Antimicrobial resistance and stewardship

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Objectives

- Describe mechanisms by which bacteria become resistant.
- Describe how antibiotic resistance arises and is selected for.
- Name and describe the most problematic resistant organisms in current UK practice.
- Explain principles and importance of good antibiotic stewardship and prescribing.

Antibiotic Resistance Awareness

AMR Worldwide

14,000 Patients Die
of *C.difficile* infection annually in the USA.[1] The use of antibiotics was a major contributing factor in up to 85% of cases.[2]

2,000,000 Infections
per year contain bacteria that are resistant to one or more antibiotics in the USA.[1]

25,000 Patients Die Each Year as a result of antibiotic-resistant infections in Europe.[3]

480,000 People Infected
by drug-resistant TB strains in 2013 Worldwide.[4]

23,000 Patients Die Each Year as a result of antibiotic-resistant infections in the USA.[1]

11,000 Estimated Deaths
caused by methicillin-resistant Staphylococcus aureus (MRSA) each year in the USA.[5]

400,000 Infections
per year with the 6 most frequent multi-drug resistant (MDR) bacteria, in 4 types of infection, in Europe.[6]

1 Child Dies Every 9 Minutes
from an infection caused by antibiotic-resistant bacteria in India.[7]

MY ROLE MATTERS
IN FIGHTING ANTIMICROBIAL RESISTANCE

(1) Antibiotic Resistance Threats in the United States, 2013. Centers for Disease Control and Prevention (CDC)
(2) Cheng HT et al. Infect Control Hosp Epidemiol, 2007; 28:926-931
(3) EMW 2013-04-10 European Report on patient safety
(4) Global Tuberculosis Report. World Health Organization, 2014
(5) WHO Antimicrobial Resistance Fact sheet N°194. Updated April 2015.
(6) Antibiotic Resistance: Implications for Global Health and Novel Intervention Strategies. Washington, DC. The National Academies Press. 2010 (Source ECDC / EMEA 2009)
(7) Laxminarayan et al. Antibiotic resistance - the need for global solutions. Lancet Infect Dis 2013; 13:1057-98

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11 March 2013 Last updated at 13:36

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

COMMENTS (1034)

- 2013 – antibiotic resistance placed on national risk register of civil emergencies
- 2016 – United Nations hold a general assembly and sign a declaration on antimicrobial resistance
- By 2050, antibiotic resistant organisms expected to kill more than cancer

Antibiotics

Antibiotic resistance could spell end of modern medicine, says chief medic

Prof Dame Sally Davies says action is needed around the world to tackle 'hidden' problem that is already claiming lives

Press Association

Friday 13 October 2017 08.41 BST

‘the end of modern medicine’

Professor Dame Sally Davies, UK CMO

Without antimicrobials, the rate of post-operative infection for clean surgery could be 0-50% and that about 30% of those with a serious infection will die.

Resistant Infections

- Delay in appropriate antibiotic therapy
  - Worse patient outcomes
  - Death
- Increased hospital length of stay
- Alternative antibiotics need to be used
  - Increased likelihood of adverse effects
  - Cost implications
  - Oral antibiotics may not be available

Bacteria develop antibiotic resistance quickly….

https://vimeo.com/180908160

The great principle of antimicrobial resistance is

'Survival of the Fittest'

Darwin C. On the Origin of Species by Means of Natural Selection. London: Murray, 1859.

Three ways bacteria can be antibiotic resistant:

INHERENT RESISTANCE

MUTATION

GENE TRANSFER

INHERENT RESISTANCE

This is mostly a problem in hospitals, where there are many patients with underlying disease who are prone to infection by ‘opportunist’ bacteria.

For example:

The bacterial species does not contain the target molecule of the antibiotic

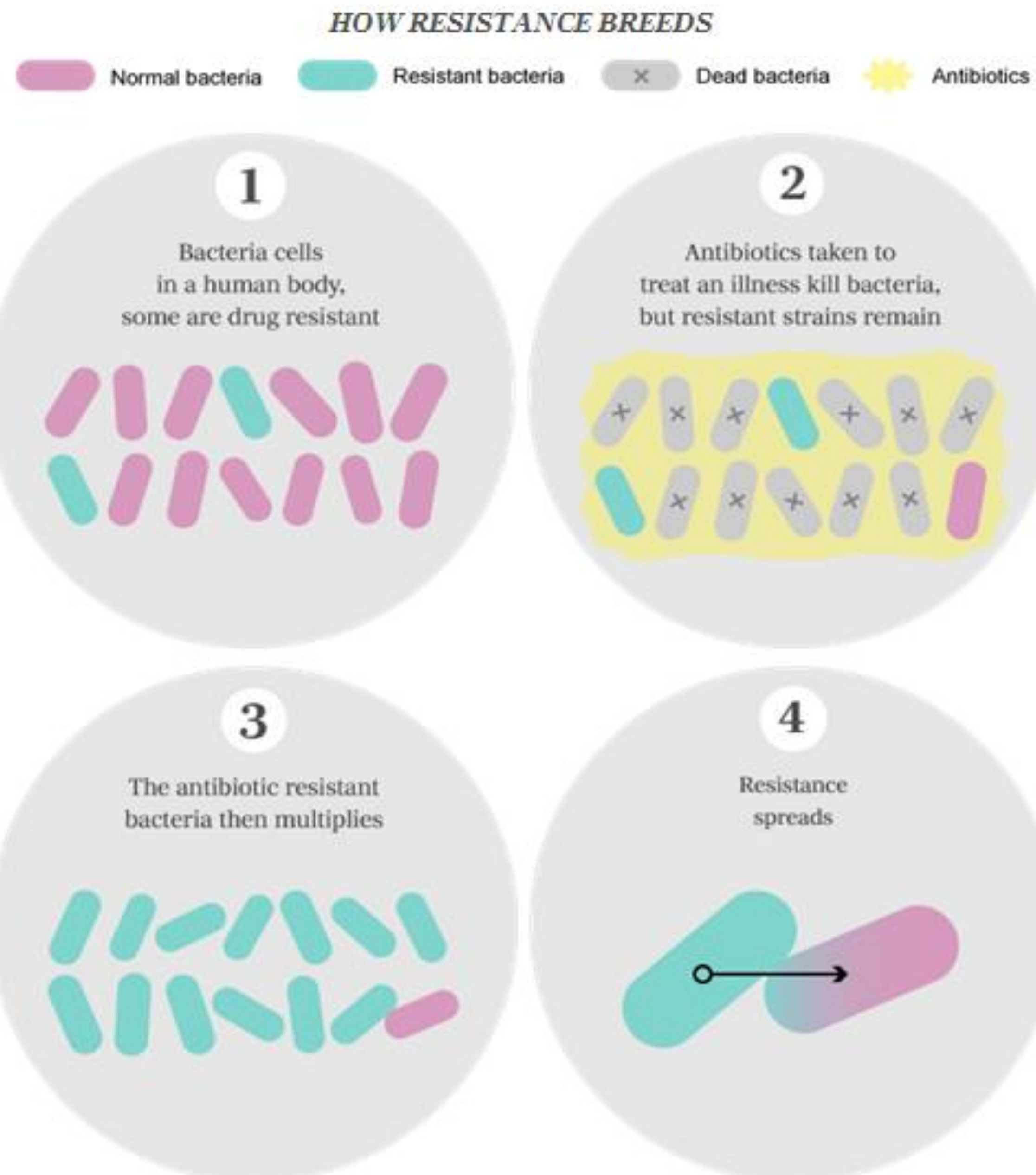
or the antibiotic cannot cross the bacterial membrane for that species

Pseudomonas is an example of an organism that is inherently resistant to many antibiotics

