University Hospitals of Leicester NHS
NHS Trust

FIGHT INFECTIONS

Antibiotic stewardship as part of the prevention strategy

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THE EVOLUTION OF RESISTANCE IS DRIVEN BY ANTIBACTERIALS

A chronology for the emergence of resistance

Date antibiotic introduced into clinical practice		Date antibiotic resistance identified
	1940	penicillin resistant *Staphylococcus*
penicillin	1943	
tetracyclines	1948	
erythromycin	1952	
vancomycin	1958	
	1959	tetracycline resistant *Shigella*
methicillin	1960	
	1962	methicillin resistant *Staphylococcus aureus* (MRSA)
	1965	penicillin resistant *Streptococcus pneumoniae*
	1968	erythromycin resistant *Streptococcus*
gentamicin	1971	
	1979	gentamicin high level resistant *Enterococcus*
imipenem, ceftazidime	1985	
	1987	ceftazidime resistant Enterobacteriaceae
	1988	vancomycin resistant *Enterococcus*
levofloxacin	1996	levofloxacin resistant *Streptococcus pneumoniae*
	1998	imipenem resistant Enterobacteriaceae
linezolid	2000	XDR tuberculosis
	2001	linezolid resistant *Staphylococcus*
	2002	vancomycin resistant *Staphylococcus*
daptomycin	2003	
	2004	PDR Acinetobacter and Pseudomonas
	2009	ceftriaxone resistant *Neisseria gonorrhoeae*, PDR Enterobacteriaceae
ceftaroline	2010	
	2011	ceftaroline resistant *Staphylococcus*

Adapted from CDC, Antibiotic resistance threats in the United States, 2013,

ANTIBACTERIAL RESISTANCE ACCUMULATES

G28 SUM3 Collect.:12/06/2012 Recd.:12/06/2012 N
, 6286222308 S0357918
Specimen No : MG043114Y Microbiology <PgUp/PgDn> for more

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ref lab no H1 2250 0354

Further report
Klebsiella pneumoniae subsp. pneumoniae

We confirm this isolate as pan-resistant and do not find any available sensitivities. The key features of an NDM-carrying isolate are pan-cephalosporin- / carbapenem- / aminoglycoside-resistances with significant potentiation of Imipenem by EDTA. Resistance to Aztreonam suggests underlying ESBL and possibly AmpC activity, as these determinants are often co-located with b1aNDM.

Antibiotic	MIC (mg/L)	S/I/R	Breakpoint (mg/L)
Amikacin	>64	R	8 & 16
Gentamicin	>32	R	2 & 4
Tobramycin	>32	R	2 & 4
Amoxicillin/ Clavulanate	>64	R	8
Ampicillin	>64	R	8
Aztreonam	>64	R	
Cefotaxime	>256	R	1 & 2
Cefotaxime/ clav-ESBL test	>32	X	
Cefoxitin	>64	R	8
Cefpirome	>64	R	1
Ceftazidime	>256	R	1 & 8
Ceftazidime/ Clav-ESBL test	>32	X	
Ertapenem	>16	R	0.5 & 1
Imipenem	128	R	2 & 8
Imipenem/ EDTA-MBL test	1	X	
Meropenem	>32	R	2 & 8
Piperacillin	>64	R	16
Piperacillin	>64	R	16
Sulbactam	>32	R	
Temocillin	>128	R	
Cefpirome/Clav	>32	X	
Cefotaxime/ cloxacillin	>256	X	
Colistin	>32	R	2
Ciprofloxacin	>8	R	0.5 & 1
Minocycline	32	R	
Tigecylcine	4	R	1 & 2
Fosfomycin	64	R	
Rifampicin	>32	R	

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ANTIBACTERIAL USE SELECTS FOR ANTIBACTERIAL RESISTANCE

Resistant bacteria in primary care following antibacterial treatment

Systematic review and meta-analysis of relationship between prior antibacterial exposure and resistance in individual patients in primary care

- 24 studies
- Antibiotics for urinary tract or respiratory tract infections linked with increased rates of carriage of resistant bacteria in recipient patients for up to 12 months (pooled odds ratio=2.5 at 2 months post antibiotics)
- Longer durations and multiple courses associated with higher resistance rates

Costelloe C et al. British Medical Journal 2010;340:c2096

ANTIBACTERIAL RESISTANCE COSTS LIVES AND HEALTHCARE RESOURCES

Estimates of burden of antibacterial resistance

European Union
population 500m

25,000 deaths per year

2.5m extra hospital days

Overall societal costs
(€ 900 million, hosp. days)
Approx. €1.5 billion per year

United States
population 300m

>23,000 deaths per year
>2.0m illnesses

Overall societal costs
Up to $20 billion direct
Up to $35 billion indirect

Thailand
population 70m

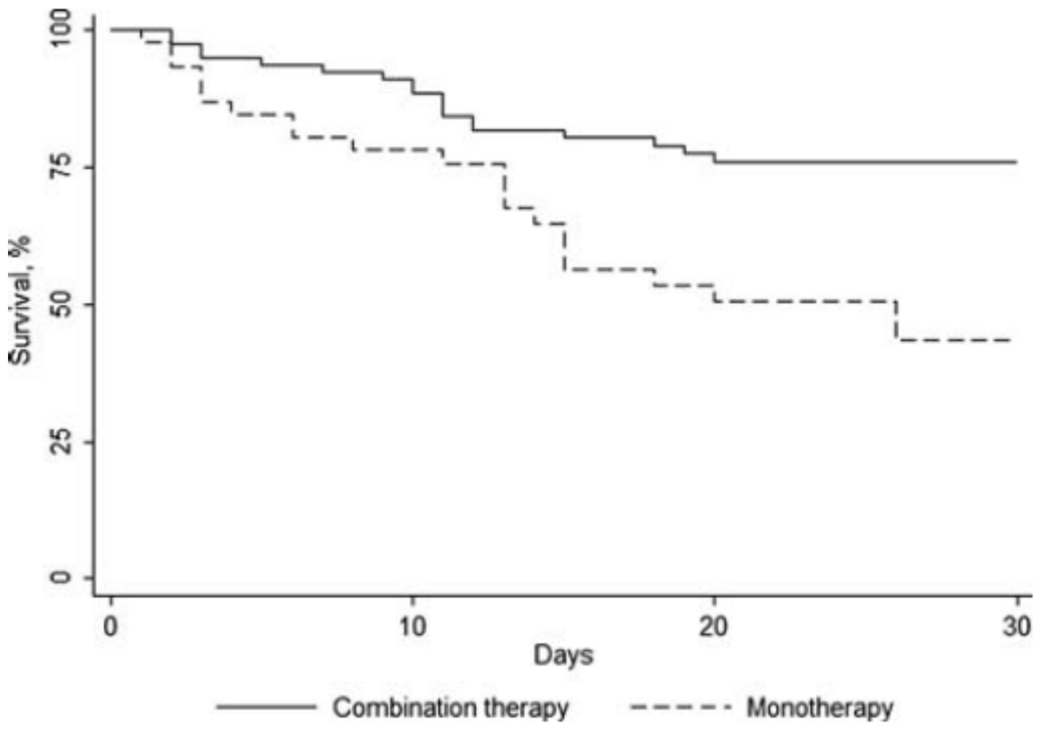
>38,000 deaths >3.2m hospital days

Overall societal costs
US$ 84.6–202.8 million Direct
>US$1.3 billion indirect

Adapted from World Health Organisation, Antimicrobial resistance: global report on surveillance (2014)

