# Antimicrobial Resistance and Stewardship

Professor Angharad Davies



## PA Induction
## Sept 2021

Swansea University Medical School
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# Antimicrobial Resistance – a slow-moving pandemic

‘COVID is the lobster dropped into boiling water where it makes a lot of noise and everyone notices, and it’s dead. AMR is the lobster put in cold water slowly heating up so it doesn’t make noise and people aren’t noticing’

Professor Dame Sally Davies, UK Special Envoy on Antimicrobial Resistance

- Discovery of penicillin 1929.
  - Sir Alexander Fleming.
  - Accidental mould contamination.

- Chinese, Egyptians, Europeans used mouldy food to treat infections.

Eber Papyrus c 1500 BC

https://upload.wikimedia.org/wikipedia/commons/8/8b/Ebers7766.jpg

https://www.flickr.com/photos/ajc1/3288245384/

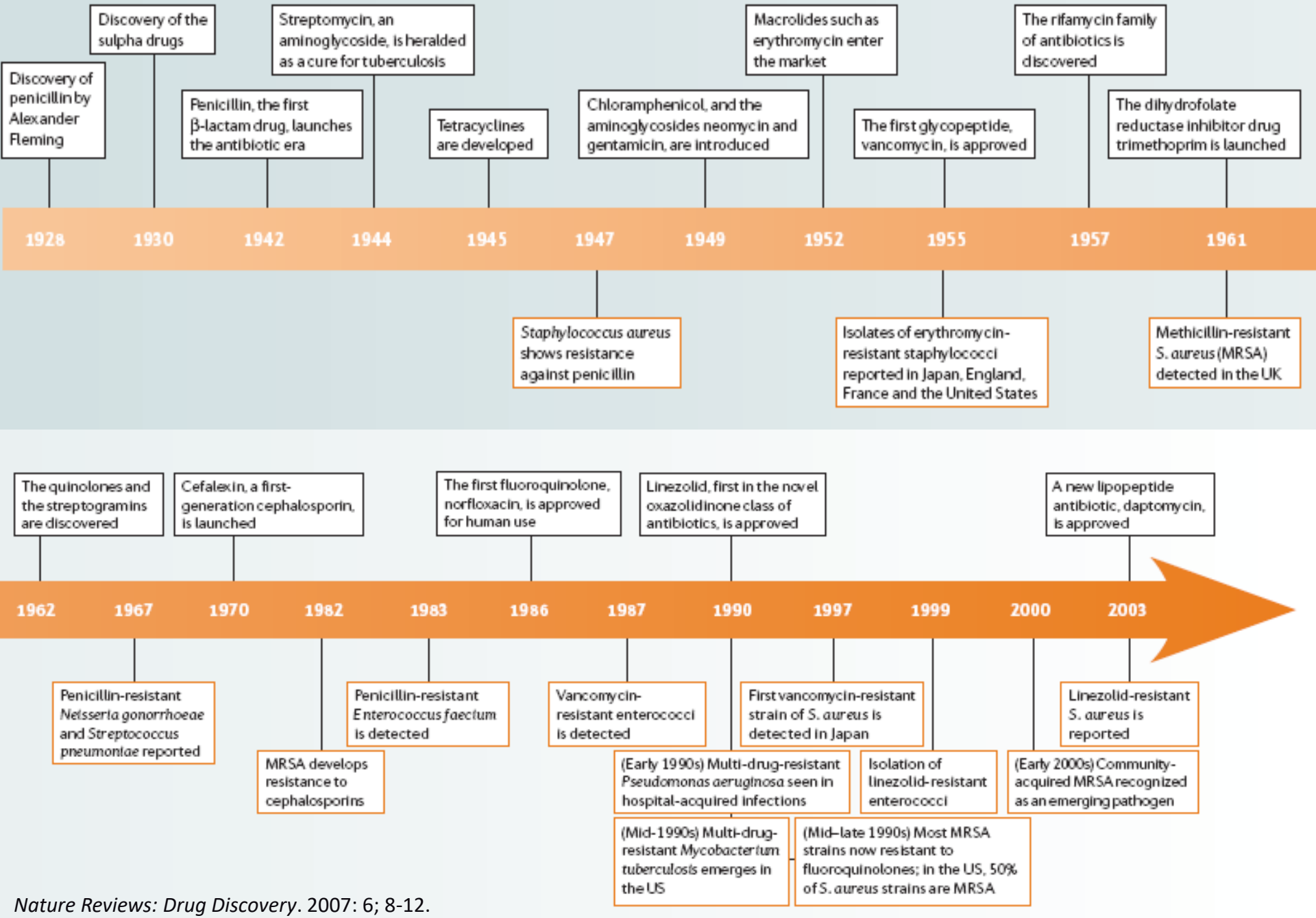

**1947**

***Staphylococcus aureus* documented resistant to penicillin**

**Extract f[illegible] dre[illegible]**

'I would like to sound one note of warni[illegible]cillin is t[illegible]ents and purpo[illegible]s non-poisonous so there is no need to worry about giving [illegible]verdose and p[illegible]oning the patient. … The time may come when penicillin can be bought by a[illegible]ne in the shops. Then there is the danger that the ignorant man may by exposing his micro[illegible]es to non-lethal quantities of the drug make them resistant. Here is a hypothetical illustration. Mr. X. has a sore throat. He buys some penicillin and gives himself…enough to educate them to resist penicillin. He then infects his wife. Mrs. X gets pneumonia and is treated with penicillin. As the streptococci are now resistant to penicillin the treatment fails. Mrs. X dies. Who is primarily responsible for Mrs. X's death? Why Mr. X whose negligent use of penicillin changed the nature of the microbe.

Timeline | **Race against time: the introduction of new antibiotic classes and the emergence of resistance**




