Antimicrobial Stewardship in Hospitals-the Evidence Base

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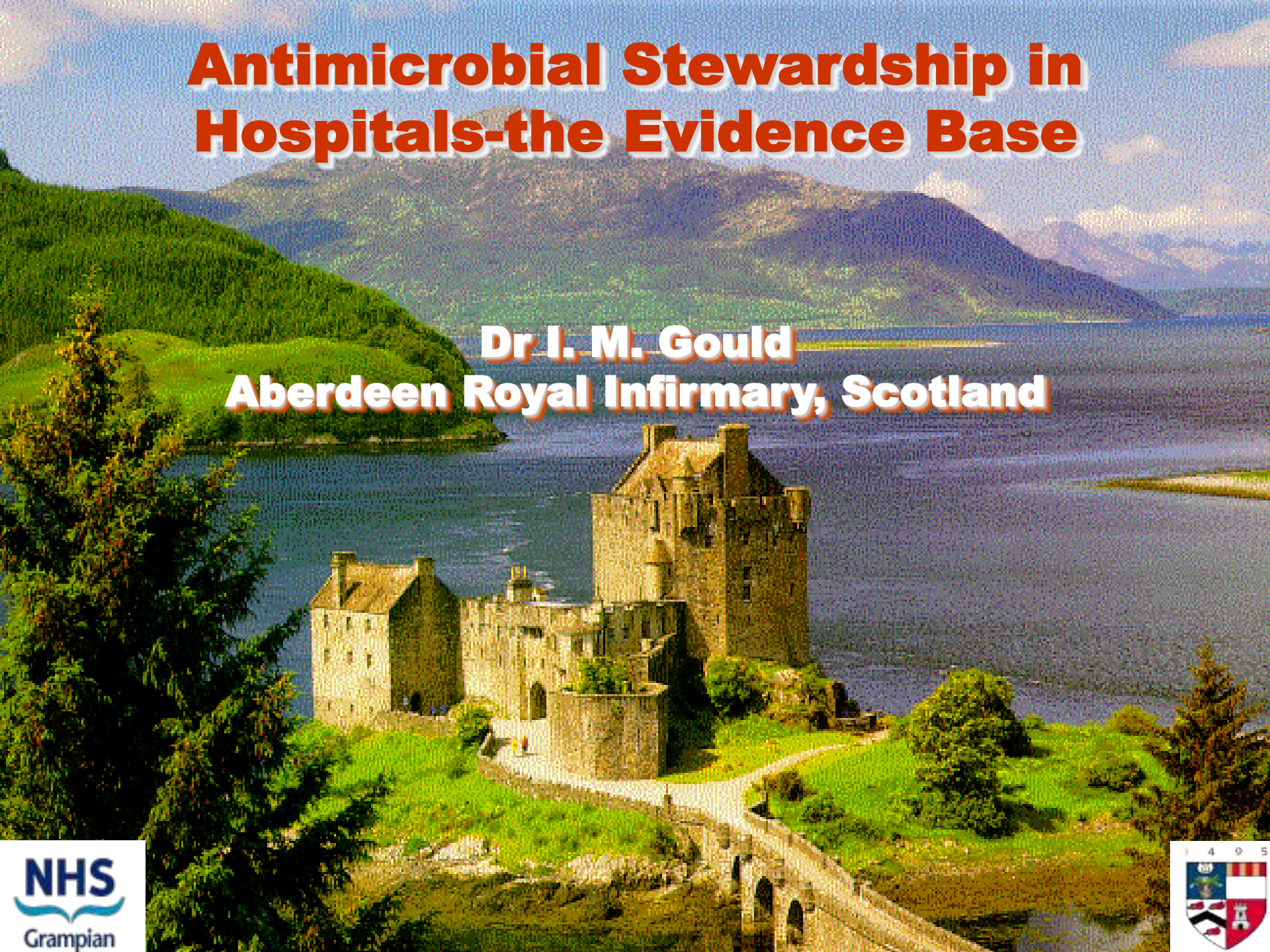


Agenda

(1) Why we need evidence

(2) Hospital: Cochrane Systematic Review

(3) Hospital: Cochrane Meta-analysis

(4) Since the review

Summary

(1) Why we need evidence

(1) Effective population level interventions

(2) Global and ethical issue that will be politicised

Antibiotics resistance 'as big a risk as terrorism' - medical chief

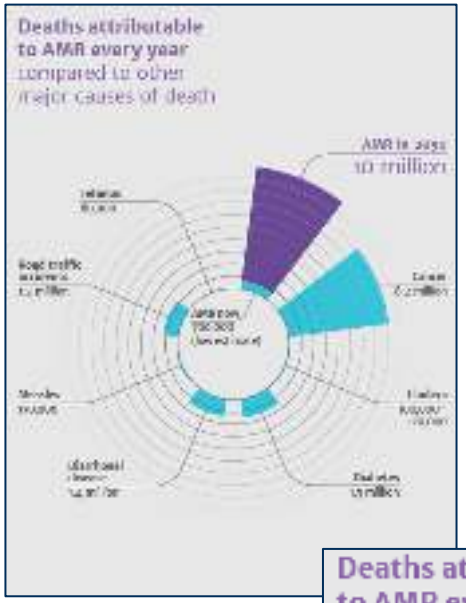
(3) There is a human face to resistance

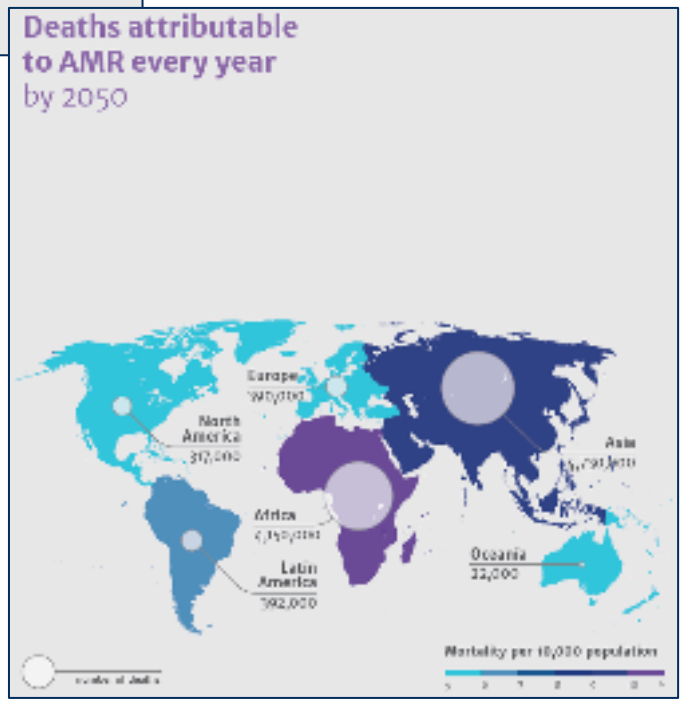
Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations

The Review on Antimicrobial Resistance
Chaired by Jim O'Neill
December 2014

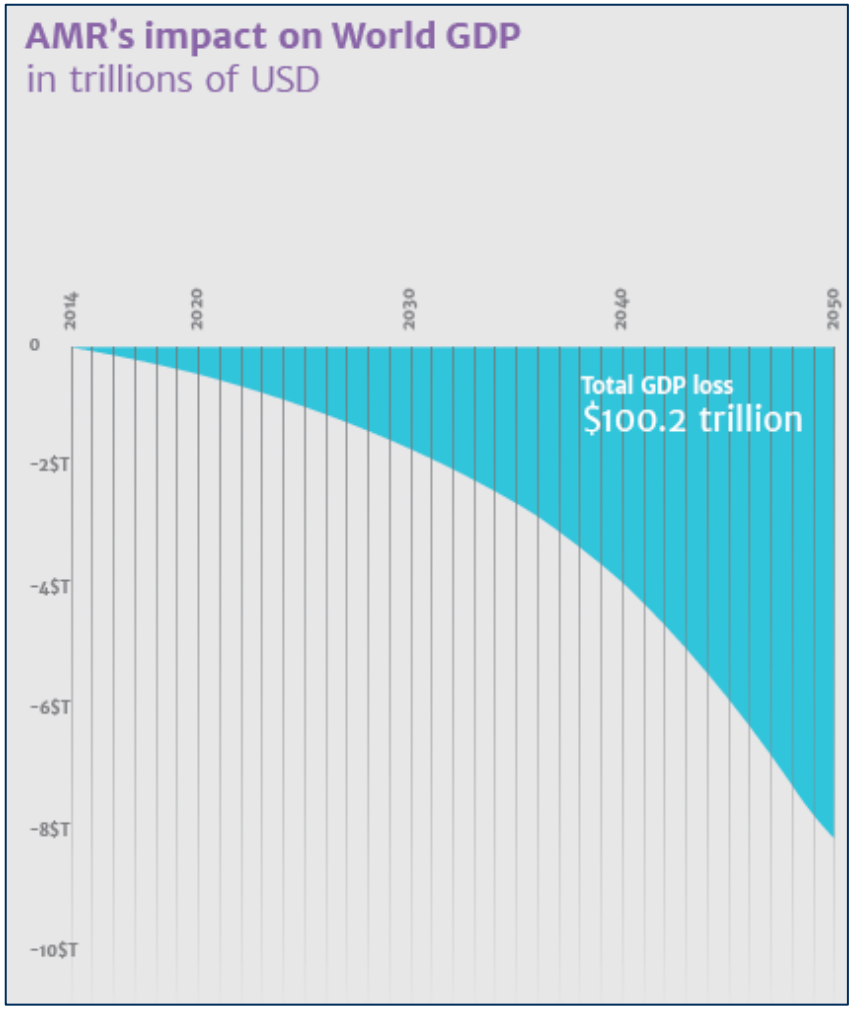




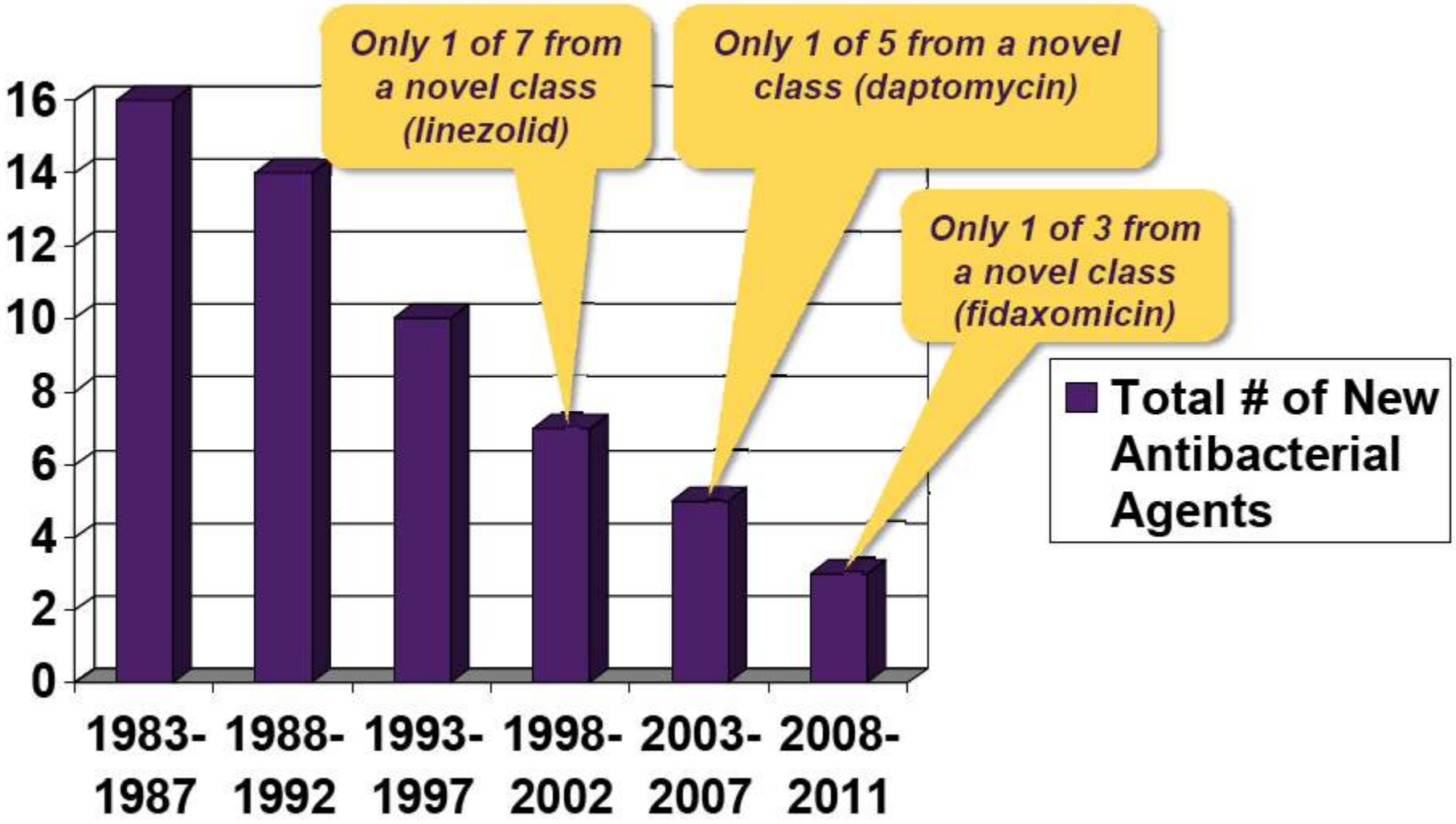
Left unchecked, the current trend in rising drug resistance is a crisis of global scale

Jim O'Neill 2014

Money talks: if nothing is done, AMR will cost 100 trillion USD by 2050



Steady decline in the No. of FDA approvals



But: Actions on the way

- AMR on the global agenda
- Actions are initiated
- Antibiotic stewardship programs (incl national) a key component.

