014;35(2):190-192

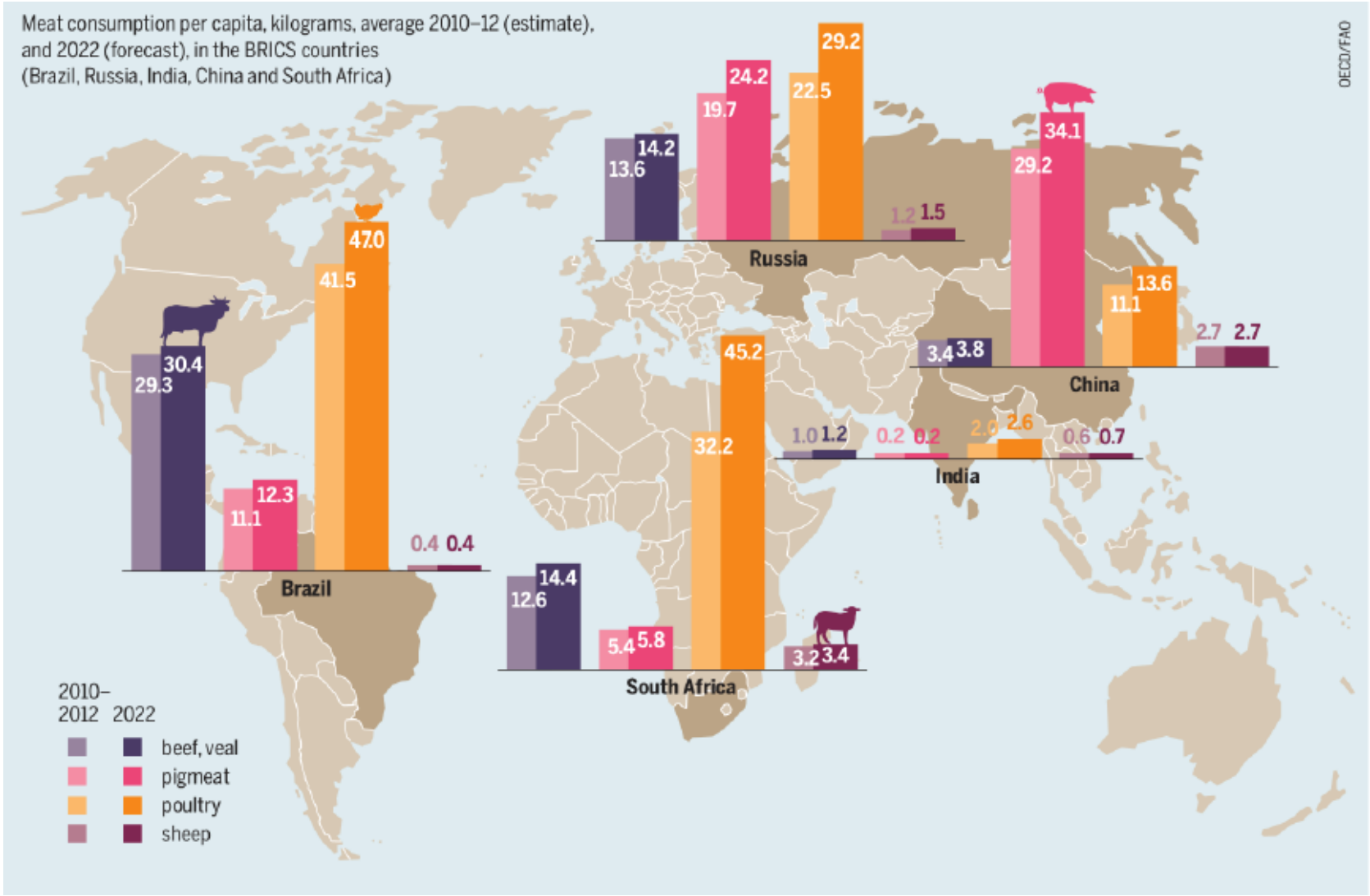


World population to reach ~8 billion by 2025 with increasing urbanization



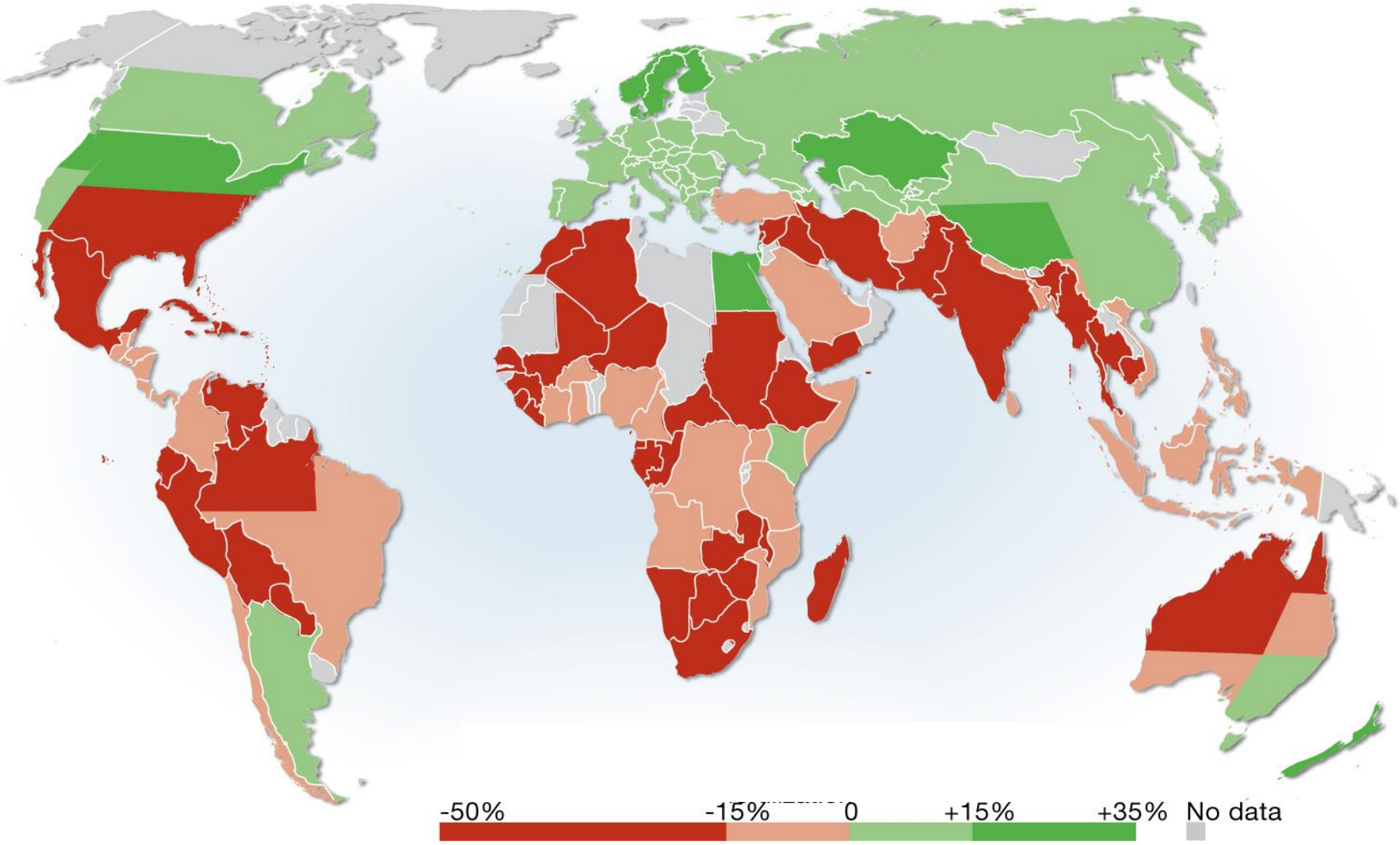
http://homosapienssaveyourearth.blogspot.com/2011/07/world-population-growth-map-2008-2050.html

Demand for meat is increasing in developing countries



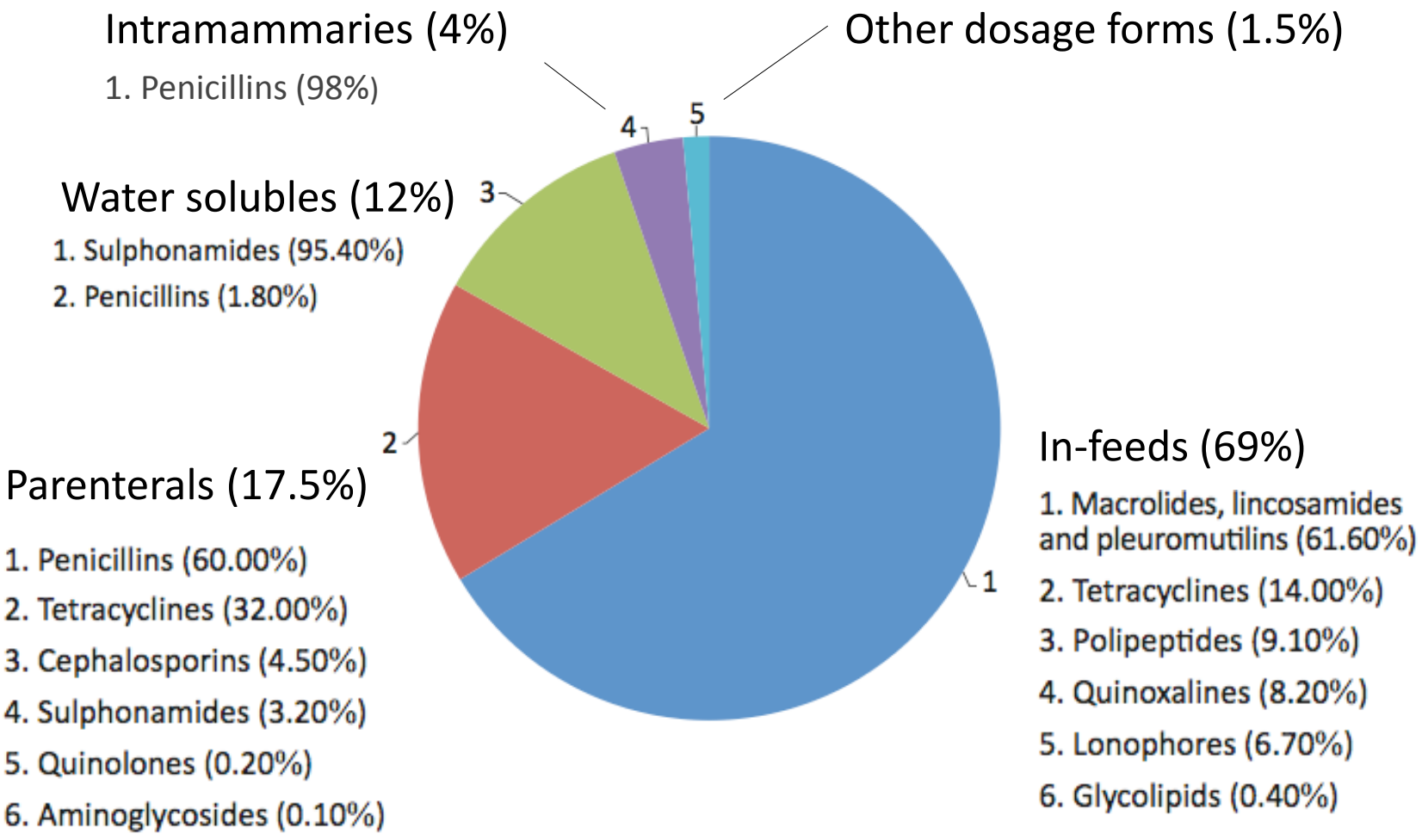
Slide courtesy of Henk Jan Ormel, FAO

Projected Change in Agricultural Productivity by 2080 due to climate change, incorporating the effects of carbon fertilization