*Nature Reviews: Drug Discovery*. 2007: 6; 8-12.

## Analysis: Antibiotic apocalypse

By James Gallagher
Health editor, BBC News website

19 November 2015 | Health

## Superbugs to kill 'more than cancer' by 2050

Fergus Walsh
Medical correspondent

11 December 2014 | Health

# New 'superbug' found in UK

By Michelle Roberts
Health reporter, BBC News

11 August 2010 | Health

**A new superbug that is resistant to even the most powerful antibiotics has entered UK hospitals, experts warn.**

They say bacteria that make an enzyme called NDM-1 have travelled back with NHS patients who went abroad to countries like India and Pakistan for treatments such as cosmetic surgery.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Health

## Bug resistant to all antibiotics kills woman

By James Gallagher
Health and science reporter, BBC News website

13 January 2017 | Health

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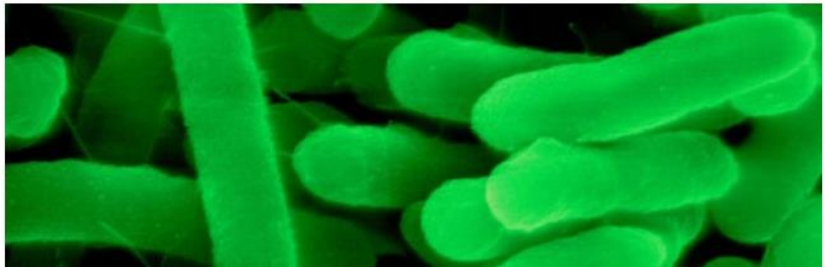

# Antibiotic Resistance Awareness

## 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]

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

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

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

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

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

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

**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) Chang HT et al. Infect Control Hosp Epidemiol, 2007; 28:1026-1031
(3) EMA 2011-04-13 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


www.myrolematters.com

# What the UK CMOs say.....

‘The harsh reality is that infections are increasingly developing that cannot be treated. The rapid spread of multi-drug resistant bacteria means that we could be close to reaching a point where we may not be able to prevent or treat everyday infections or diseases’

Prof Dame Sally Davies previous CMO


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11 March 2013 Last updated at 13:36