Antibiotic treatment of KPC-producing Klebsiella pneumoniae bacteraemia

Study: Retrospective cohort study of association between antibiotic regimen and survival to 30 days after diagnosis of KPC-producing *Klebsiella pneumoniae* bacteraemia
Setting: Three large Italian teaching hospitals



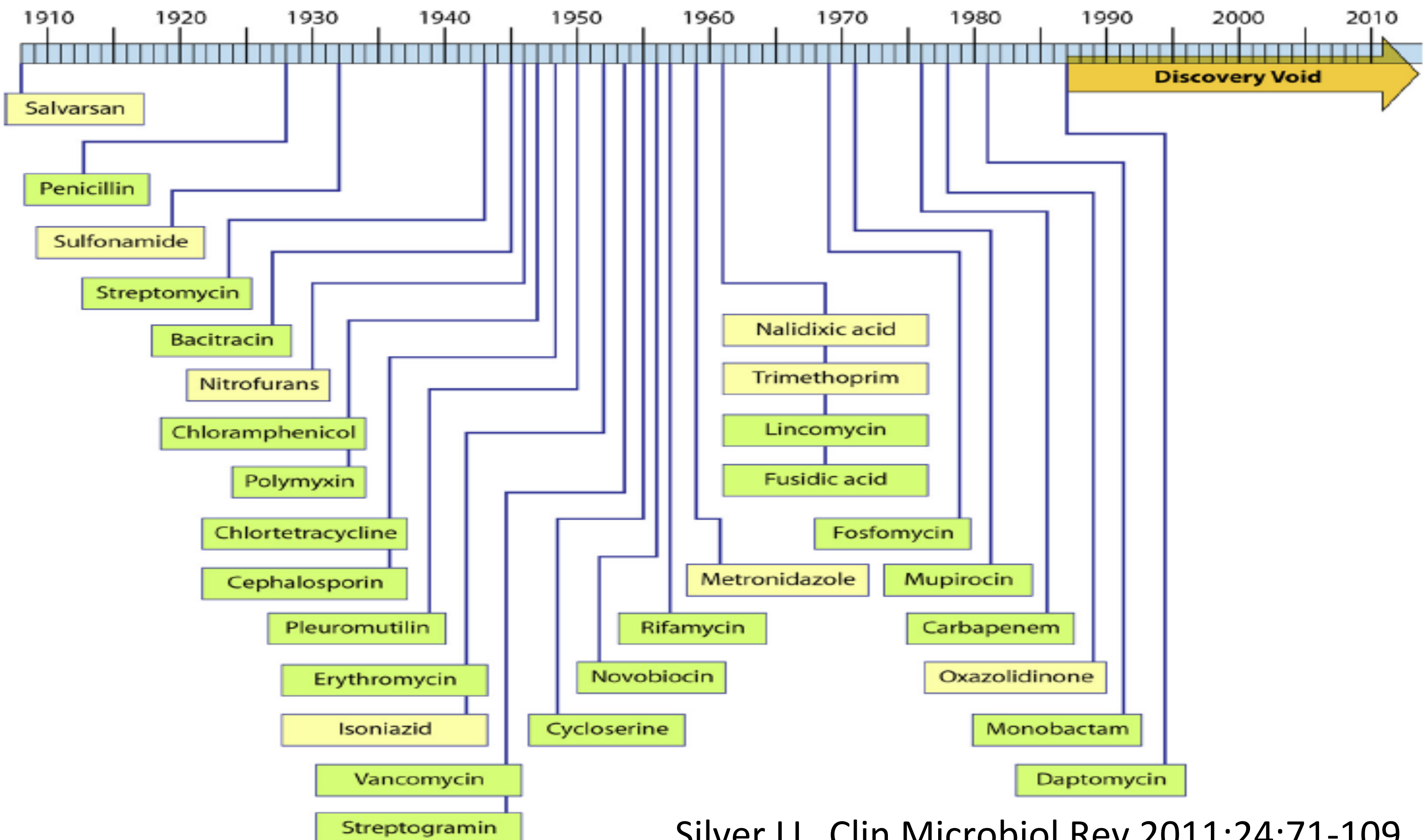
antibiotic regimen	Mortality odds ratio (95%CI)
monotherapy	1.59 (1.06-2.38)
2-drug combination	0.97 (0.64-1.48)
3-drug combination	0.36 (0.15-0.92)