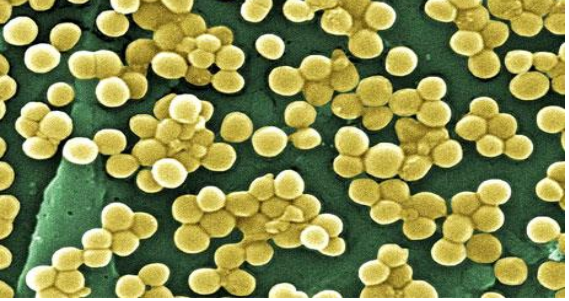


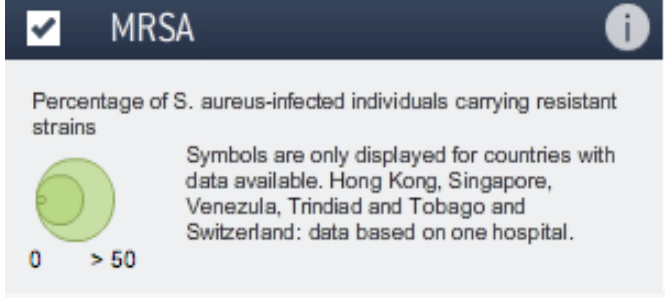
http://climatecart.wordpress.com/climate-change-as-justice/

Different forms of antibiotics sold for animal use during 2002 - 2004



Eagar et al. J S Afr Vet Assoc. 2012;83(1)





MRSA bloodstream infections

24-59% *S. aureus* isolates in public hospitals, 2010 (Bamford et al. South Afr J Epidemiol Infect 2011;26:243)

72% HA-MRSA at Red Cross Hospital, 2007-2011 (Naidoo et al. PLoS ONE. 2013; 8(10); e78396)

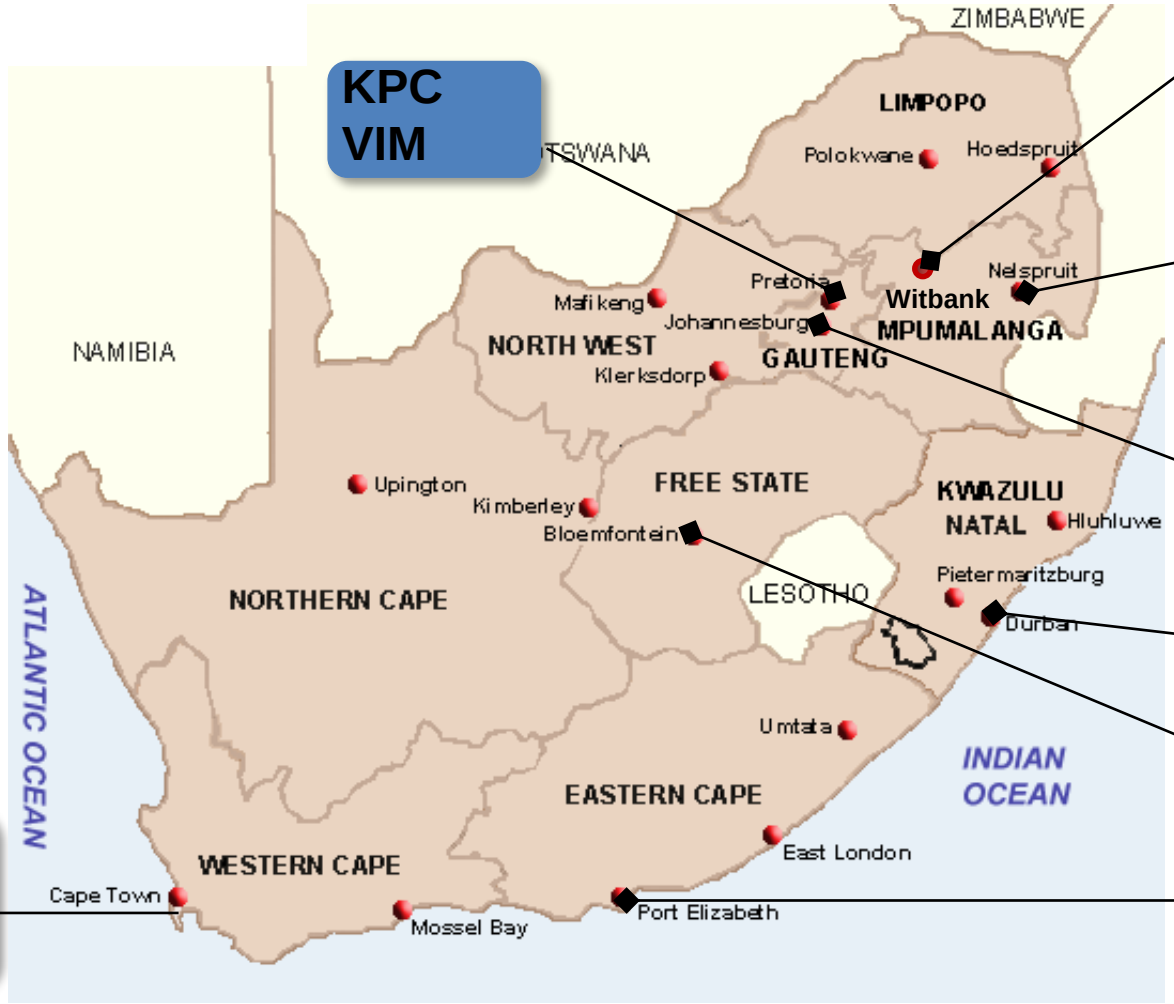
ESBL rates in South Africa

Study	Source	*K. pneumoniae*	*E. coli*
SMART[1]* 2004-2009	Complicated intra-abdominal infections	41.2%	7.6%
SASCM[2] public sector hospitals, 2010	Blood cultures	55-74%	3-17%
GERMS-SA[3] Sentinel sites Jan-Jul 2012	Blood cultures	75%	-

*Study for the Monitoring of Antimicrobial Resistance Trends

[1]Brink et al. Surg Infect 2012;13:1-7 [2]Bamford et al. *SAJEI* 2011;26:243-250 [3]GERMS-SA Annual Report 2012

Spread of Carbapenemase Producing *Enterobacteriaceae* (CPE) in South Africa



KPC
VIM

GES
NDM
VIM

NDM

NDM
KPC
OXA-48-like
VIM

NDM

GES

OXA-48-like
GES

OXA-48-like
GES
NDM

SAMJ 2012; 102(7): 599-601 J Clin Micro 2013; 51(1): 369-72

Slide courtesy of Adrian Brink

Emergence of OXA-48 and OXA-181 Carbapenemases among *Enterobacteriaceae* in South Africa and Evidence of *In Vivo* Selection of Colistin Resistance as a Consequence of Selective Decontamination of the Gastrointestinal Tract

- Unstable patient admitted MVR & CABG
- OXA-181-producing *Klebsiella pneumoniae*
  - S - tigecycline and colistin from urine
- Colistin monotherapy
- Still colonized 15 days later
- Cardiac surgery postponed
- Colistin 2MU 8hrly + Meropenem
  + SDD (oral colisitin & tigecycline 22 days)
- **Pan-resistant *K. pneumoniae***

Brink AJ. J Clin Microbiol 2013; 51(1): 360-72

BMJ 2013;346:f1493 doi: 10.1136/bmj.f1493 (Published 11 March 2013)

ANALYSIS

The true cost of antimicrobial resistance

Richard Smith and **Joanna Coast** argue that current estimates of the cost of antibiotic resistance are misleading and may result in inadequate investment in tackling the problem

Richard Smith *professor of health system economics* [1], Joanna Coast *professor of health economics*[2]

[1]London School of Hygiene and Tropical Medicine, London WC1H 9SH, UK; [2]School of Health and Population Sciences, University of Birmingham. Birmingham, UK

"We estimate that without antimicrobials, the rate of postoperative infection in [total hip replacements] is 40-50% and about 30% of those with an infection will die."