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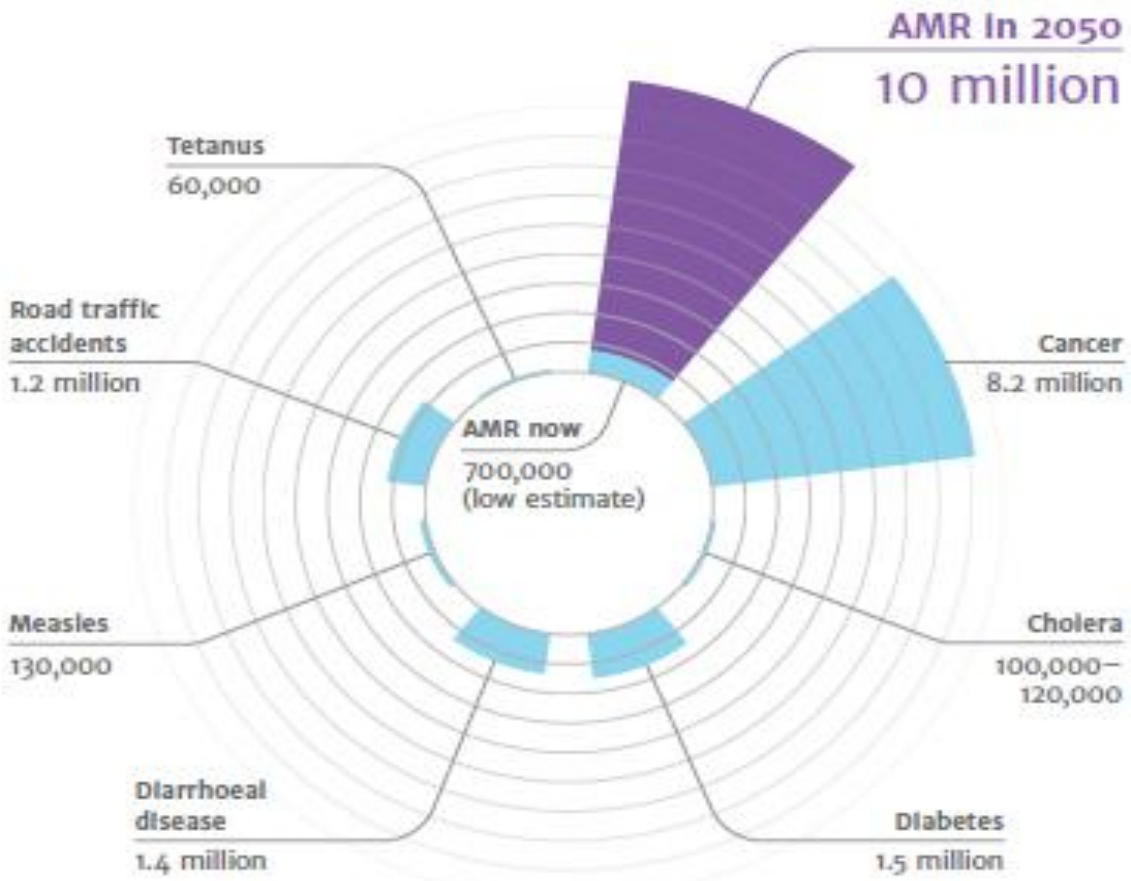
Antibiotics resistance 'as big a risk as terrorism' - medical chief

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

# DEATHS ATTRIBUTABLE TO AMR EVERY YEAR

***"The death toll could be a staggering one person every three seconds"***




**TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY:** FINAL REPORT ANDRECOMMENDATIONS
**THE REVIEW ONANTIMICROBIAL RESISTANCE** *CHAIRED BY JIM O'NEILL*MAY 2016

# Antibiotic resistance as big a threat as climate change - chief medic

**Dame Sally Davies calls for Extinction Rebellion-style campaign to raise awareness**

**Fiona Harvey**
*Environment correspondent*

Mon 29 Apr 2019
13.17 BST

2147

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

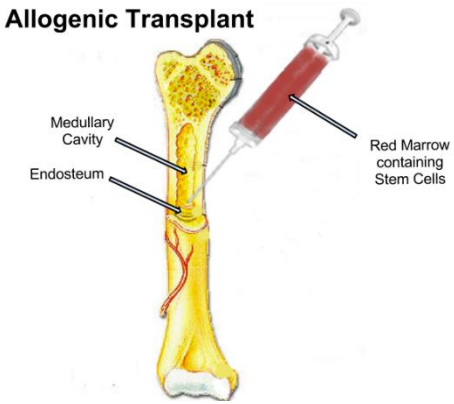
4,232

Press Association

Friday 13 October 2017 08.41 BST

‘the end of modern medicine’

