Antimicrobial Drug Resistance: A global perspective

Nick Day

Manipal 10th August 2019

“Let us not, however, flatter ourselves overmuch on account of our human victories over nature. For each such victory, nature takes its revenge on us. Each victory, it is true, in the first place brings about the results we expected, but in the second and third places it has quite different, unforeseen effects which only too often cancel the first.”

Friedrich Engels 1876

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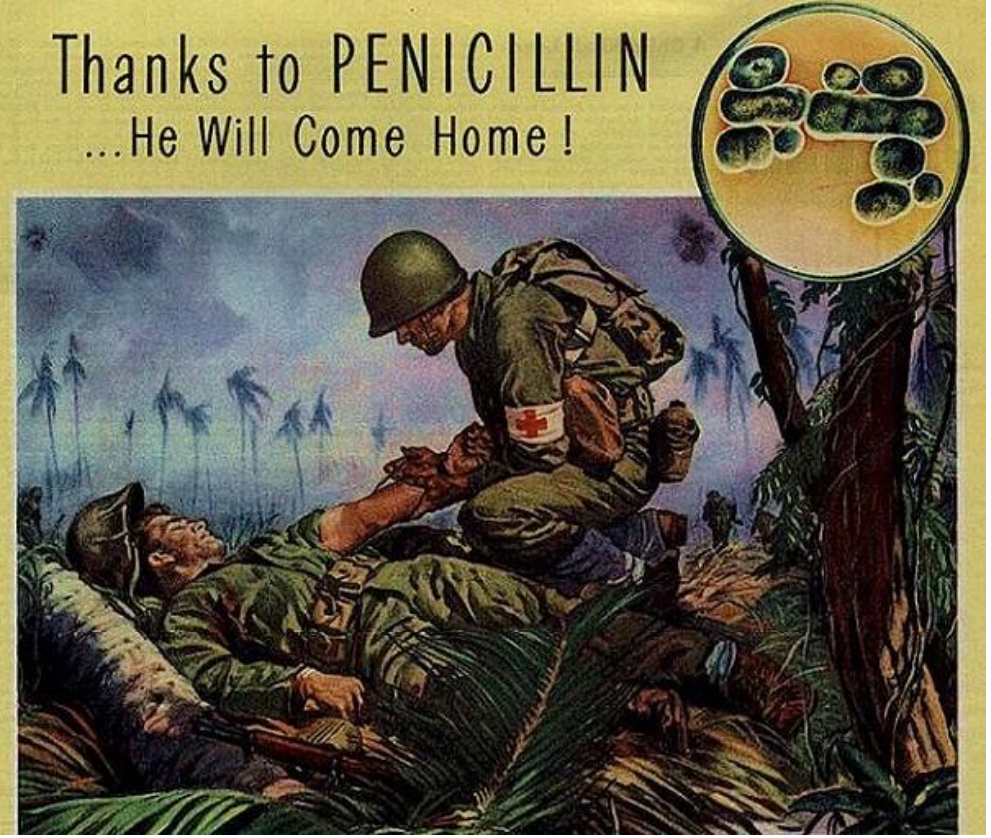
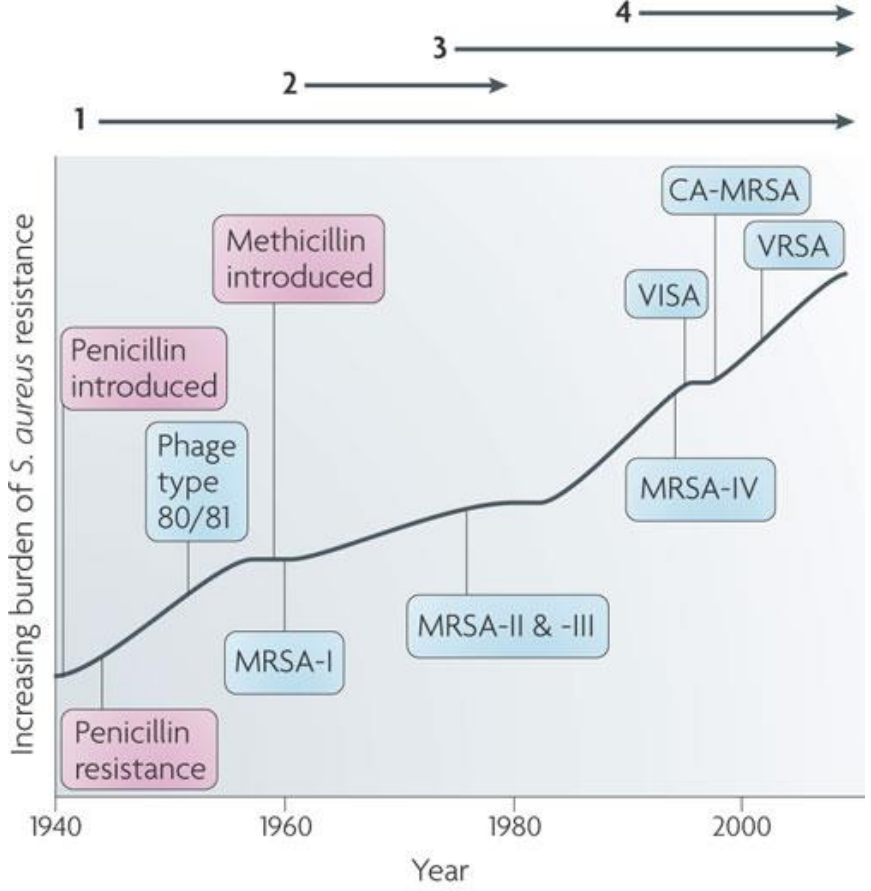
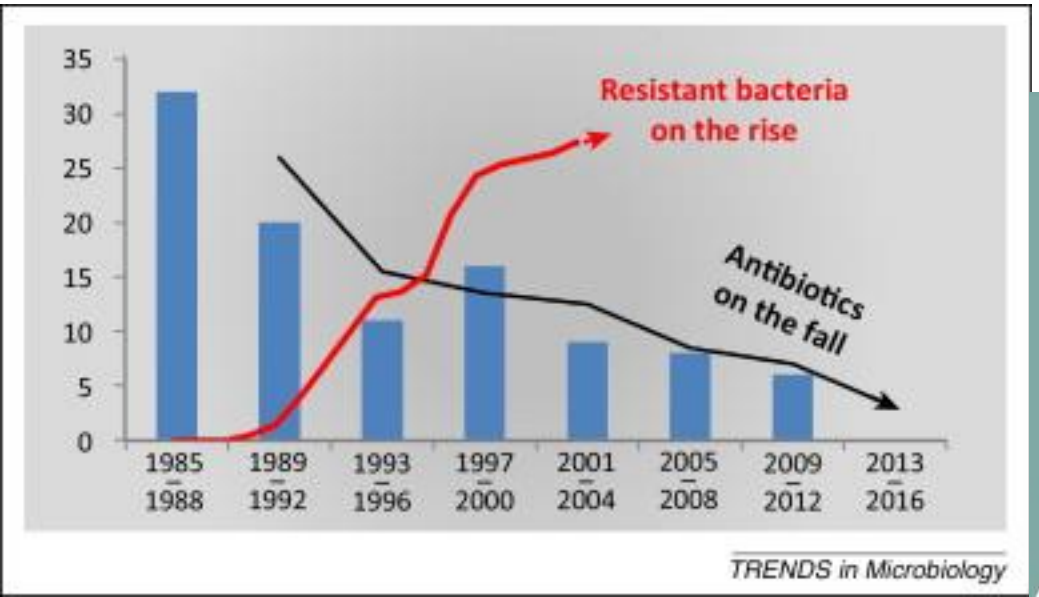

Thanks to PENICILLIN
...He Will Come Home!


4
3
2
1
Increasing burden of S. aureus resistance
Penicillin resistance
Penicillin introduced
Phage type 80/81
Methicillin introduced
MRSA-I
MRSA-II & -III
VISA
CA-MRSA
VRSA
MRSA-IV
1940
1960
1980
2000
Year


35
30
25
20
15
10
5
0
Resistant bacteria on the rise
Antibiotics on the fall
1985 1988
1989 1992
1993 1996
1997 2000
2001 2004
2005 2008
2009 2012
2013 2016
TRENDS in Microbiology


Stephen Jeffrey

Antibiotics – universal access is a fundamental human right

- Access to antibiotics has been a major contributor to the 50% reduction in maternal and child deaths since 1990
- (but many septic neonates and older children with pneumonia still dying because of drug resistant pathogens)
- Azithromycin MDA reduces all cause mortality in African children
- (but caused an increase in macrolide resistant *S. pneumoniae*)
- Many antibiotics promote growth in children
- (in animals too, but with massive increases in resistance)

Mendelson *et al*. *Lancet* 2016; 387: 188-98
Doan *et al. N Engl J Med* 2019; 380: 2271-2273