Antibiotic Resistance - The emerging Pandemic

Super BUGs

MDR/Nosocomial

Gm +

MRSA

Gm –

Klebsiella

E.Coli

Pseudomonas

Acinetobacter

ESBLs

Asia, a priority to tackle AMR

- High population densities (and 50% world population)
- Rising middle class, affluence and ‘demand for better’
- Rising healthcare including private
- Uncontrolled access to antibiotics

Agenda

(1) Why we need evidence

(2) Hospital: Cochrane Systematic Review

(3) Hospital: Cochrane Meta-analysis

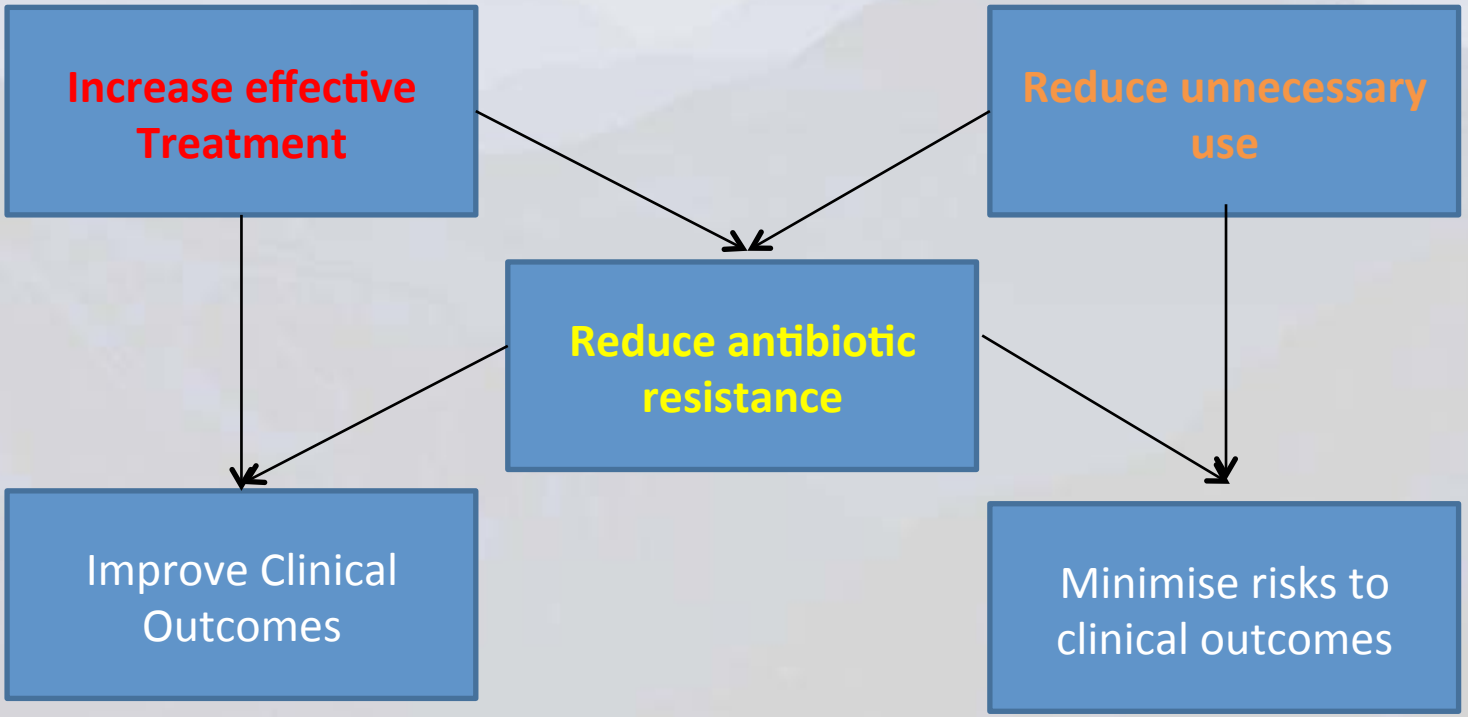
(4) Since the review

Summary

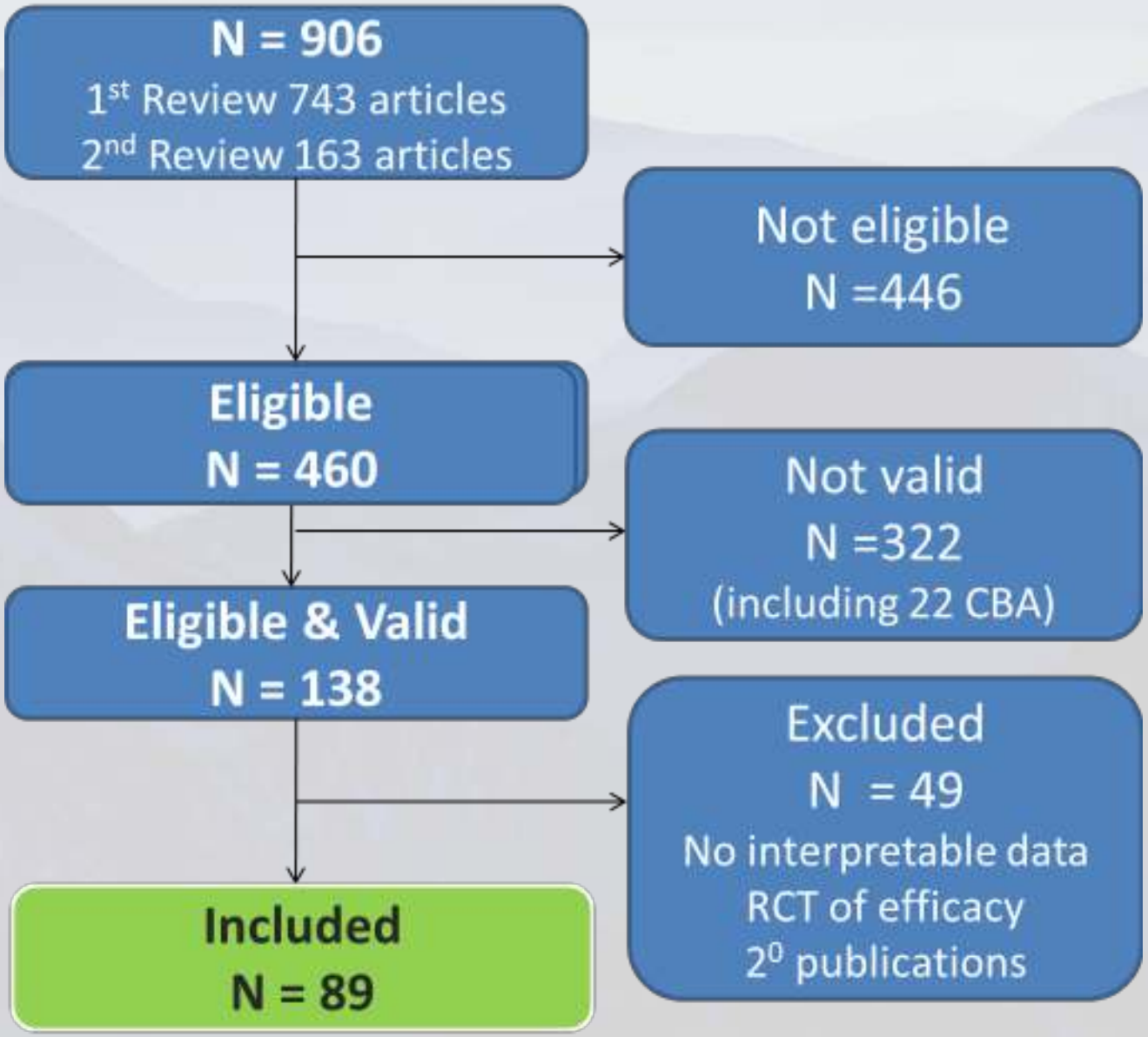
(2) Hospital: Cochrane Systematic Review

Aim:

'To evaluate the impact of interventions from the perspective of antibiotic stewardship'.



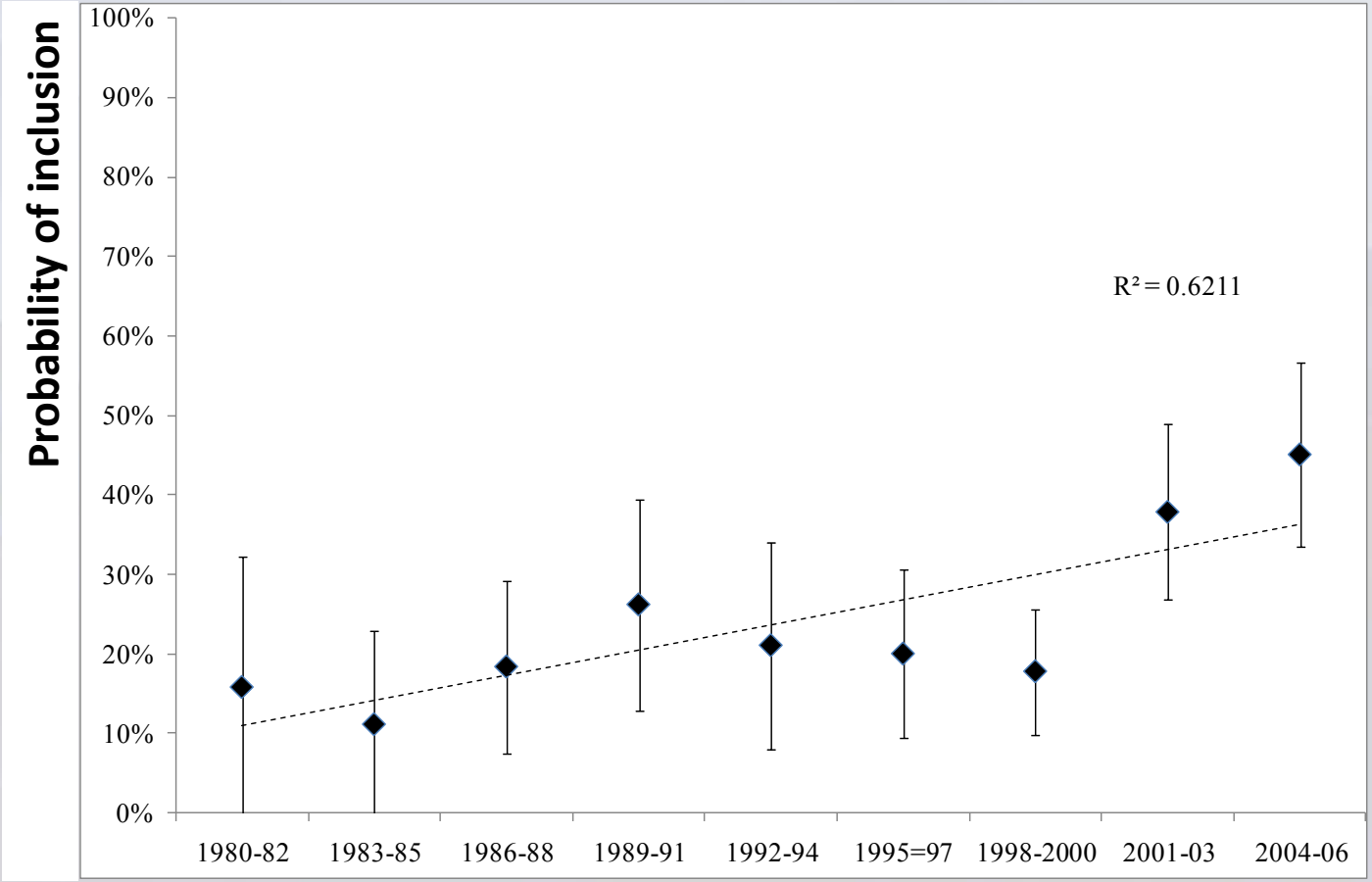
(2) Hospital: Cochrane Systematic Review



(2) Hospital: Cochrane Systematic Review

Study Quality:

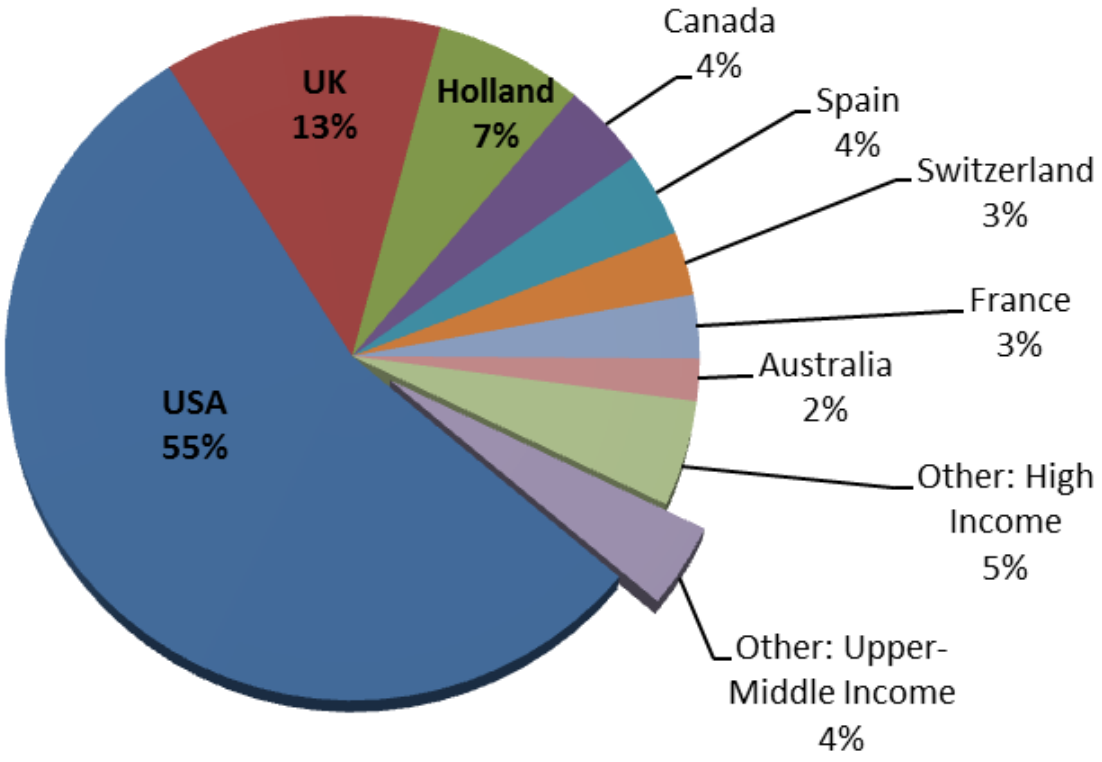
- 1st Review – Low quality
- Revision – improving.