Combination therapy with tigecycline, colistin and meropenem

Tumbarello M et al. Clin Infect Dis. 2012;55:943-50

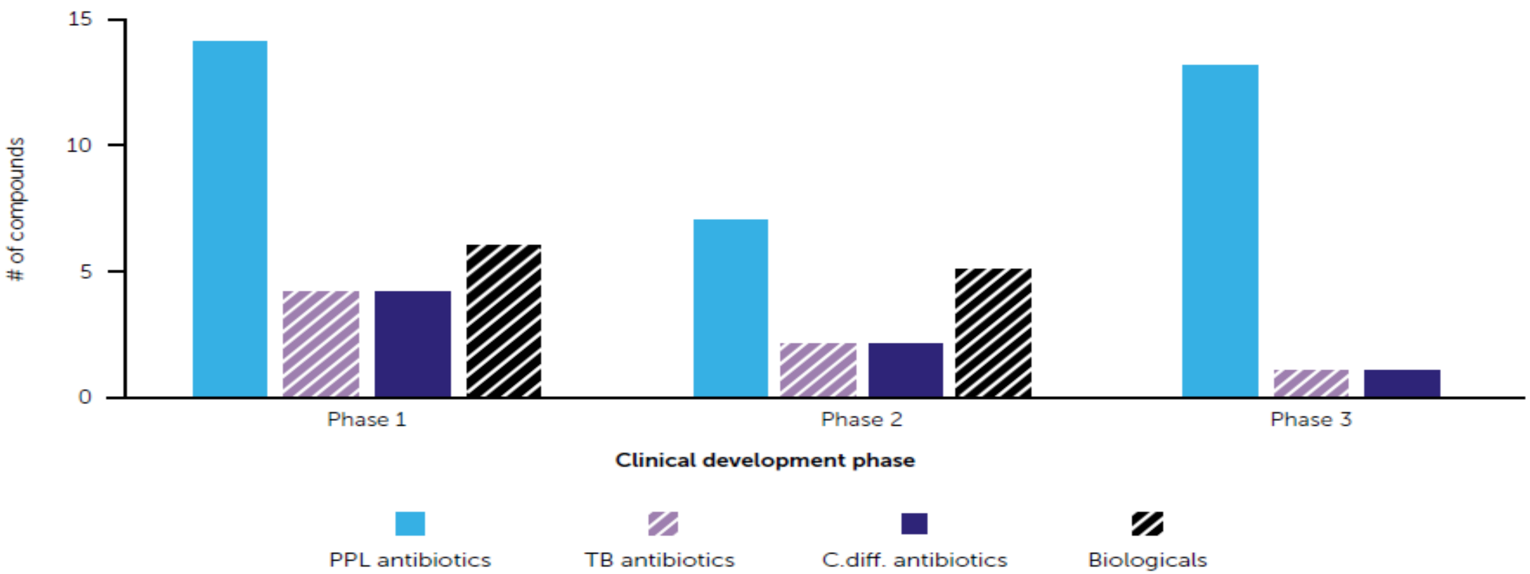
THERE ARE FEW NEW ANTIBACTERIALS

The discovery void



Silver LL. Clin Microbiol Rev 2011;24:71-109

Antibacterials currently in phase 1-3 of development



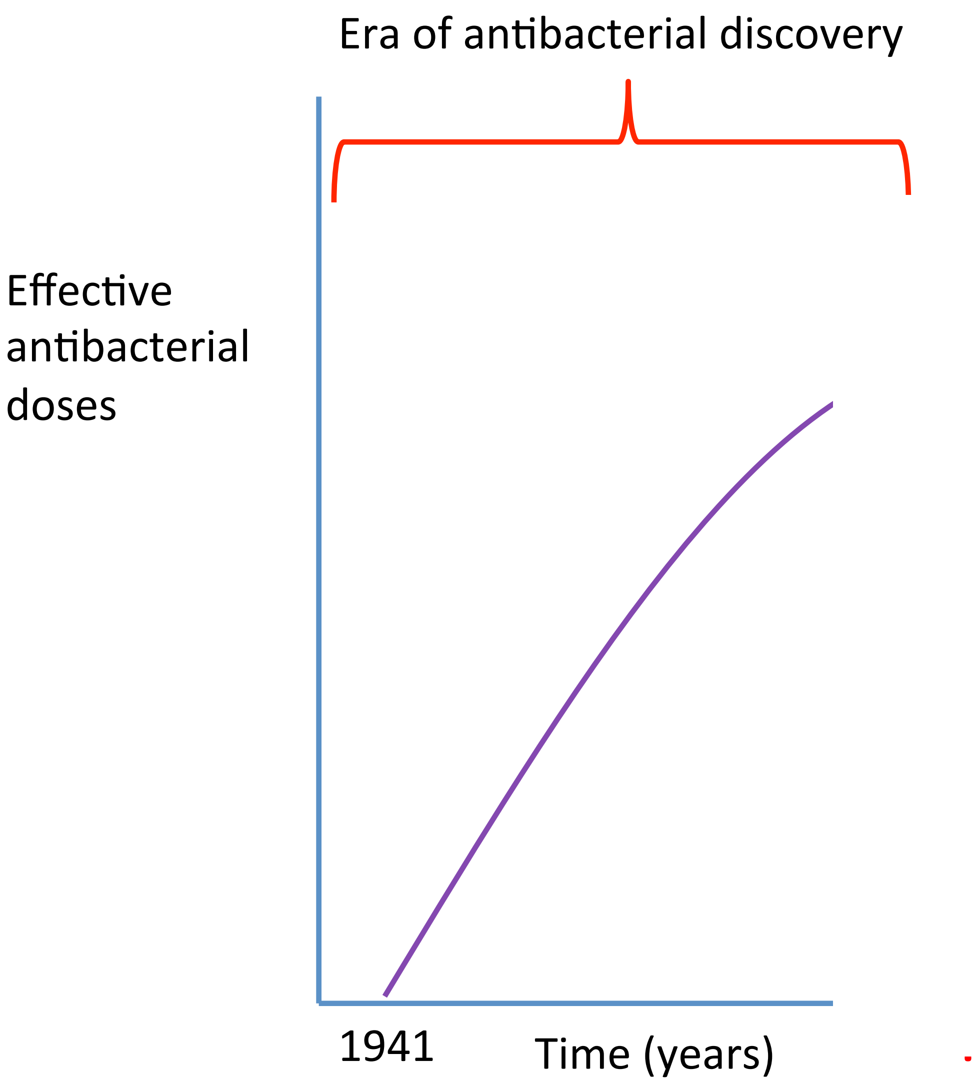
Gram positive priority pathogens: 16 products, including 2 new antibiotic classes and 7 biological agents (monoclonal antibodies and endolysins)

Gram negative priority pathogens: Almost all products are modifications of existing classes, active against limited range of bacteria

Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. WHO, 2017

ARE WE RUNNING OUT OF EFFECTIVE ANTIBACTERIAL DOSES?

Has the world passed peak antimicrobial efficacy?