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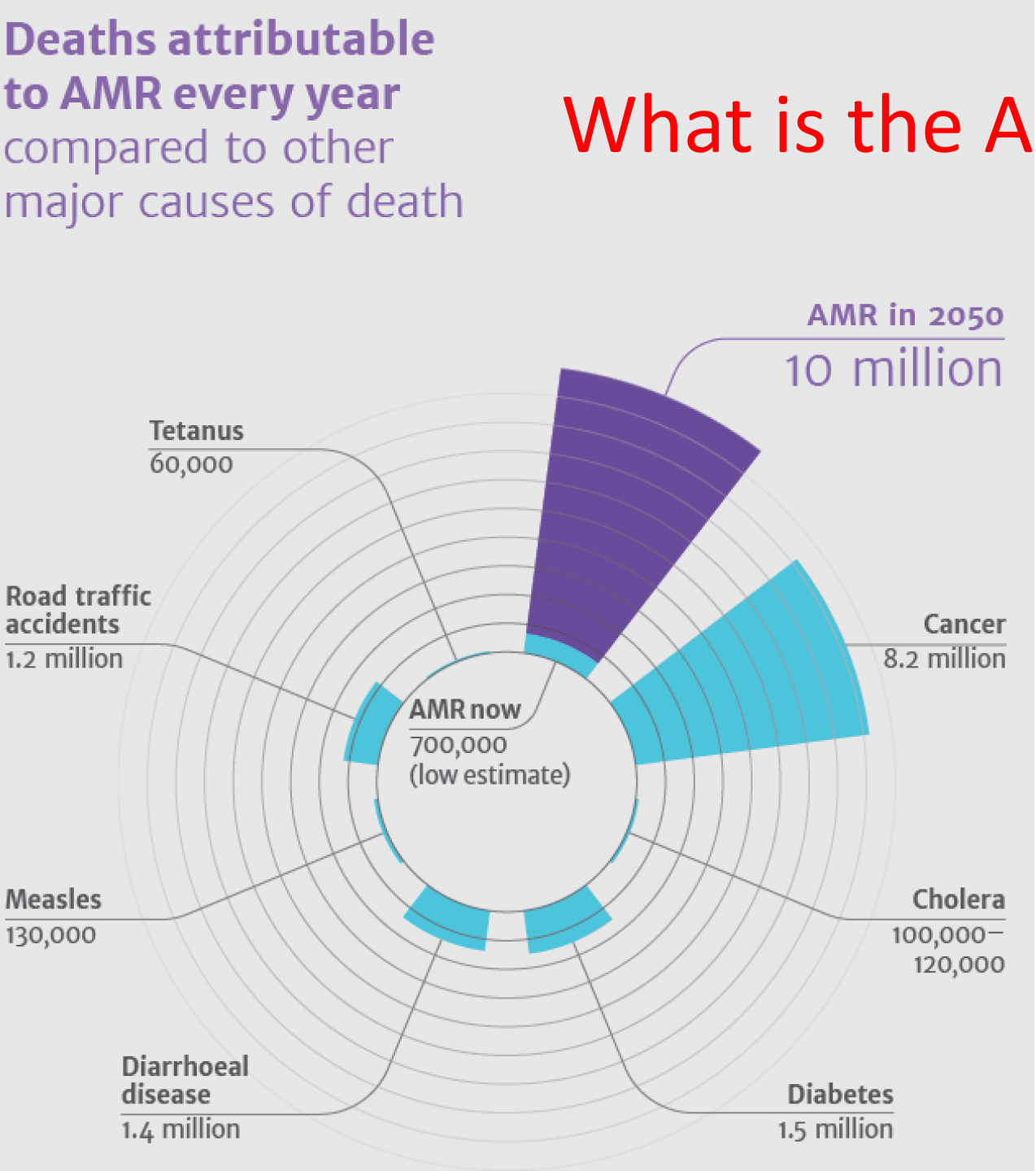
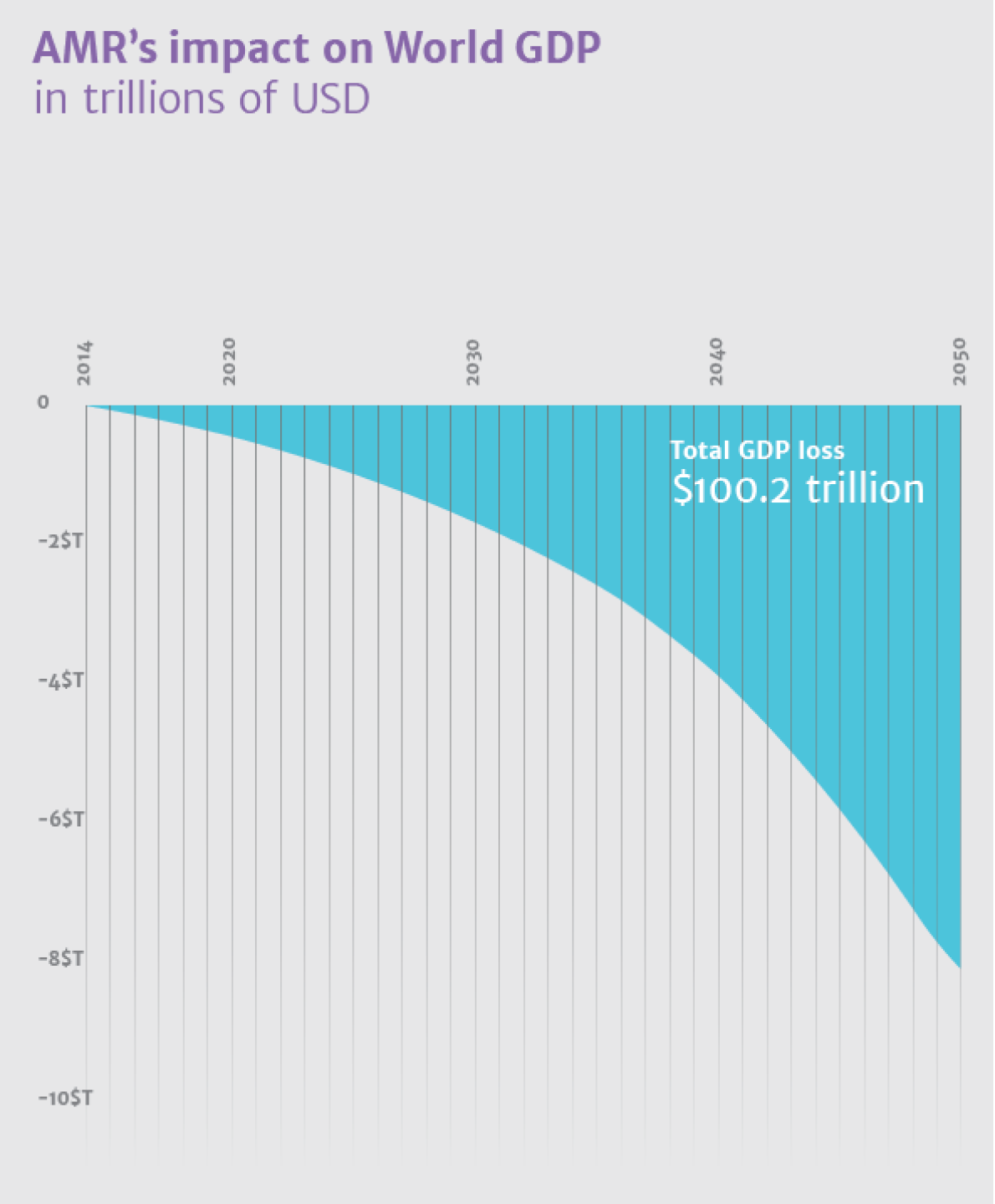
What is the AMR burden?



UK Government

Review on Antimicrobial Resistance

Chair: Jim O'Neill
December 2014

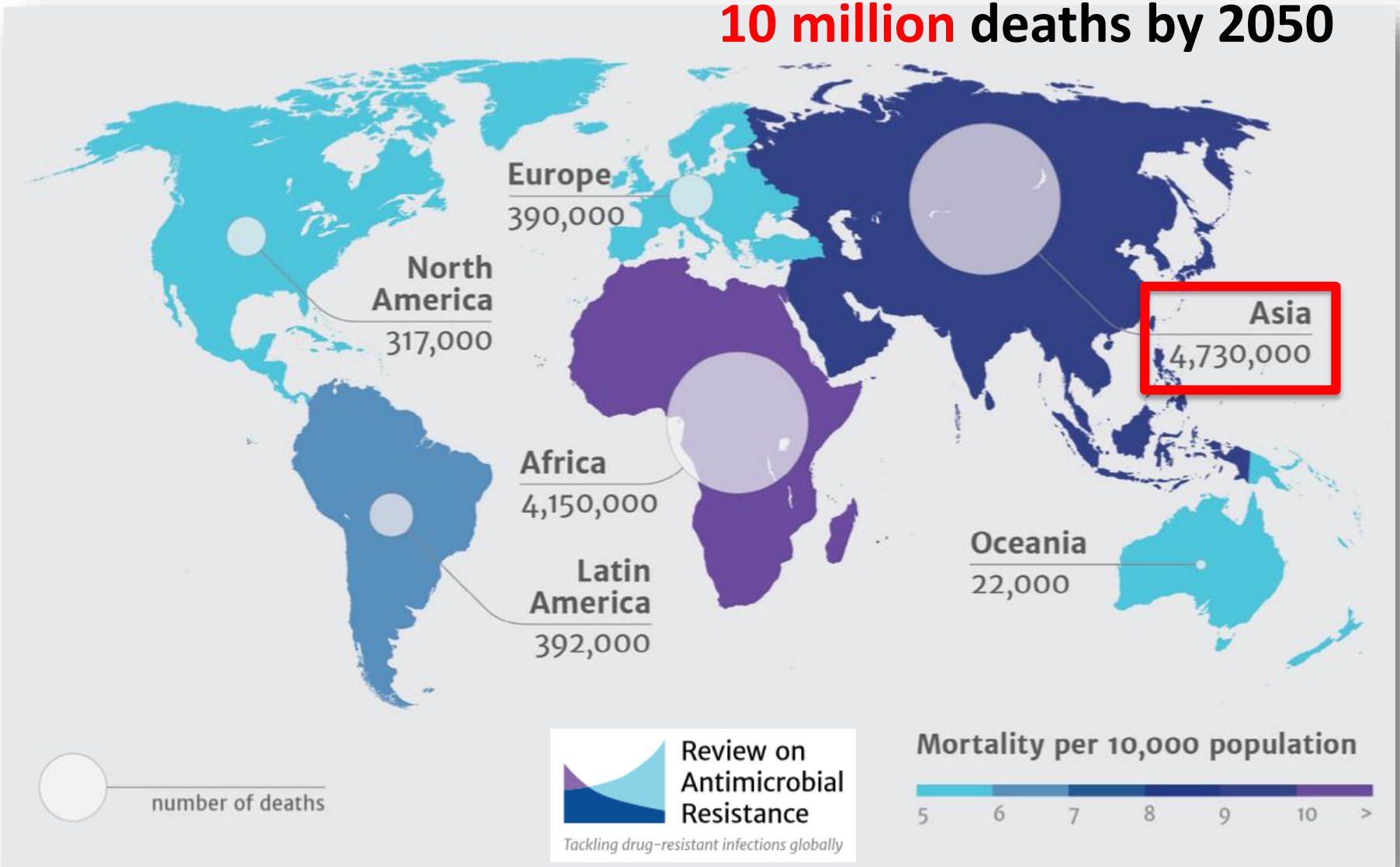


UK Government

Review on Antimicrobial Resistance

Chair: Jim O'Neill
December 2014

10 million deaths by 2050



Currently 700,000 deaths (low estimate) due to antimicrobial resistant infection

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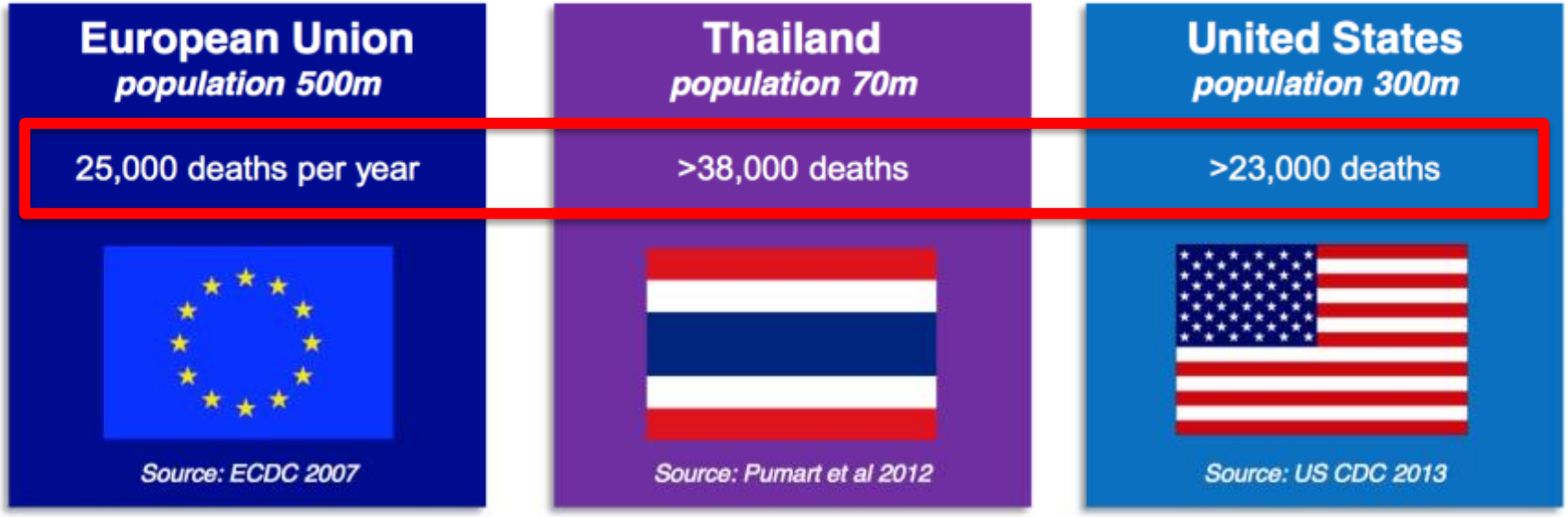
Estimates of Burden of Antibacterial Resistance

European Union *population 500m*	Thailand *population 70m*	United States *population 300m*
25,000 deaths per year	>38,000 deaths	>23,000 deaths
		
Source: ECDC 2007	*Source: Pumart et al 2012*	*Source: US CDC 2013*

Global information is insufficient to show complete disease burden impact and costs

Estimates of Burden of Antibacterial Resistance



Global information is insufficient to show complete disease burden impact and costs

| Antimicrobial Resistance
Global Report on Surveillance 2014

World Health Organization

38,000 in Thailand is "total mortality"

However, it's not comparable - "attributable mortality" should be used

Epidemiology and burden of multidrug-resistant bacterial infection in a developing country

Cherry Lim[1†], Emi Takahashi[1†], Maliwan Hongsuwan[1], Vanaporn Wuthiekanun[1], Visanu Thamlikitkul[2], Soawapak Hinjoy[3], Nicholas PJ Day[1,4], Sharon J Peacock[1,5,6], Direk Limmathurotsakul[1,4,7*]

[1]Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand; [2]Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [3]Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand; [4]Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom; [5]London School of Hygiene and Tropical Medicine, London, United Kingdom; [6]University of Cambridge, Addenbrooke's Hospital, Cambridge, United Kingdom; [7]Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