Outbreak of Oxa-181 *Klebsiella pneumoniae* on a Heaematology Transplant Unit

Slide courtesy of Colleen Bamford

Outbreak of Fatal MDR *Pseudomonas aeruginosa* on a Heaematology Transplant Unit

Slide courtesy of Colleen Bamford

The Global Action Plan

World Health Organization

EXECUTIVE BOARD
134th session
Agenda item 10.6

EB134/CONF./1
20 January 2014

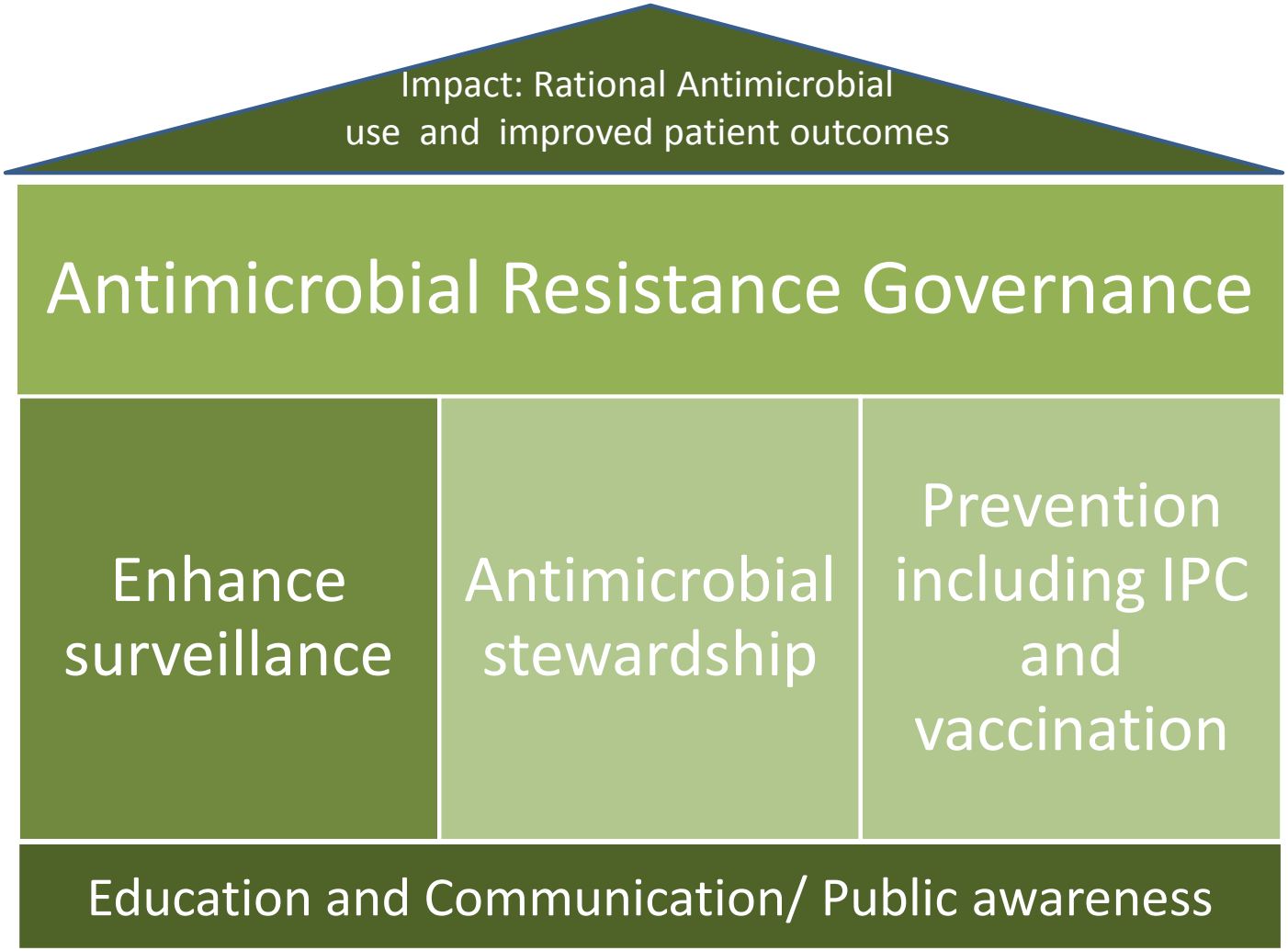
Combating antimicrobial resistance, including antibiotic resistance[1]

Draft resolution proposed by Australia, China, Costa Rica, Ghana, Japan, Libya, Mexico, Netherlands, Qatar, Sweden, Thailand, United Kingdom of Great Britain and Northern Ireland and United States of America

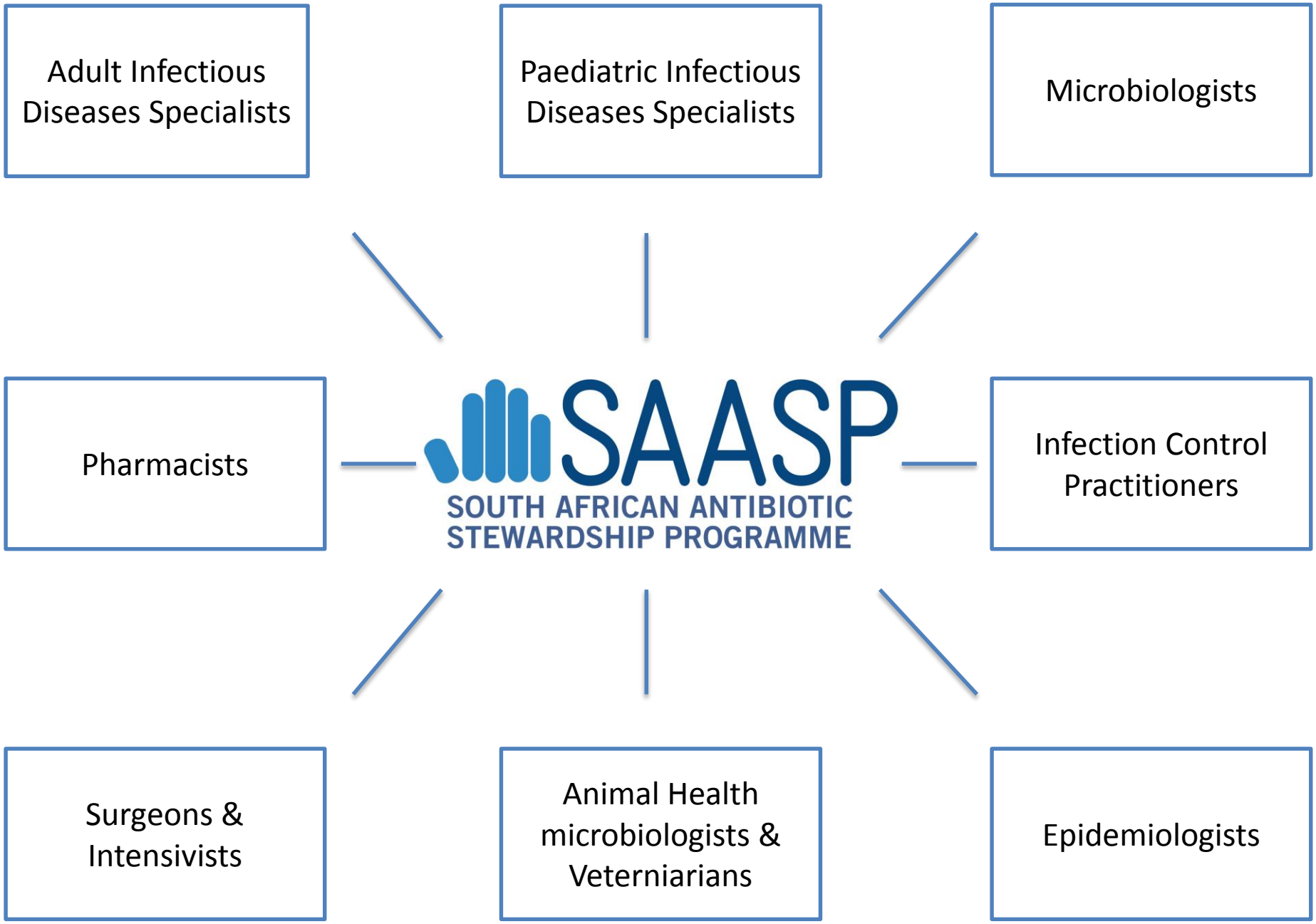
Responsibilities of members states

1. Political awareness and leadership to enable appropriate use
2. Strengthening of Infection prevention and control
3. Develop national strategic plans and international collaboration
4. Strengthen pharmaceutical management systems
5. Mobilize human and financial resources
6. Improve awareness of threat posed and required interventions
7. R&D through collaborative financial models
8. Collaborate with WHO secretariat to develop the GAP
9. Develop AMR surveillance in hospital inpatients; outpatients and community; animals and non-human usage

The South African strategic plan for AMR




agriculture, forestry & fisheries
Department: Agriculture, Forestry and Fisheries
REPUBLIC OF SOUTH AFRICA
health
Department: Health
REPUBLIC OF SOUTH AFRICA
education
Department of Education
REPUBLIC OF SOUTH AFRICA
Academia
Military
Intersectoral Ministerial Advisory Committee
Private Hospital groups
Civil Society Key NGOs
science & technology
Department: Science and Technology
REPUBLIC OF SOUTH AFRICA
Professional Societies & Bodies
the dti
Department: Trade and Industry
REPUBLIC OF SOUTH AFRICA


Adult Infectious Diseases Specialists
Paediatric Infectious Diseases Specialists
Microbiologists
Pharmacists
SAASP
SOUTH AFRICAN ANTIBIOTIC STEWARDSHIP PROGRAMME
Infection Control Practitioners
Surgeons & Intensivists
Animal Health microbiologists & Veterniarians
Epidemiologists

What lessons have we learned [are we learning] from the loss of antibacterials that have relevance to the future of antiretroviral use?