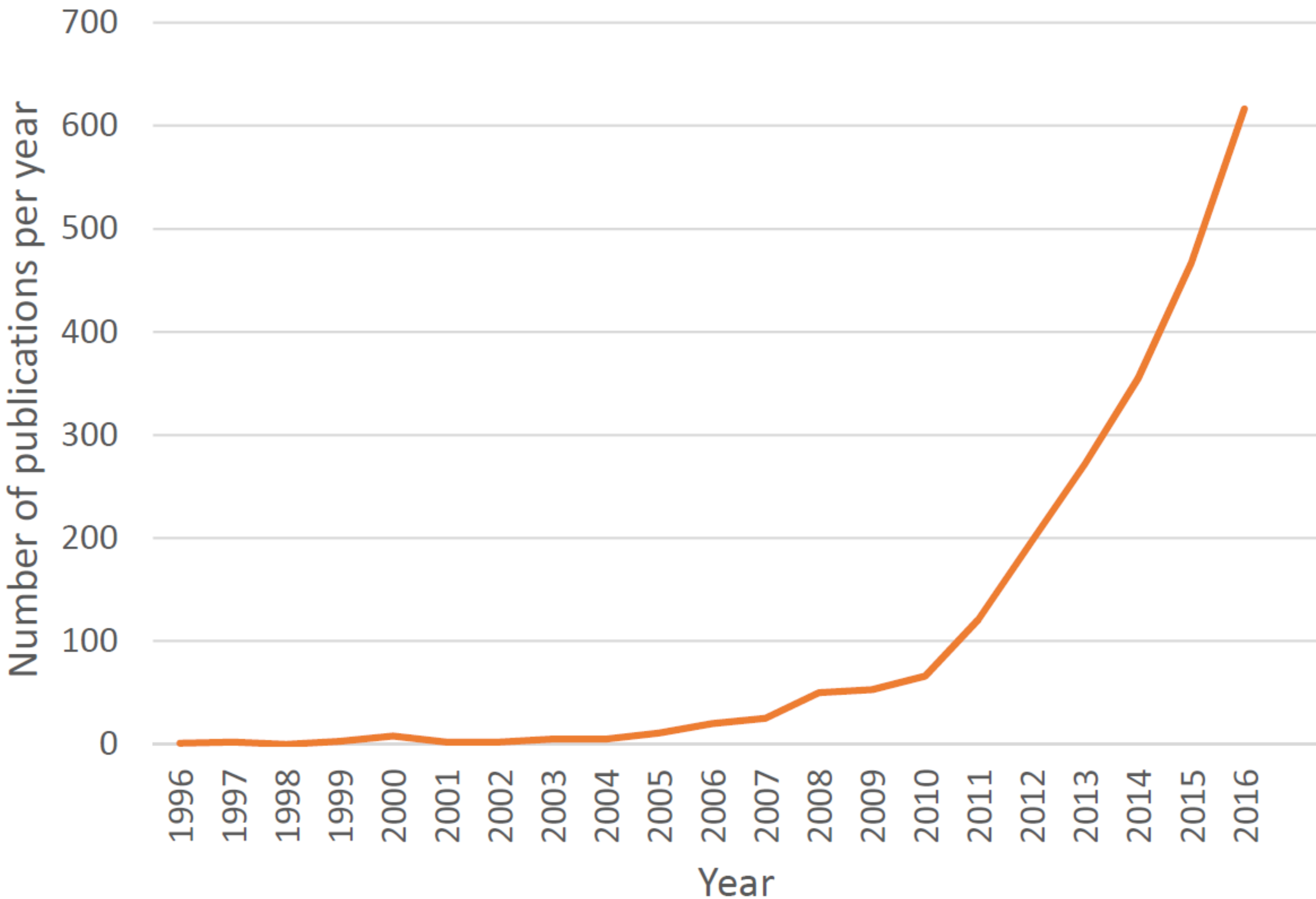


IS ANTIBACTERIAL STEWARDSHIP THE ANSWER?

IDSA description of antimicrobial stewardship

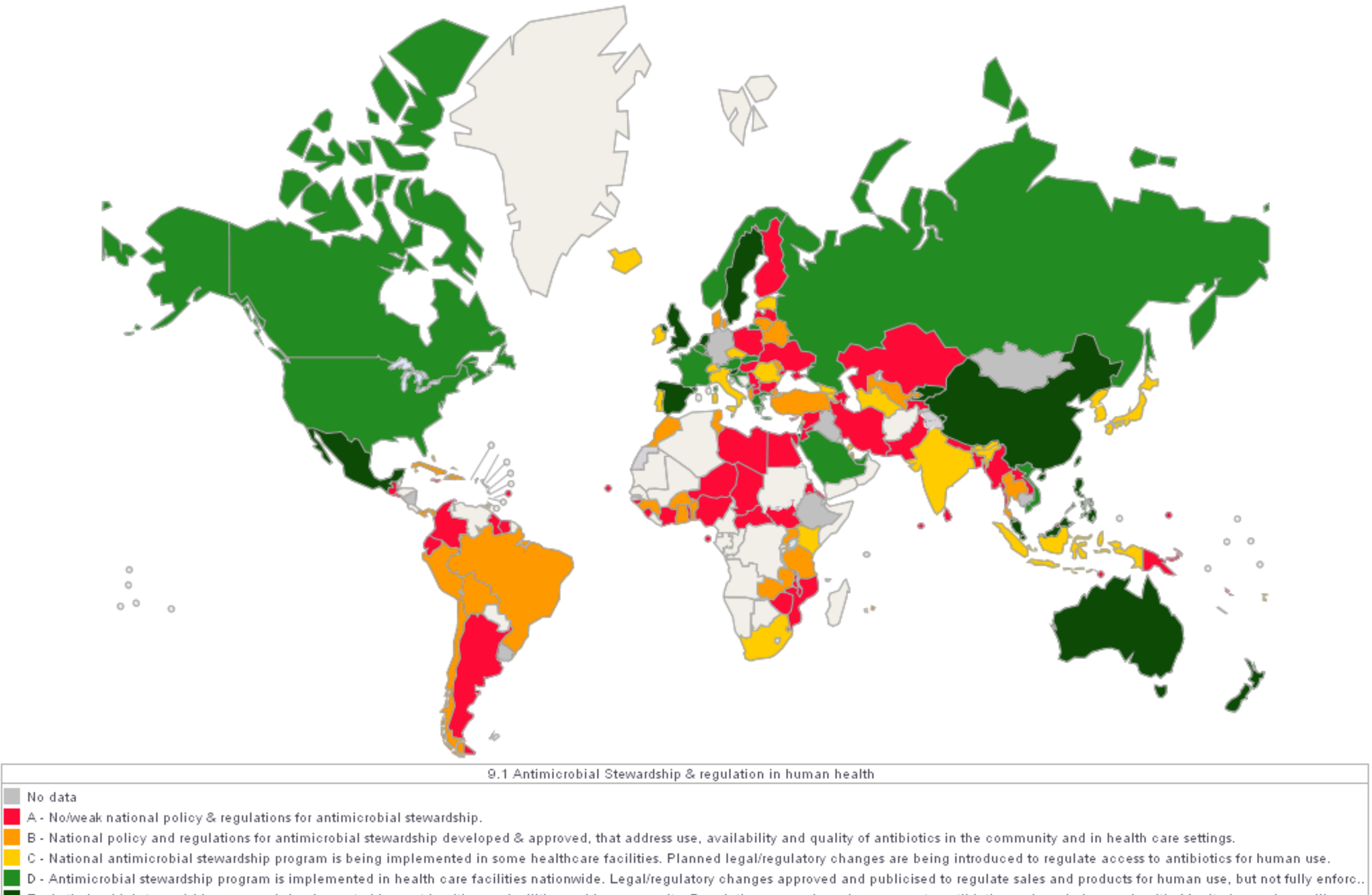
- Coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration. Antimicrobial stewards seek to achieve optimal clinical outcomes related to antimicrobial use, minimize toxicity and other adverse events, reduce the costs of health care for infections, and limit the selection for antimicrobial resistant strains.

The growth of interest in antimicrobial stewardship – PubMed citations



Dyar OJ et al. Clinical Microbiology and Infection 2017, in press

Antimicrobial stewardship and regulation in human health



http://www.who.int/antimicrobial-resistance/global-action-plan/database/en/

Stewardship intervention types

- **Persuasive**
  - Education
  - Consensus
  - Opinion leaders
  - Reminders
  - Audit
  - Feedback
- **Restrictive**
  - Restricted susceptibility reporting
  - Formulary restriction
  - Prior authorisation
  - Automatic stop orders
- **Structural**
  - Computerised records
  - Rapid lab tests
  - Expert systems
  - Quality monitoring

Davey P et al. Cochrane Database of Systematic Reviews 2013

Cochrane Library

Cochrane Database of Systematic Reviews

Interventions to improve antibiotic prescribing practices for hospital inpatients (Review)

Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, Gould IM, Ramsay CR, Michie S

Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: CD003543.