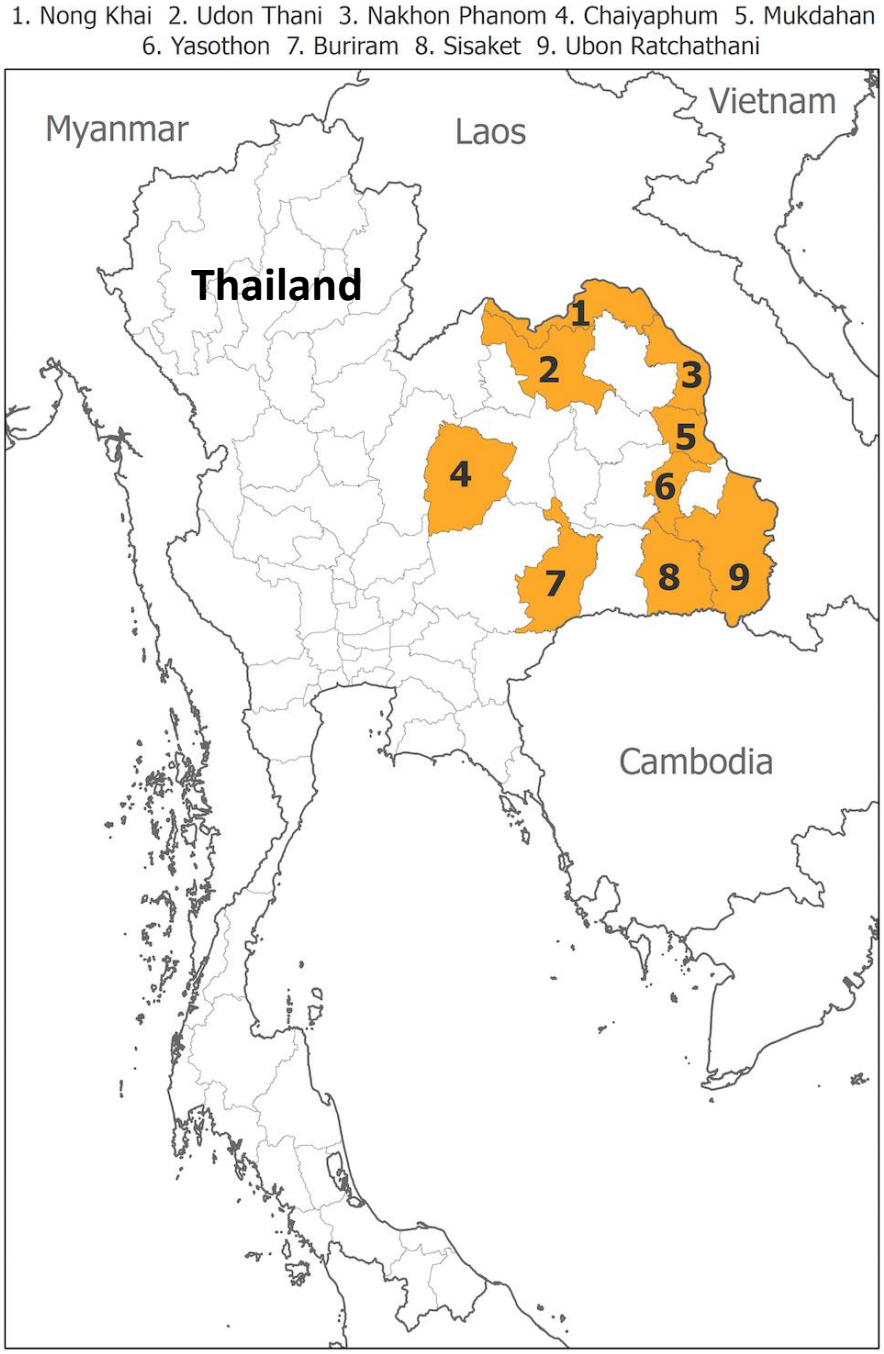
Contributors

- Bacterial Infection in Northeast Thailand (BINET) network
- Ministry of Interior, Thailand

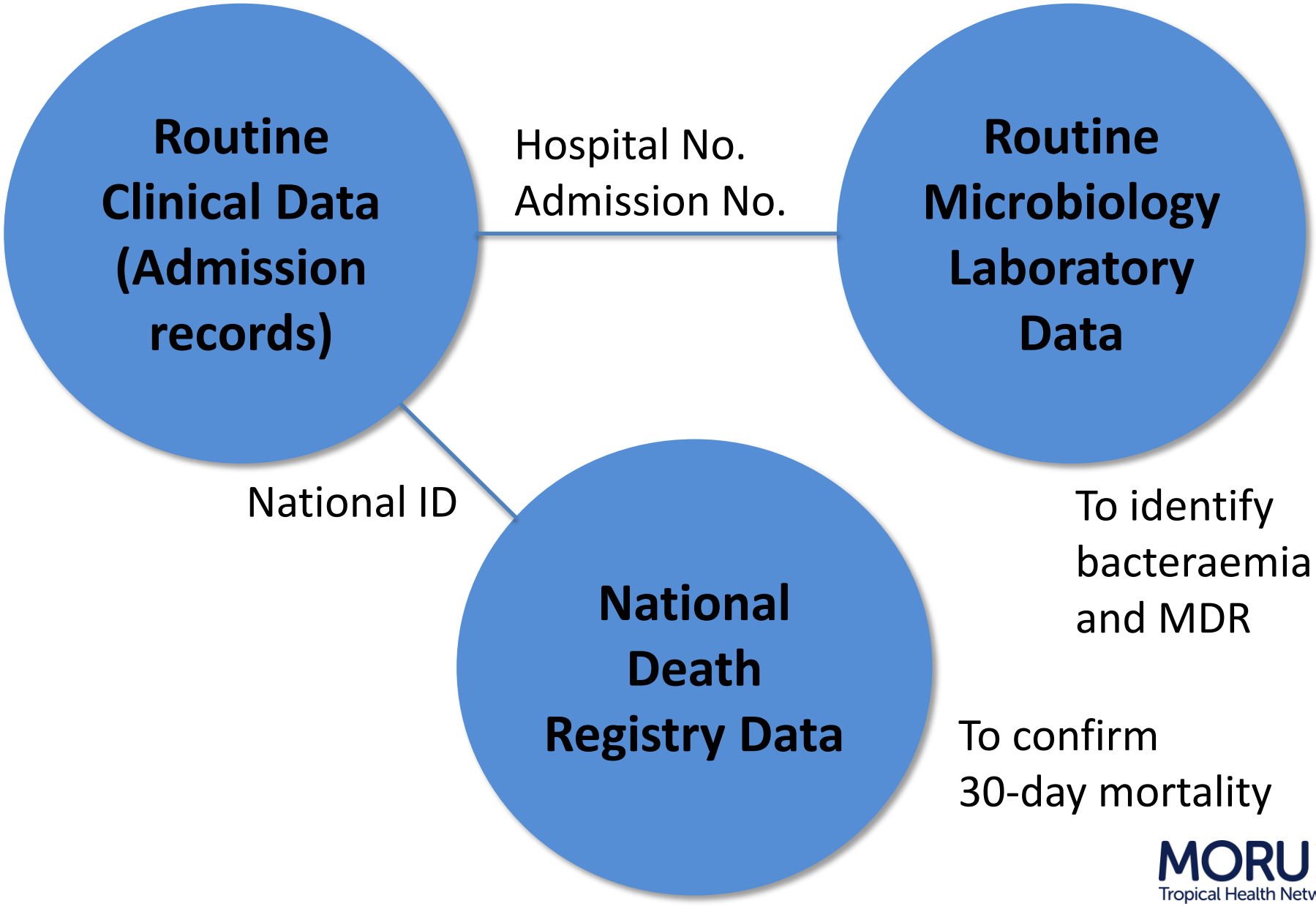
https://elifesciences.org/content/5/e18082 2016

Study Design

- Retrospective, multicentre surveillance study
- Bacteraemia cases
- Jan 2004 - Dec 2010
- 9 provincial hospitals in Northeast Thailand



Methods - Data sources



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Methods

Mortality attributable to MDR
in hospital-acquired bacteraemia (our study)

← Correction factors

Martone WJ., at al. 1998.

Mortality attributable to MDR
in hospital-acquired infections (all sites)

← National statistics of nosocomial MDR infections

Pumart P., et al. 2012.

Mortality attributable to MDR
in hospital-acquired infections **in Thailand**

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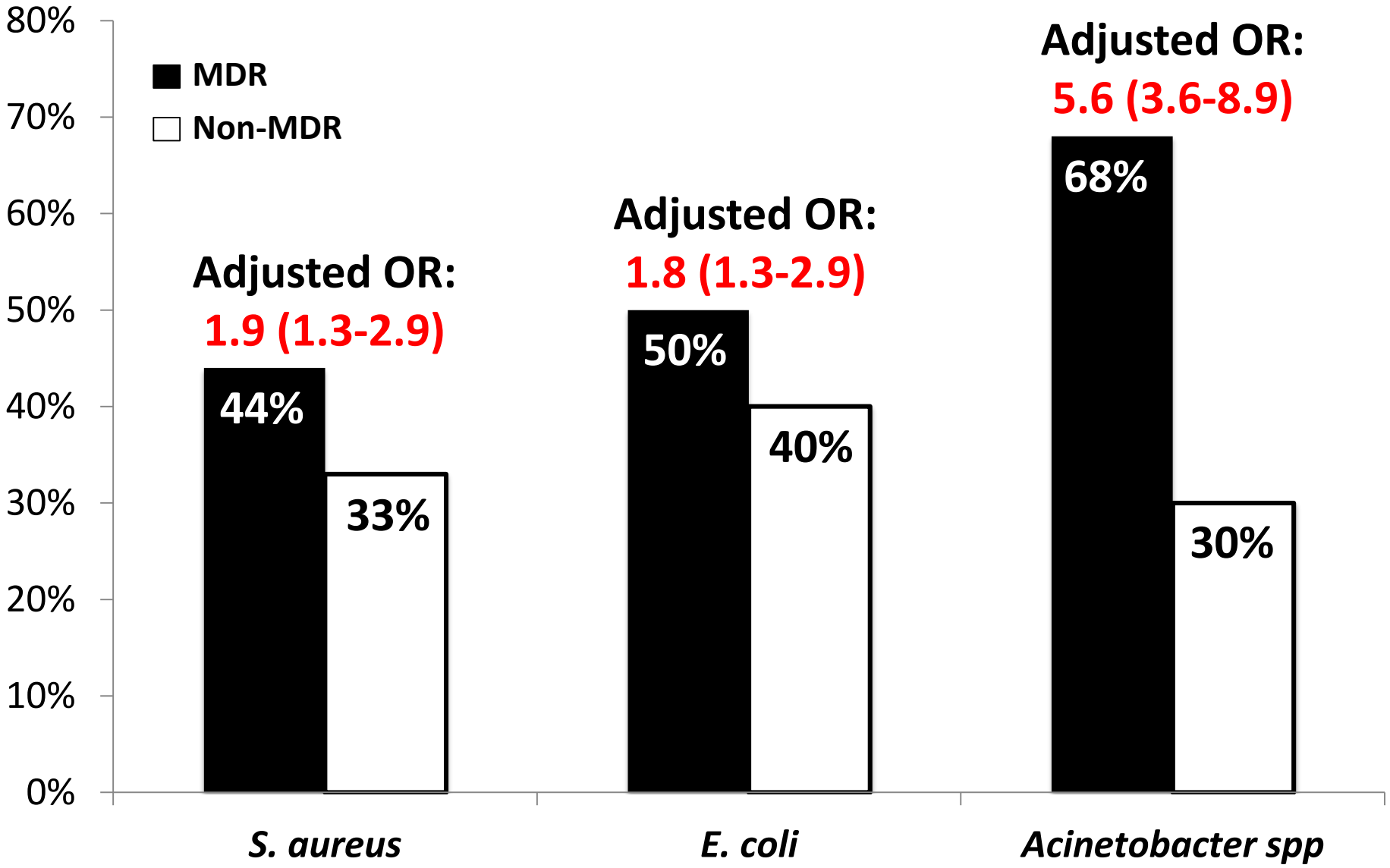
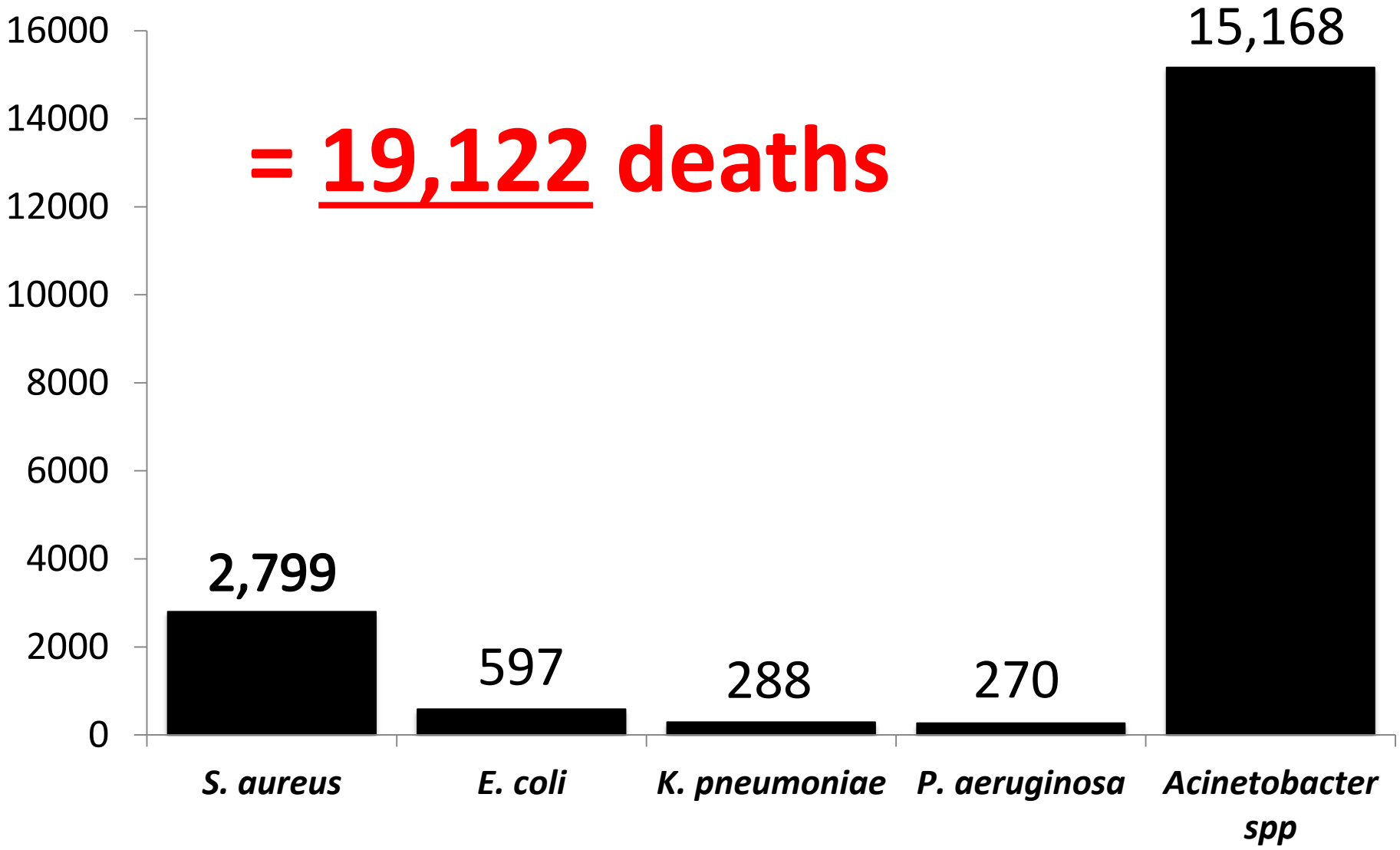
Results – 30 day mortality in patients with hospital-acquired bacteraemia