MUTATION

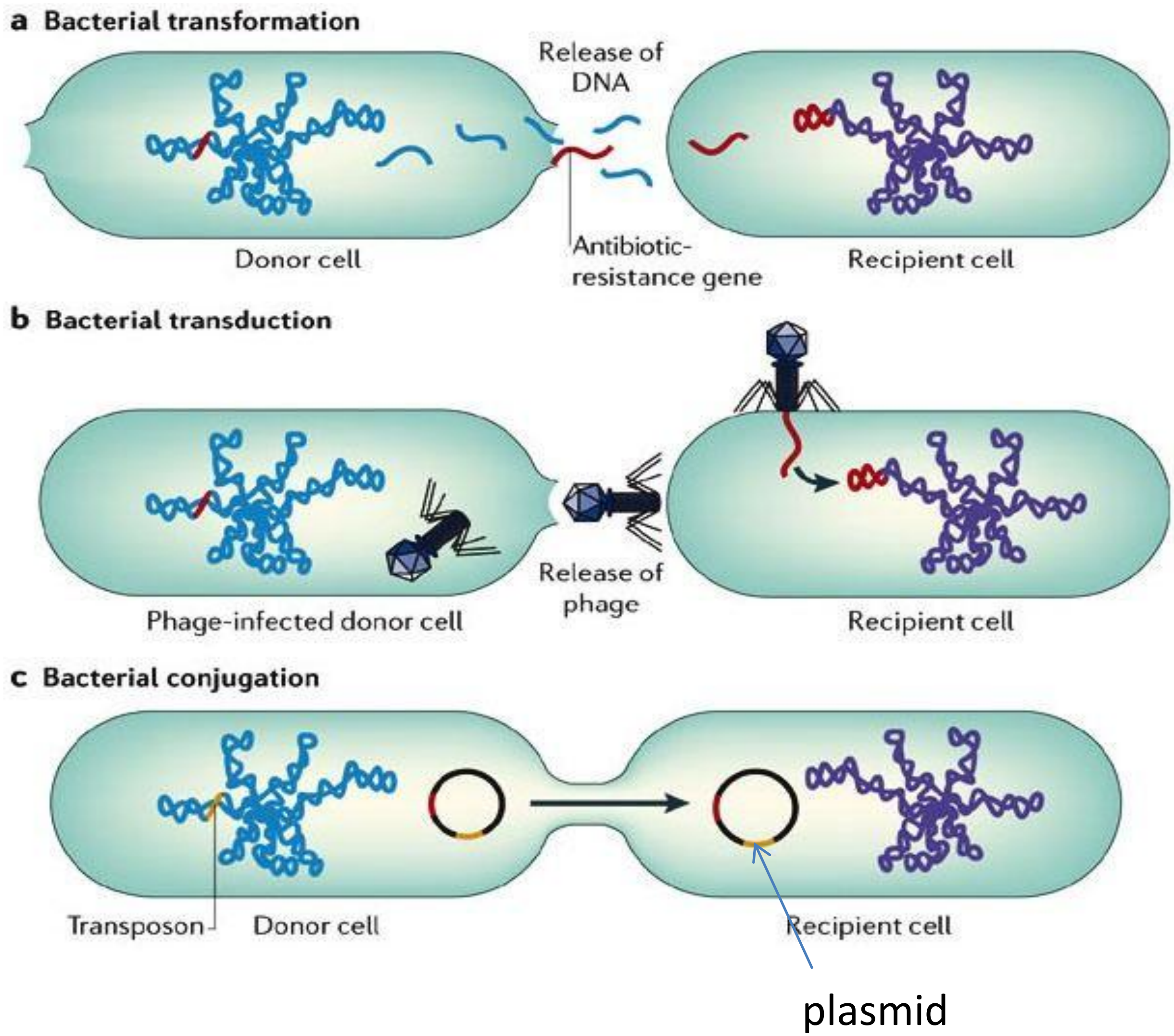
Mutations are spontaneous genetic changes, arising **randomly**, **all the time.**

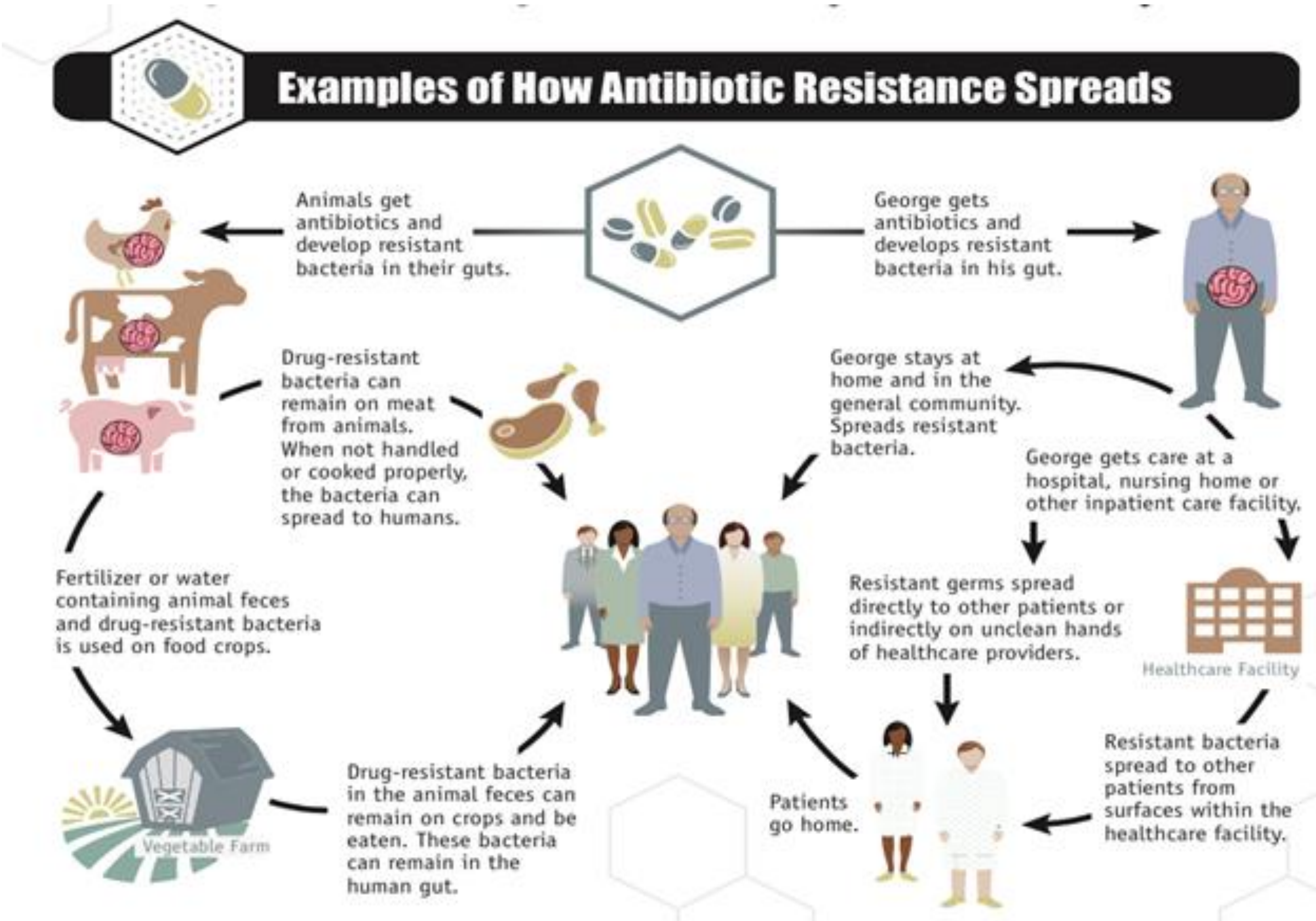
•


HOW RESISTANCE BREEDS
Normal bacteria
Resistant bacteria
Dead bacteria
Antibiotics
1
Bacteria cells
in a human body,
some are drug resistant
2
Antibiotics taken to
treat an illness kill bacteria,
but resistant strains remain
3
The antibiotic resistant
bacteria then multiplies
4
Resistance
spreads

GENE TRANSFER

Bacteria can exchange genetic information (DNA) by several mechanisms.