221 studies:	**58 randomised controlled trials, 163 non-randomised studies**	
	North America	96
	Europe	87
	Asia	19
	South America	8
	Australia	8
	East Asia	3

Interventions to improve antibiotic prescribing practices for hospital inpatients (Review)

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Outcome	Absolute effect	
	Without intervention	With intervention
% of patients treated according to antibiotic prescribing guidelines	43%	58%
Duration of antibiotic therapy	11.0 days	9.1 days
Mortality	11%	11%
Length of hospital stay	12.9 days	11.8 days

Davey P et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database of Systematic Reviews. 2017;2.

AN EXAMPLE OF ANTIBACTERIAL STEWARDSHIP AIMED AT REDUCING RESISTANCE

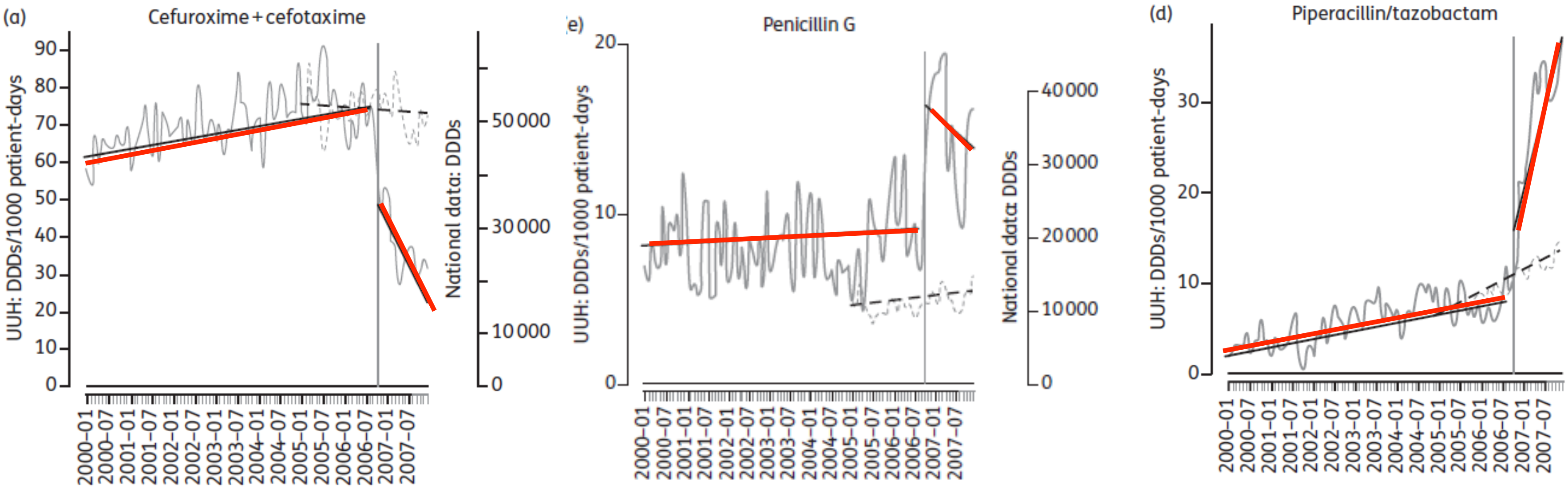
Changing prescribing practice through education to tackle an ESBL- Klebsiella pneumoniae outbreak

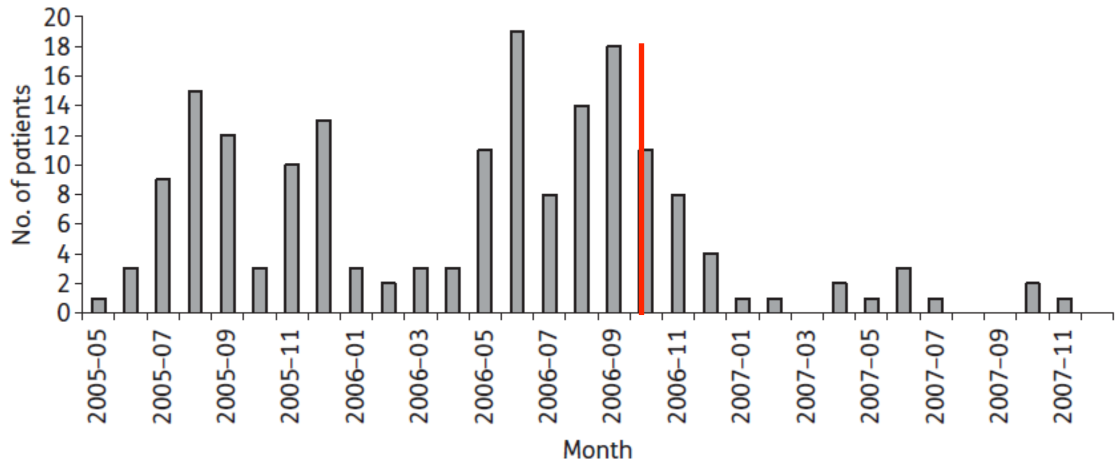
- Hospital clonal outbreak of ESBL-producing K. pneumoniae (ESBL-KP)
- Educational antibiotic intervention
  - Primary aim: reduce prescriptions of second and third-generation cephalosporins
  - Secondary aim: avoid increased consumption of fluoroquinolones and carbapenems.

New treatment protocols to replace cephalosporins	
Diagnosis	Recommended antibiotic treatment
Abdominal infections	Piperacillin/tazobactam
Community-acquired pneumonia	Penicillin G (+ moxifloxacin if septic)
Hospital-acquired pneumonia	Piperacillin/tazobactam
Febrile urinary tract infection	Piperacillin/tazobactam or cefotaxime
Septic shock	Imipenem or meropenem
Severe sepsis in patients with known ESBL carriage	Imipenem or meropenem

Tangden T et al. J Antimicrob Chemother 2011;66:1161-1167

Changing prescribing practice through education to tackle an ESBL- Klebsiella pneumoniae outbreak





However…

…the causal effect of the antibiotic intervention is difficult to evaluate because of an unknown natural course of the outbreak and other simultaneous actions, including hygienic measures

Tangden T et al. J Antimicrob Chemother 2011;66:1161-1167

Microbial outcomes of AMS programmes

- 26 interrupted time series studies
  - prescribing outcomes at 6 months and microbial outcomes (AMR, CDI) at 12 months post-intervention
- 20 planned interventions
- 6 unplanned interventions
  - responding to outbreaks
  - associated with **greater effects on microbial outcomes than planned interventions**

Davey P et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database of Systematic Reviews. 2017;2.