Excess deaths due to MDR in hospital-acquired infections in Thailand



Estimates of Burden of Antibacterial Resistance

European Union *population 500m*	Thailand *population 70m*	United States *population 300m*
25,000 deaths per year	19,000 deaths per year	>23,000 deaths
		
Source: ECDC 2007	*Source: Lim 2016*	*Source: US CDC 2013*

Global information is insufficient to show complete disease burden impact and costs

| Antimicrobial Resistance
Global Report on Surveillance 2014

World Health Organization

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2015

2017-2018

Acinetobacter spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, *Salmonella* spp., *Shigella* spp., *Staphylococcus aureus*, and *Streptococcus pneumoniae*

"Limitations with data quality and representativeness"

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WHO-GLASS Participation December 2018

Allows both isolate-based and case-based reports

However, mortality data is not included

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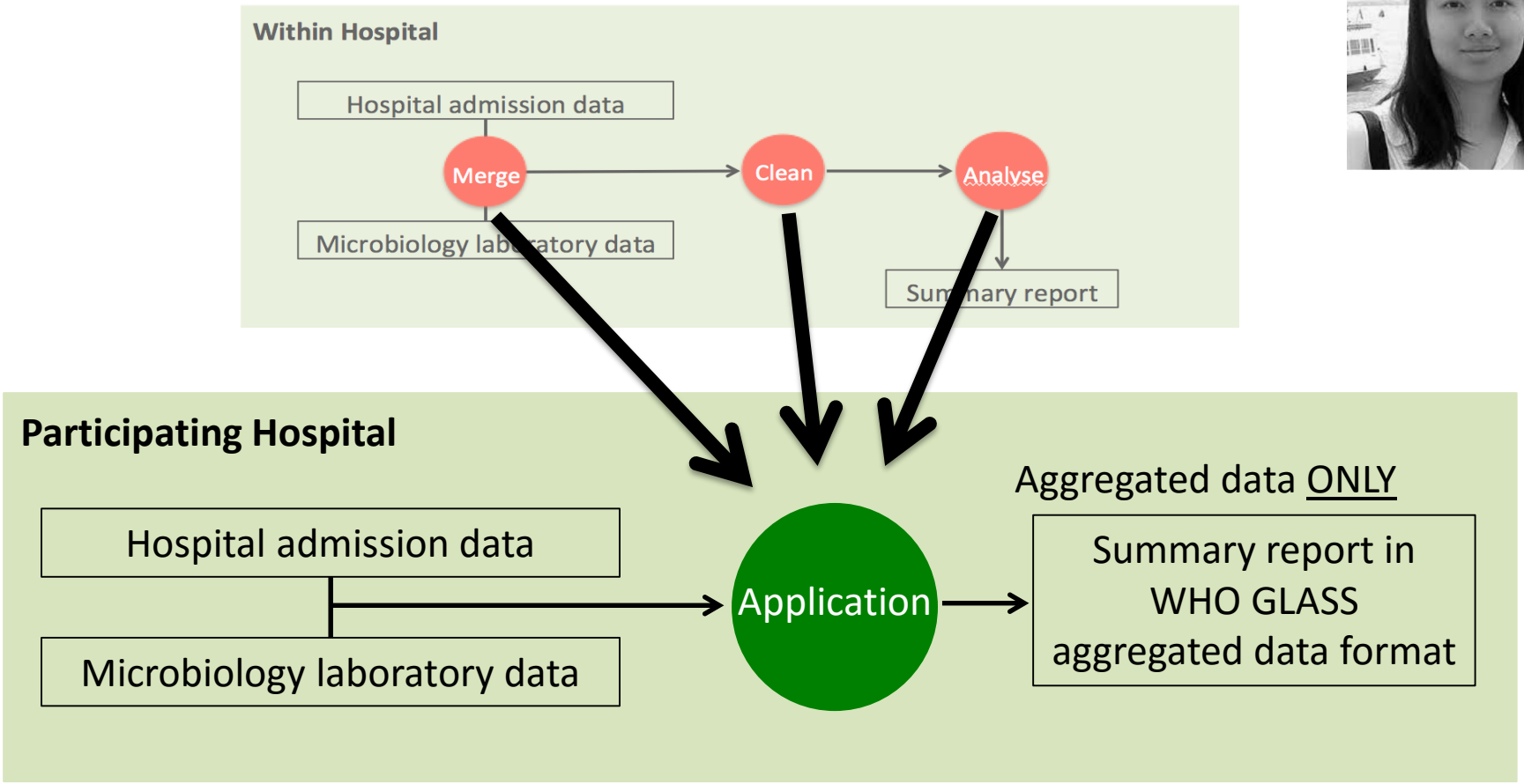
Plan - **easy-to-use application** allowing hospitals to analyse their own data, and produce summary reports for monitoring deaths related to AMR in their own hospitals



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ACORN - A Clinically Oriented antimicrobial Resistance Network

Objectives	Outcome Measures
Primary: **To develop, implement and assess a hospital-based system for patient-centred surveillance of Drug Resistant Infections (DRI)**	A protocol and guideline for implementation of this system for further roll-out in other sites
Secondary: **To systematically characterize drug-resistant infections based on important clinical syndromes, to adequately inform treatment guidelines**	Antimicrobial susceptibility data with both pathogen and clinical denominators, including predefined subgroups
To implement clinical syndrome-guided diagnostic stewardship of patients with suspected infection	Proportion of timely and correctly sampled patients per syndrome
To determine the duration, cost of hospitalisation and patient outcome of DRI and non-DRI	Antimicrobial susceptibility data, cost estimates, 28 day mortality data
Tertiary: **To evaluate the feasibility and acceptability of the surveillance system and package of tools**	Results of clinician and laboratory technician surveys

Led by Paul Turner, Director of Cambodia-Oxford Medical Research Unit

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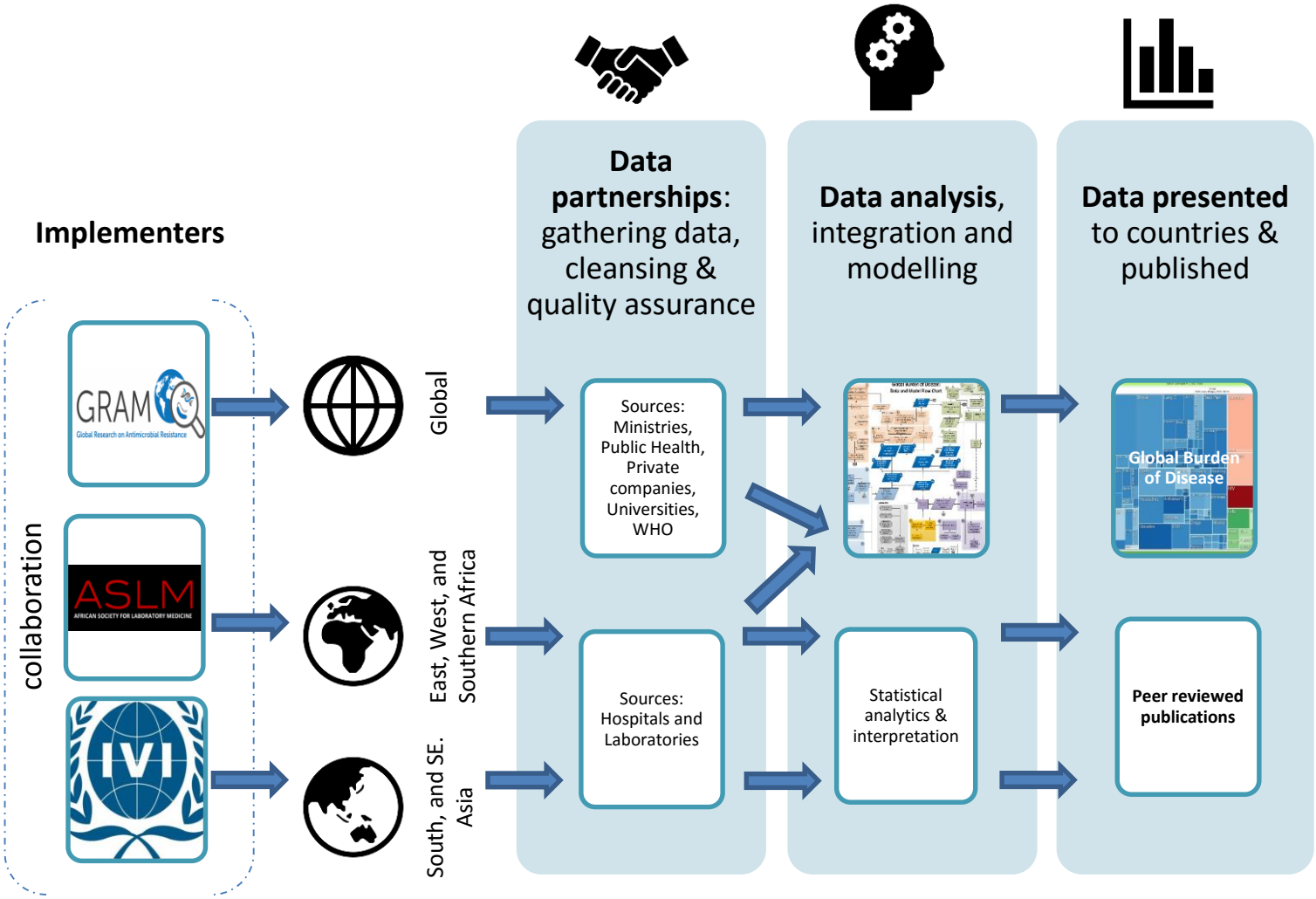
Fleming Fund data-focussed project collaboration: GRAM and Regional Grants Round 1.