Professor Dame Sally Davies, ex UK CMO

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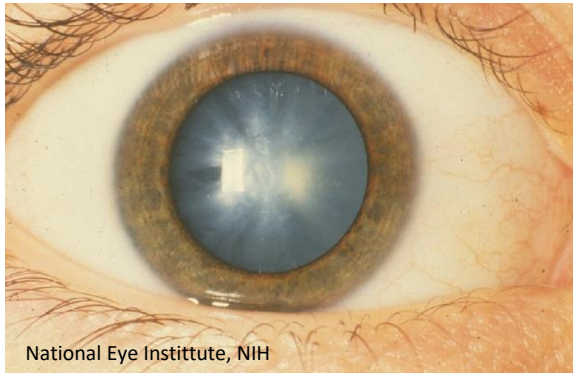
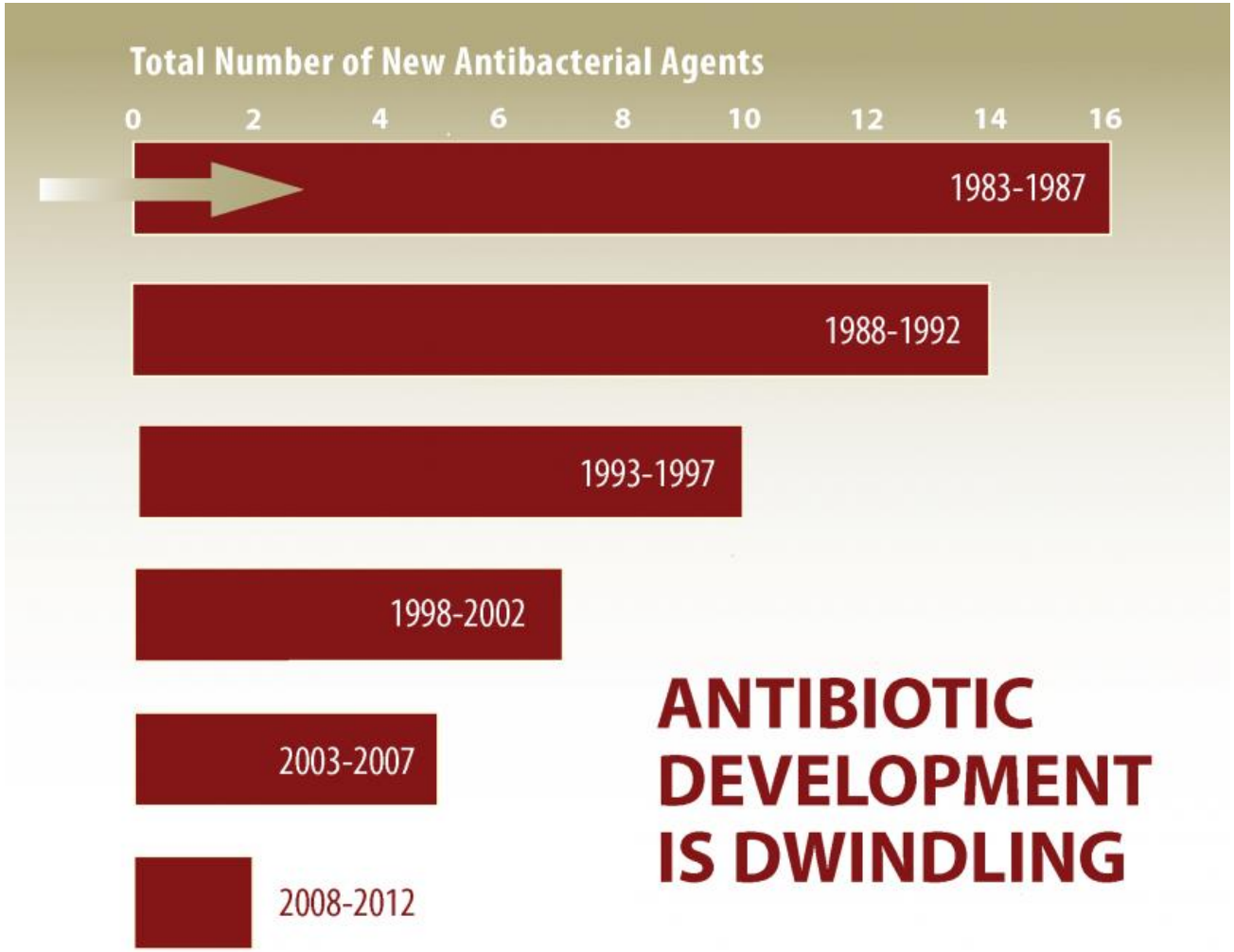