Examples of How Antibiotic Resistance Spreads
Animals get antibiotics and develop resistant bacteria in their guts.
George gets antibiotics and develops resistant bacteria in his gut.
Drug-resistant bacteria can remain on meat from animals. When not handled or cooked properly, the bacteria can spread to humans.
George stays at home and in the general community. Spreads resistant bacteria.
George gets care at a hospital, nursing home or other inpatient care facility.
Fertilizer or water containing animal feces and drug-resistant bacteria is used on food crops.
Resistant germs spread directly to other patients or indirectly on unclean hands of healthcare providers.
Healthcare Facility
Vegetable Farm
Drug-resistant bacteria in the animal feces can remain on crops and be eaten. These bacteria can remain in the human gut.
Patients go home.
Resistant bacteria spread to other patients from surfaces within the healthcare facility.

Mechanisms by which organisms can resist antibiotics

1. Enzyme inactivation of the antibiotic - eg beta-lactamase producers
2. Decreased permeability
3. Efflux pumping of the antibiotic
4. Modification of the antibiotic target
5. Alteration of the metabolic pathway

Some important antibiotic classes

Class	Examples	Target
Beta-lactams	Penicillin, flucloxacillin, cephalosporins, meropenem	Cell wall synthesis
Tetracyclines	Tetracycline, doxycycline	ribosome
Glycopeptides	Vancomycin	Cell wall synthesis
Macrolides	Erythromycin, clarithromycin	ribosome
Quinolones	ciprofloxacin	DNA gyrase
aminoglycosides	gentamicin	ribosome
trimethoprim	Trimethoprim	Folate synthesis

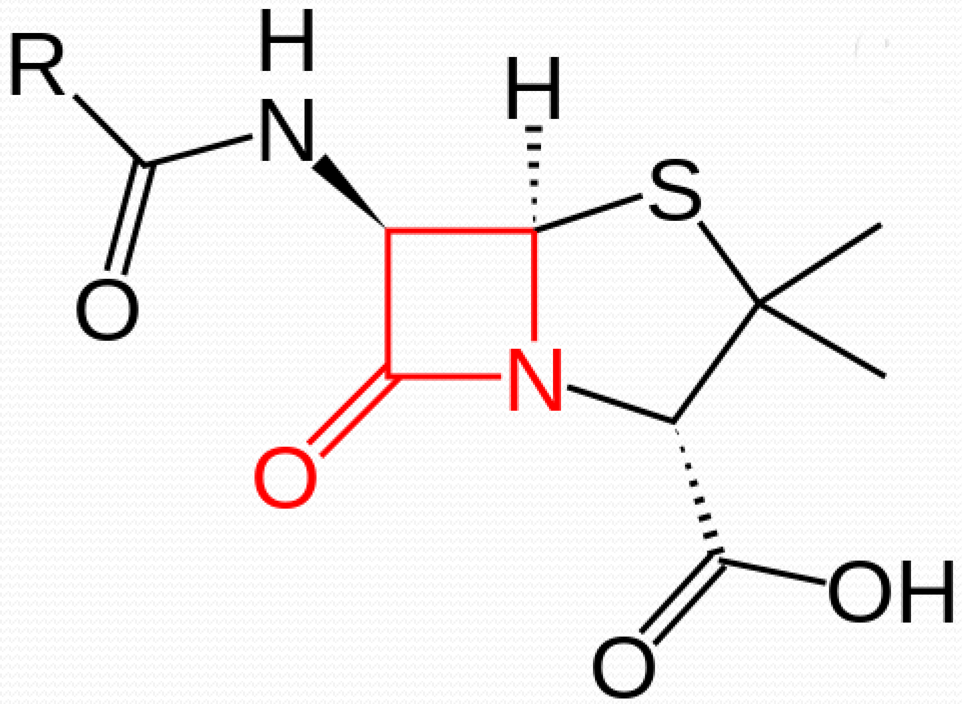
A closer look at 3 important antibiotic classes

- Beta-lactams
- Aminoglycosides
- Glycopeptides

Beta-lactams

- Penicillins
- Cephalosporins
- Carbapenems

Beta-lactam ring



Beta-lactams: penicillins

- **Penicillin**
  - Narrow spectrum - streptococci
- **Flucloxacillin**
  - Narrow spectrum - *Staphylococcus aureus*
- **Ampicillin/amoxycillin**
  - Broader spectrum penicillin

Penicillins combined with beta-lactamase inhibitors

- **Amoxycillin + clavulanate***
  - **'Co-amoxiclav' (Augmentin**®)
  - Gram +, many Gram – and anaerobes
- **Piperacillin + tazobactam***
  - **'Piptazo-bactam' (Tazocin**®)
  - Similar co-amoxiclav but broader cover and also *Pseudomonas aeruginosa* (PSA)
  - Not active against MRSA/VRE

*clavulanate and tazobactam are beta-lactamase inhibitors

Beta lactams: cephalosporins

- Discovered from *Cephalosporium* mould from Sardinian sewage 1945
- Widely introduced in 1980's
- Broad spectrum, G+ and G-
- Reputation for causing *C. difficile*

disease

Beta-lactams: carbapenems

- Imipenem, meropenem
- **Very broad spectrum** – G+ and G-
- Critical care 'big guns'
- ICUs/bone marrow transplant/chemotherapy units now very reliant on them

Aminoglycosides

- Example: gentamicin
- Discovered in 1963 – product of *Micromonospora* sp.
- On WHO list of essential medicines
- inexpensive

Aminoglycosides continued

- Spectrum: usually used for **Gram-negatives**
- Bactericidal
- Toxicity: kidneys and inner ear hair cells (nephrotoxic and ototoxic)
- Need to measure blood levels to avoid toxicity

Glycopeptides

- Example: Vancomycin
- Produced by *Streptomyces* from a sample of dirt from Borneo, 1952
- ‘Mississipi mud’
- Named vancomycin – from ‘vanquish’

Glycopeptides

- Spectrum: **Gram-positive** cover only; cover nearly all Gram-positives
- Common uses: critical care
- Toxicity – renal; ‘red man’ syndrome
- Need to measure blood levels to ensure adequate dosing while avoiding toxicity

Important examples of drug resistance – Gram positive

- MRSA – methicillin resistant *Staphylococcus aureus*
  - Resistant to flucloxacillin
  - Serious infections treated with glycopeptides (e.g. vancomycin)

- GRE/VRE – glycopeptide resistant enterococci/vancomycin resistant enterococci
  - Glycopeptides (like vancomycin)

  are ineffective

Today’s story is Gram negative

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WHO names 12 bacteria that pose the greatest threat to human health

Antibiotic resistance could make c-sections, transplants and chemotherapy too dangerous to perform, warns World Health Organisation

Monday 27 February 2017 17.49 GMT

Priority 1

Acinetobacter baumanni
Pseudomonas aeruginosa
Enterobacteriacieae

Priority 2

Enterococcus faecium
Staphyloccus aureus
Helicobacter pylori
Campylobacter spp
Salmonellae
Neisseria gonorrheae