Lesson 1

The international mindset still sees antimicrobials as private goods

Responsible use requires acknowledging that antimicrobials are a Global Public Good

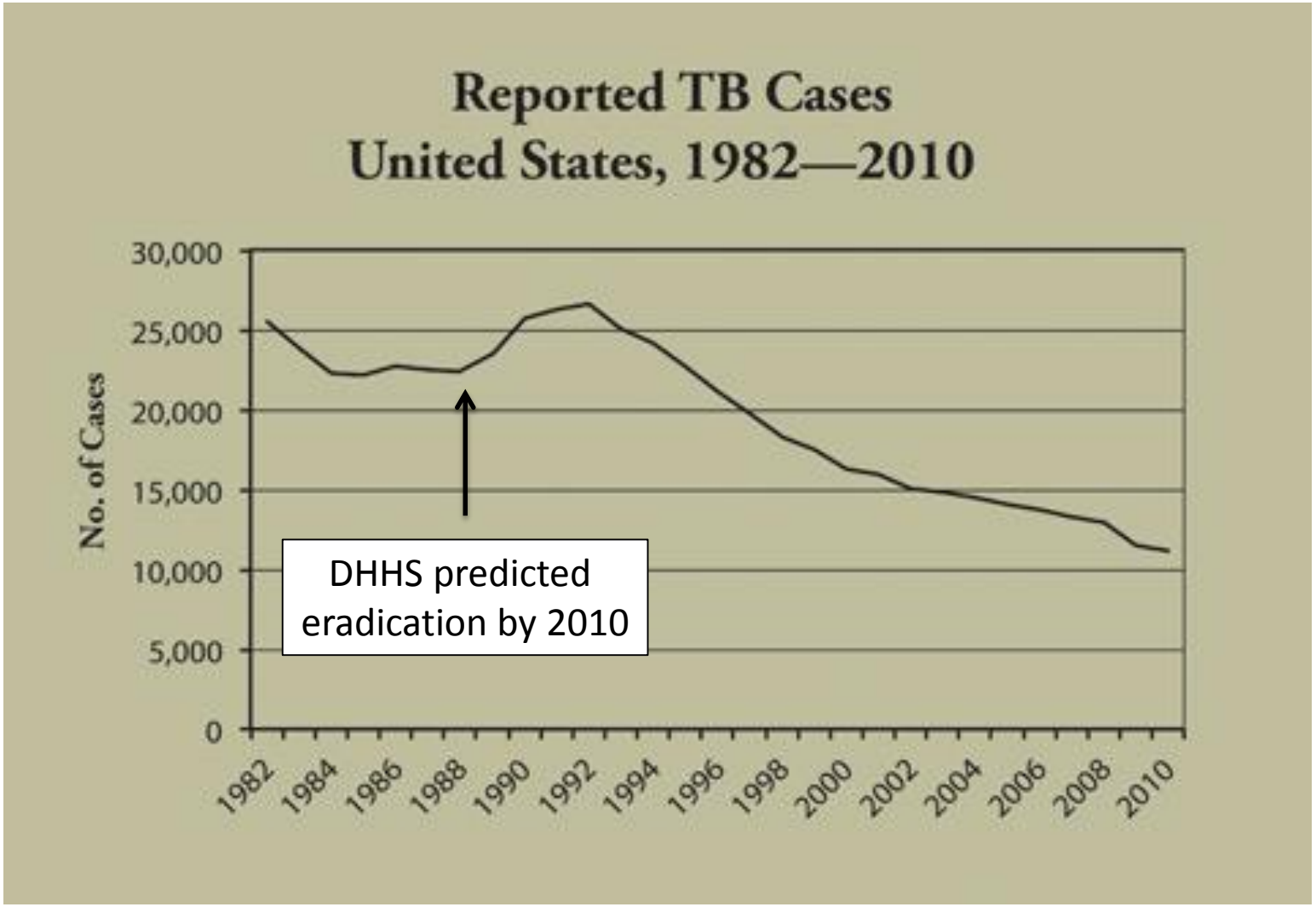
Keiji Fukuda - Assistant Director-General for Health Security

A ‘Global Public Good’ is both non-excludable and non-rival in consumption

Global governance failure exists because of ‘free riders’

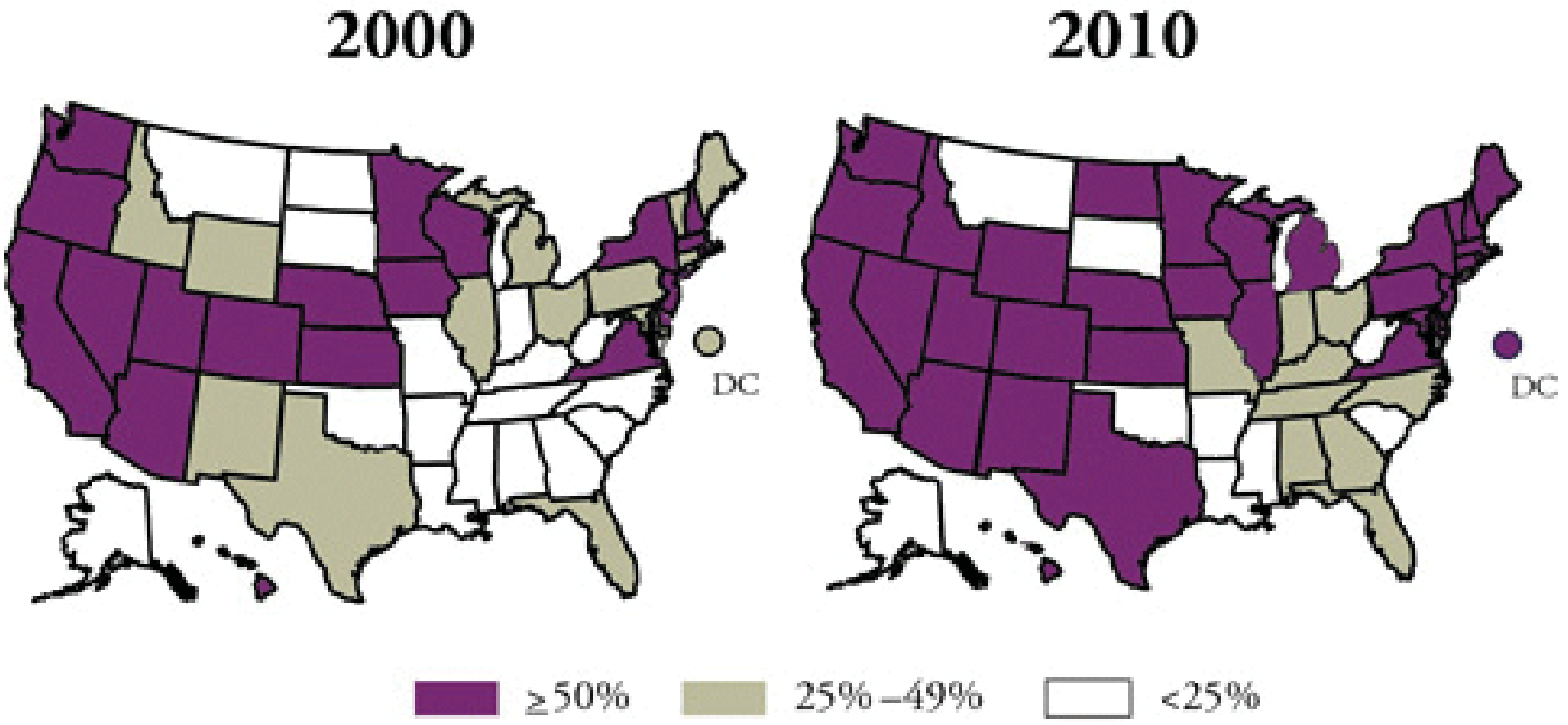
Lesson 2
Complacency and Profits

“Tuberculosis will be eradicated”



Funding for TB research and treatment 1960 = $40 million → 1989 = $283,000

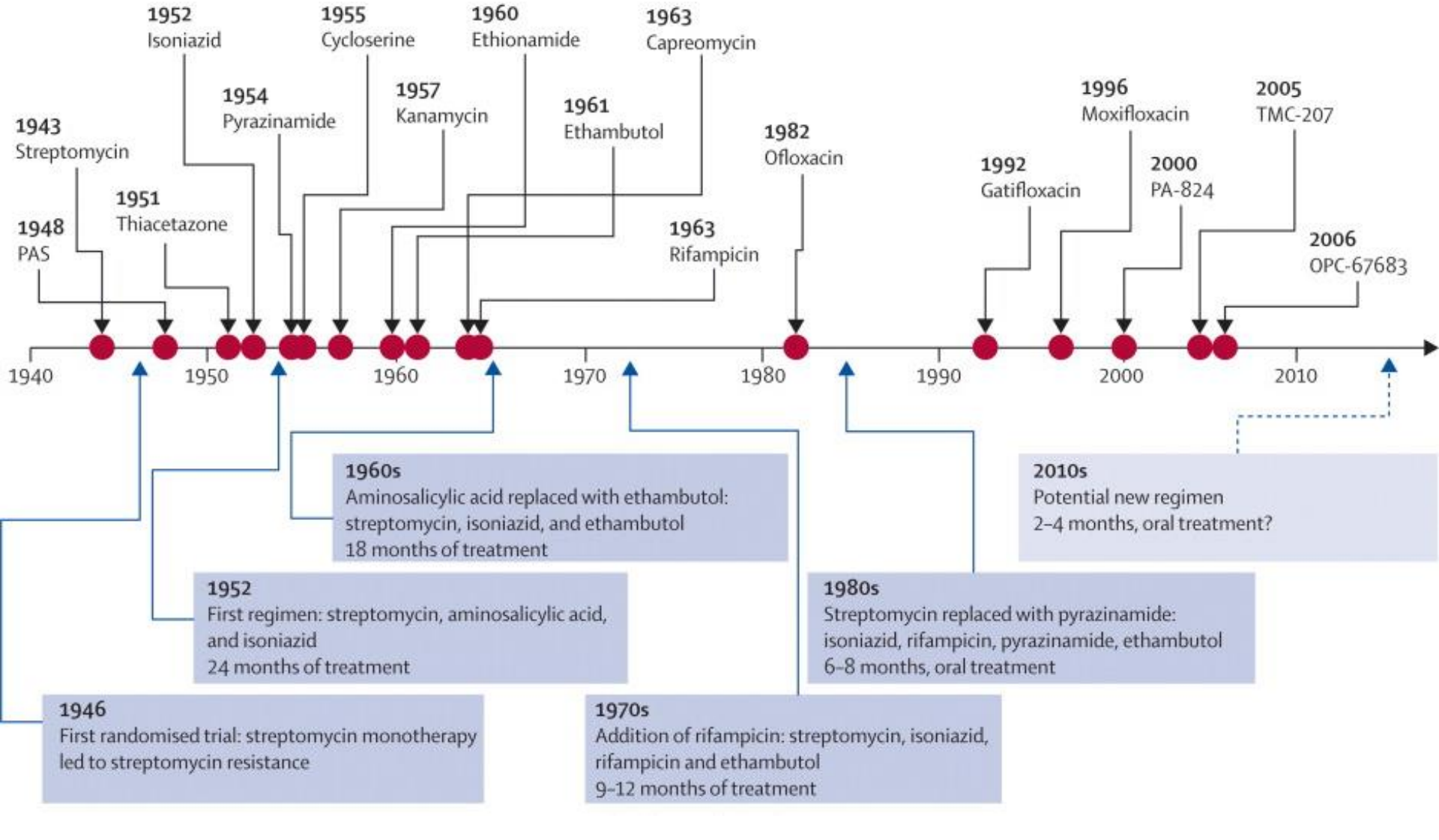
Percentage of TB Cases Among Foreign-born Persons, United States*