The Fleming Fund



The Global Research on AntiMicrobial Resistance (GRAM) study

an Oxford University / Institute of Health Metrics & Evaluation Partnership

- GRAM is the flagship project of the Oxford GBD (Global Burden of Disease) Group
- The Oxford GBD Group is a partnership between the University of Oxford Big Data Institute (BDI) and the Institute of Health Metrics & Evaluation (IHME) at the University of Washington.
- Goal is to provide robust, comprehensive and timely evidence of the burden of AMR globally, in order to:
  - drive awareness of AMR
  - support better surveillance of AMR
  - prompt policy action to control AMR, including facilitating antimicrobial stewardship
- GRAM was launched with support from the UK Department of Health's Fleming Fund, the Wellcome Trust and the Bill and Melinda Gates Foundation.

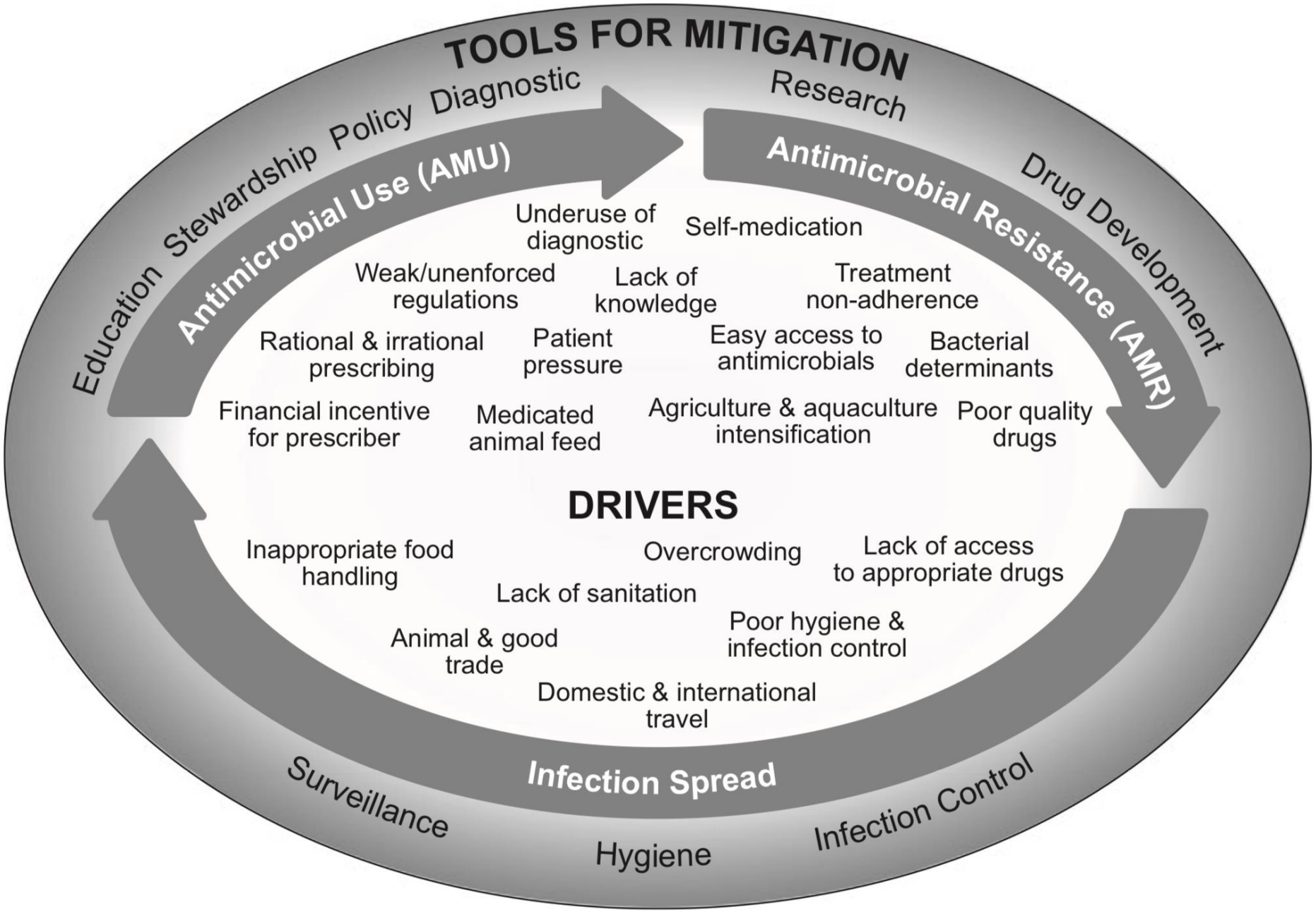
The Global Research on AntiMicrobial Resistance (GRAM) study

an Oxford University / Institute of Health Metrics & Evaluation Partnership

Objectives

1. Consolidate, review and analyse all available data and scientific information on AMR worldwide
2. Produce granular geospatial maps of AMR burden as detailed as the data will allow
3. Incorporate the mortality and morbidity attributable to AMR bacterial pathogens into the GBD Study estimates

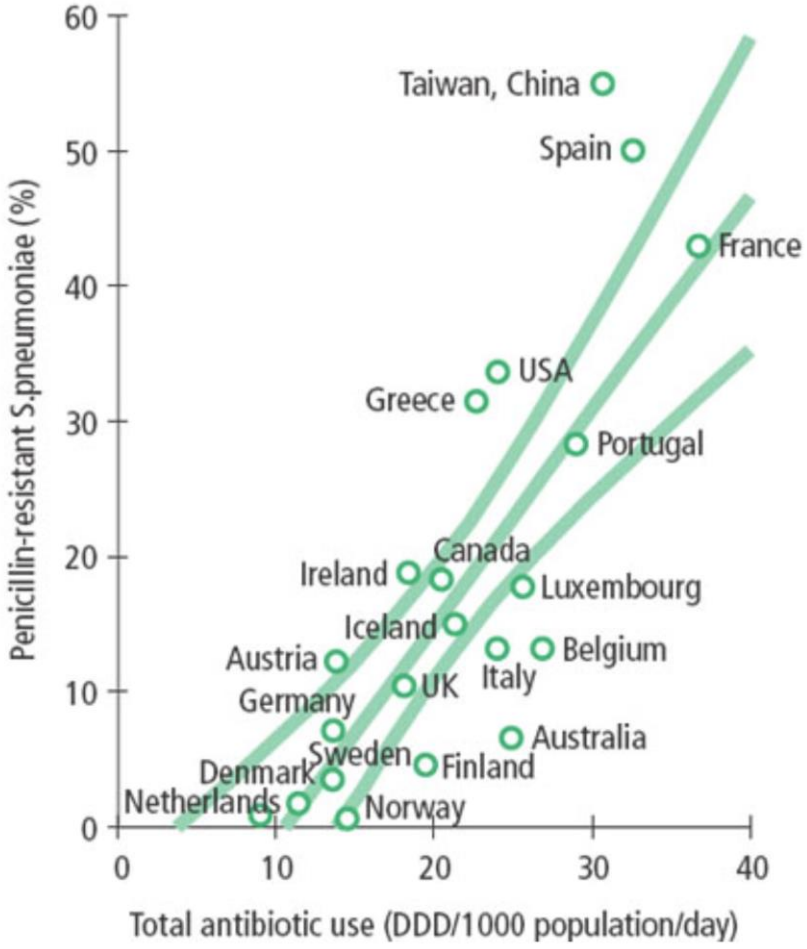
UNIVERSITY of WASHINGTON IHME BIG DATA INSTITUTE UNIVERSITY OF OXFORD MORU Tropical Health Network

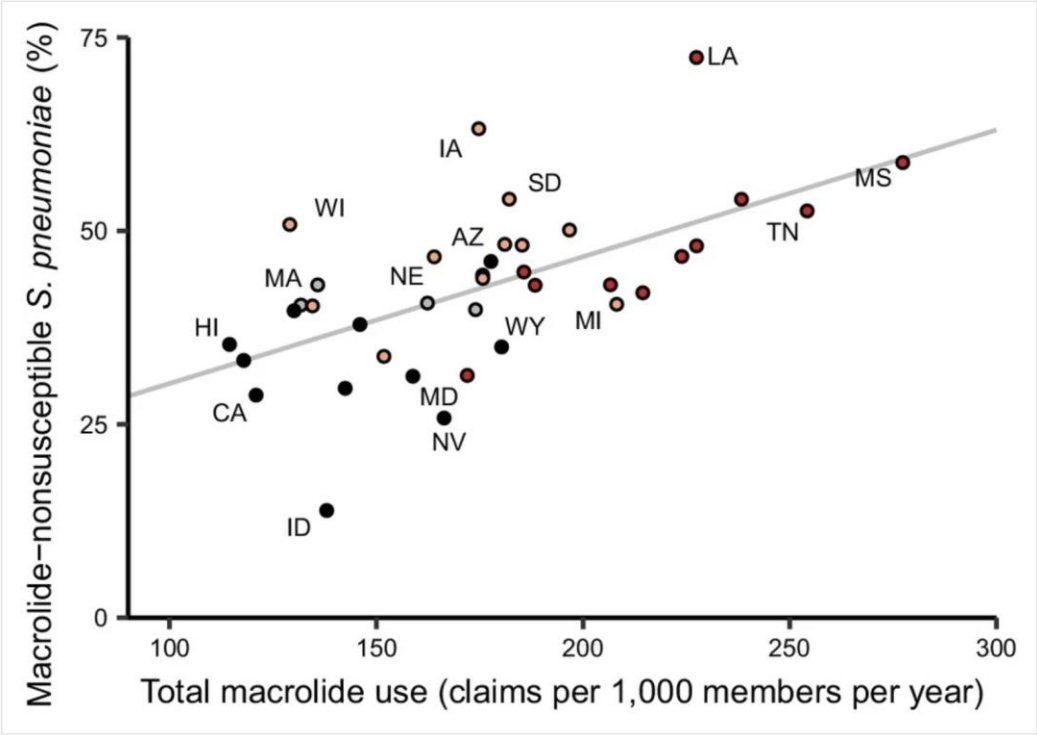


J Antimicrob Chemother 2017; 72: 2963–29

Access vs Excess

Antibiotic use drives antimicrobial resistance





Olesen *et al*. *eLife* 2018;7:e39435

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The distribution of antibiotic use and its association with antibiotic resistance