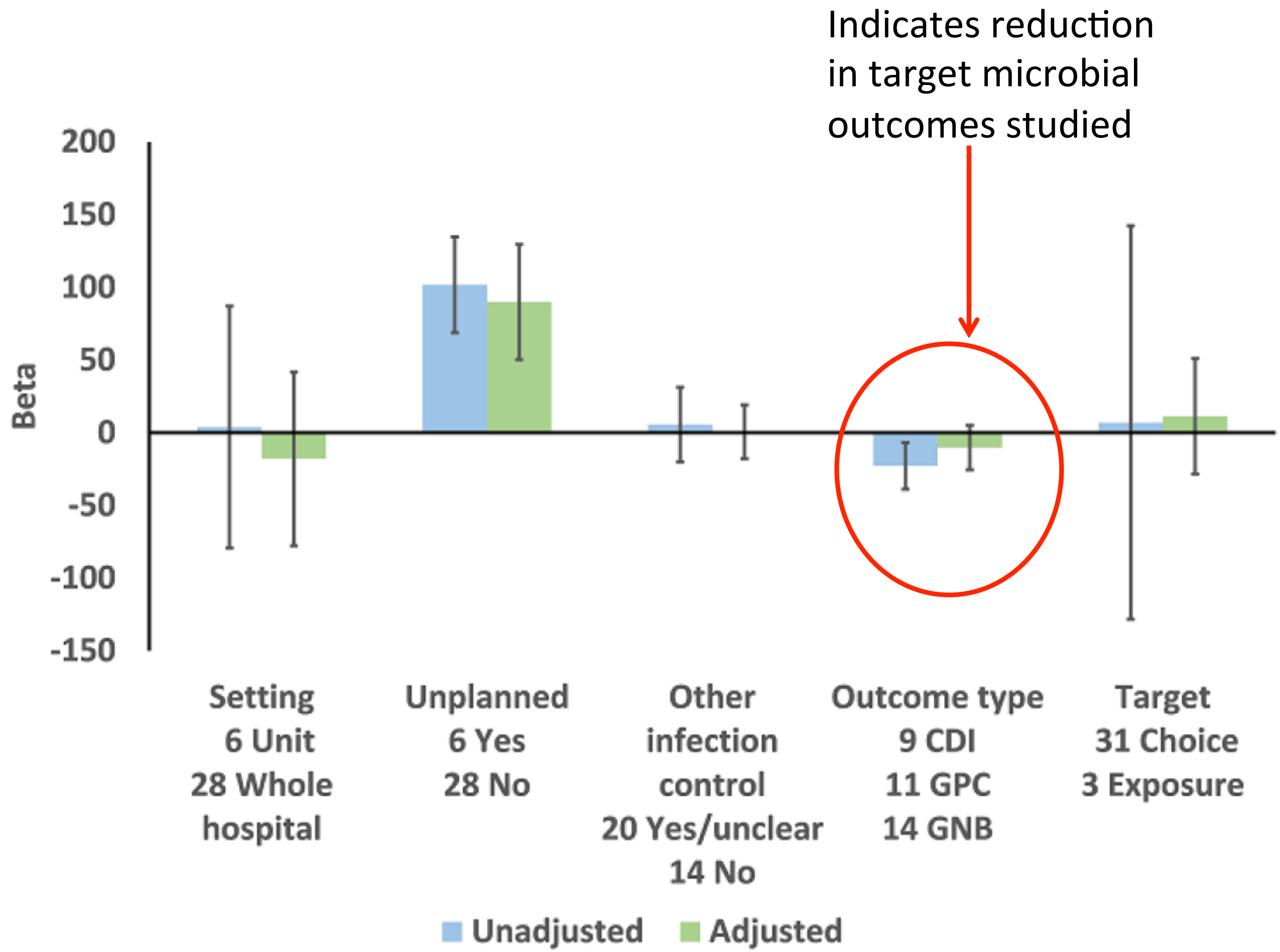
Interventions to improve antibiotic prescribing practices for hospital inpatients (Review)

Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, Gould IM, Ramsay CR, Michie S

- Uncertainty about the effects of interventions on resistant gram-negative and gram-positive bacteria

Davey P et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database of Systematic Reviews. 2017;2.

Impact of AMS interventions on microbial outcomes (Clostridium difficile, MDR-GPC, MDR-GNB)



Davey P et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database of Systematic Reviews. 2017;2.

WHY IS IT DIFFICULT TO SHOW THAT ANTIMICROBIAL STEWARDSHIP REDUCES RESISTANCE?

Why is it difficult to show that antimicrobial stewardship reduces resistance?

Possible technical explanations

- Variance obscured benefits
- Too few pre-intervention data points
- Inappropriate selection of prescribing outcomes when more than one reported
- Choice of prescribing and microbial outcomes time points possibly inappropriate

Possible systemic explanations

- AMS programmes need to be more effective
  - 15% average increase in adherence to mean 58% is insufficient to deliver microbial effect?
- "Wrong" choice of interventions
- AMS ineffective, at least by itself

IMPROVING EFFECTIVENESS OF AMS PROGRAMMES – ENGAGING CLINICIANS

What do clinicians think about stewardship?

In depth interviews with respiratory doctors and nurses in Australia

- Perceptions of stewardship:
  - **AMS as a challenge to clinical specialty-specific ownership**
  - AMS as a challenge to established hierarchies and consultation etiquette
  - Barriers to nursing roles in AMS
  - Interspecialty and interprofessional dynamics

- Unsolicited AMS advice, invading clinical territory.
- "I can usually fix pneumonia without any input from them. My feeling just is that ID understand bugs very, very well, but they don't understand lungs very well."

Broom J et al. J Hosp Infect 2017;96:316-322

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- When approval processes involved senior respiratory doctors requesting antibiotic approval from a more junior AMS doctor, the process was viewed as insulting.
- "[AMS] ..is rude...offensive...suggesting we're incompetent and that we have no expertise"

Broom J et al. J Hosp Infect 2017;96:316-322

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  - **Barriers to nursing roles in AMS**
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- Some nurses unaware what the term "antimicrobial stewardship" meant.
- Fear of adverse clinical outcomes, legal implications
- "Withholding that antibiotic"..."It's not something I want to risk my registration for".