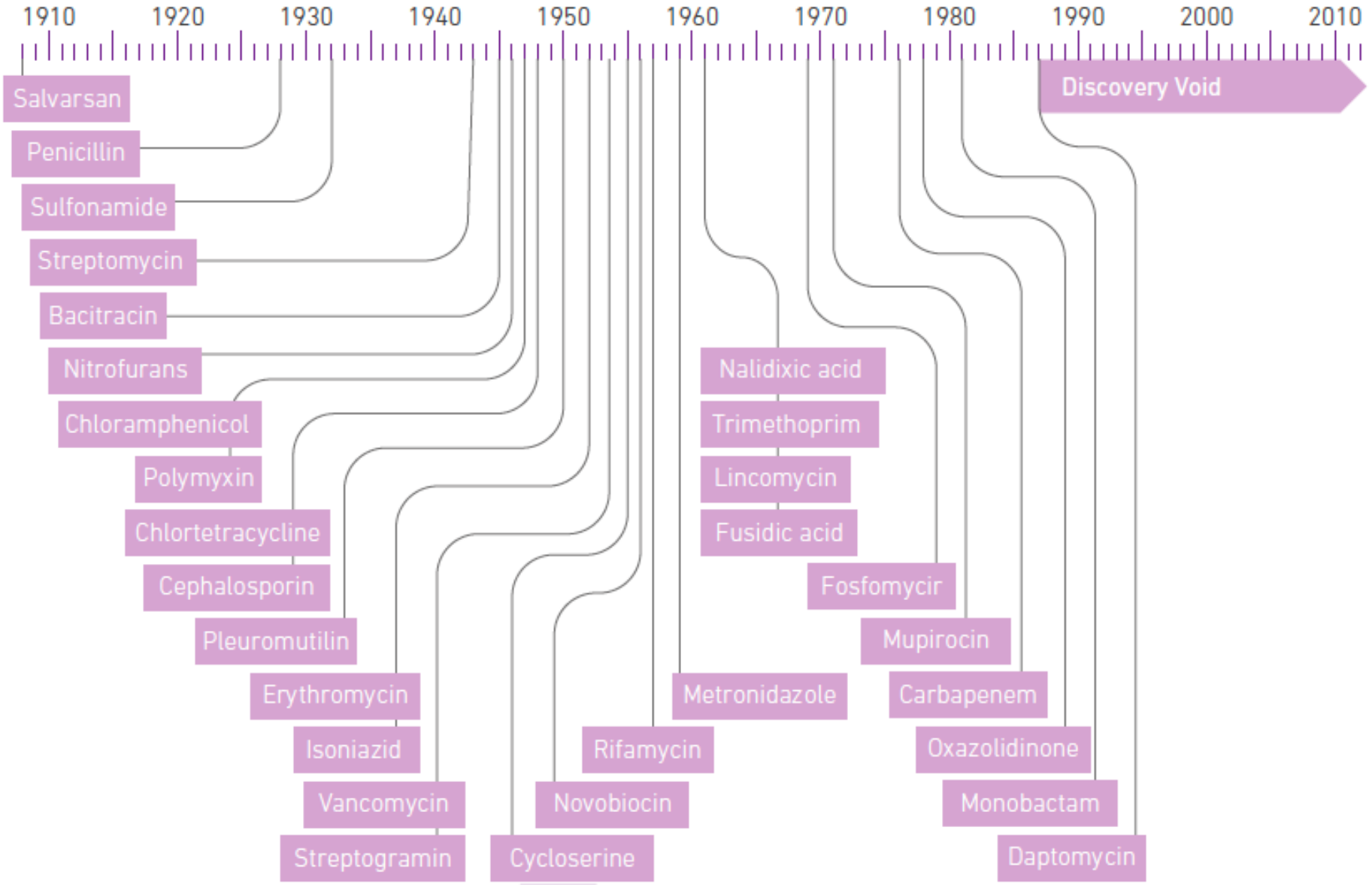
*Updated as of July 21, 2011.

CDC, 2012

Discovery of drugs for tuberculosis



Dates of discovery of distinct classes of antibacterial drugs



Adapted from Silver 2011 (1) with permission of the American Society of Microbiology Journals Department.

WHO AMR Report 2014

The Gram negative antibiotic pipeline for the next 10-15 years

http://www.mistymountaingraphics.com/gallery6.html

Antiretroviral Pipeline 1987 - 2003

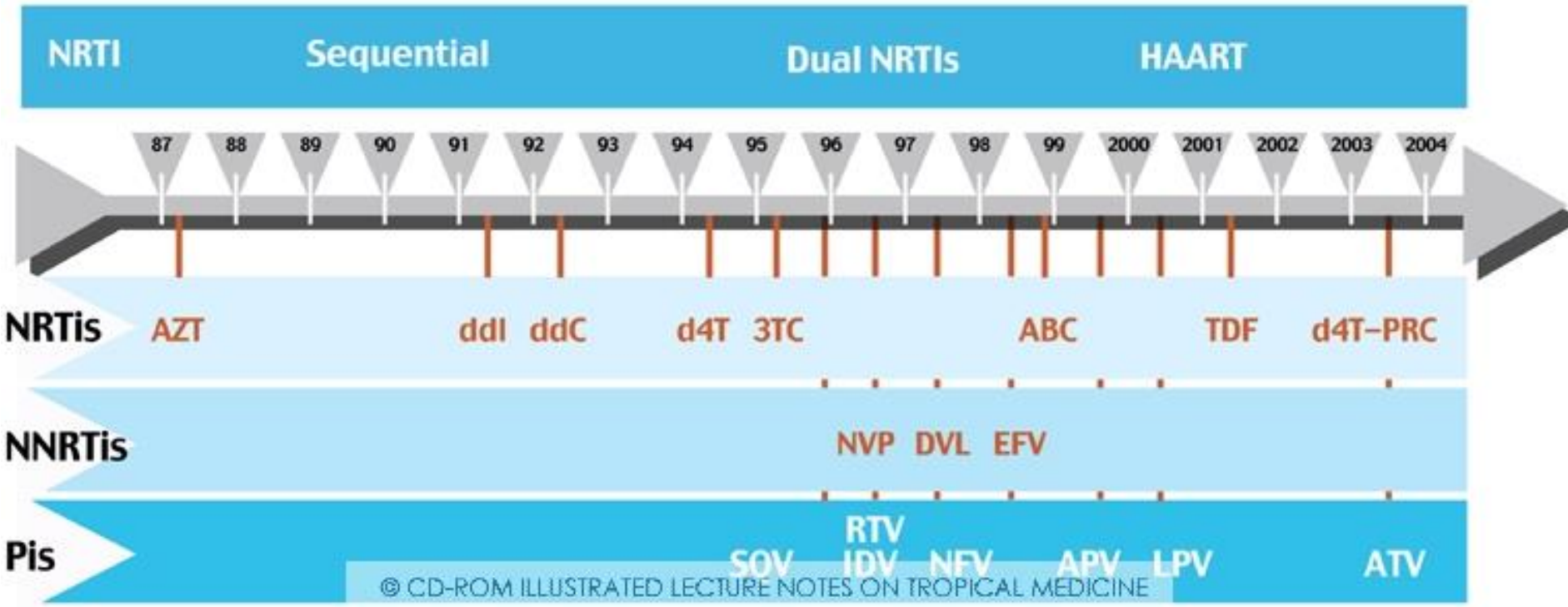


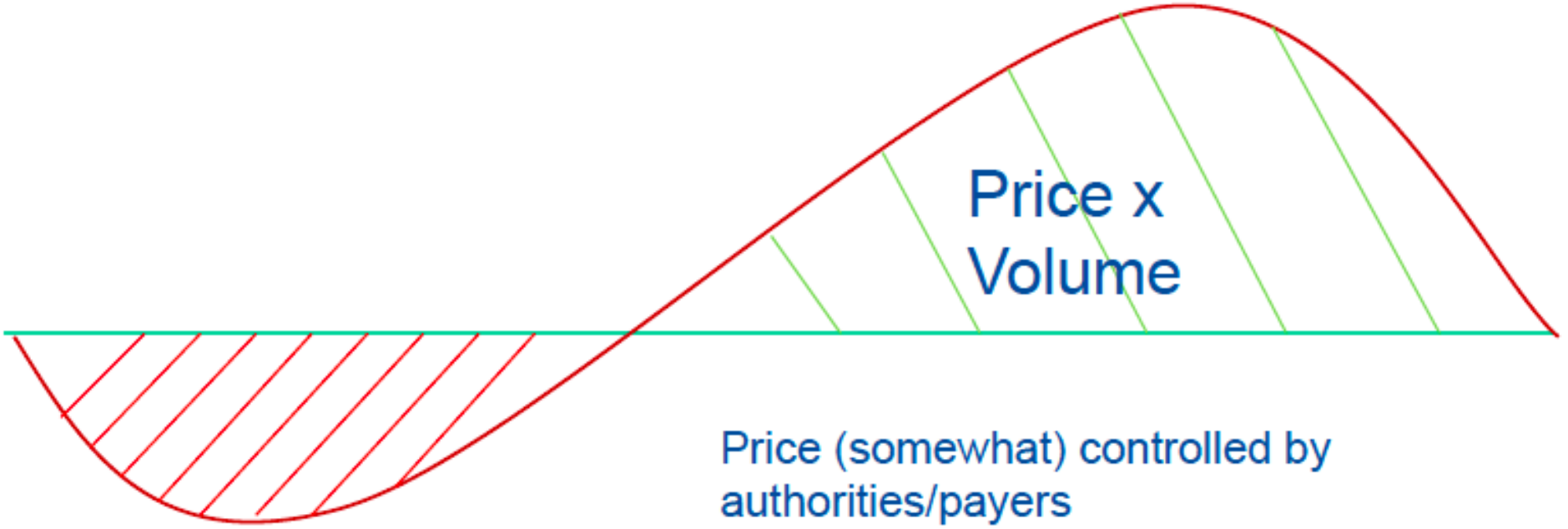
Table 1A. HIV treatment pipeline, 2003–2013: Drugs approved, submitted, or active in phase II/III