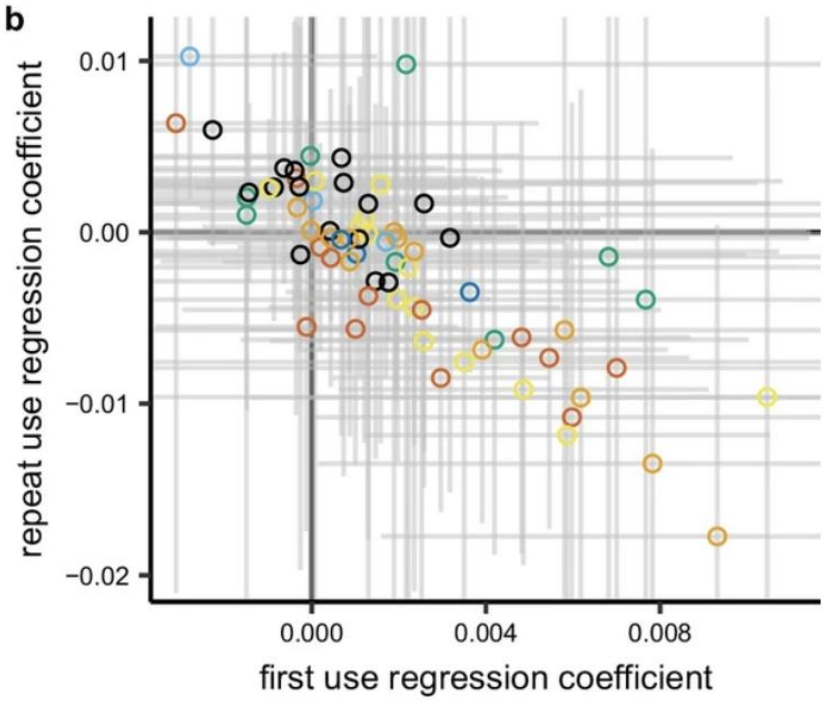
eLIFE elifesciences.org

eLife 2018;7:e39435

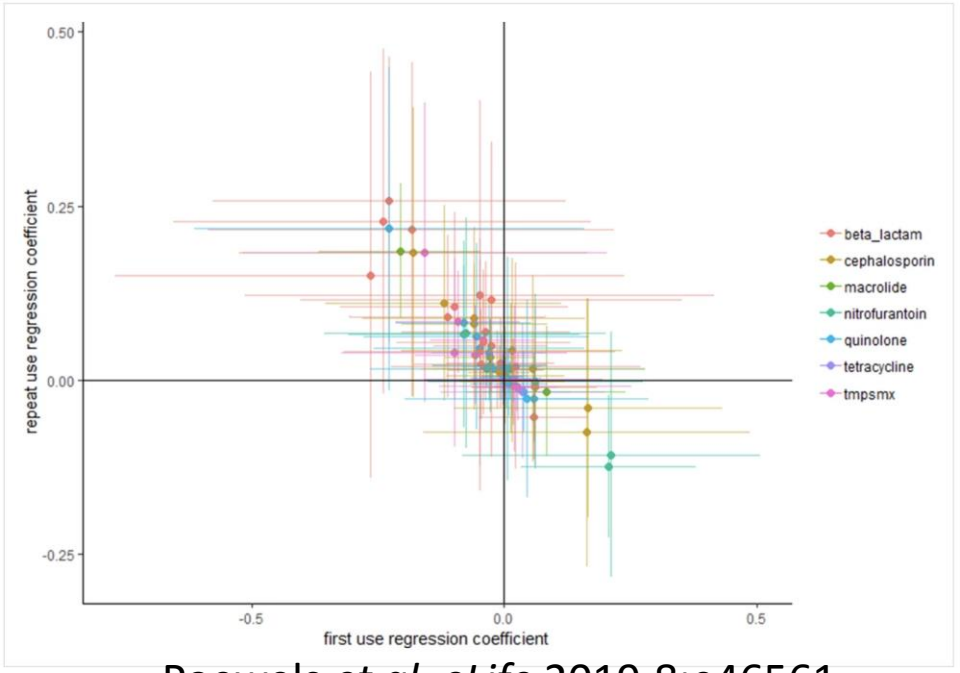
Scott W Olesen, Michael L Barnett, Derek R MacFadden, John S Brownstein, Sonia Hernández-Díaz, Marc Lipsitch, Yonatan H Grad

Harvard T.H. Chan School of Public Health, United States; Brigham and Women's Hospital, Harvard Medical School, United States; University of Toronto, Canada; Boston Children's Hospital, United States; Harvard Medical School, United States

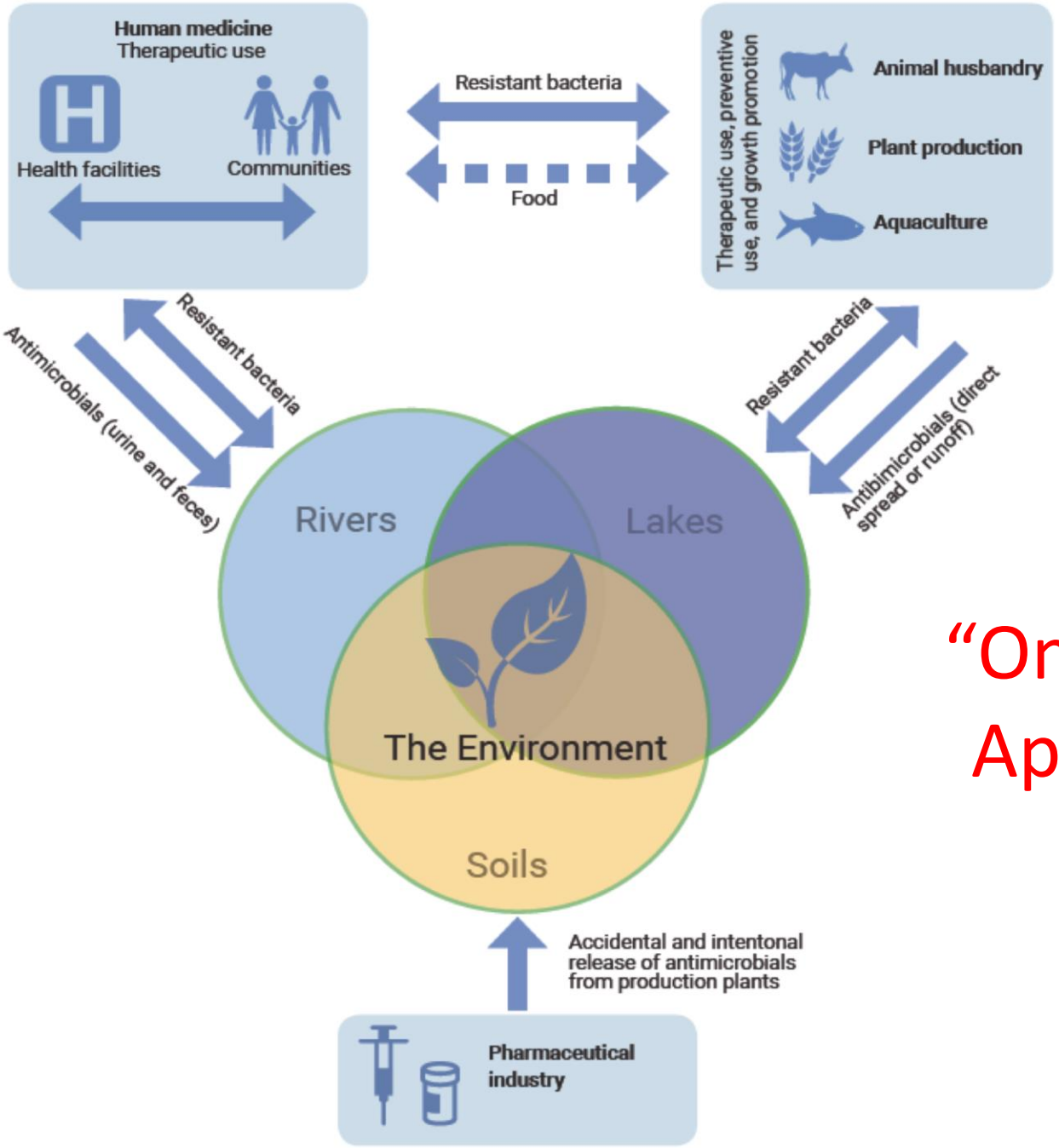
Broad use of antibiotics more important than intensive, repeated use



Intensive, repeated use of antibiotics more important than broad use when controlled for first use of ANY antibiotic



Poewels *et al*. *eLife* 2019;8:e46561



"One Health Approach"

OPINION

The EPA's latest bad idea: Spraying streptomycin on our citrus fruits | Commentary

By NATHAN DONLEY
GUEST COLUMNIST | JAN 09, 2019 | 10:55 AM

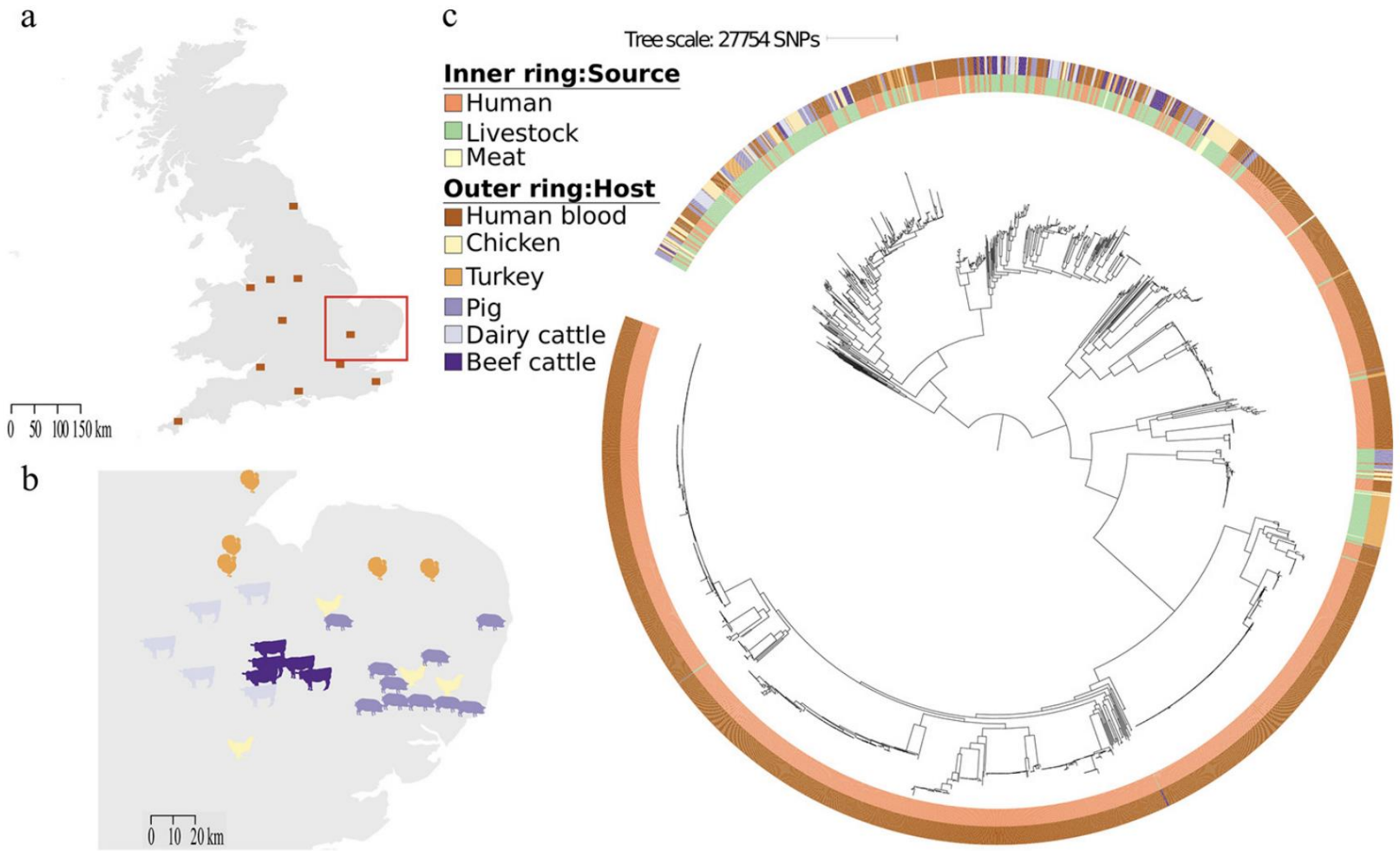
A citrus grove is pictured in Clermont, The EPA recently approved the spraying of streptomycin on nearly half a million acres of the nation's citrus. (Orlando Sentinel)