Broom J et al. J Hosp Infect 2017;96:316-322

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  - Barriers to nursing roles in AMS
  - **Interspecialty and interprofessional dynamics**

- Junior medical participants "caught in the middle" between their own respiratory team and the AMS team.
- "Pharmacy will only dispense one dose if the approval is not put in."
- "We're getting pressure from the medical team and we're just pushing it on to the pharmacist"

Broom J et al. J Hosp Infect 2017;96:316-322

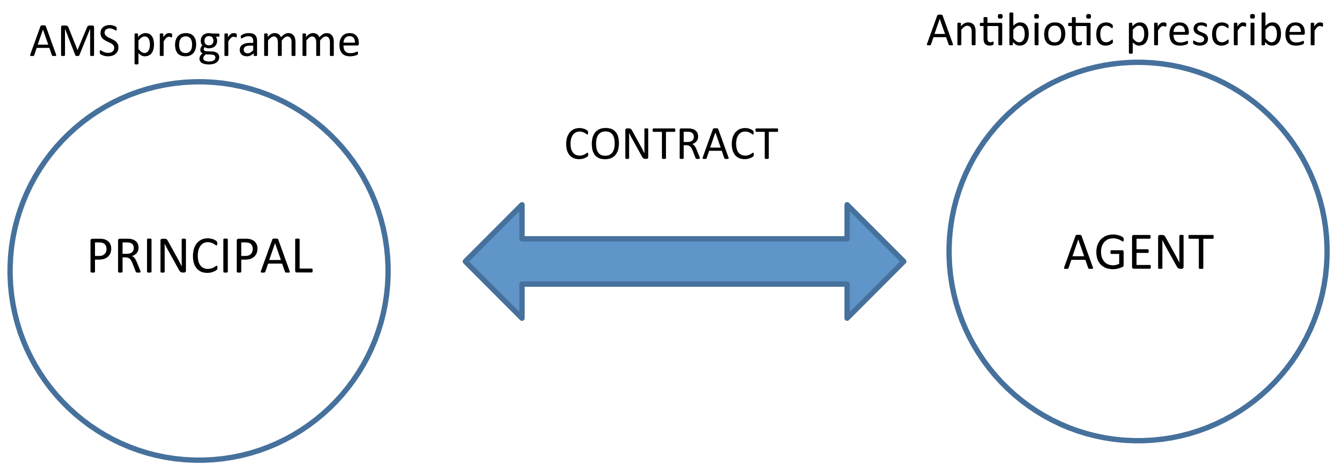
Antimicrobial prescribing is more than choosing the right drug at the right dose at the right time

"...in the case of antimicrobial prescribing, prescribing etiquette is a key determinant of behaviour, with prescribing decisions influenced not only by clinical and therapeutic goals but also by a host of cultural determinants and clinical groups across different specialties."

Charani E et al. Clinical Infectious Diseases 2013;57:188–96

AMS NEEDS AN UNDERLYING THEORY TO EXPLAIN AND PREDICT PRESCRIBING BEHAVIOUR

Principal-Agent theory



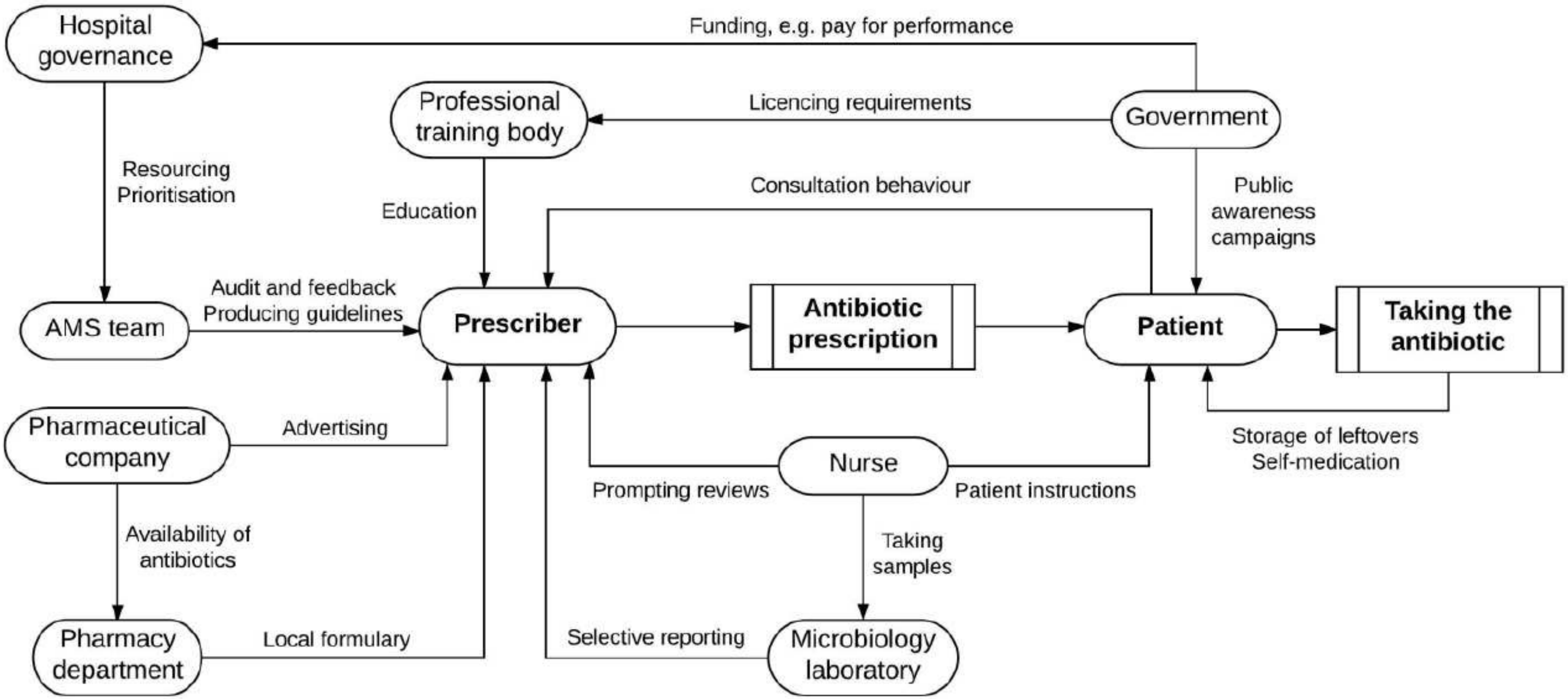
- How to ensure agents perform in the way principals expect them to. (Adverse selection)
- How to align the conflicting goals of principals and agents. (Moral hazard)

Problems arise when it is difficult or expensive for the principal to verify what the agent is doing