National Eye Institute, NIH




Source: *The Epidemic of Antibiotic-Resistant Infections*, CID 2008:46 (15 January)
Clin Infect Dis. (2011) May 52 (suppl 5): S397-S428. doi: 10.1093/cid/cir153

‘There are only about 500 scientists in industry working on AMR around the world…there are 3500 working in oncology for Cancer Research UK alone’

The Telegraph, January 2019

# BLADE OF GRASS IS RESPONSIBLE FOR LOSS OF FOOT

C. W. Jones, athletic director of the Athens Y. M. C. A. yesterday suffered the loss of his right foot, the member having been amputated just above the ankle.

Mr. Jones, it seems, recently was exercising on a plot of grass, dew on a blade of grass cutting him slightly just under the little toe. The cut did not heal as quickly as it should have and medical attention was called, but to no avail. Blood poisoning had set in, and it was imperative that the foot be amputated to prevent the poison spreading further.

*Weekly Banner*, 18 July 1899, p. 2, col. 2.

©Athens-Clarke County Heritage Room, 2011.

http://accheritage.blogspot.com/2011_07_01_archive.html

- 66 different antibiotics prescribed - top 15 account for 98% in general practice and 88% in hospitals .

- 35 million courses of antibiotics are prescribed by GPs in England each year.

- 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

# Contributing factors to development of resistance

- Misuse of antibiotics in human medicine
- Inadequate infection control eg in hospitals
- Use of antimicrobials in animal husbandry & agriculture – 40% of antibiotic use in UK
- Over the counter access
- Poor quality drugs (not UK)
- International travel
- Medical tourism
- ‘contagion’ – the spread of resistant strains and resistance genes
  - Poor sanitation
  - Access to clean water
  - Public health expenditure