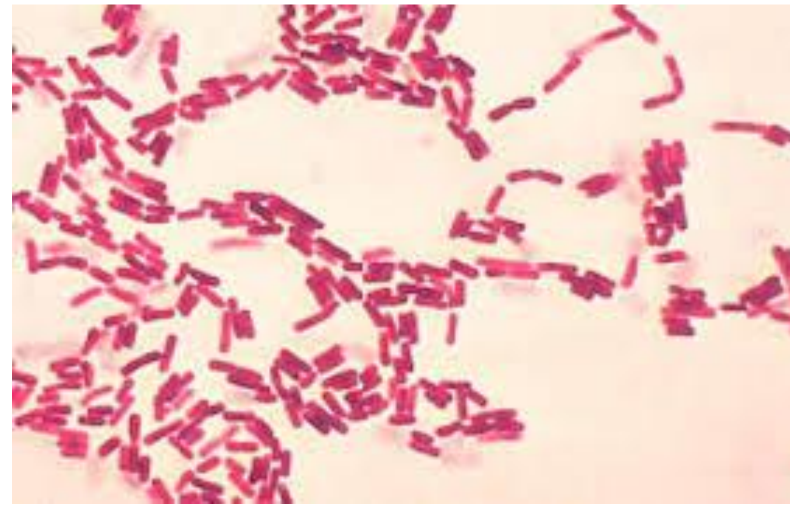
Priority 3

Streptococcus pneumoniae
Haemophilus influenzae
Shigella spp

GIG CYMRU NHS WALES | Iechyd Cyhoeddus Cymru Public Health Wales

A Report from Public Health Wales
Antimicrobial Resistance Programme Surveillance Unit:

Antibacterial Resistance
In Wales 2005-2014



- *E. coli* bacteraemia (secondary care)
- UTI (primary care)

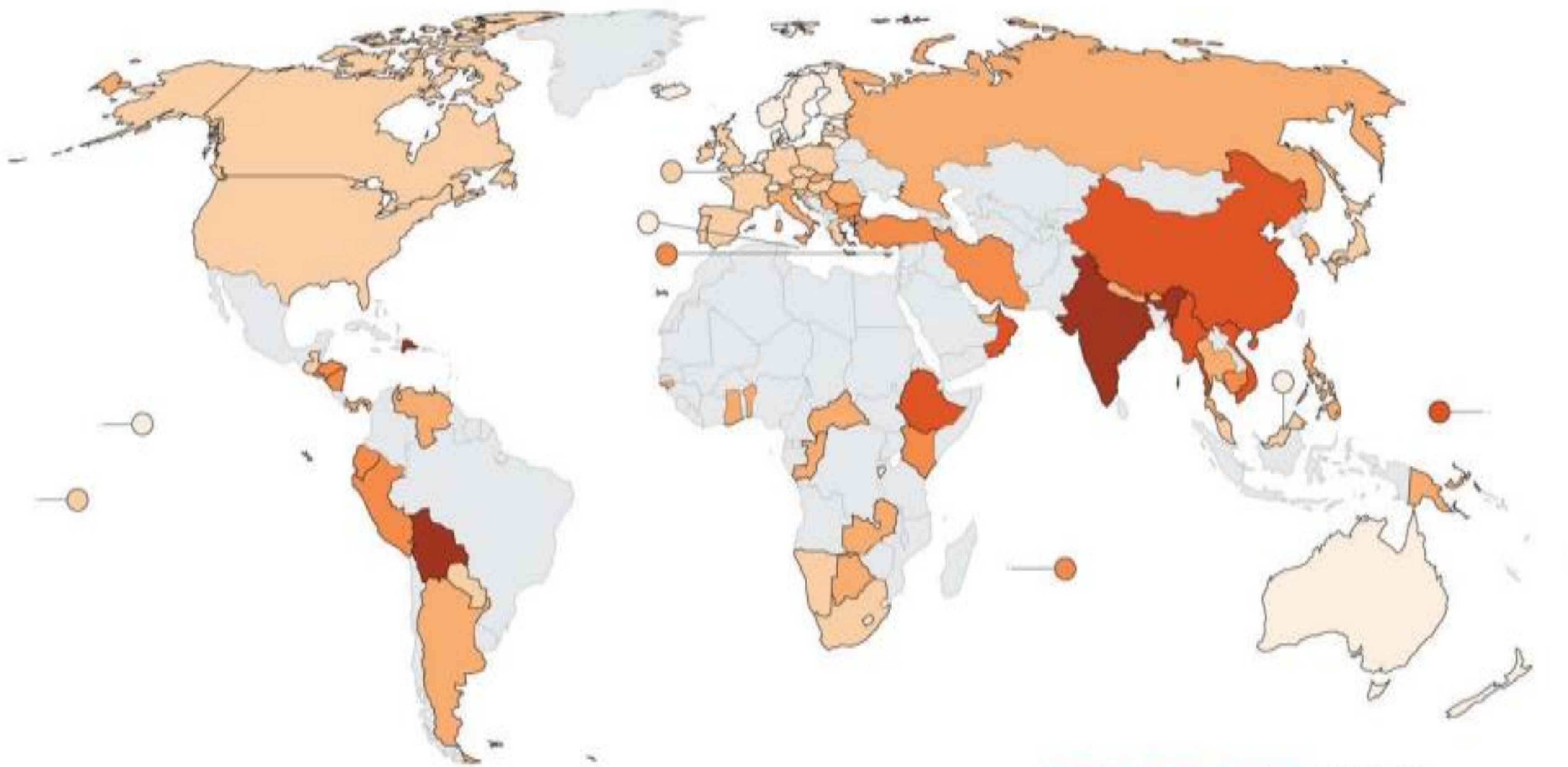
Gram negatives - the problem in a nutshell

- Enzymes!

For example

- ESBLs
  - ‘Extended spectrum beta-lactamases’
  - Resistant to penicillins and cephalosporins
  - *E. coli* and *Klebsiella*
- CPE
  - ‘Carbapenemase-producing enterobacteracieae’
  - Mainly *Klebsiella*

Percentage of extended-spectrum beta-lactamase producing *Escherichia coli**, by country (most recent year, 2011-2014)



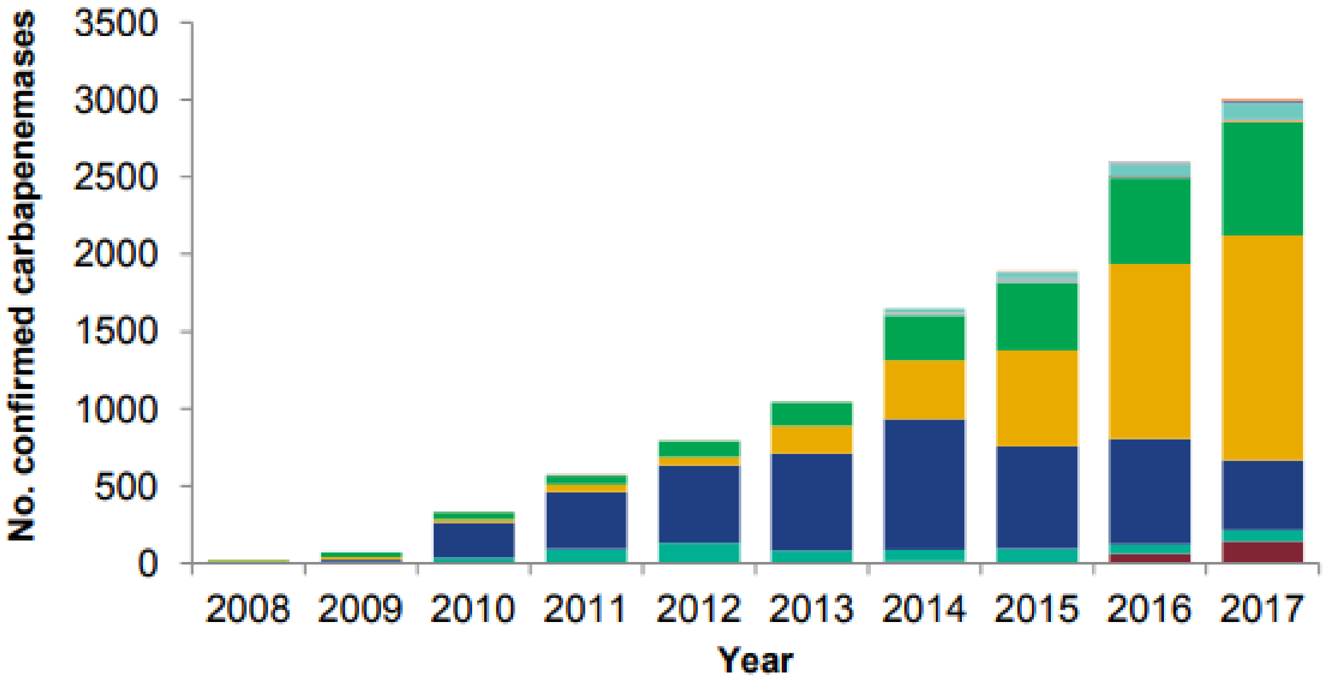
0-9 | 10-19 | 20-39 | 40-59 | 60-79 | 80-100 | No data