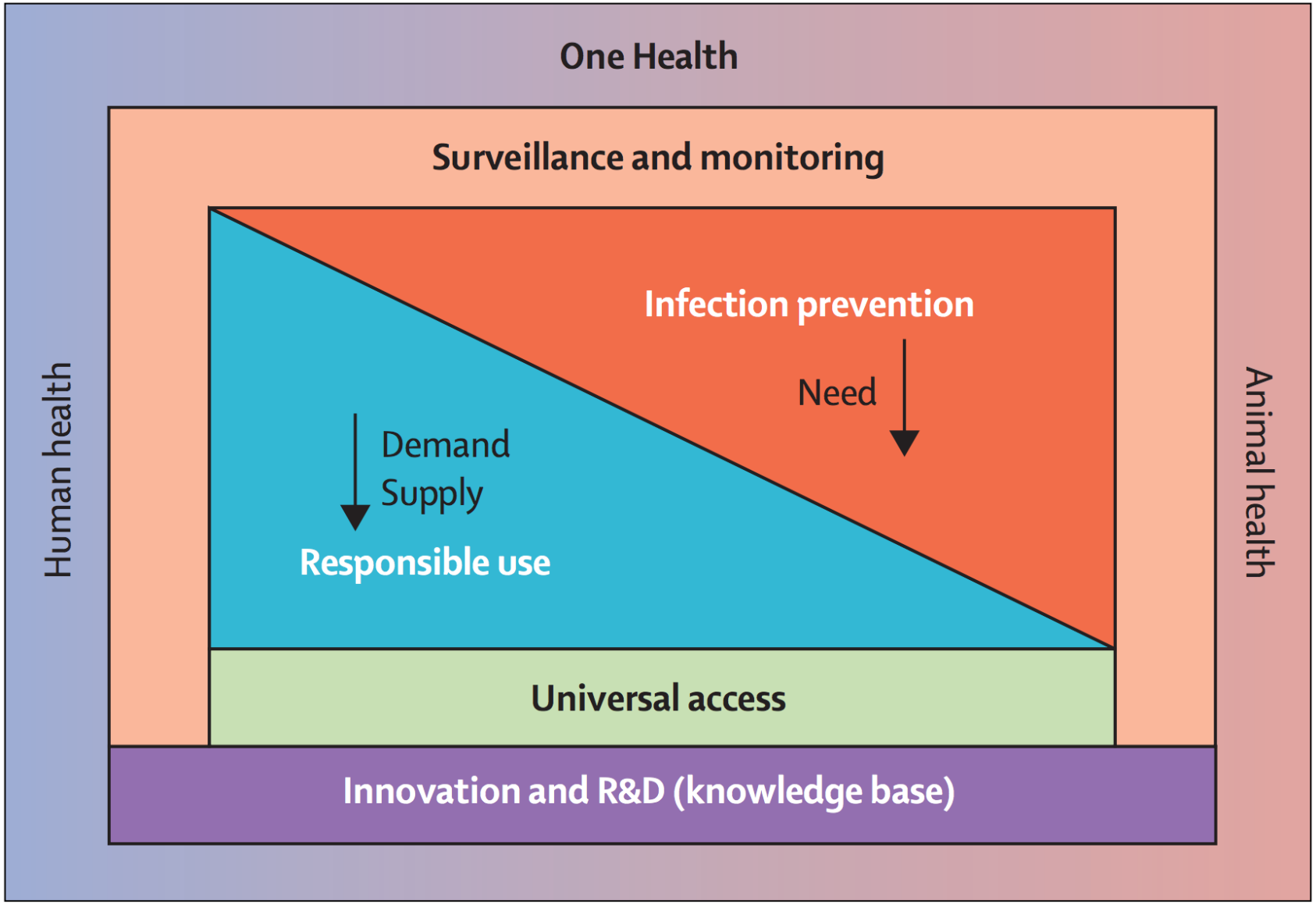
As a scientist and former cancer researcher, I'm the family pusher when it comes to fresh veggies and fruit.

And like millions of other American families, my family loves citrus fruits. Oranges,

One Health Genomic Surveillance of *Escherichia coli* Demonstrates Distinct Lineages and Mobile Genetic Elements in Isolates from Humans versus Livestock

Catherine Ludden,[a,b] Kathy E. Raven,[c] Dorota Jamrozy,[b] Theodore Gouliouris,[c,d,e] Beth Blane,[c] Francesc Coll,[a,b] Marcus de Goffau,[b] Plamena Naydenova,[c] Carolyne Horner,[f] Juan Hernandez-Garcia,[g] Paul Wood,[h] Nazreen Hadjirin,[g] Milorad Radakovic,[g] Nicholas M. Brown,[d,e,f] Mark Holmes,[g] Julian Parkhill,[b] Sharon J. Peacock[a,b,c]





Policy framework for sustainable access to effective antimicrobials

Dar *et al*. *Lancet* 2016; 387: 285–95

What communication strategy should we use for AMR?

COMMENT

PALAEONTOLOGY How teeth, diet and environment shaped human evolution p.28 | MICROBIOLOGY A life of Frederick Novy, forgotten bacteriology and education pioneer p.28 | PUBLISHING A call for one submission system to rule them all p.30 | SUSTAINABILITY Restore earthworm workforce to rebuilt topsoil p.30

A physician examines a man with TB. Like the bacteria behind other common infections, *Mycobacterium tuberculosis* has become increasingly resistant to drugs.

Antibiotic resistance has a language problem

A failure to use words clearly undermines the global response to antimicrobials' waning usefulness. Standardize terminology, urge **Marc Mendelson** and colleagues.

Clinicians have long known that microbes such as bacteria, viruses and fungi are becoming alarmingly resistant to the medicines used to treat them. But a global response to this complex health threat — commonly termed 'antimicrobial resistance' — requires engagement from a much broader array of players, from governments, regulators and the public, to experts in health, food, the environment, economics, trade and industry.

People from these disparate domains are talking past each other. Many of the terms routinely used to describe the problem are misunderstood, interpreted differently or loaded with unhelpful connotations.

On 16 March, the United Nations formed an interagency group to coordinate the fight against drug resistance[1]. We urge that, as one of its first steps, this group coordinate a review of the terminology used by key actors. Such an effort could improve understanding across the board and help to engender a consistent and focused global response.

BLINDED BY SCIENCE

A 2015 survey by the World Health Organization (WHO) in 12 countries highlighted people's unfamiliarity with the language of antibiotic resistance[2]. Fewer than half of the nearly 10,000 respondents had heard of the term 'antimicrobial resistance'. Only one-fifth were aware of its abbreviated form 'AMR'.

4 MAY 2017 | VOL 545 | NATURE | 23

Nature. 2017 May 3;545(7652):23-25

- "War against superbugs"
- "Fight against AMR"
- "Please stop the misusing antibiotics"
- AMR vs Drug Resistant Infections
- Who? Action? Nudge?
- Market-Message-Medium?

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Antibiotic Footprints

Antibiotic Footprint can be used to attribute antibiotic consumption to **different human activities**

Limmathurotsakul *et al. J Antimicrob Chemother*. 2019 Aug; 74(8): 2122–2127.

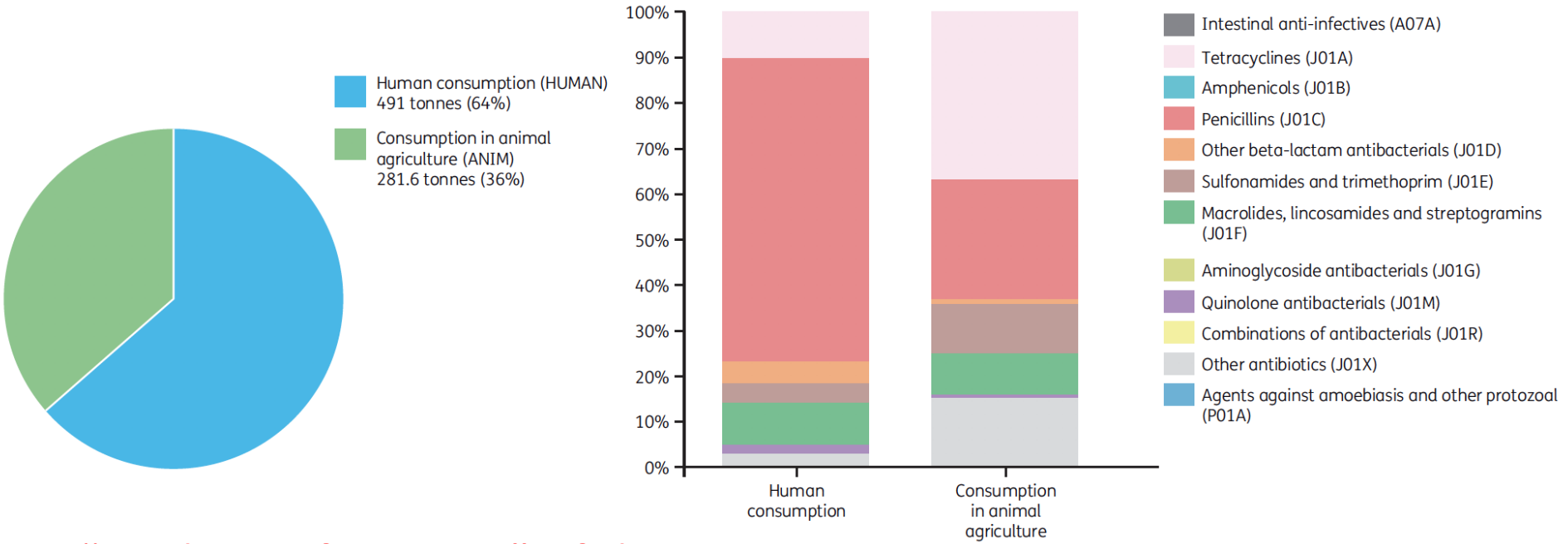
MORU Tropical Health Network

J Antimicrob Chemother 2019; **74**: 2122–2127
doi:10.1093/jac/dkz185 Advance Access publication 10 May 2019

Journal of Antimicrobial Chemotherapy

'Antibiotic footprint' as a communication tool to aid reduction of antibiotic consumption

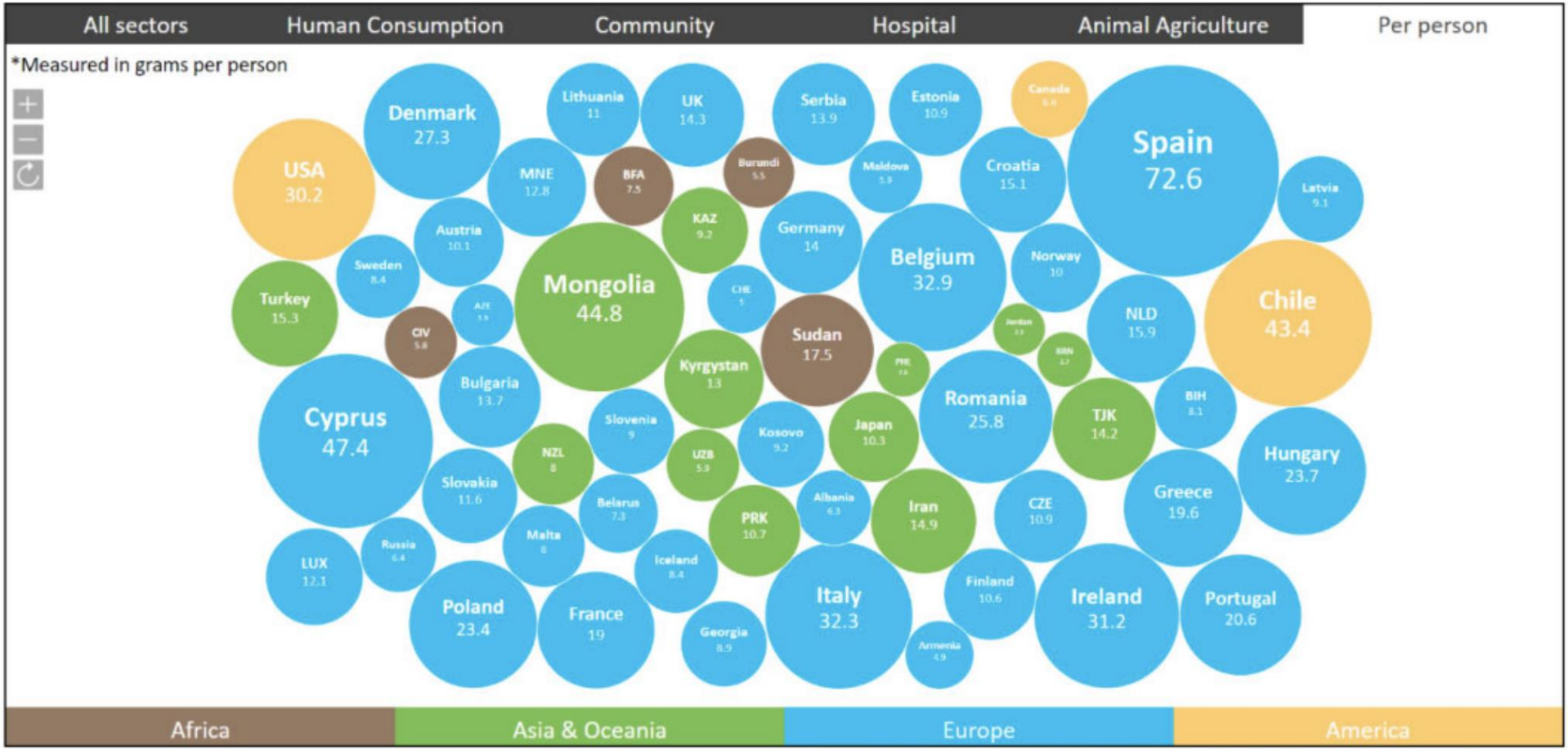
Direk Limmathurotsakul [1–3]*, Jonathan A. T. Sandoe[4,5], David C. Barrett[6], Michael Corley[5], Li Yang Hsu[7,8], Marc Mendelson[9,10], Peter Collignon[11,12], Ramanan Laxminarayan[13,14], Sharon J. Peacock [15] and Philip Howard[4,5]



"Antibiotic footprint" of the UK in 2017

Tropical Health Network

www.antibioticfootprint.net



Limmathurotsakul *et al. J Antimicrob Chemother*. 2019 Aug; 74(8): 2122–2127.