[Davey et al, personal correspondence]

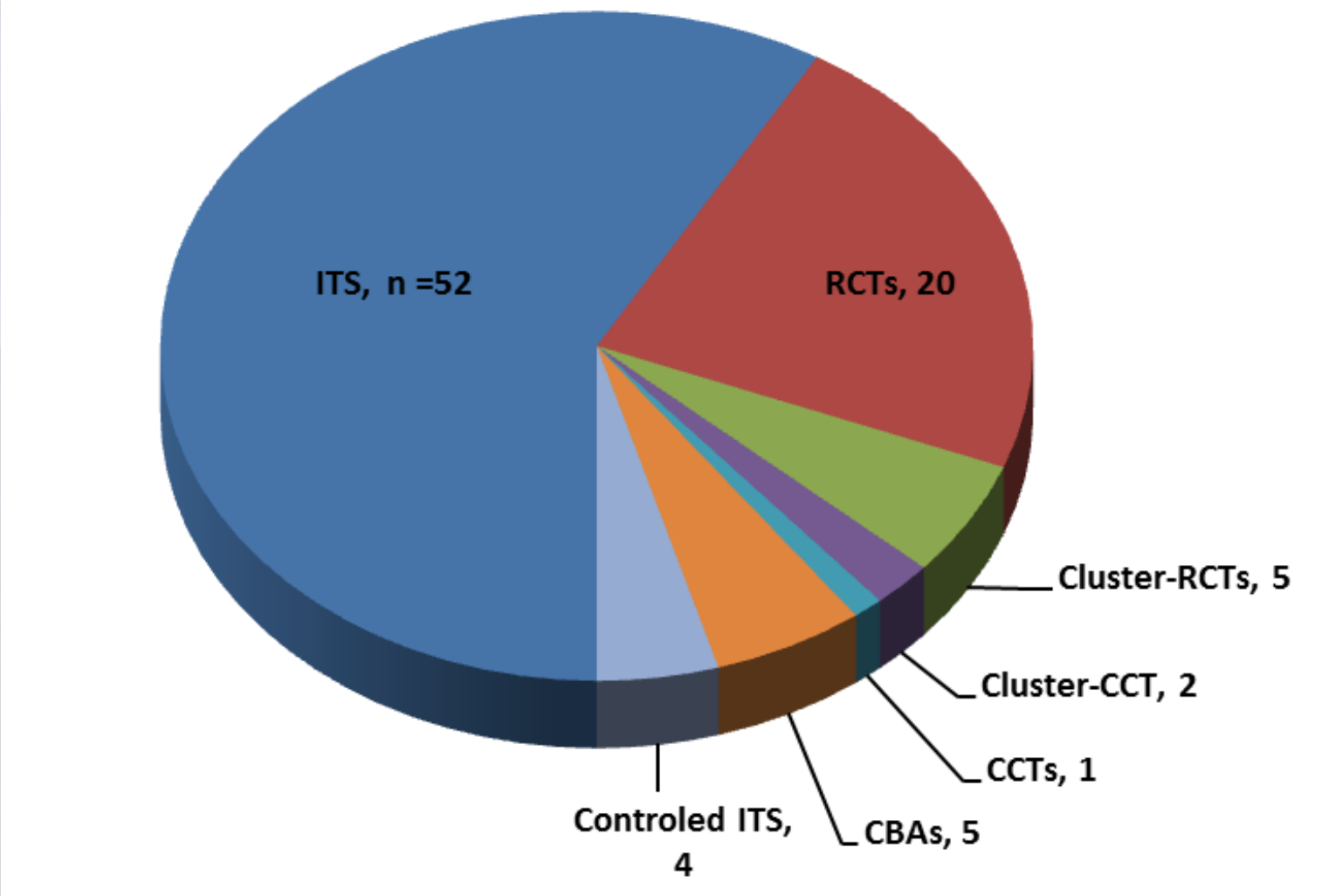
(2) Hospital: Cochrane Systematic Review

- **Where?**
  - 96% High-Income countries
  - 0% from Low- or Lower-Middle-Income



(2) Hospital: Cochrane Systematic Review

Study Type?



[Davey et al, personal correspondence]

(2) Hospital: Cochrane Systematic Review

- **New Risk of Bias criteria for CBA:**
  - ≥2 intervention and control sites
  - Allocation sequence adequately generated?
  - Allocation concealed?

- **Controlled ITS**
  - Historic and other site act as controls
  - Low bias/contamin.

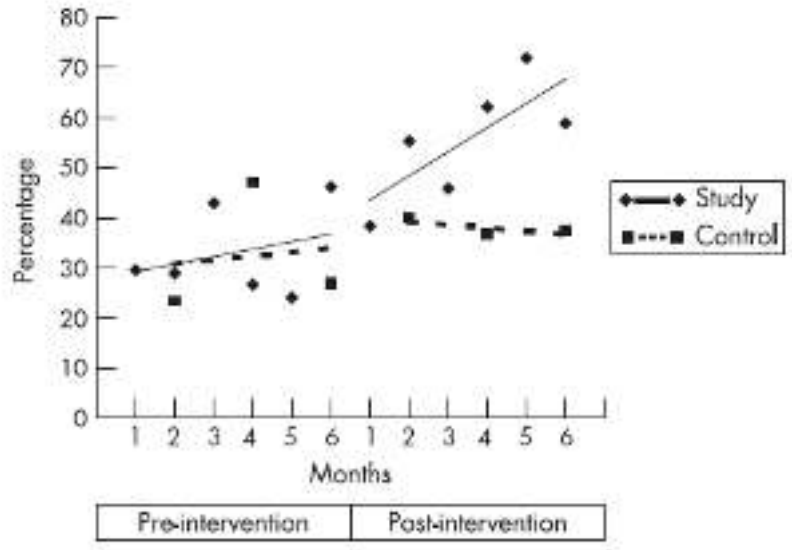


Figure 1 Changes over time in the percentage of patients receiving appropriate antibiotics within 4 h of admission. Data from the intervention site are shown monthly. Data from the control site are shown bimonthly.

[Barlow, et al 2007*Thorax 62(1): 67-74*]

(2) Hospital: Cochrane Systematic Review

- **What interventions?**
- Persuasive

Direct contact with prescriber	Intervention	Studies	Multi-faceted	ITS median Drug Outcome (%)
Least	Educational materials & meetings	2	0	11%
	Reminders	8	88%	20%
	Audit and feedback	10	100%	33%
	Educational outreach			46%
	Academic detailing	6	100%	
Most	Review & recommend change	18	78%	
	TOTAL	**48**	**77%**	**42%**

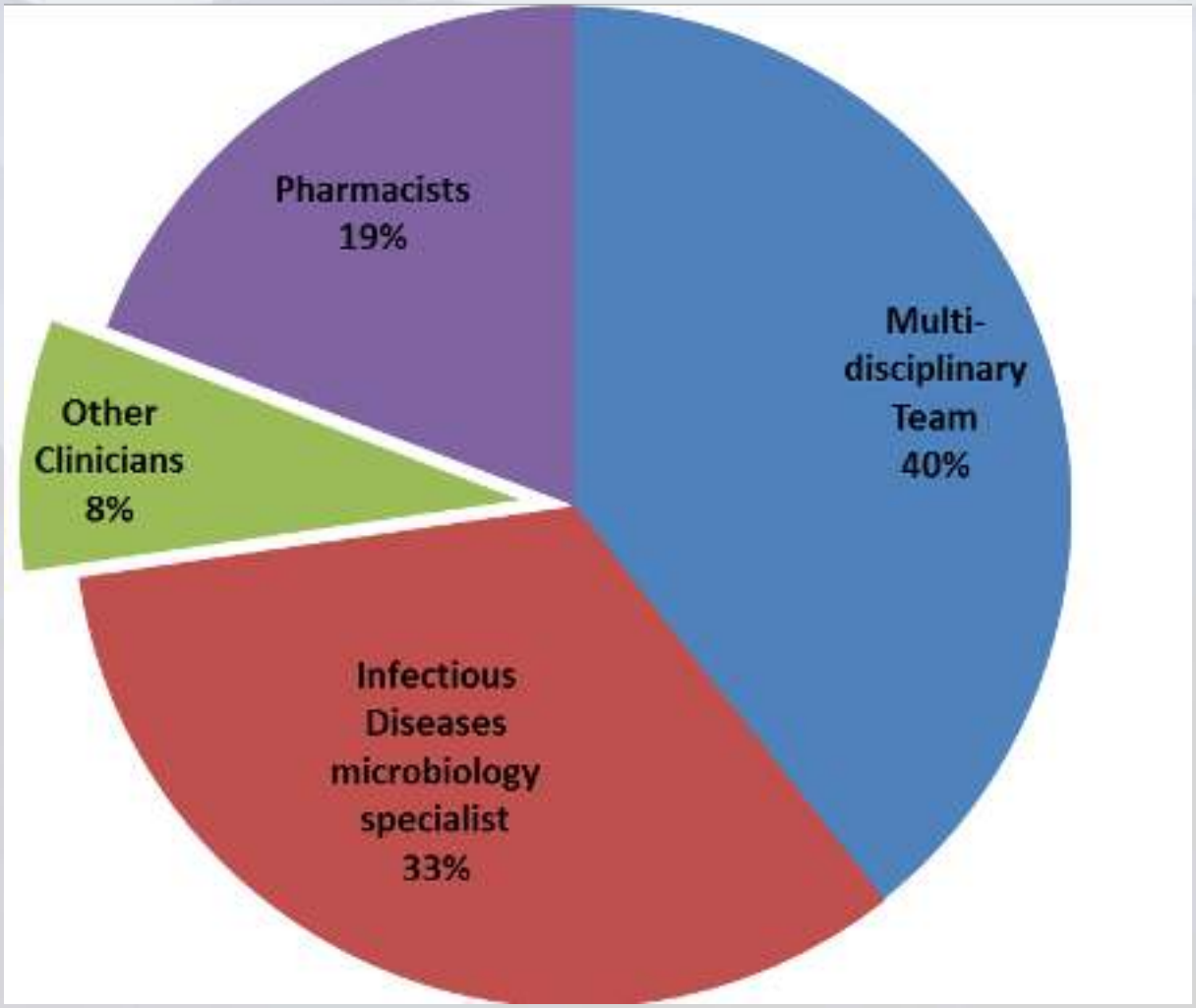
(2) Hospital: Cochrane Systematic Review

- **What interventions?**
- Restrictive

Direct contact with prescriber	Intervention	Studies	Multi-faceted (+Persuasive)	ITS median effect (%)
Least	Compulsory order form	5	100%	7%
	Expert approval	15	25%	24%
	Removal from clinical areas	14	50%	61%
Most	Review and make change	4	50%	94%
	TOTAL	**38**	**50%**	**35%**

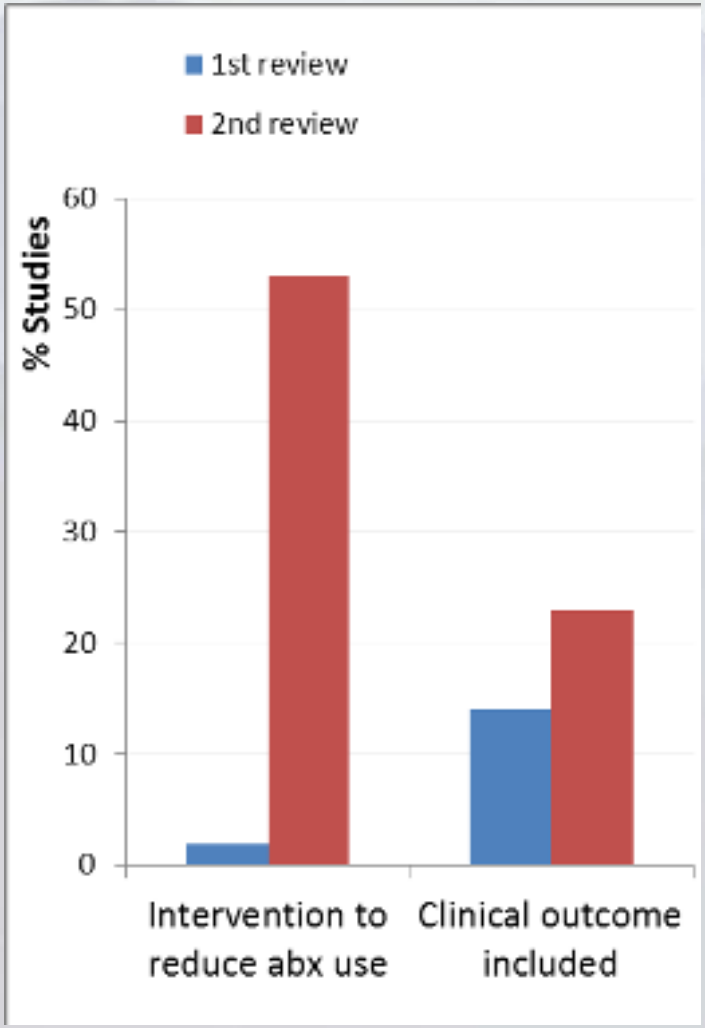
(2) Hospital: Cochrane Systematic Review