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

Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

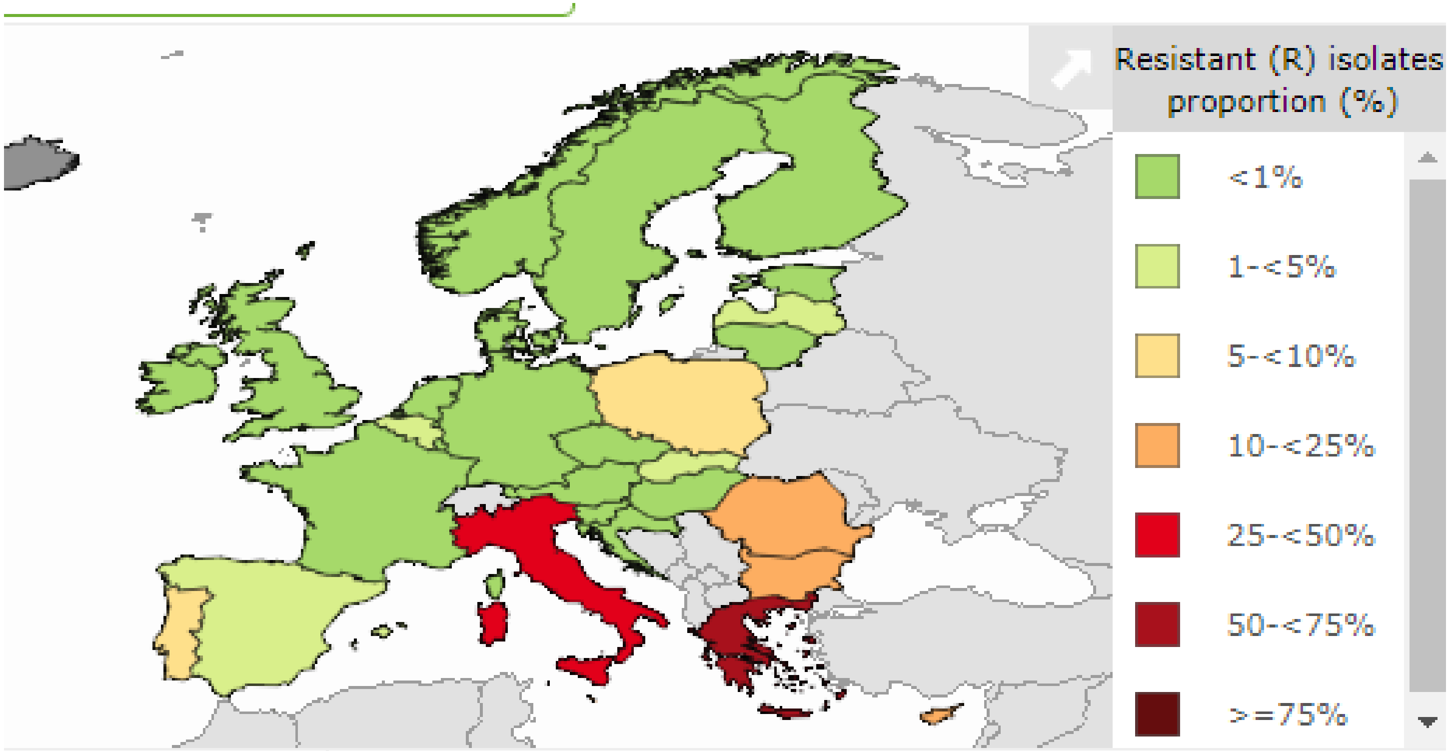
CPEs – a new threat

CPEs sent to AMRHAI (PHE) from UK clinical laboratories, 2008- 2017



https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/759975/ESPAUR_2018_report.pdf

CPEs, Europe (EARS-Net) 2017



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Bwrdd Iechyd Prifysgol Abertawe Bro Morgannwg University Health Board

Infection Prevention & Control Standard Operating Protocol

Preventing the Spread of Carbapenem Resistant Gram negative Bacteria

Public Health England

Acute trust toolkit for the early detection, management and control of carbapenemase-producing Ente


World Health Organization

Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in health care facilities

Clinical case*

A 65 years old male undergone pylorus preserving pancreaticoduodenectomy (PPPD) procedure on May 2016 that was complicated by duodenal stump leak with drain placement.

He was treated with **multiple antibiotics** including **Meropenem for 2 weeks**.

Re-admitted 10 days after discharge with fever, dehydration and acute renal failure, a blood culture taken was positive for *K. pneumoniae* with the following susceptibility pattern:

*courtesy of Dr Ben-Ismaeil, CMM, PHW Swansea

Antibiotic/Culture:	KPNE
Ampicillin	R
Ceftazidime	R
Ciprofloxacin	R
Cephalexin	R
Cefotaxime	R
Ertapenem	R
Gentamicin	I
Imipenem	R
Meropenem	R
Piperacillin/Tazobactam	R
Amikacin	R
Amoxicillin	R
Amoxicillin/Clavulanate	R

Management?

- **What antimicrobial agent would you select?**

Colistin (a polymyxin)

Available for >50 yrs — not trialled under conditions of modern drugs

- No standardized dosing
- No detailed trials on pharmacology or pharmacokinetics

Neurotoxic and ototoxic...including sudden apnoea >> how often??