Generic Name (Acronym)	Brand Name	Sponsor	Status	Date	Class
Approved (16)					
atazanavir	Reyataz	BMS	Approved	2003	PI
emtricitabine (FTC)	Emtriva	Gilead	Approved	2003	NRTI
enfuvirtide (T-20)	Fuzeon	Roche	Approved	2003	FI
fosamprenavir	Lexiva	GSK	Approved	2003	PI
abacavir/lamivudine (ABC/3TC)	Epzicom	GSK	Approved	2003	NRTI 2-FDC
emtricitabine/tenofovir (FTC/TDF)	Truvada	Gilead	Approved	2004	NRTI 2-FDC
tirpanavir	Aptivus	BI	Approved	2005	PI
darunavir	Prezista	Janssen	Approved	2006	PI
efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF)	Atripla	BMS/Gilead	Approved	2006	NNRTI/2NRTI 3-FDC
maraviroc	Selzentry	Pfizer	Approved	2007	CCR5RI
raltegravir	Isentress	Merck	Approved	2007	InI
etravirine	Intelence	Janssen	Approved	2008	NNRTI
nevirapine-XL	ViramuneXR	BI	Approved	2011	NNRTI
rilpivirine	Edurant	Janssen	Approved	2011	NNRTI
rilpivirine/emtricitabine/tenofovir	Complera	Janssen/Gilead	Approved	2011	NNRTI/2NRTI 3-FDC
elvitegravir/cobicistat/emtricitabine/tenofovir	Stribild	Gilead	Approved	2012	InI/PK booster/2NRTI 4-FDC
Submitted (3)					
elvitegravir	–	Gilead	Submitted	2012	InI (single-agent approval postponed; approved in Stribild 2012)
cobicistat	–	Gilead	Submitted	2012	PK booster (single-agent approval postponed; approved in Stribild 2012)
dolutegravir	–	ViiV/GSK	Submitted	2013	InI
Active in Phase III (1) or Phase II (9)					
tenofovir alafenamide (TAF)	–	Gilead	In phase III	2013	NtRI
BMS-986001	–	BMS	In phase II	2013	NRTI
BMS-663068	–	BMS	In phase II	2013	AI
cenicriviroc	–	Tobira	In phase II	2013	CCR5RI
doravirine (MK-1439)	–	Merck	In phase II	2013	NRTI
GSK1265744	–	GSK/Shionogi	In phase II	2013	InI (injectable LA)
rilpivirine-LA	–	Janssen	In phase II	2013	NNRTI (injectable LA)
darunavir/cobicistat/emtricitabine/ tenofovir alafenamide	–	Janssen/Gilead	In phase II	2013	PI/PK booster/2NRTI 4-FDC
dolutegravir/abacavir/lamivudine (572-Trii)	–	GSK/ViiV	In phase II	2013	PI/2NRTI 3-FDC
elvitegravir/cobicistat/emtricitabine/ tenofovir alafenamide	–	Gilead	In phase II	2013	InI/PK booster/2NRTI 4-FDC

Table 1B. HIV treatment pipeline, 2003–2013: drugs stopped or stalled in phase II/III

Generic Name (Acronym)	Sponsor	Last Active Year	Class
Stopped in Phase III (3)			
capravirine (AG-1549)	Pfizer	2005	NNRTI
vicriviroc (SCH 417690)	Schering	2010	CCR5I
lersivirine (UK-453,061)	Pfizer	2013	NNRTI
Stalled in Phase II (2)			
PRO 140	Progenics/Cytodyn	2010	AI mAb
ibalizumab (TNX-355)	Tanox/Biogen	2011	anti-CD4 mAb
Stopped in Phase II (13)			
DPC-083 (AI-183)	BMS	2004	NNRTI
PRO 542	Progenics	2004	AI mAb
SCH-C	Schering	2004	CCR5RI
calanolide A	Advanced L.S.	2005	NNRTI
reverset (D-D4FC)	Incyte	2006	NRTI
brecanavir	GSK	2007	PI
alovudine (FLT)	Mefuvir Beijing	2008	NRTI
BILR 355/r BS	BI	2008	NNRTI
elvucitabine	Achillion	2008	NRTI
racivir	Pharmasset	2008	NRTI
amdoxivir (DAPD)	Gilead	2010	NRTI
apricitabine	Avexa	2010	NRTI
bevirimat (PA-457)	Panacos/Myriad	2010	AI

Typical Pharmaceutical Economic Model: Return is driven by sales volume



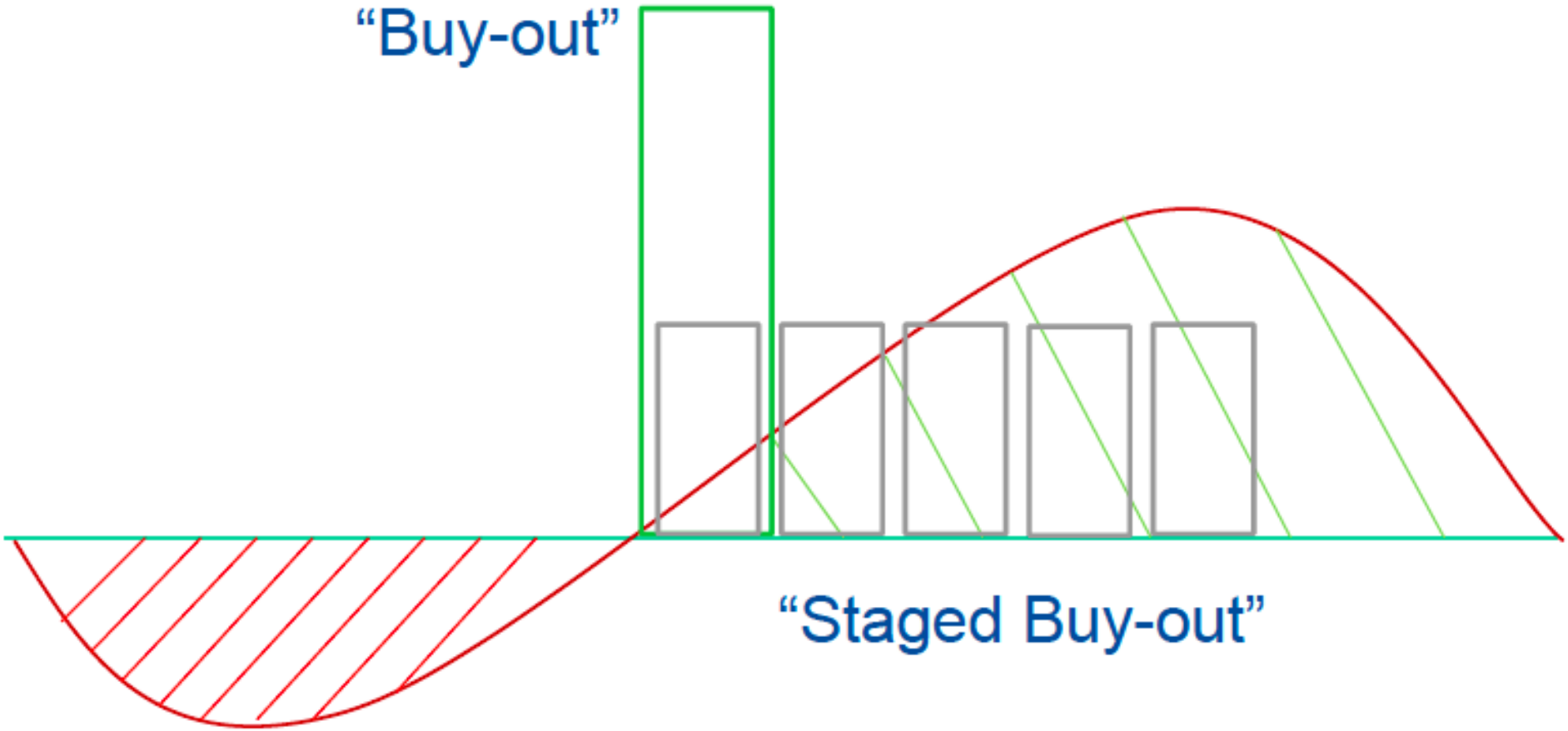
Price (somewhat) controlled by authorities/payers