KM Eisenhardt Acad Management Rev 1989;14:57-74

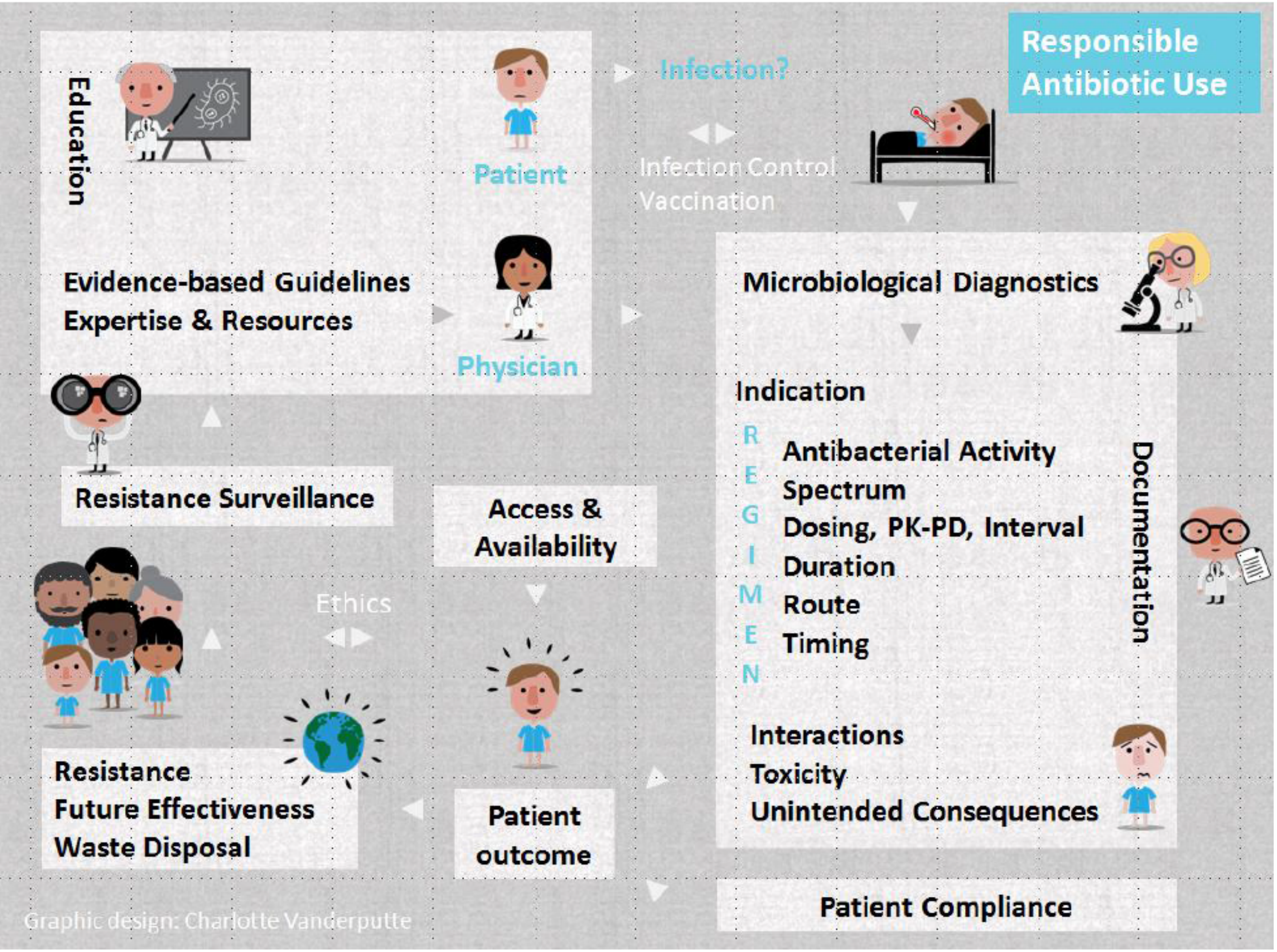
AMS IS MORE THAN ABOUT ANTIBACTERIAL PRESCRIBING

Stewardship actors and actions



Dyar OJ et al. Clinical Microbiology and Infection 2017, in press

22 elements of responsible antibiotic use



http://drive-ab.eu/wp-content/uploads/2015/06/Definition_RU_07042017final.pdf

CAN YOU BELIEVE THE SENSITIVITY RESULTS FROM YOUR MICROBIOLOGY LABORATORY?

Variation in antibacterial disc quality

“The results, some good, some appalling...”

Antimicrobial disk	Bio-Rad		Liofilchem		BD		Abtek		SirScan		Oxoid		HiMedia		Bioanalyse		Mast	
	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
Benzylpenicillin 1 unit					L				H	H			NA	NA	H	H		
Amoxicillin-clav. 30 µg	H	H*					L						H	H		L		
Piperacillin-tazo. 36 µg							L	L	H				NA	NA				
Oxacillin 1 µg			L		L				L				H	H	L			
Mecillinam 10 µg							L		H				H		H			
Cefotaxime 5 µg[1]							NA		L				NA	NA				
Cefoxitin 30 µg[2]	H*	H*	H	H*			NA	L					L*	L*		L		
Ceftazidime 10 µg							L	L					L	H				
Meropenem 10 µg[1]	H		H*				L	L			H		H					
Ciprofloxacin 5 µg[2]	L				L		L	L					H	H*		L	L	
Norfloxacin 10 µg							L		L				H*	H				
Pefloxacin 5 µg			L	L	L		NA	NA	NA				H					
Gentamicin 10 µg					H		L		NA				H	H				
Tobramycin 10 µg	NA	NA	H										H*	H*				
Erythromycin 15 µg			L		L		L		L				H	H	L*	L		
Tetracycline 30 µg			L	L*	L*		L		L*					L	L		L	

Mean value within ± 1 mm of the target value
Mean value >1 mm but within ± 2 mm of the target value
Mean value >2 mm from target value but still within the QC range
Mean value out of the QC range
Disk included in first study, but not supplied for second study

NA = Not Available
H = High, mean value >1 mm above target
L = Low, mean value >1 mm below target
* One or more readings out of QC range

See: Kahlmeter G. Clin Microbiol Infect 2016;22:211-212

DO YOUR ANTIBIOTICS WORK?

Antibacterial quality: co-trimoxazole from Ghana, Nigeria and United Kingdom

Country of purchase	Number of samples	MiniLab		HPLC content analysis adherence	Dissolution test compliance
		colorimetric test	Thin-layer chromatography		
Ghana (1 sample made in India)	5	5/5 pass	4/5 pass	0/5 pass	2/5 pass
Nigeria	9	9/9	8/9	0/9	3/9
United Kingdom	1	1/1	1/1	1/1	1/1

Fadeyi I et al. Am J Trop Med Hyg. 2015;92(suppl 6):87-94

The role of infection prevention and control in AMS

A broader view of stewardship

- Oversight and guidance of a system
- Ensuring strategic policy frameworks exist , combined with effective oversight
- Coalition –building
- Regulation
- Attention to system-design
- Accountability

Wiysonge CS et al. Public stewardship of private for-profit healthcare providers in low and middle-income countries. Cochrane Database of Systematic Reviews 2016, 8.

A strategic approach to stewardship

- A coherent set of actions designed to use antimicrobials responsibly
  - Ranges from individual level actions to global actions
  - Not restricted to writing prescriptions

Dyar OJ et al. Clinical Microbiology and Infection 2017, in press

Conclusions

- AMS is not yet proven to be an effective strategy to counter challenge of resistance
- Foundational AMS theory is required to support effectiveness of interventions
- Greater understanding needed of optimal interventions
- AMS should be more than about prescribers and prescribing