- **What other measures need to be taken?**

Strict patient isolation & use of contact precautions by all HCWs

Screening will be required to detect if he is still carrying the bacterium

THE LANCET Infectious Diseases

 Volume 16, No. 2, p161–168, February 2016

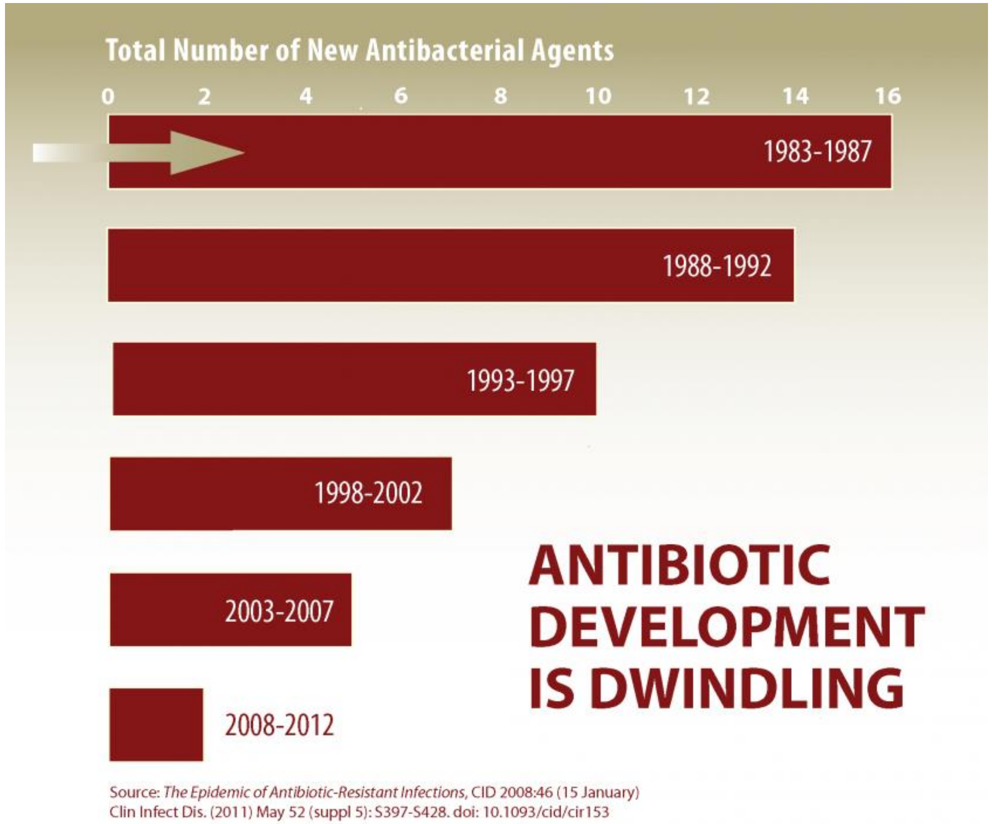
Articles

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, BS[†], Yang Wang, PhD[†], Prof Timothy R Walsh, DSc, Ling-Xian Yi, BS, Rong Zhang, PhD, James Spencer, PhD, Yohei Doi, MD, Guobao Tian, PhD, Baolei Dong, BS, Xianhui Huang, PhD, Lin-Feng Yu, BS, Danxia Gu, PhD, Hongwei Ren, BS, Xiaojie Chen, MS, Luchao Lv, MS, Dandan He, MS, Hongwei Zhou, PhD, Prof Zisen Liang, MS, Prof Jian-Hua Liu, PhD, Prof Jianzhong Shen, PhD

[†] Contributed equally

Published: 18 November 2015



‘The development pipeline for new antibiotics is at an all-time low. We must therefore conserve the antibiotics we have left by using them optimally’

Professor Dame Sally Davies, UK CMO

What factors contribute to development of antimicrobial resistance?

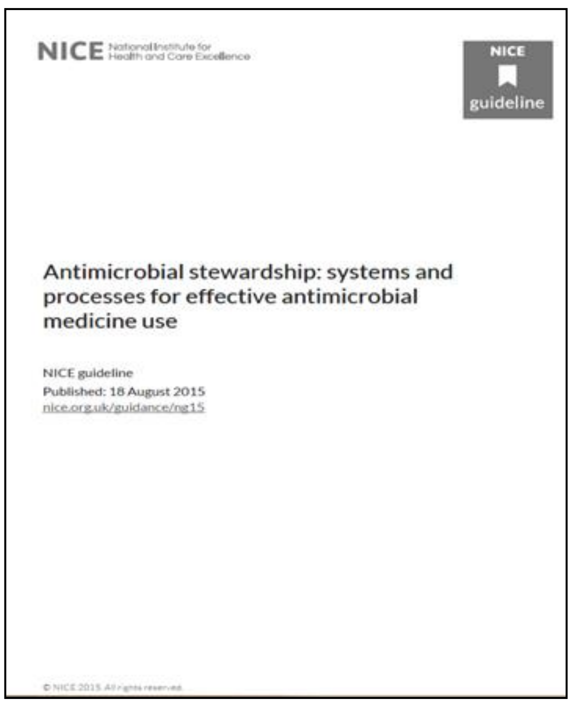
- Misuse of antibiotics in medicine – in Wales, an estimated 20-50% of prescriptions are unsuitable
- Lack of control of use of antibiotics
- Lack of effective infection control procedures
- Use of antibiotics in animal husbandry and agriculture – 40% of UK antibiotic use is in animals
- Over the counter medicines
- Lack of laboratory capacity and tests too slow
- Low quality pharmaceuticals
- International travel
- ‘Medical tourism’

What is misuse of antibiotics?

- Prescribing antibiotics unnecessarily
- Delaying antibiotic treatment unnecessarily in critically ill patients
- Using broad spectrum antibiotics too generously or narrow-spectrum antibiotics incorrectly
- Inappropriately high or low doses in a specific patient
- Too long or short courses
- Not streamlining treatment after the culture results received
- Omitting or delaying doses of antibiotics

Antimicrobial Stewardship

- ‘healthcare-system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness'.



NICE National Institute for Health and Care Excellence

NICE guideline

Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use

NICE guideline
Published: 18 August 2015
nice.org.uk/guidance/ng15

NICE Guideline August 2015

The main principle of antimicrobial stewardship

Right Drug, Right Dose, Right Time, Right Duration

……… Every Time

Public Health England

Protecting and improving the nation's health

Start Smart - Then Focus

Antimicrobial Stewardship Toolkit for English Hospitals

Updated March 2015

“Start Smart..........”

DO NOT START ANTIBIOTICS IN THE ABSENCE OF CLINICAL EVIDENCE OF BACTERIAL INFECTION

1. Take thorough drug allergy history
2. Initiate prompt effective antibiotic treatment within one hour of diagnosis (or as soon as possible) in patients with severe sepsis or life-threatening infections[α]
3. Comply with local antimicrobial prescribing guidance
4. Document clinical indication (and disease severity if appropriate), dose[β] and route[#] on drug chart and in clinical notes
5. Include review/stop date or duration
6. Obtain cultures prior to commencing therapy where possible (but do not delay therapy)

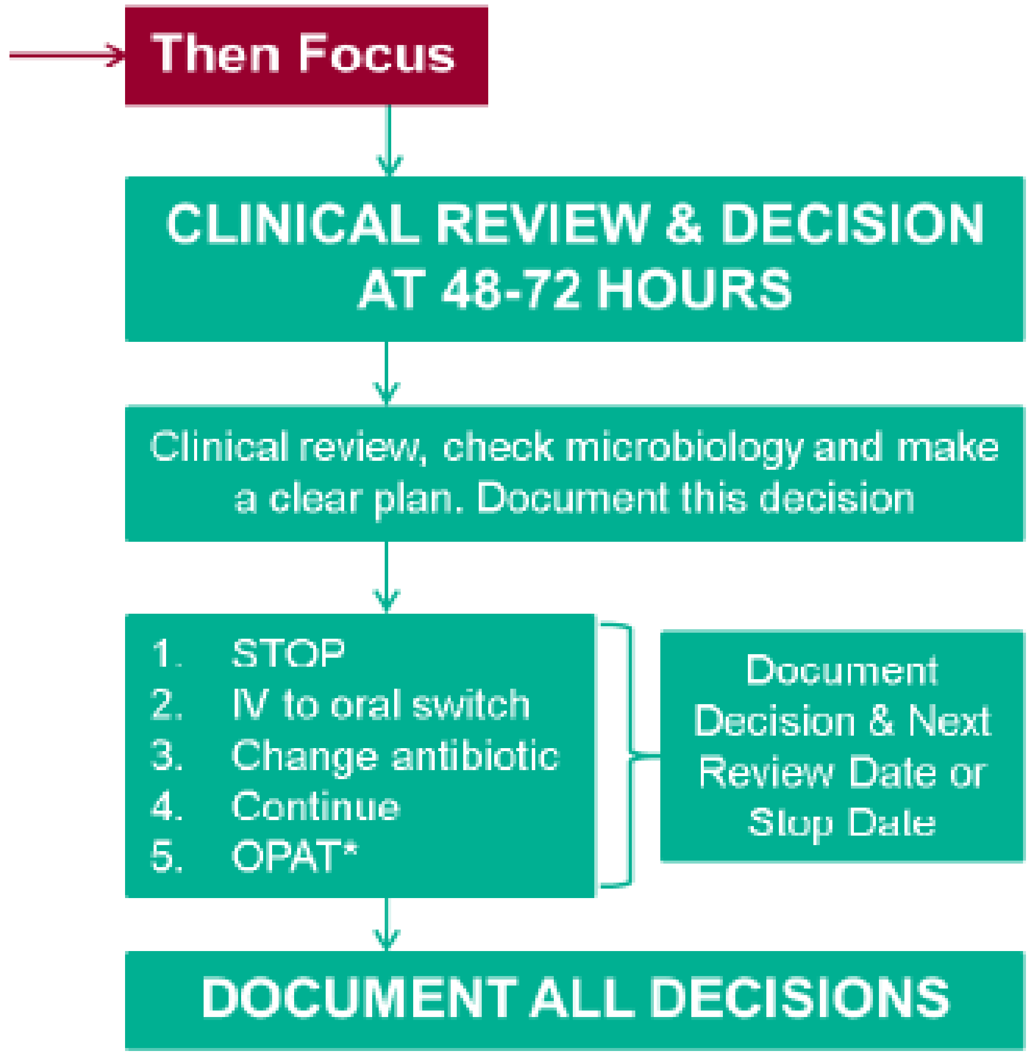
Good Antibiotic Prescribing 1

- Start antibiotics promptly **when indicated**
- Collect cultures **before** first dose of antibiotic wherever possible and ensure you review the results
  - NB: Do not treat colonisation e.g. skin flora in wound swabs
- Consult the guidelines for empirical treatment
- Consider previous resistant organisms e.g. MRSA, ESBL-producing organisms
- Be aware of adverse effects related to specific antibiotics