Volume (somewhat) driven by company and competition

Investment is largely controlled by need to demonstrate safety & efficacy

Slide courtesy of James Anderson, GSK

De-linked or de-coupled model

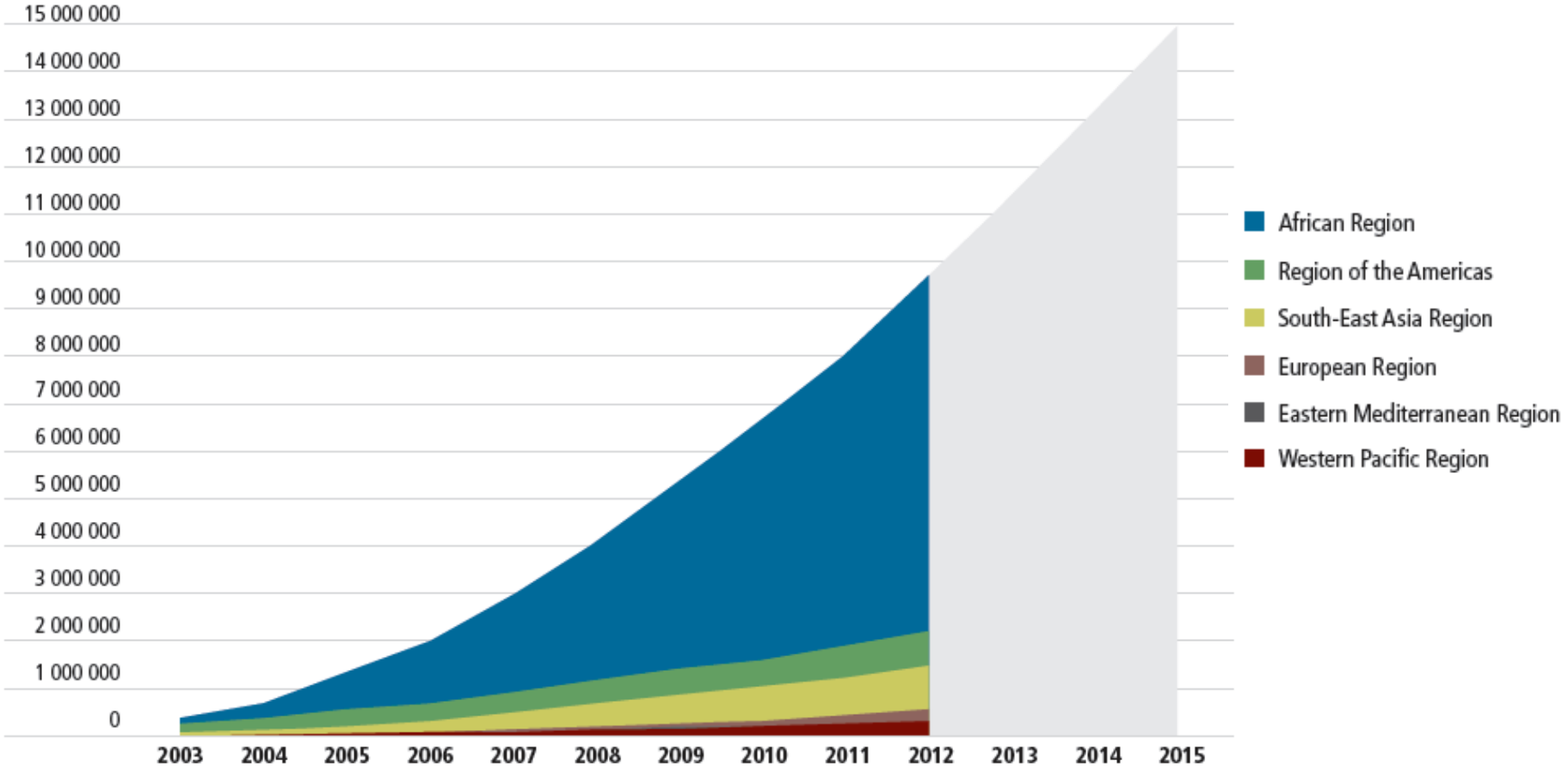


Slide courtesy of James Anderson, GSK

Recommendations for new models of pharmaceutical R&D by the WHO Consultative Expert Working Group

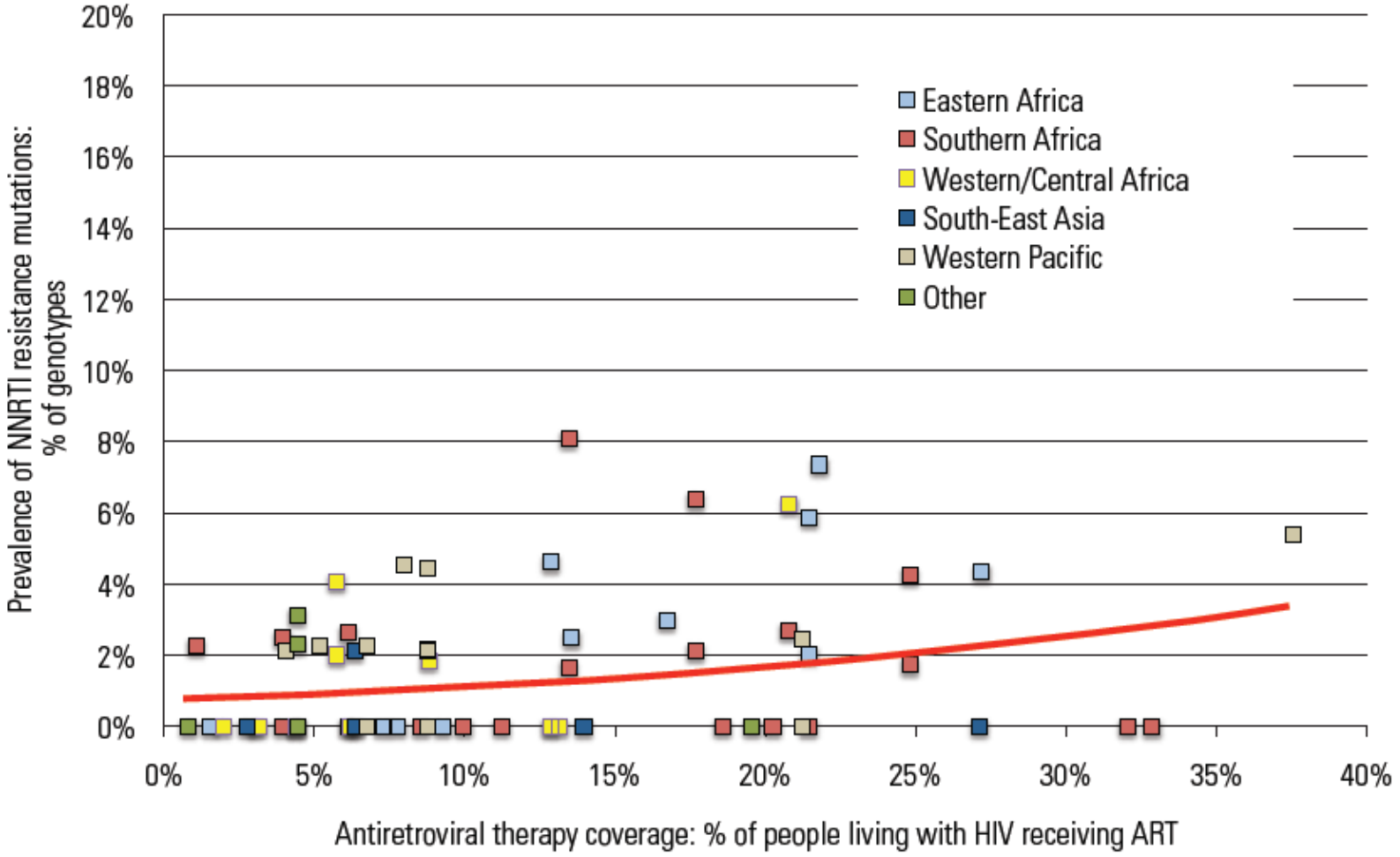
- De-linking revenues from sales
- New incentives or re-purposing off-patent medicines
- Milestone payments and advanced purchase commitments for new priority antibacterials
- Global contract for stewardship
- Agreement on tiered pricing

Actual and projected numbers of people receiving ART in LMICs, and by WHO region, 2003-2015



2013 Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS)

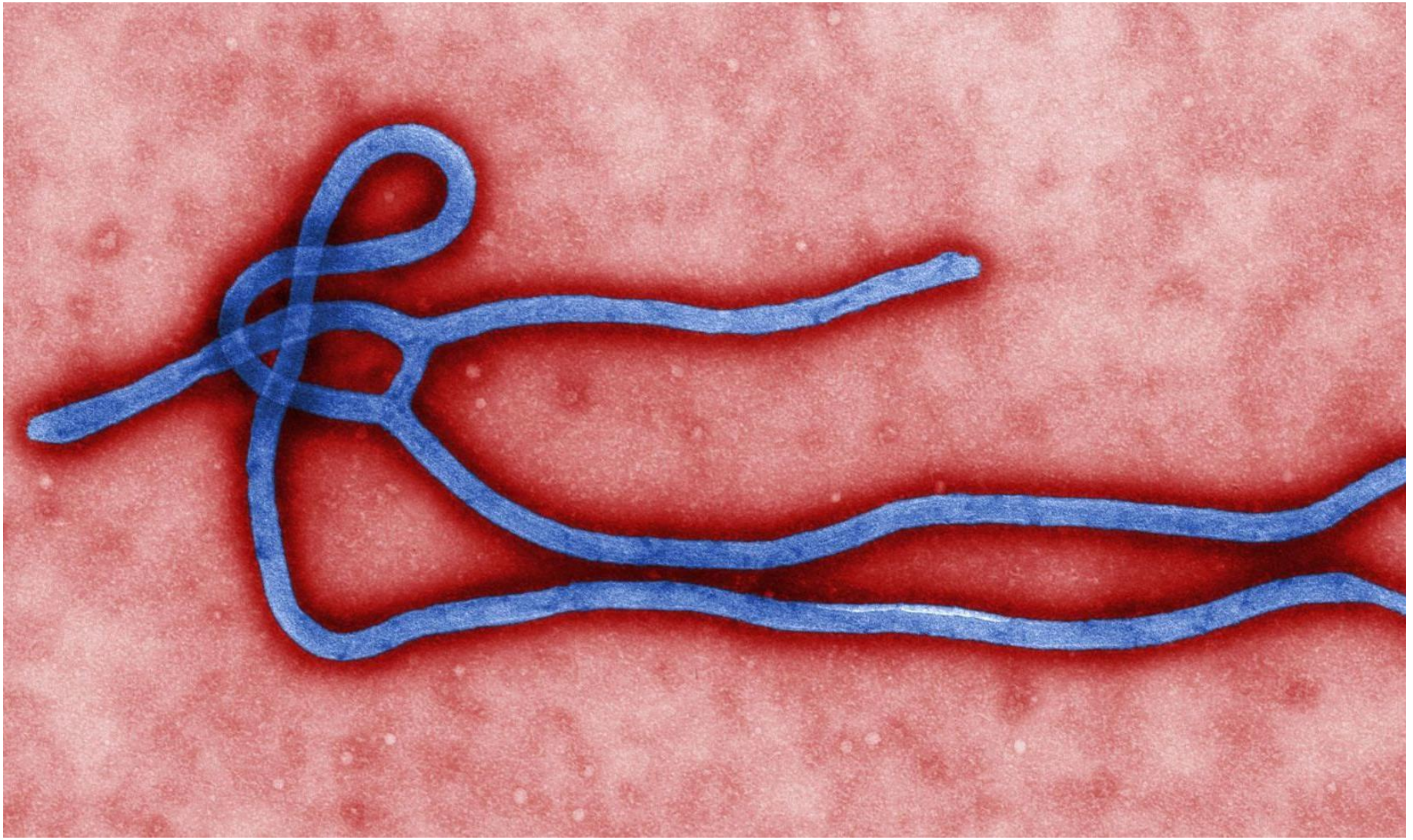
Relationship between transmitted resistance to NNRTI drugs & antiretroviral therapy coverage