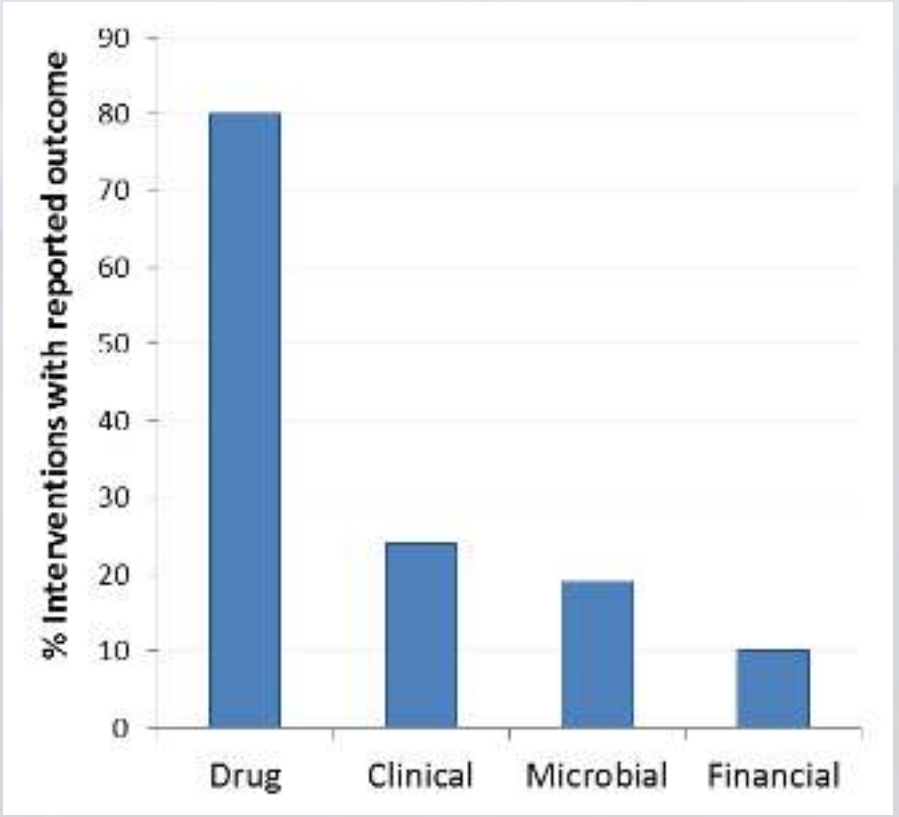
- **Who delivers?**



(2) Hospital: Cochrane Systematic Review

- **Which Outcomes?**



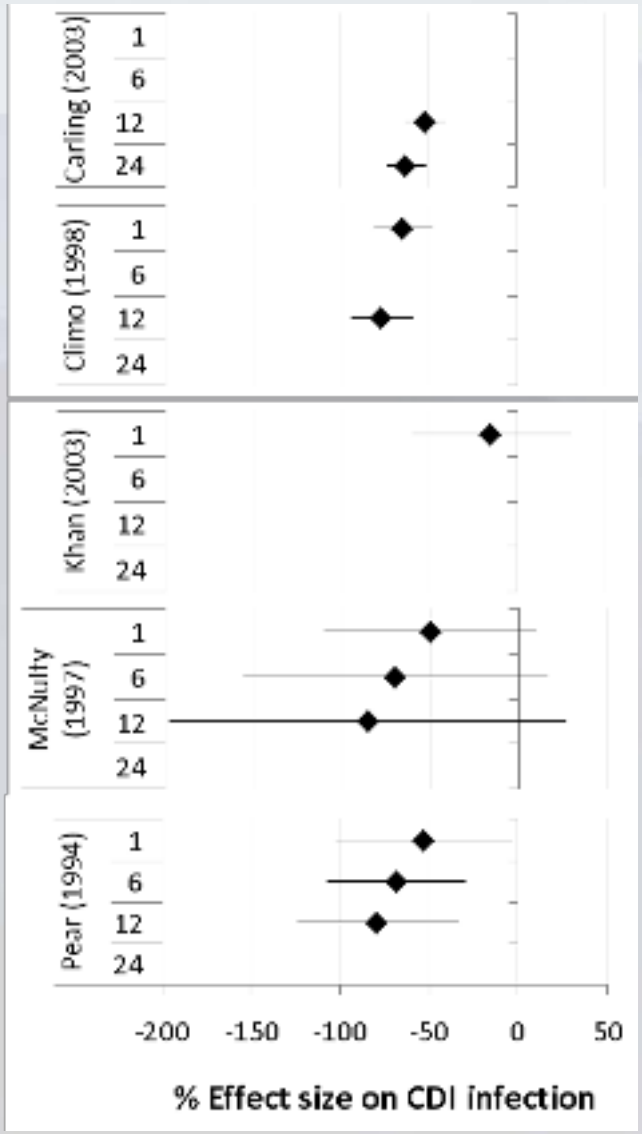


(2) Hospital: Cochrane Systematic Review

Microbial Outcomes

C.difficile infections

Study type	Number studies	Median effect
ITS	5	-68%

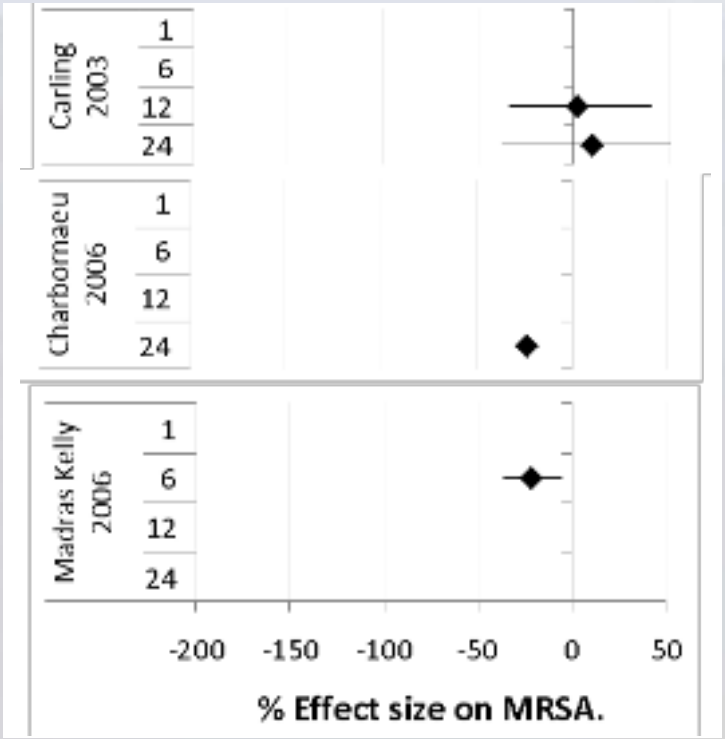


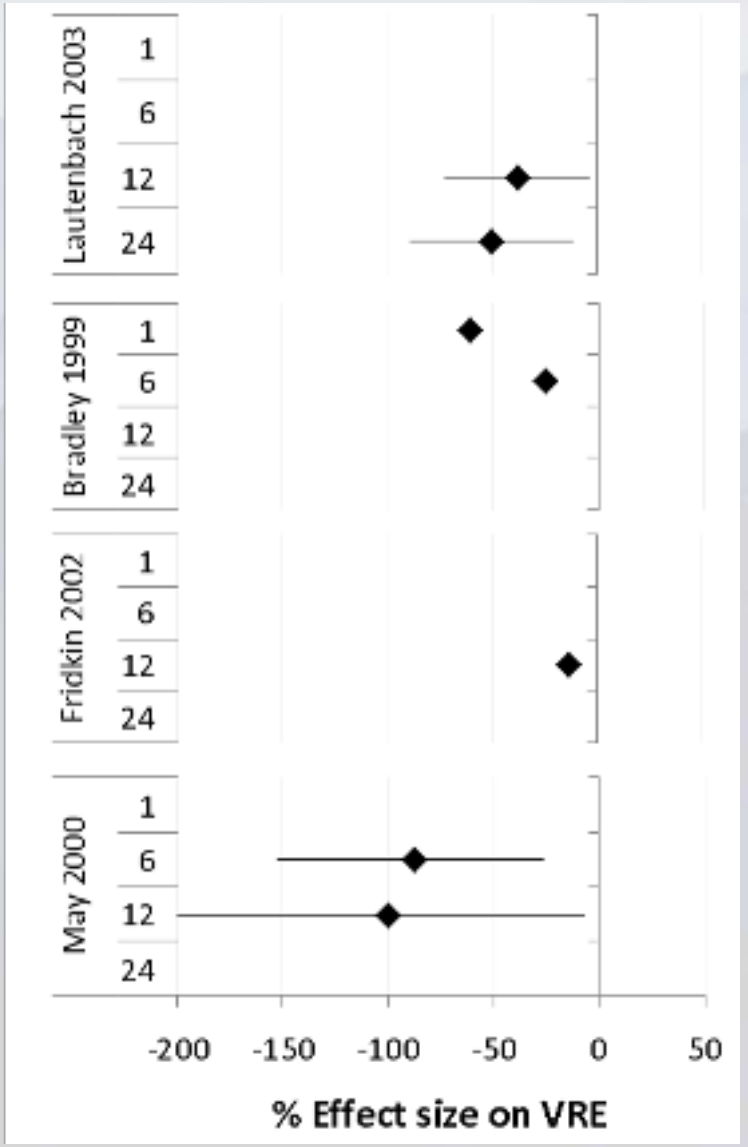
(2) Hospital: Cochrane Systematic Review

Microbial Outcomes

Gram-Positive

Study type	Number studies	Median effect
ITS	6	-24%
CBA	1	-32%



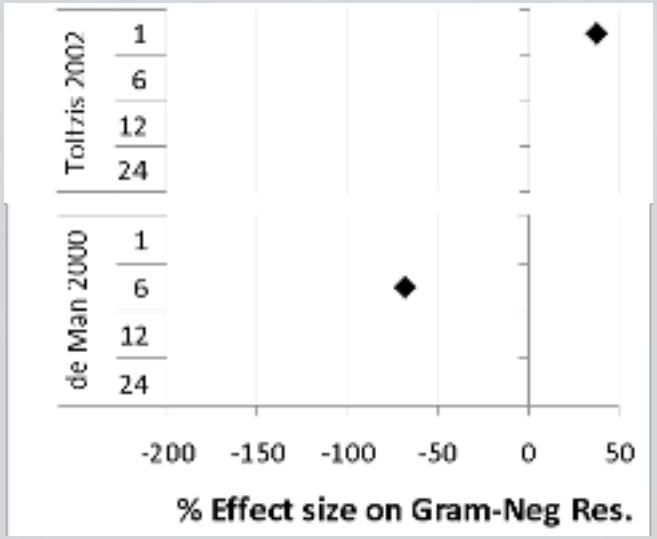


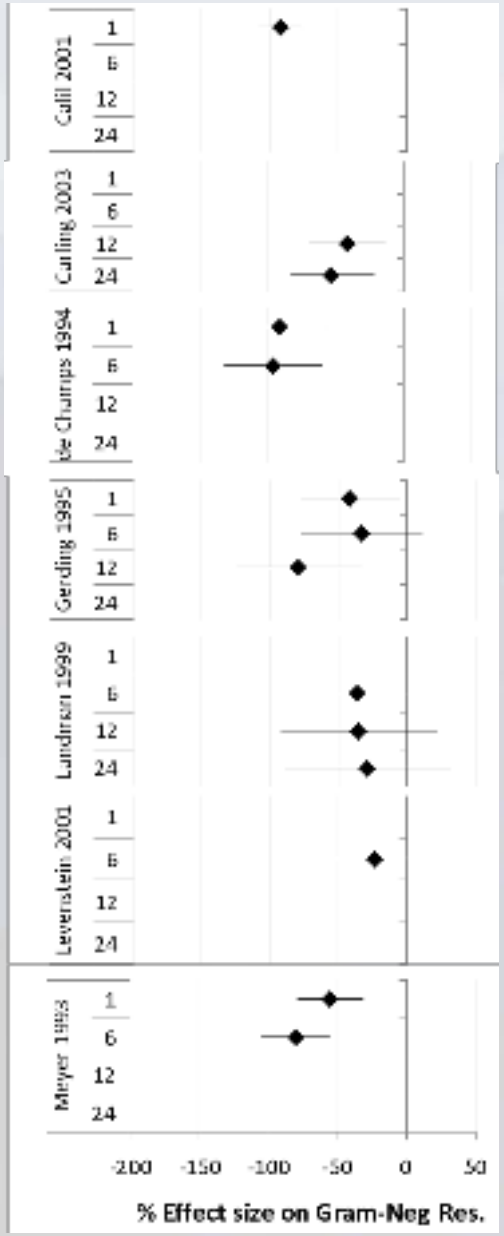
(2) Hospital: Cochrane Systematic Review