Good Antibiotic Prescribing 2

- **Document indication and stop/review date**
- Seek advice from Consultant Microbiologist if necessary

....then focus”


Then Focus
CLINICAL REVIEW & DECISION AT 48-72 HOURS
Clinical review, check microbiology and make a clear plan. Document this decision
1. STOP
2. IV to oral switch
3. Change antibiotic
4. Continue
5. OPAT*
Document Decision & Next Review Date or Stop Date
DOCUMENT ALL DECISIONS

Good antibiotic prescribing 3

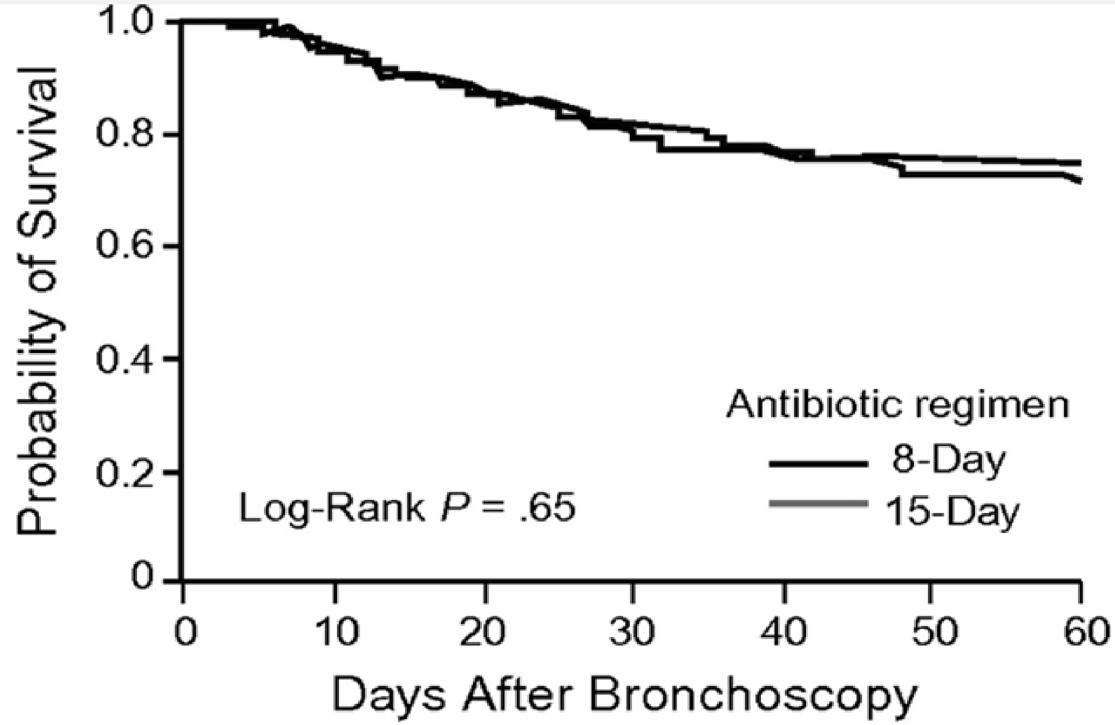
- Secondary care: **Review in 48 hours** (stop/IV→ oral switch, change antibiotic, continue)

  De-escalate if appropriate

  - Narrower spectrum agents
  - Lower *Clostridium difficile* risk

- Stop antibiotics if the culture is negative unless clinically indicated **– antibiotics can be stopped at ANY TIME if not indicated – there is no need to 'complete the course'**

Probability of survival for 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia
(Kaplan-Meier estimates)



No. at Risk							
8-Day Antibiotic Regimen	197	187	172	158	151	148	147
15-Day Antibiotic Regimen	204	194	179	167	157	151	147

Kollef M H et al. *Clin Infect Dis*. 2011;53:S33-S55

IV → Oral Switch

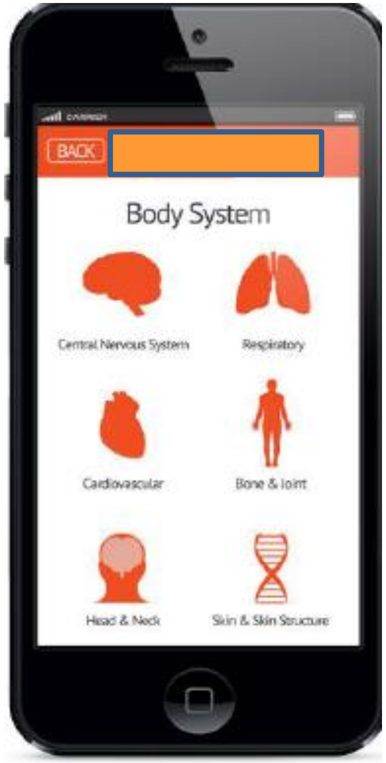
- Reduced risk of bacteraemia from line
- Reduced risk of thrombophlebitis
- Saves medical and nursing time
- Increased convenience, comfort and mobility
- Significant cost reduction
- Reduced risk of administration errors
- Earlier discharge from hospital
- Switch when patient clinically stable

Intravenous Administration

- Severe infections
- Immunocompromised
- Oral route not available
- Surgical prophylaxis

Antimicrobial Guidelines

- Check your Health Board guidelines
  - Secondary care
  - Primary care
  - Smartphone App
    - RxGuidelines



Prudent use of antibiotics can prevent the emergence and selection of antibiotic-resistant bacteria.