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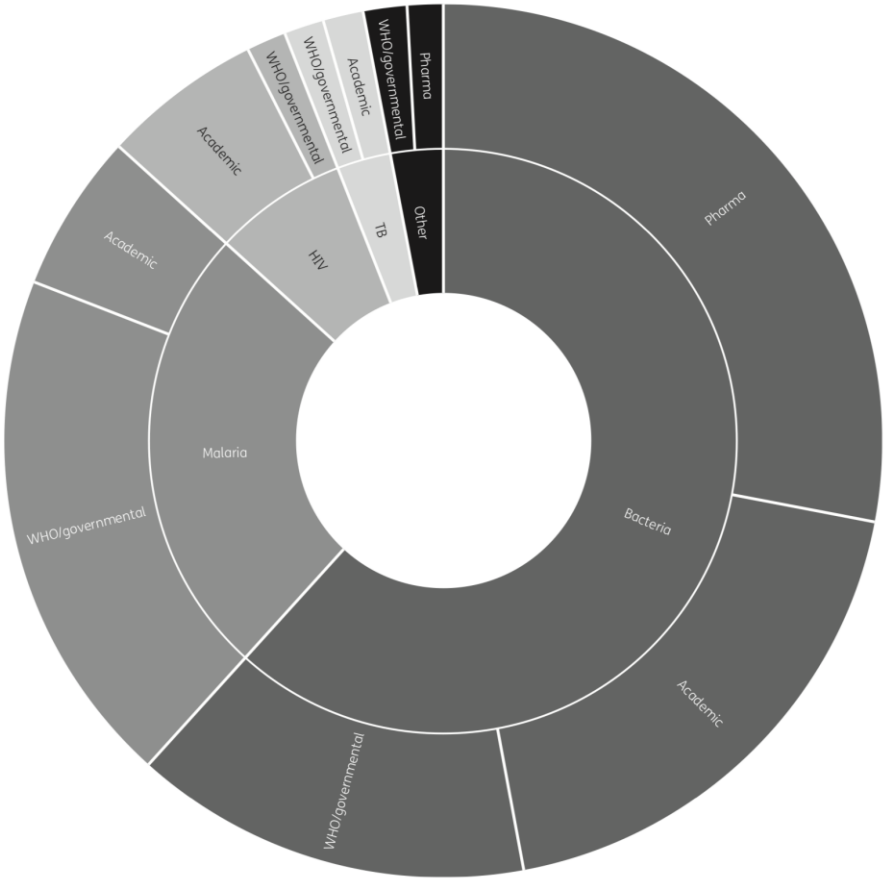
J Antimicrob Chemother 2018; **73**: 1737–1749
doi:10.1093/jac/dky026 Advance Access publication 5 March 2018

Journal of Antimicrobial Chemotherapy

An inventory of supranational antimicrobial resistance surveillance networks involving low- and middle-income countries since 2000

Elizabeth A. Ashley[1,2]*, Judith Recht[3], Arlene Chua[4], David Dance[2,5,6], Mehul Dhorda[2,3,7], Nigel V. Thomas[2,7], Nisha Ranganathan[8], Paul Turner[2,3,9], Philippe J. Guerin[2,7,10], Nicholas J. White[2,3] and Nicholas P. Day[2,3]



"Since 2000, 72 supranational networks for AMR surveillance in bacteria, fungi, HIV, TB and malaria have been created that have involved LMICs, of which 34 are ongoing."

Median survival 6 years

"Maintaining an up-to-date registry of networks would promote a more coordinated approach to surveillance."

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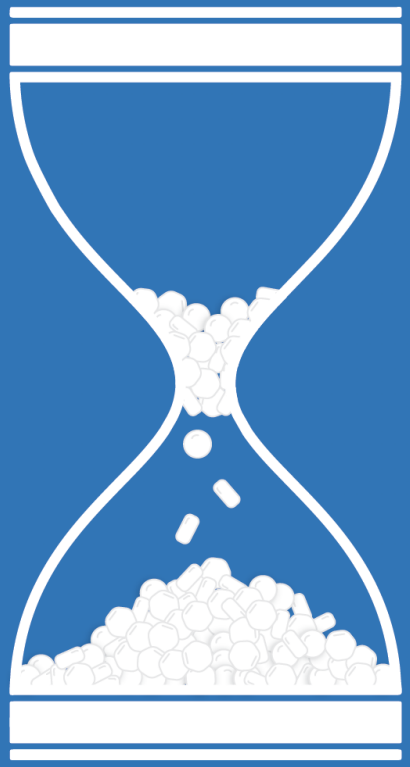
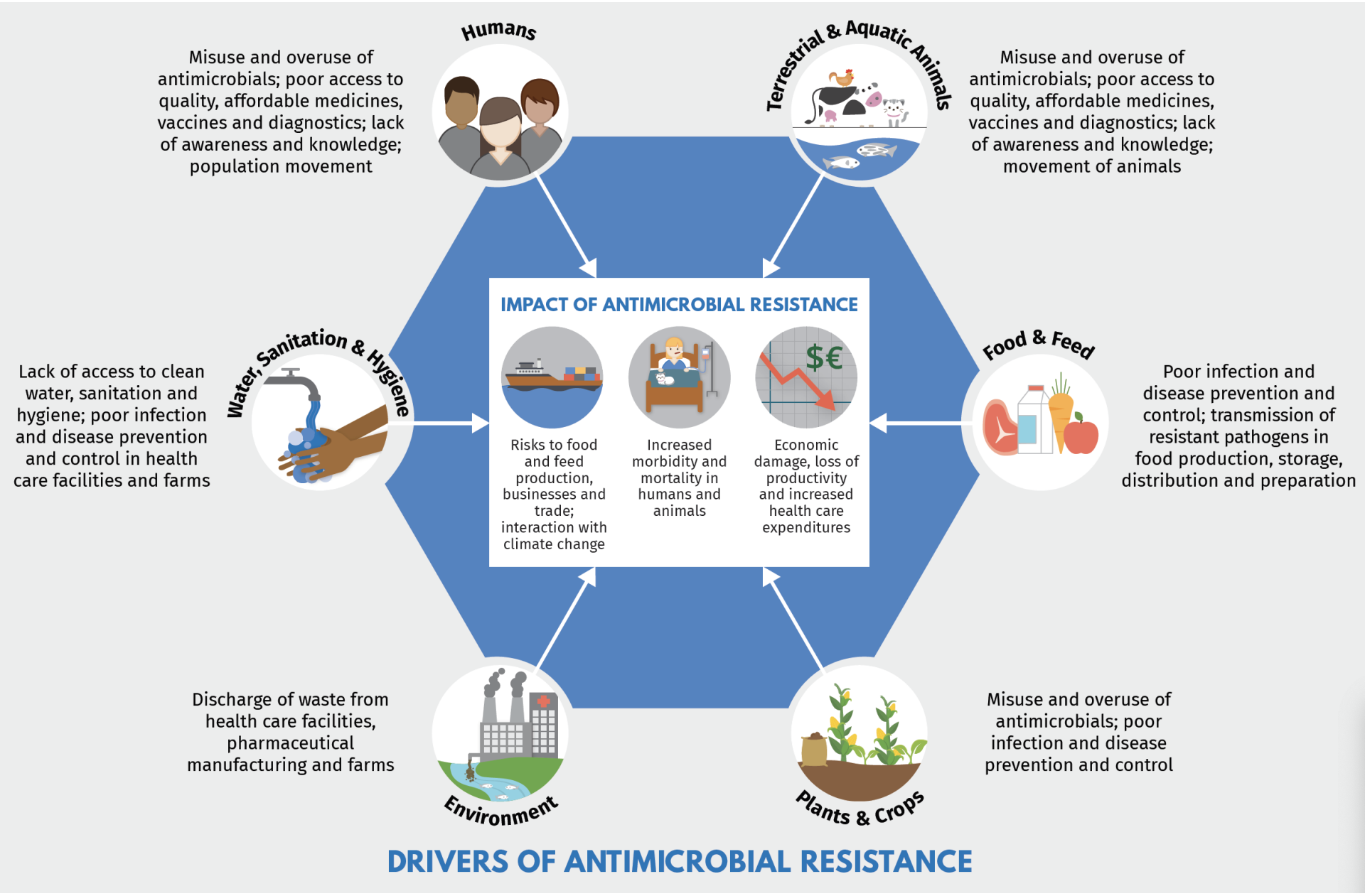


NO TIME TO WAIT:
SECURING THE FUTURE FROM DRUG-RESISTANT INFECTIONS

REPORT TO THE SECRETARY-GENERAL OF THE UNITED NATIONS

APRIL 2019

IACG | Interagency Coordination Group on Antimicrobial Resistance


Humans
Misuse and overuse of antimicrobials; poor access to quality, affordable medicines, vaccines and diagnostics; lack of awareness and knowledge; population movement
Terrestrial & Aquatic Animals
Misuse and overuse of antimicrobials; poor access to quality, affordable medicines, vaccines and diagnostics; lack of awareness and knowledge; movement of animals
Water, Sanitation & Hygiene
Lack of access to clean water, sanitation and hygiene; poor infection and disease prevention and control in health care facilities and farms
IMPACT OF ANTIMICROBIAL RESISTANCE
Risks to food and feed production, businesses and trade; interaction with climate change
Increased morbidity and mortality in humans and animals
Economic damage, loss of productivity and increased health care expenditures
$€
Food & Feed
Poor infection and disease prevention and control; transmission of resistant pathogens in food production, storage, distribution and preparation
Environment
Discharge of waste from health care facilities, pharmaceutical manufacturing and farms
Plants & Crops
Misuse and overuse of antimicrobials; poor infection and disease prevention and control
DRIVERS OF ANTIMICROBIAL RESISTANCE

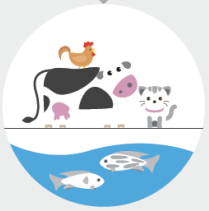
ONE HEALTH RESPONSE TO ANTIMICROBIAL RESISTANCE

Humans

Food & Feed

Plants & Crops

Environment



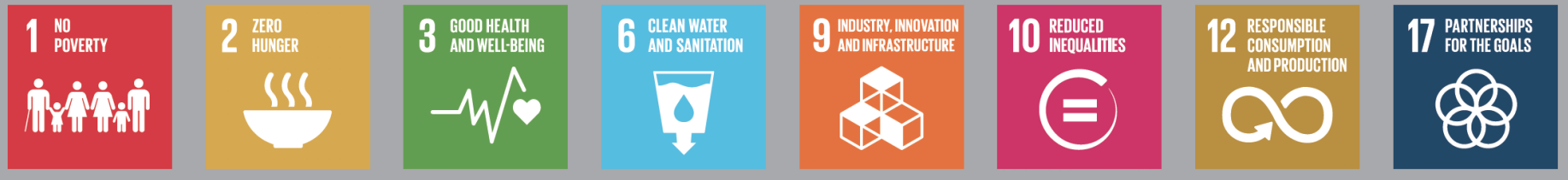
Terrestrial & Aquatic Animals

Antimicrobial resistance is a global crisis. There is no time to wait.
A sustained One Health response with a shared vision and goals is essential to tackle antimicrobial resistance and achieve the Sustainable Development Goals.

Interagency Coordination Group on Antimicrobial Resistance Recommendations

- ACCELERATE PROGRESS IN COUNTRIES
- INNOVATE TO SECURE THE FUTURE
- COLLABORATE FOR MORE EFFECTIVE ACTION
- INVEST FOR A SUSTAINABLE RESPONSE
- STRENGTHEN ACCOUNTABILITY AND GLOBAL GOVERNANCE

SUSTAINABLE DEVELOPMENT GOALS



Conclusions

- More research needed on burden and on drivers of AMR so we know what to communicate
- Still need better ways to communicate the threat of AMR
- The bandwagon has everyone on board now, but its still needs steering

Acknowledgements

- Direk Limmathurotsakul
- Susie Dunachie
- Cherry Lim
- MORU microbiology staff
- Wellcome Trust