Microbial Outcomes

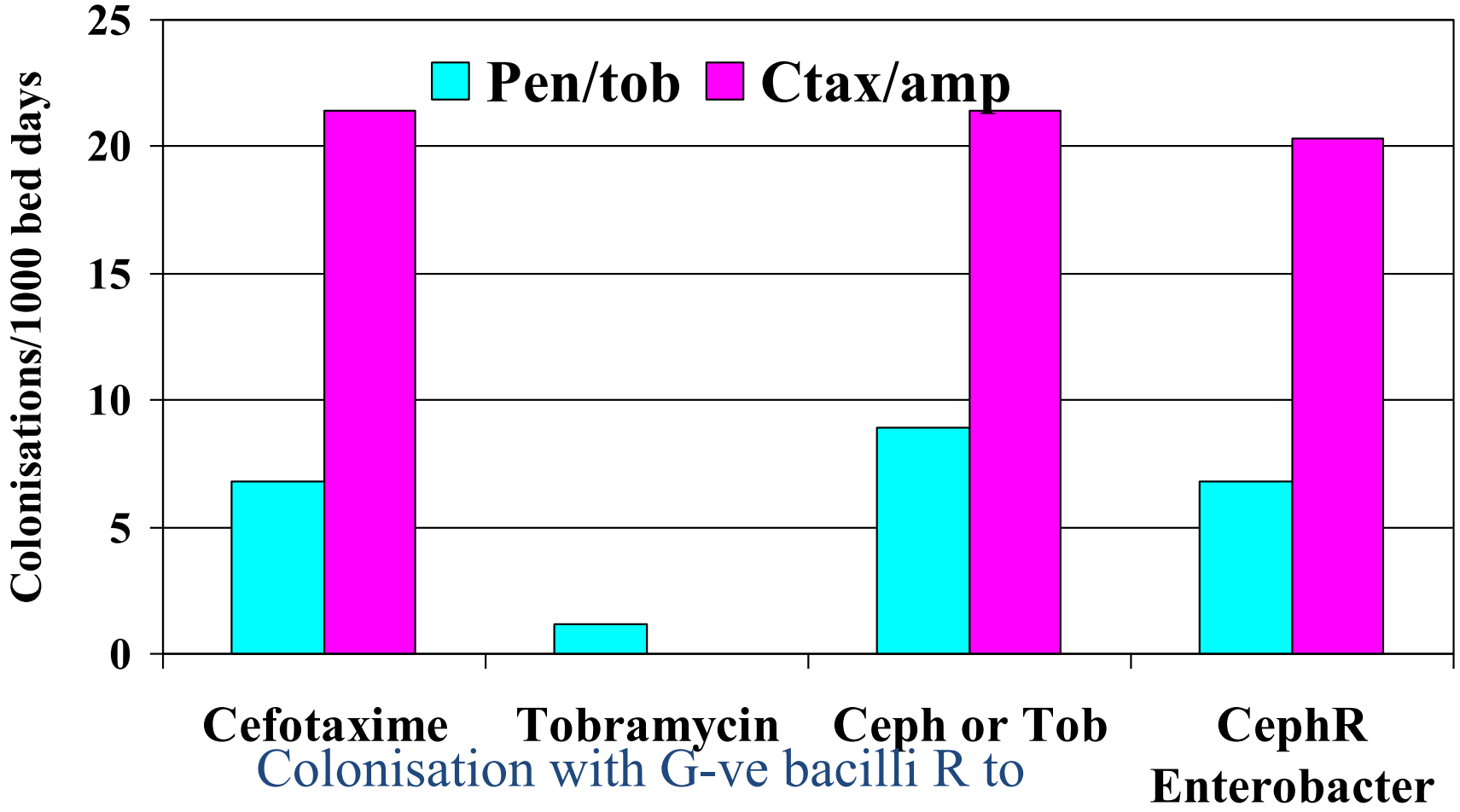
Gram-negative resistance

Study type	Number studies	Median effect
ITS	7	-47%
CCT	1	+39%
cCCT	1	-68%





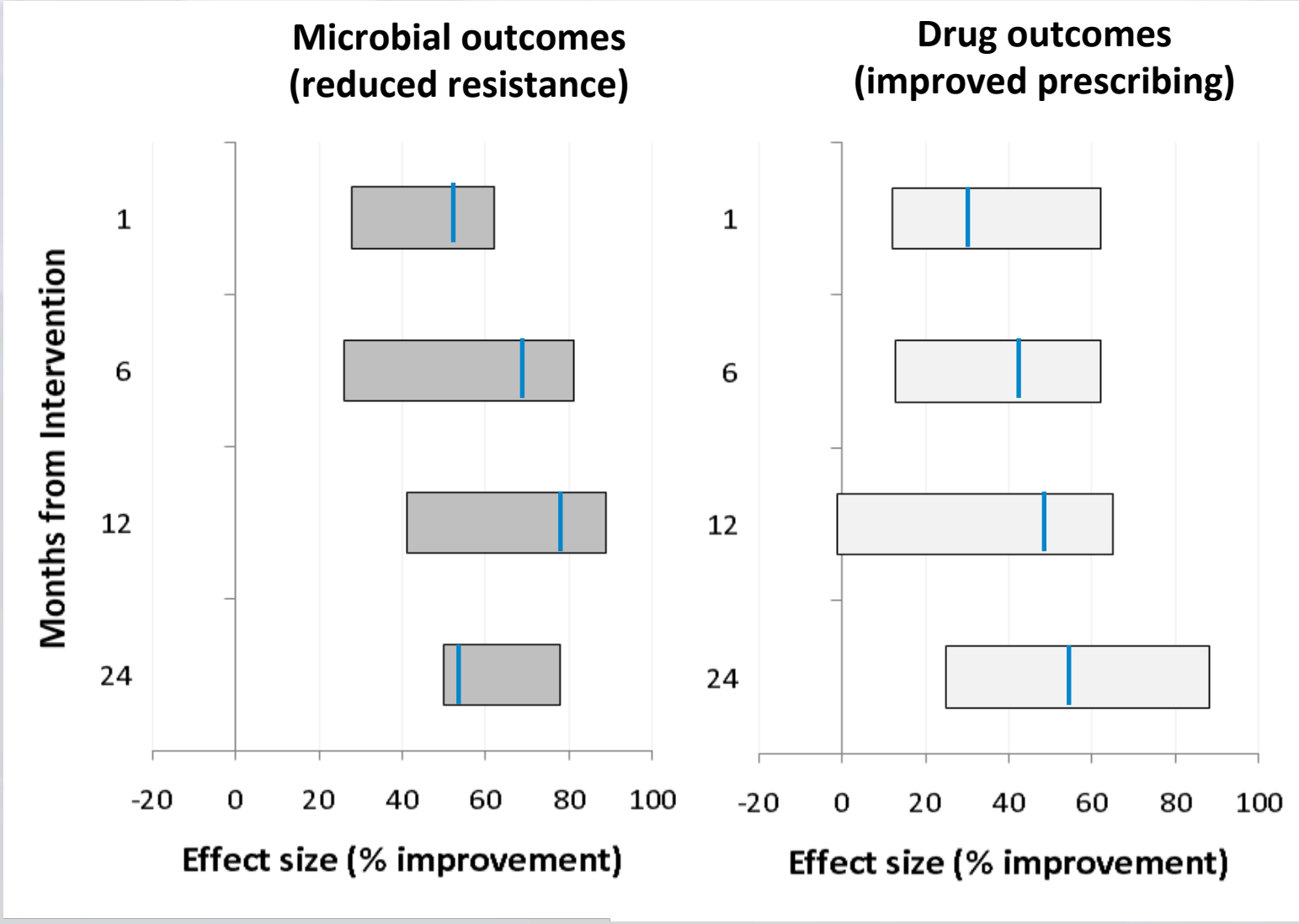
Empiric septicaemia R_x in NICU



de Man, *Lancet* 2000, **355**, 973

(2) Hospital: Cochrane Systematic Review

Overall effects by months from intervention



(3) Hospital: Cochrane Meta-analysis

Conclusions

Comparison 1: Restrictive vs. Persuasive – drug outcomes

- Restrictive greater impacts short term.
- Restrictive = Persuasive in longer term

Comparison 2: Restrictive vs. Persuasive - microbial outcomes

- As above.

Comparison 3: ↑effective antibiotics & clinical outcomes

- May reduce mortality from CAP, not in all infections.

Comparison 4: ↓ excessive antibiotic use & clinical outcomes

- No associated increases in mortality, LoS or infection-specific readmission.

Agenda

(1) Why we need evidence

(2) Hospital: Cochrane Systematic Review

(3) Hospital: Cochrane Meta-analysis

(4) Since the review

Summary

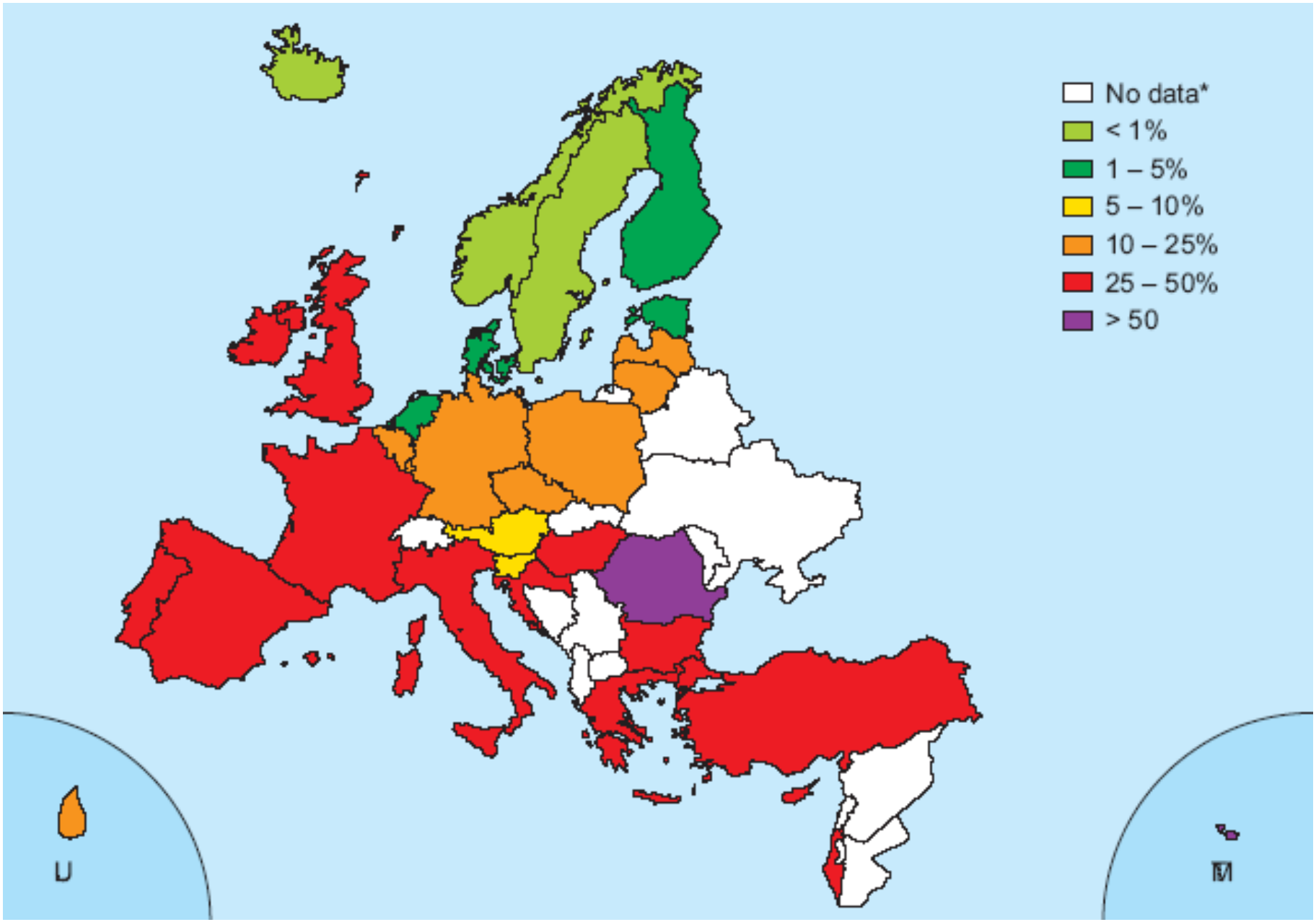
(4) Since the review

(1) More studies meeting EPOC standards

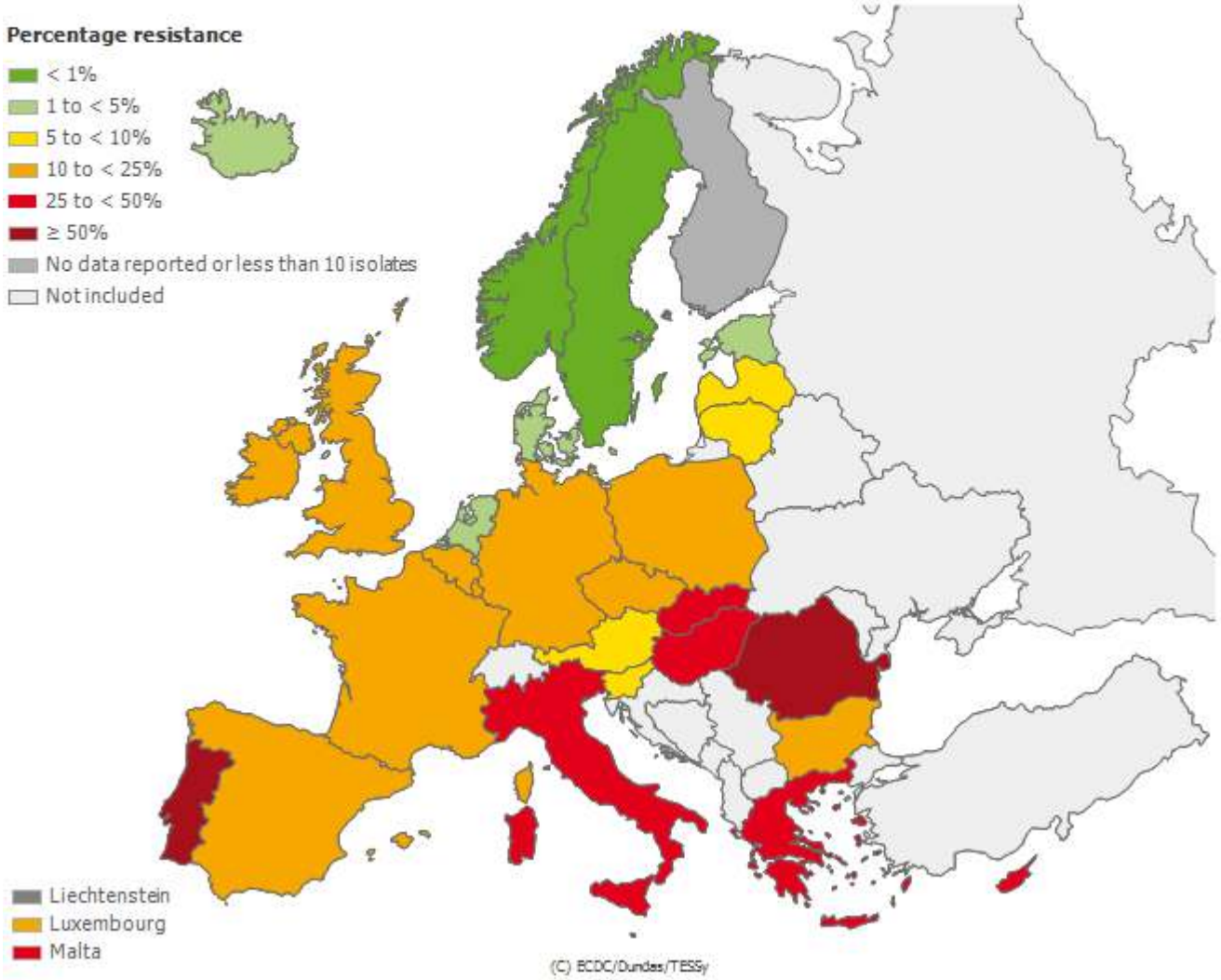
Study	Design	Location	Intervention	Outcome
Cook JHI 2006	ITS	US University Hospital-wide	↓ Cipro	↓MRSA
Avery BJ Max Fac Surg 2006	Obs	UK Max Fax Uni Hosp	Surg proph ↓2GC	↓MRSA
Bassetti ICAAC 2006	Un B/A	Italy ICU University Hosp	↑4FQ ↓3GC	↑ESBL ↓MRSA
Meyer JAC 2007	ITS	Germany	2GC Carbap BLIs ↓ Glycopep	↓MRSA (B.A)
Buising JAC 2008	ITS	Australia	Glycopep ↑ ESP Carbap 3/4GC ↓ Aminoglyc	MRSA MDR P.aerug ↓ Cefaz ® E.coli
Liebowitz JHI 2008	ITS	UK DGH	↓Cipro/3GC	↓MRSA
Aldeyab JAC 2008	ITS	UK Uni	↓3GC/4FQ Macro BLasel	↓MRSA
Vernaz JAC 2008	ITS	Swiss Uni	↓3GC4FQ Macro BLasel	↓MRSA

‘Dose-response’ (NNT to do harm) identified

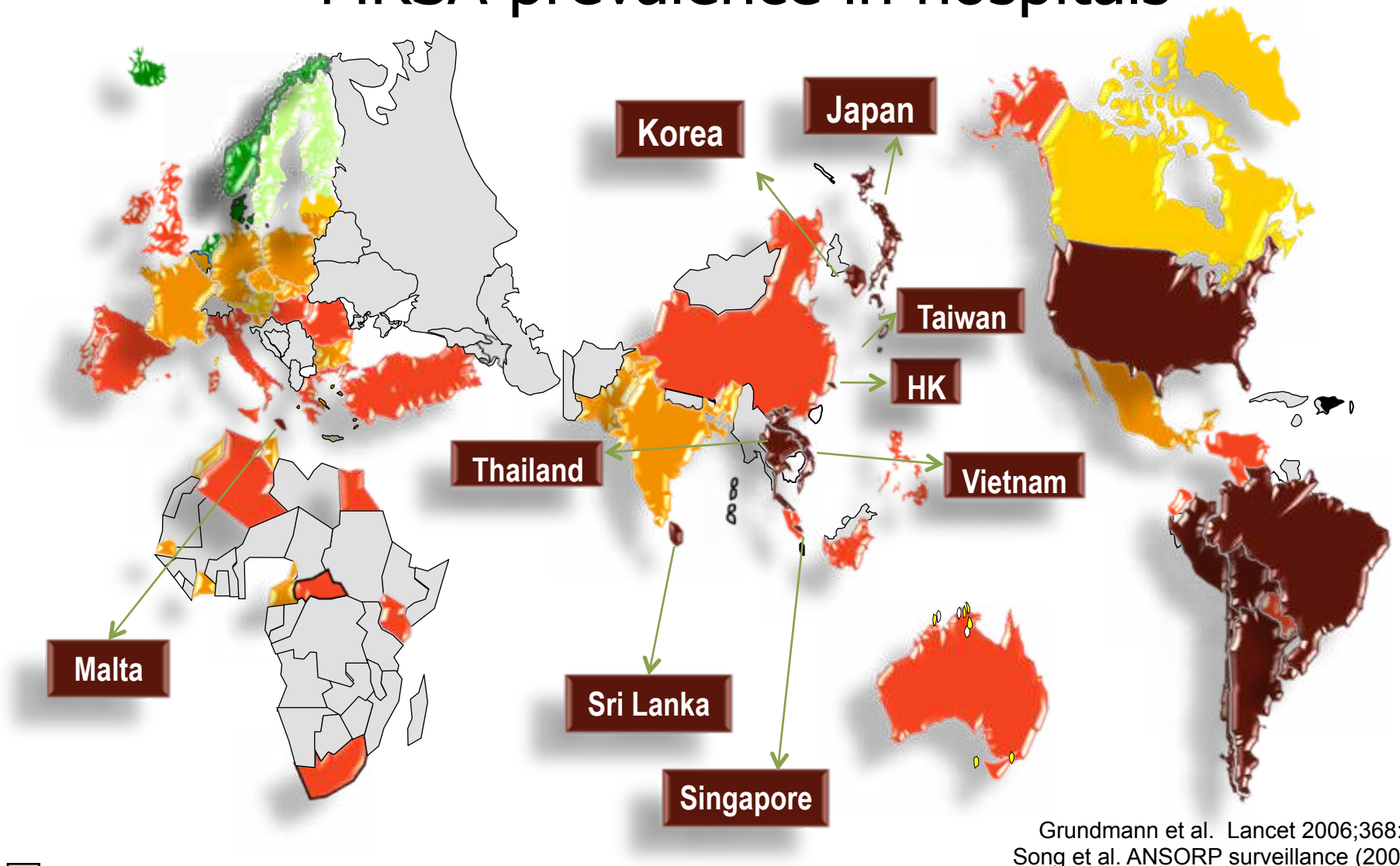
S. aureus: proportion of invasive isolates resistant to oxacillin (MRSA) in 2006