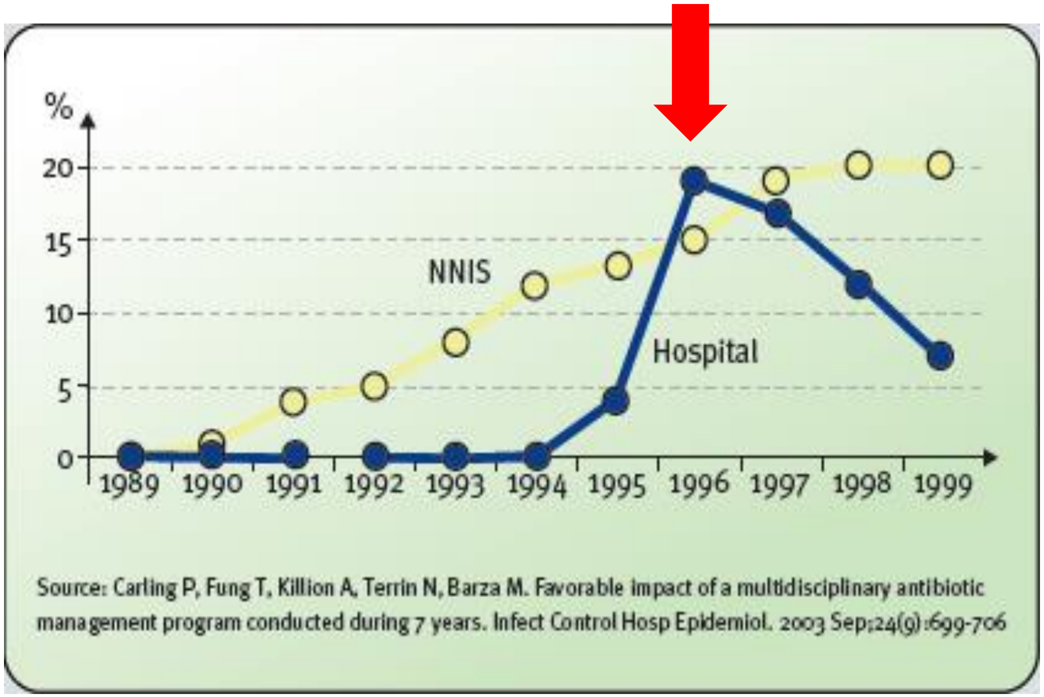
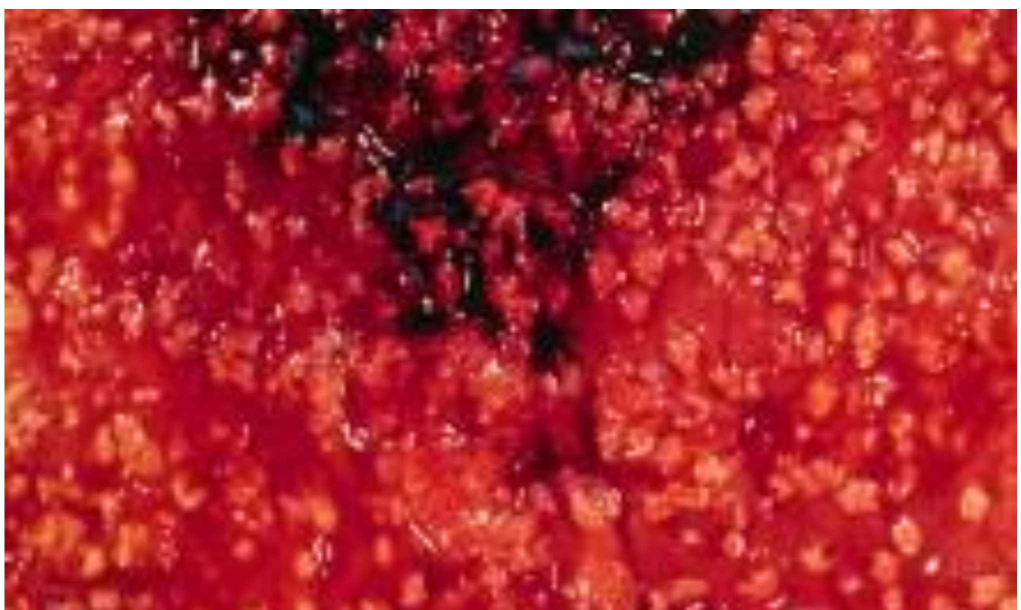


Figure 6: Rates of Vancomycin-resistant *Enterococci* in hospital before and after implementation of the antibiotic management program compared with rates in National Nosocomial Infections Surveillance (NNIS) System* hospitals of similar size. *NNIS is now the National Healthcare Safety Network (NHSN).

Clostridium difficile Infection

- Diarrhoea caused by toxin of gut bacterium *Clostridium difficile*
- Symptoms range from mild diarrhoea to severe life-threatening inflammation of the colon – 'pseudomembranous colitis



Clostridium difficile infection (CDI)

Often provoked by antibiotic therapy

- Any antibiotic may increase risk
- Risks additive with multiple antibiotics
- Risk increases with course length
- ?Risk may vary between agents

Management

- Barrier nursing
- Review/stop other antibiotics if possible
- Specific treatment:
  - Oral Vancomycin
  - Fidaxomicin if recurrent - Consultant Microbiologist approval
  - Role of FMT

- Review PPI / H_2 antagonists, stop if possible
- Anti-motility agents should not be prescribed in acute CDI

Decreasing antibiotic use have also been shown to result in lower incidence of *Clostridium difficile* infections.

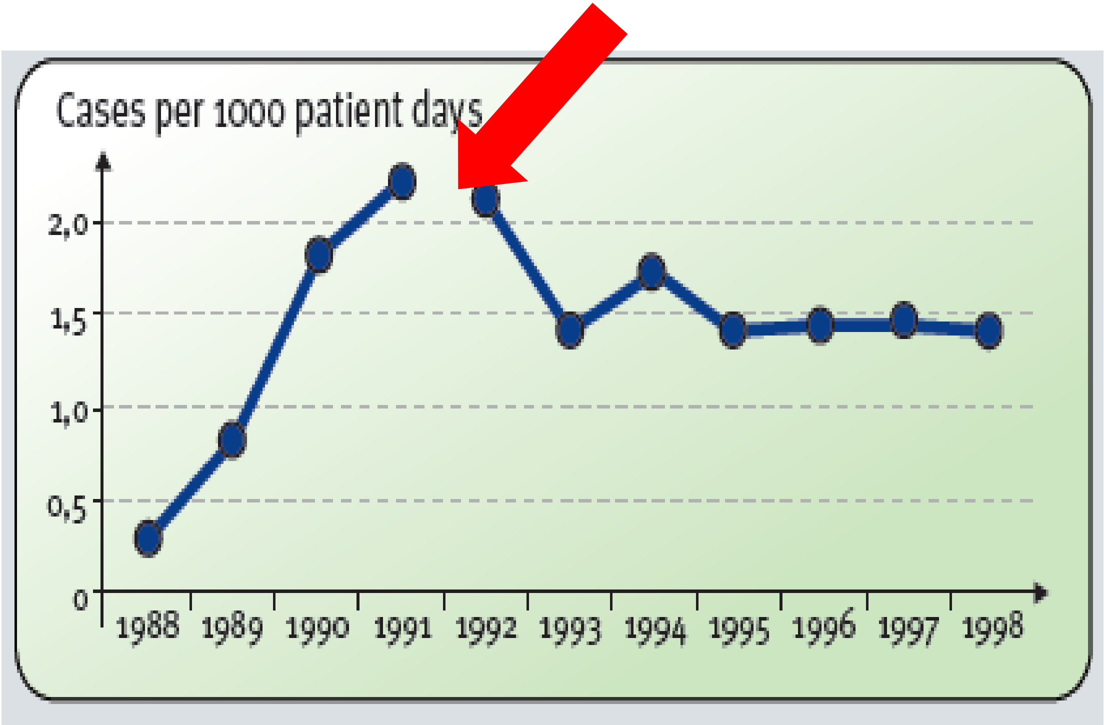


Figure 7: Rates of nosocomial *Clostridium difficile*, expressed per 1,000 patient-days, before and after implementation of the antibiotic management program.

Carling P, et. Al. Infect Control Hosp Epidemiol. 2003 Sep;24(9):699-706.

Sources of Information & Advice

- Antimicrobial guidelines
- BNF
- Renal Drug Database
- Antimicrobial pharmacist/ward pharmacist
- Microbiologist
- Medicines Information Department

ANTIBIOTIC GUARDIAN

https://antibioticguardian.com/

CURRENT PLEDGES: 32061

Antibiotic resistance is one of the biggest threats facing us today.

Why it is relevant to you: without effective antibiotics many routine treatments will become increasingly dangerous. Setting broken bones, basic operations, even chemotherapy and animal health all rely on access to antibiotics that work.

What we want you to do: To slow resistance we need to cut the unnecessary use of antibiotics. We invite the public, students and educators, farmers, the veterinary and medical communities and professional organisations, to become Antibiotic Guardians.

Call to action: Choose one simple pledge about how you'll make better use of antibiotics and help save these vital medicines from becoming