WHO HIV Drug Resistance Report 2012

Lesson 3

Healthcare professionals and the public have difficulty identifying with AMR

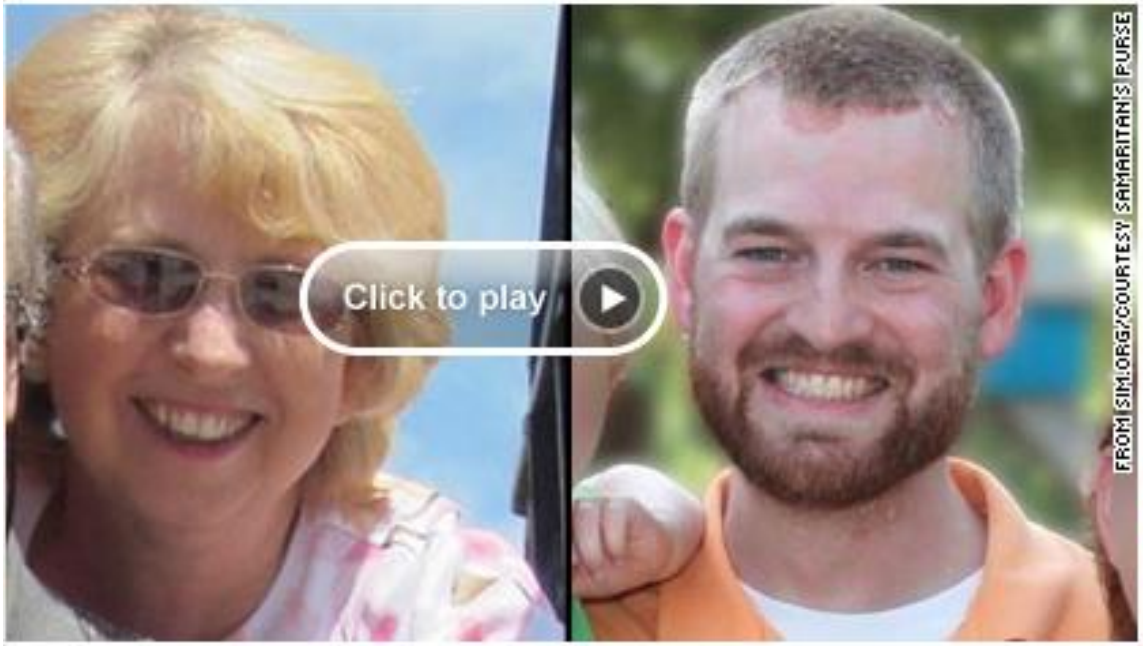



Irish Aid
EBOLA
Signs and Symptoms
FEVER
BLOODY DIARRHOEA
VOMITING BLOOD
SKIN RASH
MUSCLE OR JOINT PAIN
If You Have Fever, Diarrhoea and Vomiting With or Without Bleeding
GO IMMEDIATELY TO THE NEAREST HEALTH FACILITY
For more information call 117 (Call free)

DOMINIQUE FAGET/AFP/GETTY IMAGES

BREAKING NEWS

Coming to America



Patients will be 1st in U.S. with Ebola

The concern began just as news broke that a long-range business jet left the U.S. for Liberia, where it was to evacuate two Americans infected with Ebola. **FULL STORY**

- **Jet outfitted with isolation pod**
- **What's risk of Ebola on planes?**
- **Photos: Outbreak | Explainer**
- **Sick doc gives Ebola serum away**

How do you develop the narrative?

What do the consequences of antiretroviral treatment failure look like to you, your patients and their support networks?

26 year old cachexic HIV-HBV coinfected man

- 1st line ART after PTB diagnosis – defaulted and re-started
- Developed virological failure, 2nd line switch
- Re-presented with presumptive disseminated TB
- Alluvia not boosted
- Deteriorating on TB treatment, unidentified cause
  - rifampicin boosting and addition of MDR therapy
- Re-admitted with [probable] disseminated TB, disseminated cryptococcosis, pseudomembraneous colitis

26 year old male HIV-HBV coinfected

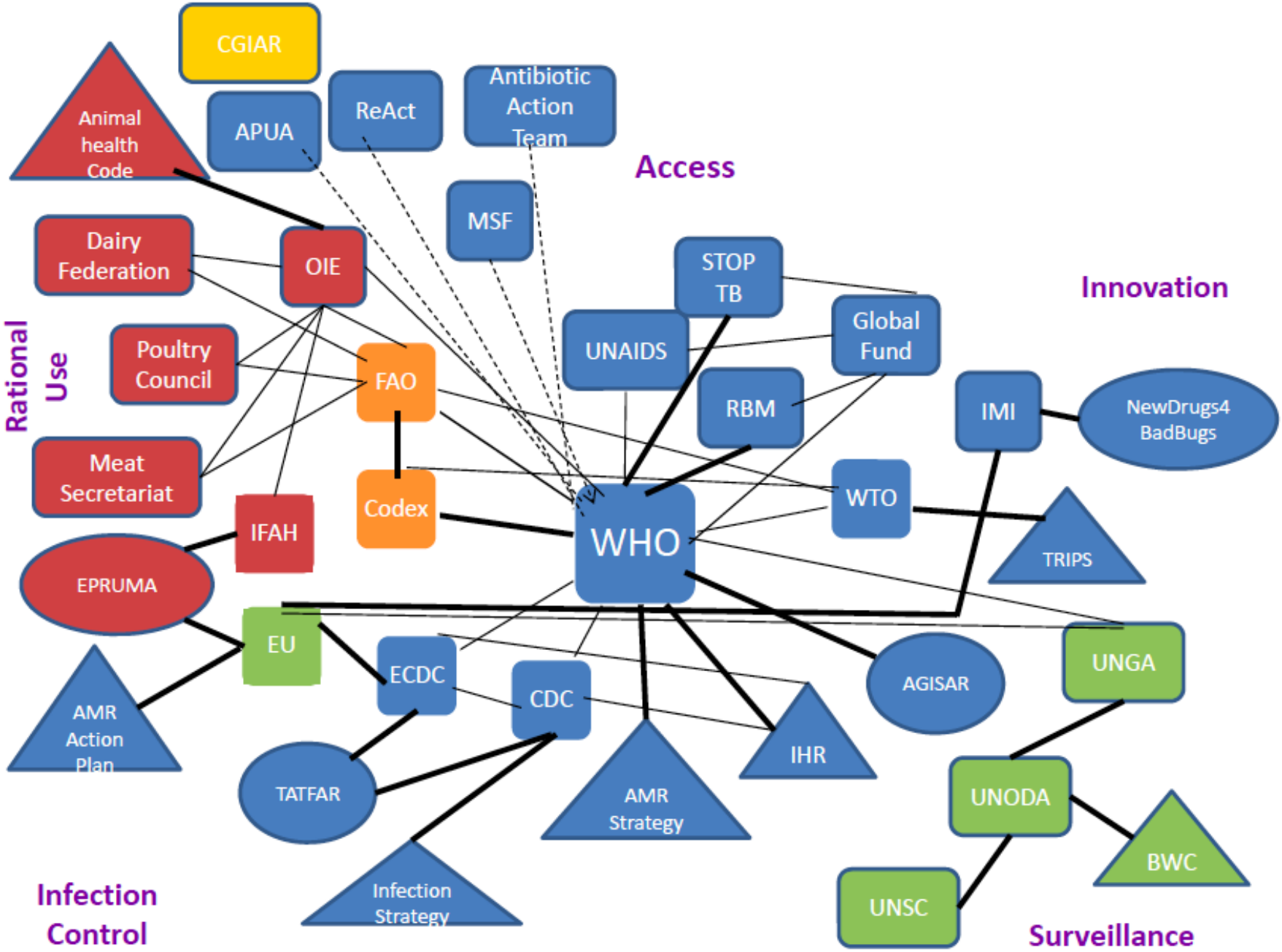
Tuberculosis	HIV, HBV	Cryptococcus	*C. difficile*
Rifampicin	Tenofovir	Amphotericin	Vancomycin
Isoniazid	Emtricitabine	Fluconazole	[oral]
Ethambutol	Aluvia (DD)		
Prazinamide	Cotrimoxazole		
Moxifloxacin			
Ethionamide			
Kanamycin			

Potential nephrotoxicity

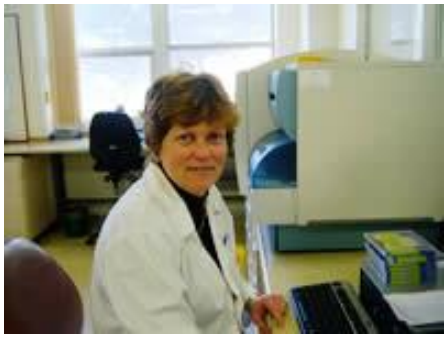
Potential hepatic toxicity

Lesson 4

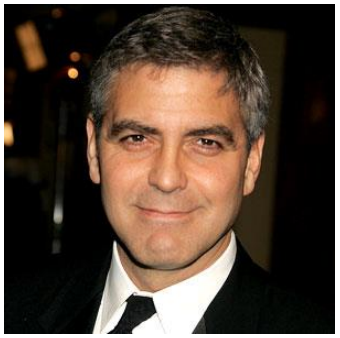
The need to work effectively as a multi-disciplinary team



Slide courtesy of Steven Hoffman




Microbiologists


Infectious Diseases Specialists

Registrars

GSH Antibiotic Stewardship Team

Pharmacists

Nurses

IPC

Intensivists

Statistician


Nurses
[Psychologist/Psychiatrist]
Social Worker
Adherence Counsellor
Treatment supporter(s)
ART Prescriber
Antiretroviral Stewardship Team
Others; Who would they be?

Lesson 5

Asking the right question

5 D'S OF DODGEBALL

Duck Dodge Dip Dive Dodge

The 5 D's of Antibiotic Stewardship

- Drug [Is an antibiotic indicated at all?]
- Dose
- Dosing interval
- Duration
- De-escalation

[And an 'R' – Route of administration]

What antiretroviral combination should I use?

That’s the easy part

“Why did we fail?”

Take Home Messages

- History has a horrible way of repeating itself, particularly when it comes to the control of infectious diseases
- Although much is being done to address ARV treatment failure, too often, the wrong question is being asked
- We need to be smarter about defining patients at risk and ensuring members of our ARV stewardship teams have the skills and time to fulfill their role

Do not go gentle into that good night
Old age should burn and rave at close of day
Rage, rage against the dying of the light

Though wise men at their end know dark is right,
Because their words had forked no lightning they
Do not go gentle into that good night

Good men, the last wave by, crying how bright
Their frail deeds might have danced in a green bay,
Rage, rage against the dying of the night

Wild men who caught and sang the sun in flight
And learn, too late, they grieved it on its way
Do not go gentle into that good night

Grave men, near death, who see the with blinding sight
Blind eyes could blaze like meteors and be gay,
Rage, rage against the dying of the light.

And you my father, there on the sad height,
Curse, bless, me now with your fierce tears I pray,
Do not go gentle into that good night.
Rage, rage against the dying of the light

Dylan Thomas, 1914 - 1953

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