Collignon et al, Lancet Planetary Health 2; e398-405

# 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

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.*

# Bacteria develop antibiotic resistance quickly….

https://vimeo.com/180908160

# What causes antimicrobial resistance in bacteria?

**INHERENT RESISTANCE**

**MUTATION**

**GENE TRANSFER**

# INHERENT RESISTANCE

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

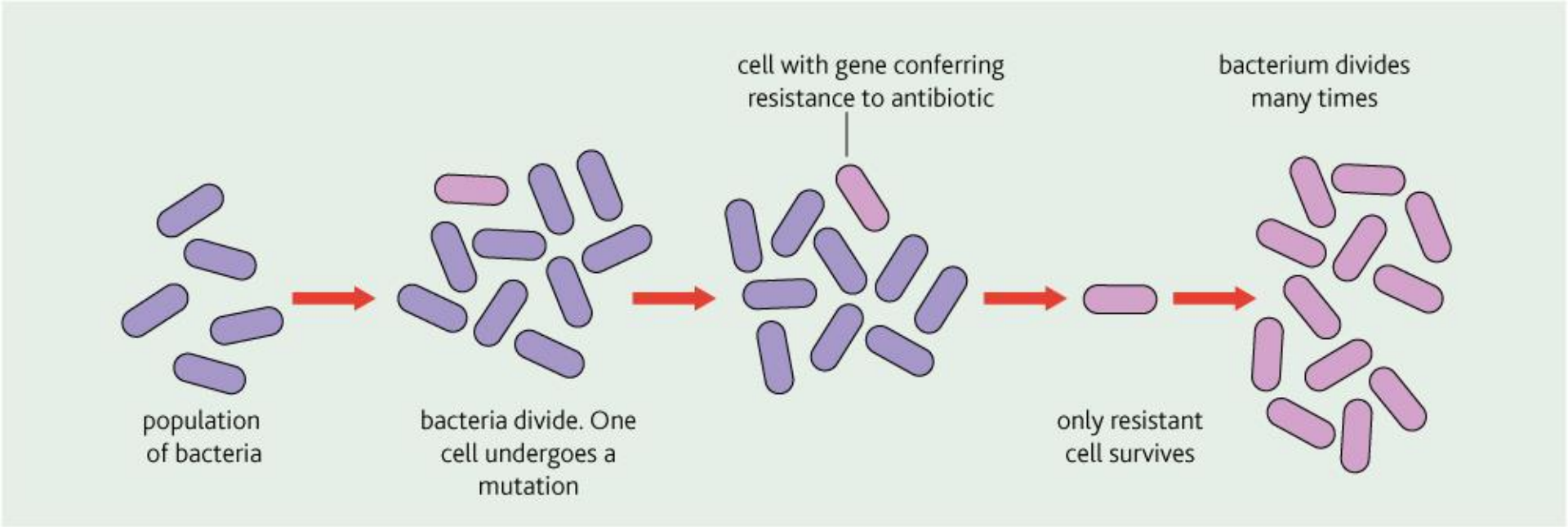
# Mutations are spontaneous genetic changes, arising randomly, all the time.

.

Bacteria multiply by the millions >> a few of these bacteria will mutate >> some mutations make the bacterium drug resistant.

In the presence of drugs >> only Drug resistant bacteria survive >> Drug resistant bacteria multiply and thrive.