Proportion of Methicillin Resistant *Staphylococcus aureus (MRSA)* Isolates in Participating Countries in 2011



MRSA prevalence in hospitals



Grundmann et al. Lancet 2006;368:874–85
Song et al. ANSORP surveillance (2005-2006)
Annual report of the EARS-Net 2009
Mejia et al. Braz J Infect Dis 2010;14 Suppl 2:S79–86

Date of preparation: November 2012
Job number: 2113204

Open Access Research

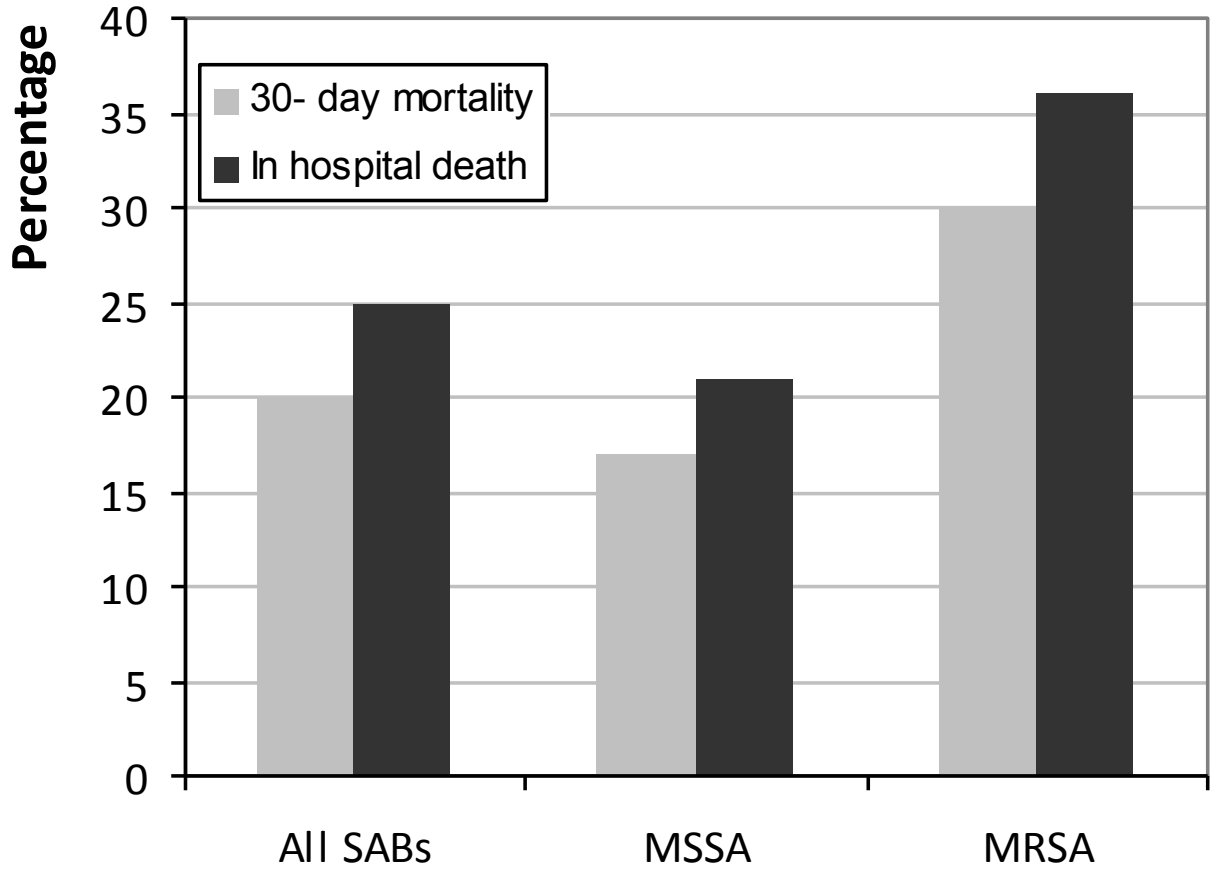
BMJ open
accessible medical research

Trends in *Staphylococcus aureus* bacteraemia and impacts of infection control practices including universal MRSA admission screening in a hospital in Scotland, 2006–2010: retrospective cohort study and time-series intervention analysis

Timothy Lawes,[1] Becky Edwards,[2] José-Maria López-Lozano,[3] Ian Gould[2]

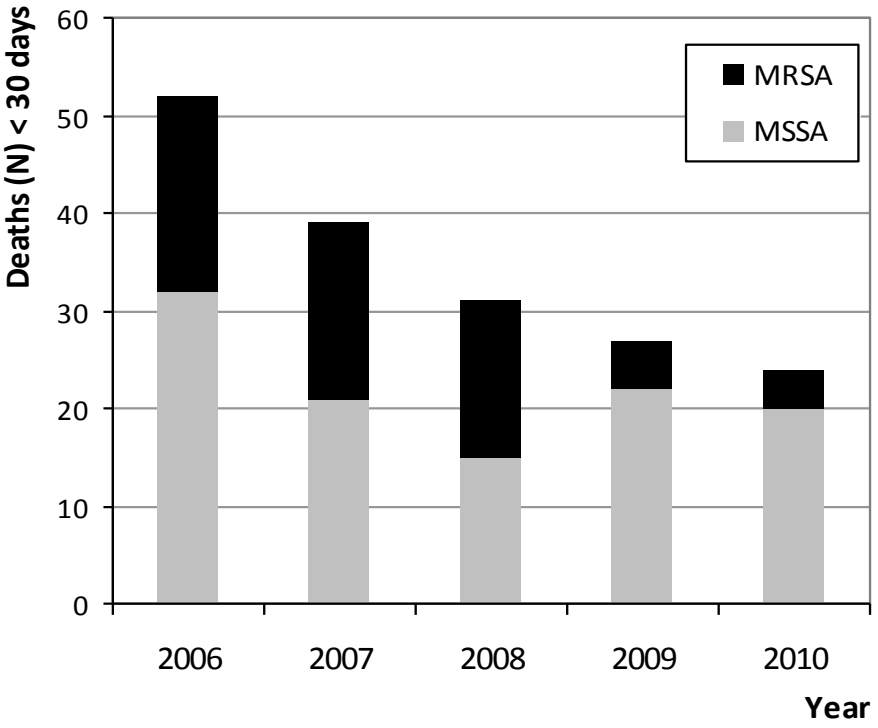
BMJ Open 2012;2:e000797 doi:10.1136/bmjopen-2011-000797

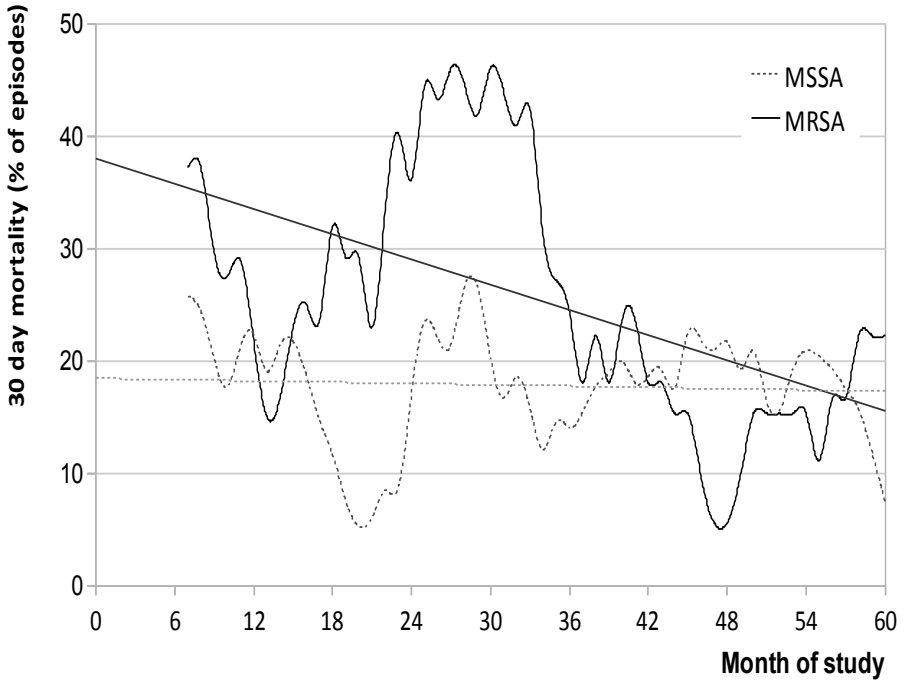
Aberdeen cohort (2006-2010)



Outcomes	All SABs	MSSA	MRSA	*P*
30-day mortality	173 (20%)	110 (17%)	63 (30%)	<0.001
In hospital death	209 (25%)	134 (21%)	75 (36%)	<0.001

Temporal Trends in 30 day mortality (2006-10)



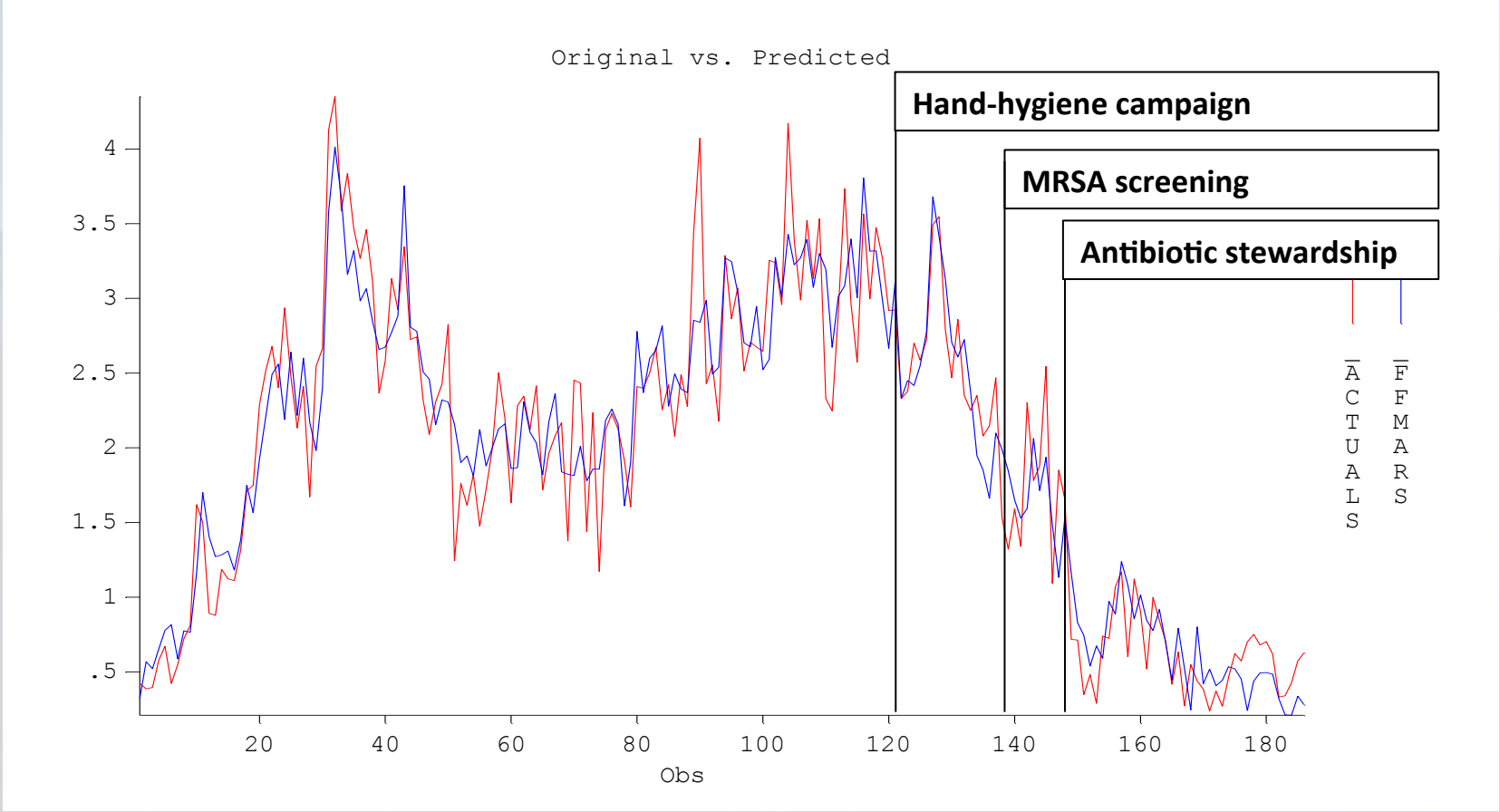


- Significant declines in 30-day and inpatient mortality ($p < 0.05$)

(4) Since the review

NHS Grampian:

Non-linear TSA (MARS) significant impact on MRSA of…



Lawes T, et al. BMJ Open 2015;5:e006596. doi:10.1136/bmjopen-2014-006596

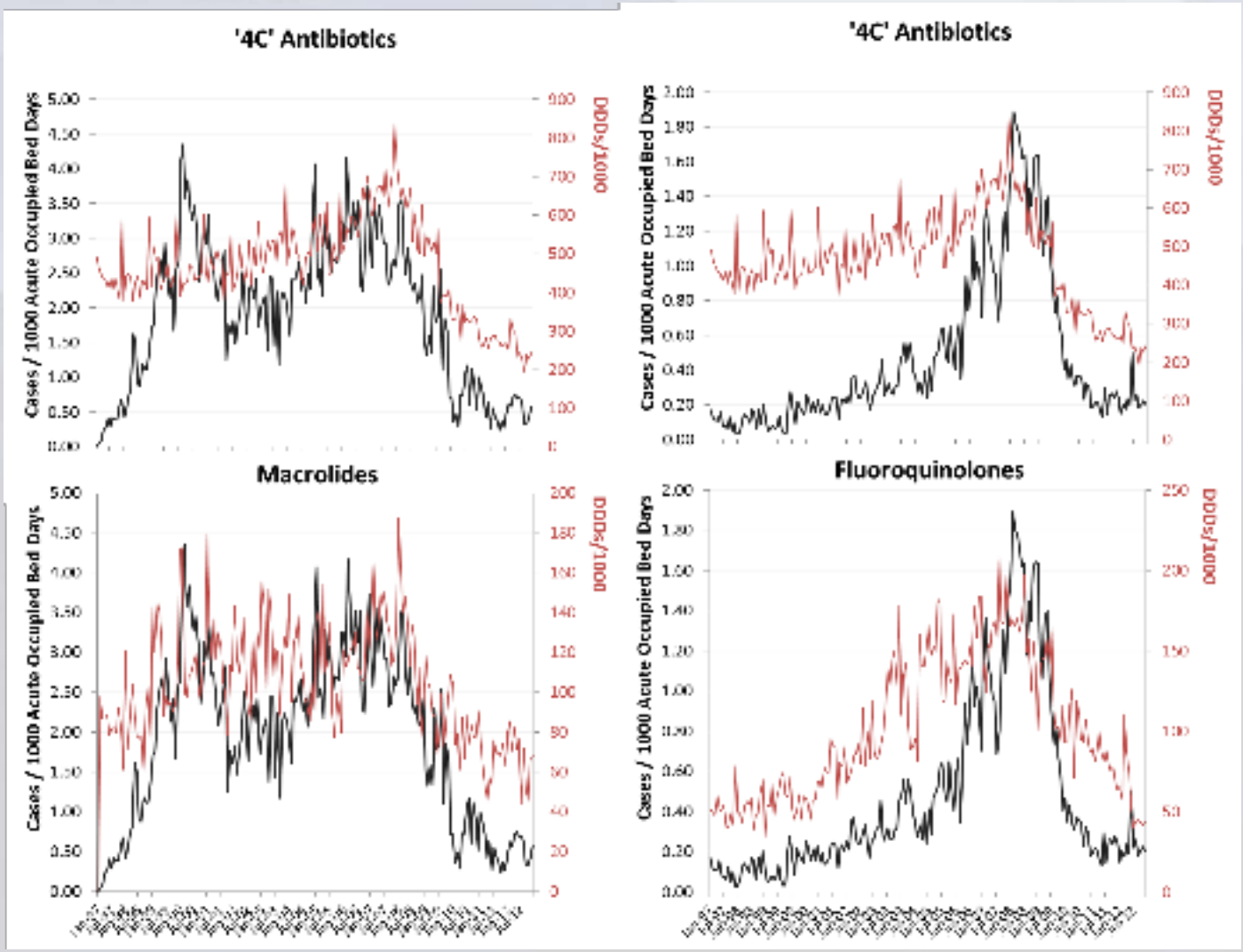
(4) Since the review

NHS Grampian:

Lawes T, et al. BMJ Open 2015;5:e006596. doi:10.1136/bmjopen-2014-006596

MRSA

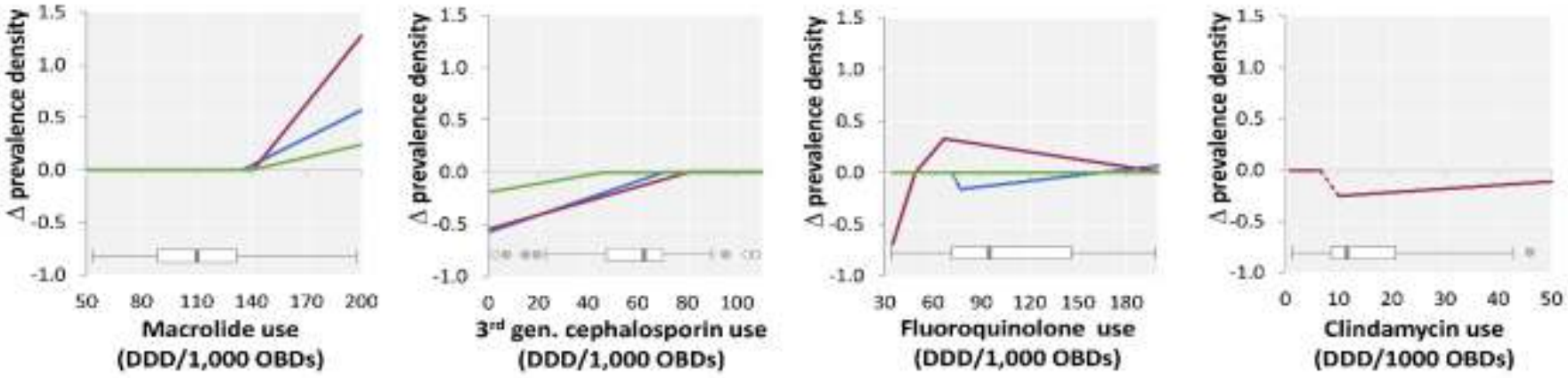
C.difficile

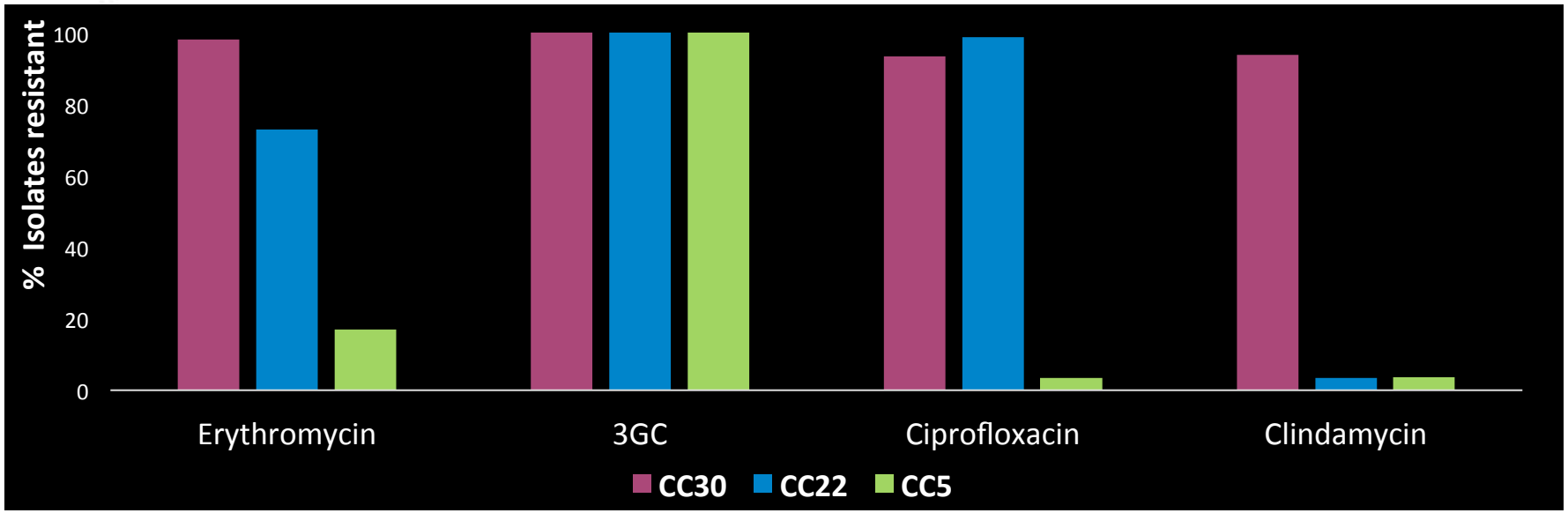


Lawes T, et al. BMJ Open 2015;5:e006596. doi:10.1136/bmjopen-2014-006596

Results

Non-linear TSA:



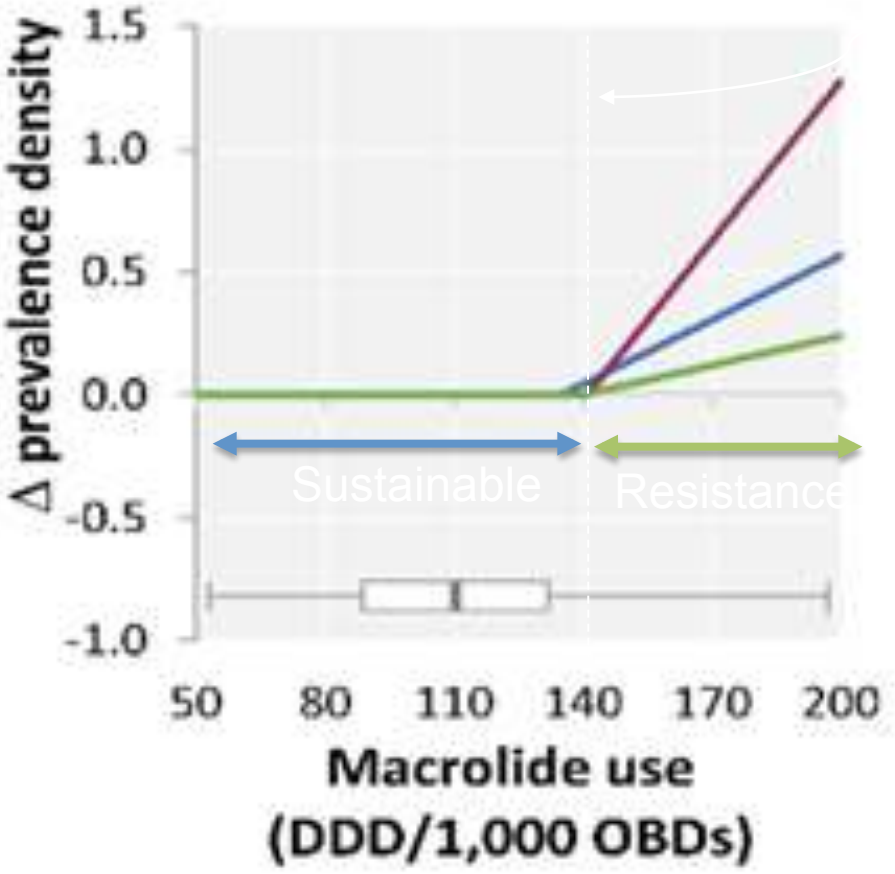


Lawes T, et al. BMJ Open 2015;5:e006596. doi:10.1136/bmjopen-2014-006596

Implications

(2) Total antibiotic use & other critical thresholds

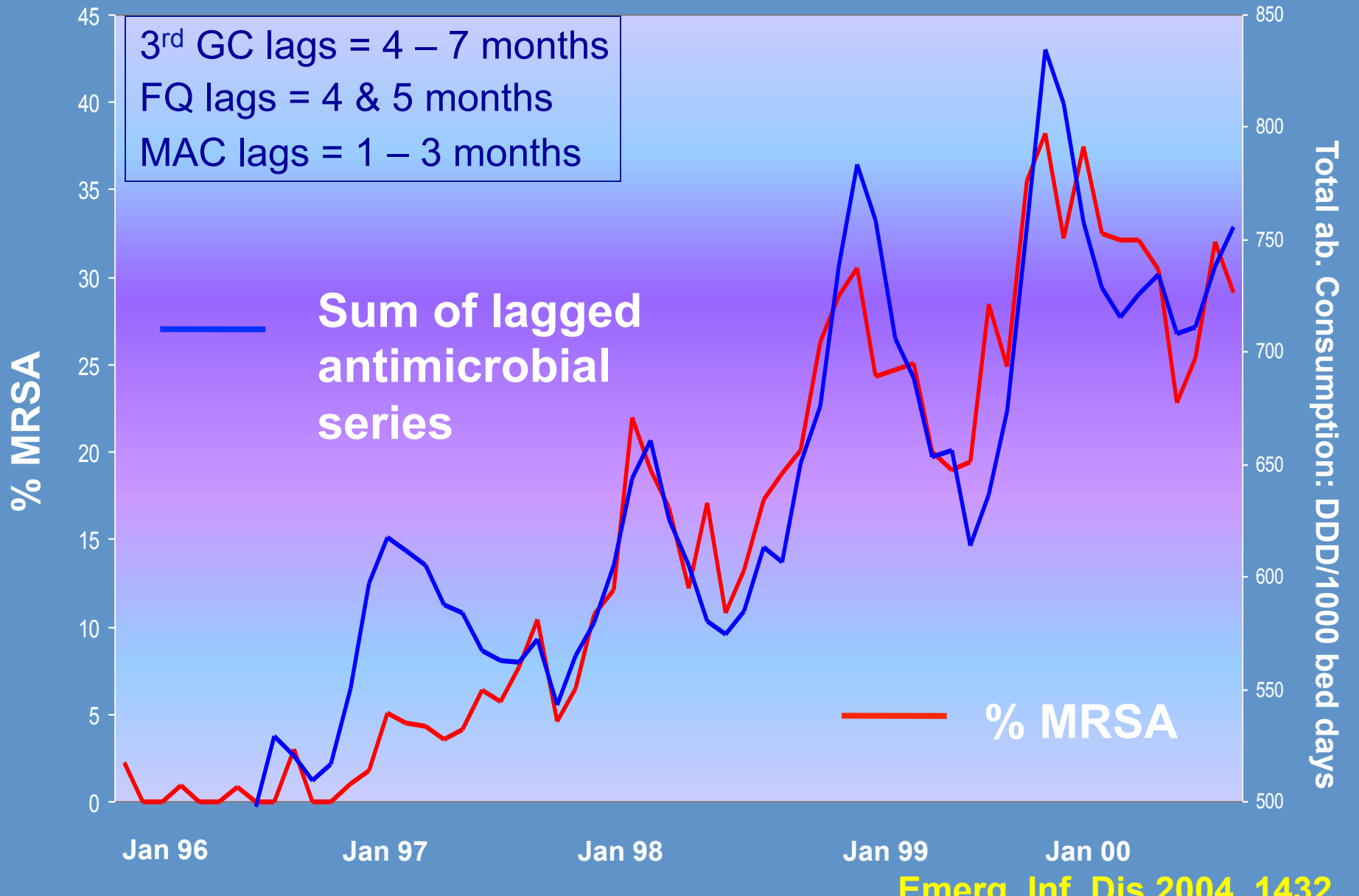
- May identify **cost-effective** level of intervention



Total Antibiotic Use Threshold:

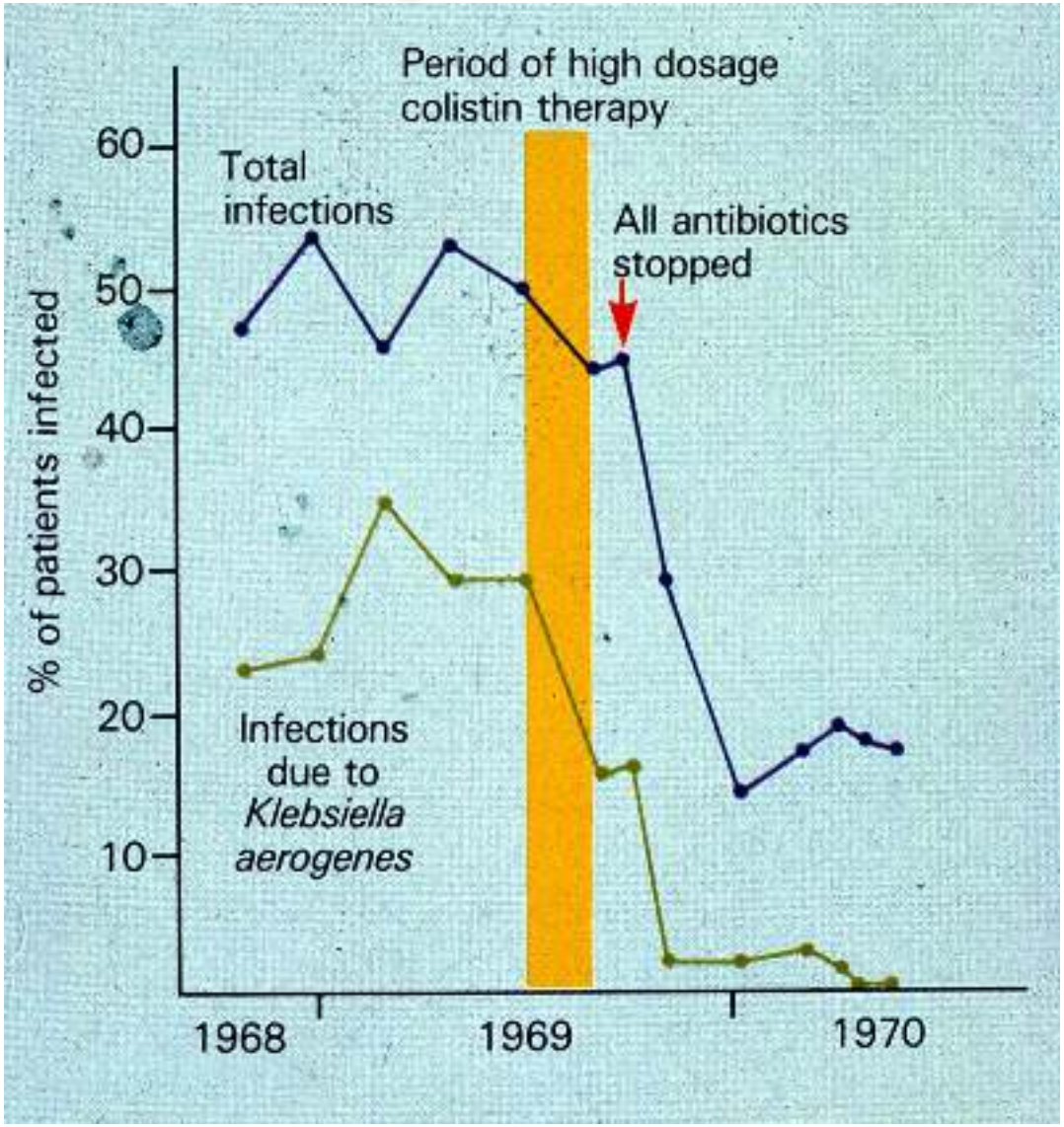
How many treatments with macrolides?	Number
DDDs per 1,000 OBDs	140
Treatment per 1,000 OBDs (7 DDDs = 1 tmt)	20
OBDs /month	21,000
OBDs / year	252,000
Person(s) treatable/month	**417**
Person(s) treatable / year	**5,000**

Relationship between % MRSA and antibiotic use. (3rd GC, FQ, MAC)



Emerg. Inf. Dis 2004, 1432

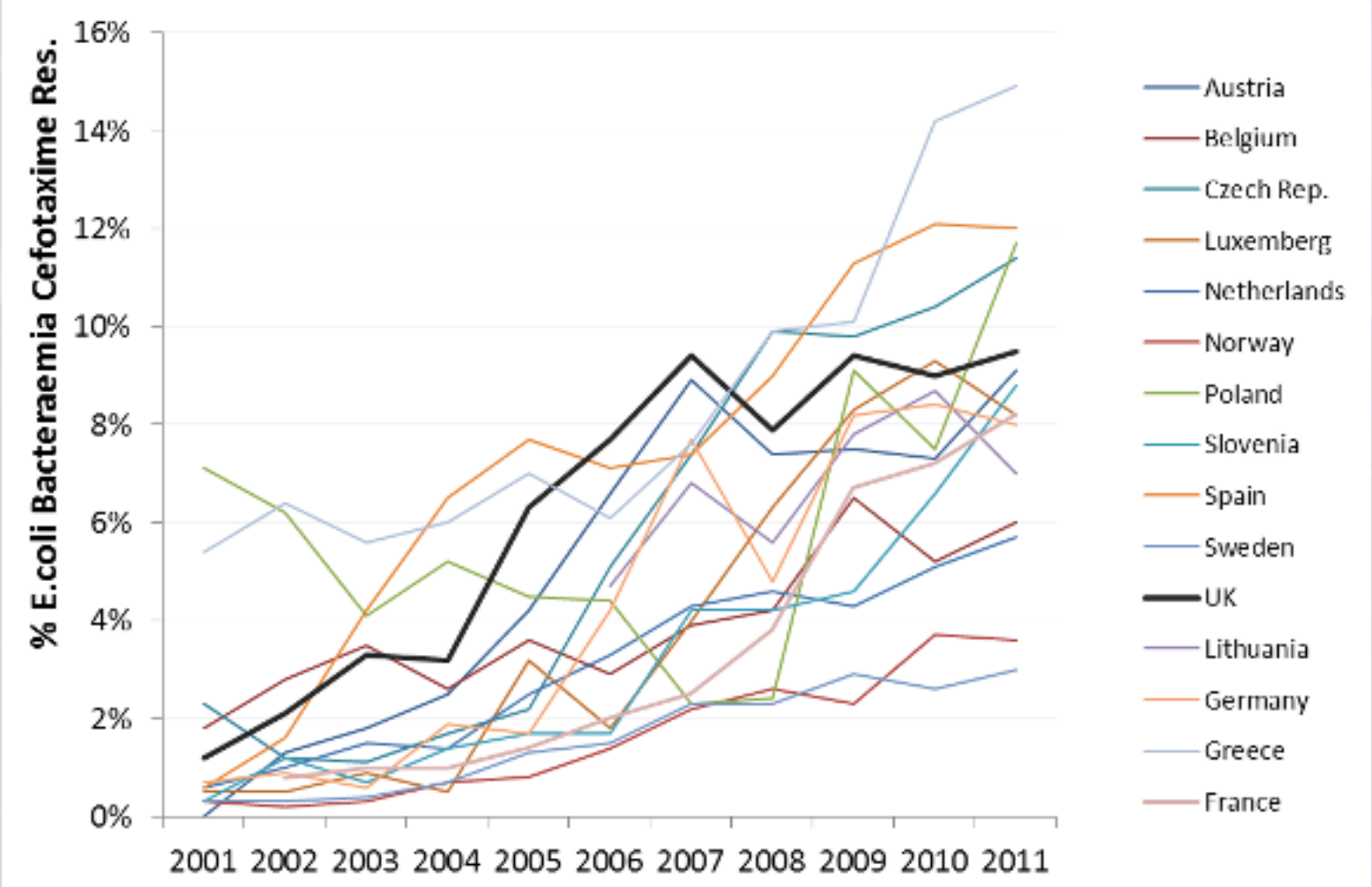
MDR K. aerogenes outbreak



Price and Sleigh Lancet 1971

(4) Since the review

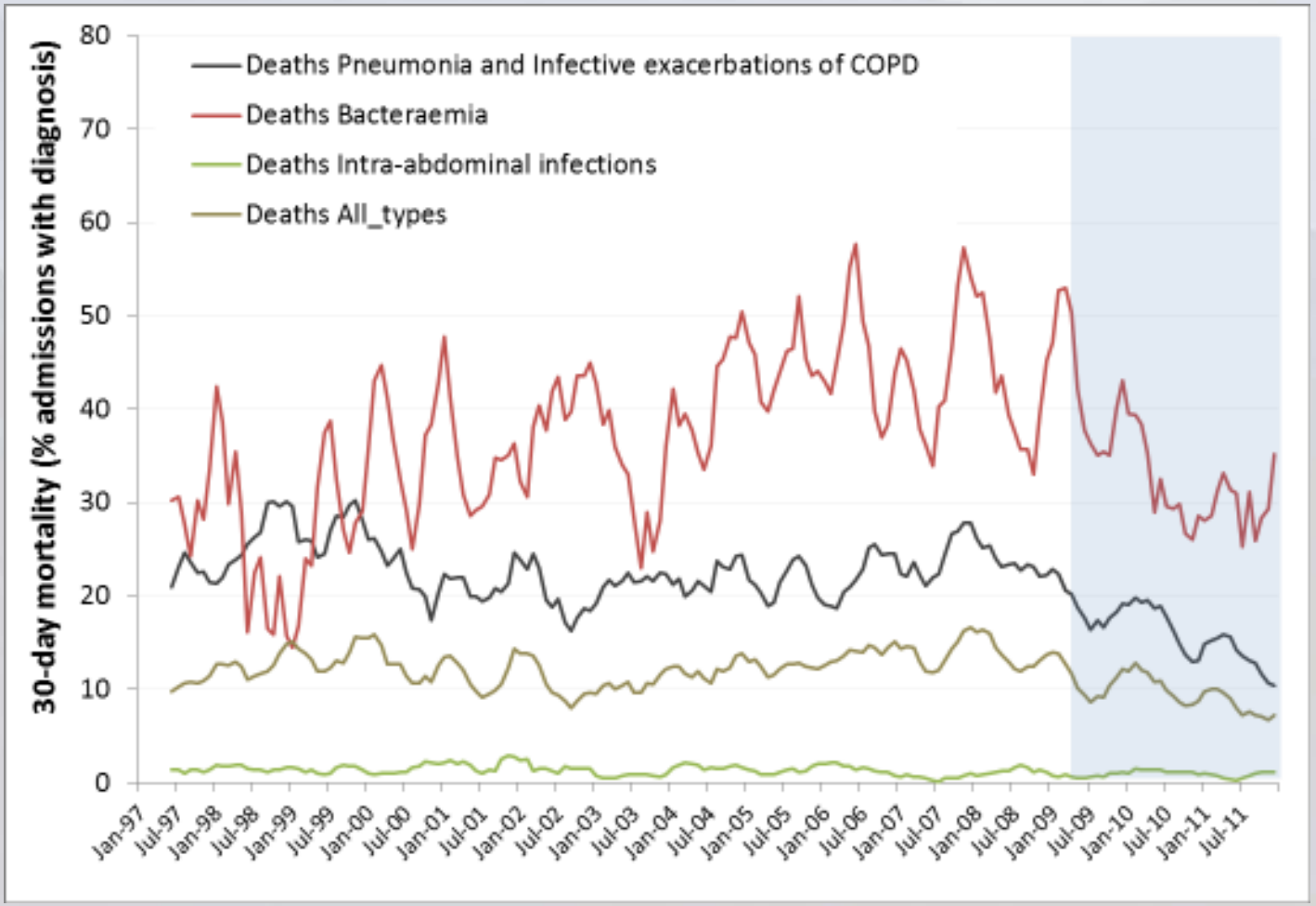
National analysis: International comparison



(4) Since the review

Monitoring for Unintended Consequences

Reduced Efficacy of Treatment?



Agenda

(1) Why we need evidence

(2) Hospital: Cochrane Systematic Review

(3) Hospital: Cochrane Meta-analysis

(4) Since the review

Summary

AM Stewardship - Goals

Goals

- Optimizing clinical outcomes while minimizing unintended consequences of antimicrobial uses.

Optimizing clinical outcomes

- All patients receive appropriate antibiotic from first dose.
- Reduce Antimicrobial resistance.
- Decrease morbidity / mortality.
- Decrease in length of stay.

AM Stewardship- The Hospital Context

Hospital context

- A program to promote evidence based usage of antibiotics by making customized treatment protocols based on the hospital's ecology & microbiology data

- Antibiotic Stewardship Program,
  - Overall understanding on all class of antibiotics & related issues of resistance.
  - Emphasis on local microbiology data to select right antibiotics.
  - Patient risk stratification to evaluate patients' condition & suspect antimicrobial resistance.
  - De-escalation strategy to optimize appropriate antibiotic right from the first dose.

Remember 4 D's of Antimicrobial therapy

- The Right Antibiotic
- The Right Dose
- Optimum Duration
- De-escalation

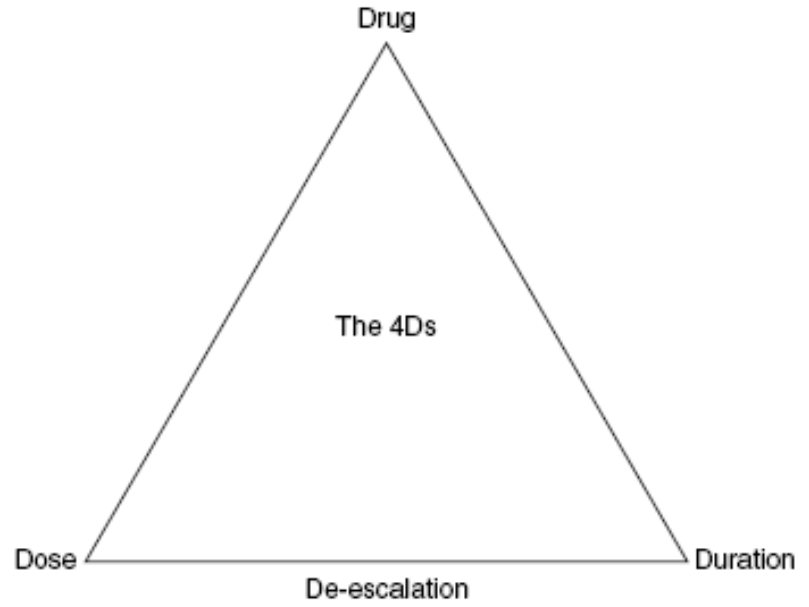


Figure 1. The 4 Ds of antimicrobial therapy: the right Drug, Dose, Duration and De-Escalation.

Glynn etal. Current Anaesthesia & Critical Care (2005) 16, 221–230

10 Stewardship Truths

- **Tailor** the intervention to the context
- **Benchmark/targets** – how much? By when?
- **Collaboration** or intervention will be circumvented
- **Pragmatism** - what benefit does the prescriber see?
- **Realism** – start with modest goals.
- **Balancing measures - unwanted consequences:**
  - Toxicity
  - Loss of effectiveness
  - New resistance 'Squeezing the balloon'

10 Stewardship Truths contd.

- Modest but sustained returns likely.
- Broad spectrum of methods work
- Balance resource intensity and impact
- Evidence base-improving

The very first guidelines are still not fully implemented!
(The 10 commandments)


THE
A TEAM

ANTIBIOTIC POLICIES

Theory and Practice

EDITED BY
IAN M. GOULD AND
JOS W. M. VAN DER MEER

FOREWORD BY STUART LEVY

ANTIBIOTIC POLICIES

Fighting Resistance

EDITED BY
IAN M. GOULD
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Foreword by John McGowan

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