# Mutation

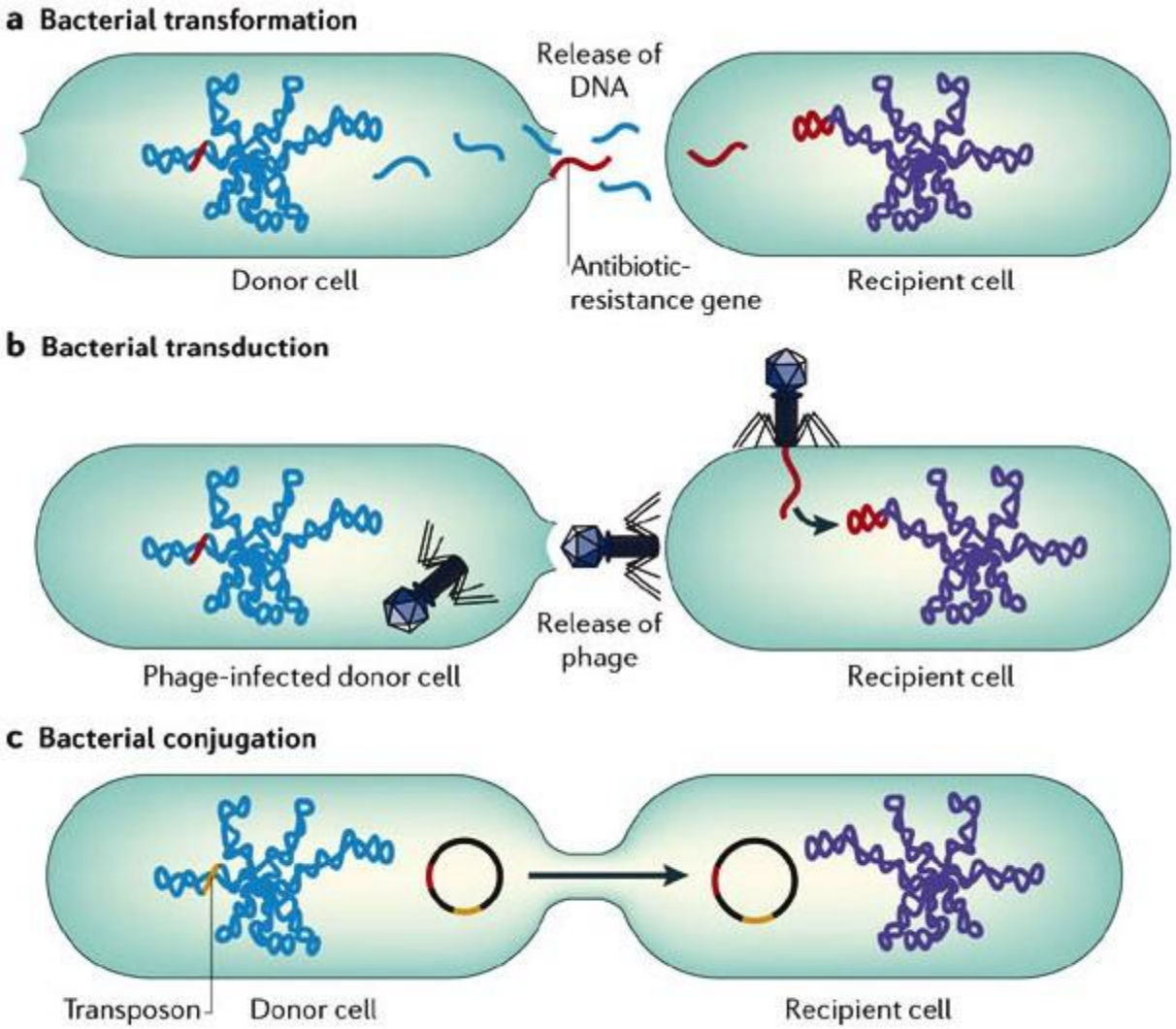



https://thealevelbiologist.co.uk/images/antibiotic-resistance.png

# HORIZONTAL GENE TRANSFER

The transfer of whole genes rather than the development and selection of mutations.

# HORIZONTAL GENE TRANSFER

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Nature Reviews | Microbiology

- Plasmid: extra-chromosomal genetic element made up of ds-DNA.
- can self replicate
- extremely common in bacteria.

- https://www.youtube.com/watch?v=Sqr39xbDPS4

- Whether resistance is inherent, achieved by mutation or by gene transfer, the same combination(s) of basic resistance mechanisms are found

# Mechanisms by which organisms can resist antibiotics

1. Inactivation of the antibiotic with enzymes - eg beta-lactamases
2. Decreased permeability – don’t let antibiotic in
3. Efflux pumping of the antibiotic - pump it out
4. Modification of the antibiotic target molecule
5. Alteration of the metabolic pathway

# Enzymatic degradation - example

- Some organisms produce enzymes which break down beta-lactams
- These are called beta-lactamases
- Arms race! drugs now developed which inhibit the beta-lactamases
- Beta-lactamase inhibitors

# Penicillins combined with beta-lactamase inhibitors

- Amoxycillin +/- clavulanate*
  - ‘Co-amoxiclav’ (Augmentin®)
  - Broad spectrum
- Piperacillin +/- tazobactam*
  - ‘Piptazo-bactam’ (Tazocin®)
  - Very broad spectrum

Newspaper of the Year

# THE INDEPENDENT

No 5,660 TUESDAY 7 DECEMBER 2004 www.independent.co.uk

## EXCLUSIVE: JANET OF THE JUNGLE

'I've given up salt, sugar and caffeine. My blood pressure is much better. And I'm more tolerant' Janet Street-Porter, in her own words PAGES 24-25

# MRSA

Each year, 100,000 people catch an infection in hospital. Of these, 5,000 die – more than are killed on the roads. It's one of the worst rates in the world. So is there a cure?

# The rise of the ‘superbug’

- 1990’s MRSA
- Methicillin resistant *Staphylococcus aureus*
- *S. aureus* which is resistant to flucloxacillin which is the usual treatment
- It is spread on **hands** and clinical equipment
- Handwashing between each patient
- Barrier nursing

- MRSA is no longer on the increase and MSSA causes more cases of sepsis

# 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

27 Chwefror 2017

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*

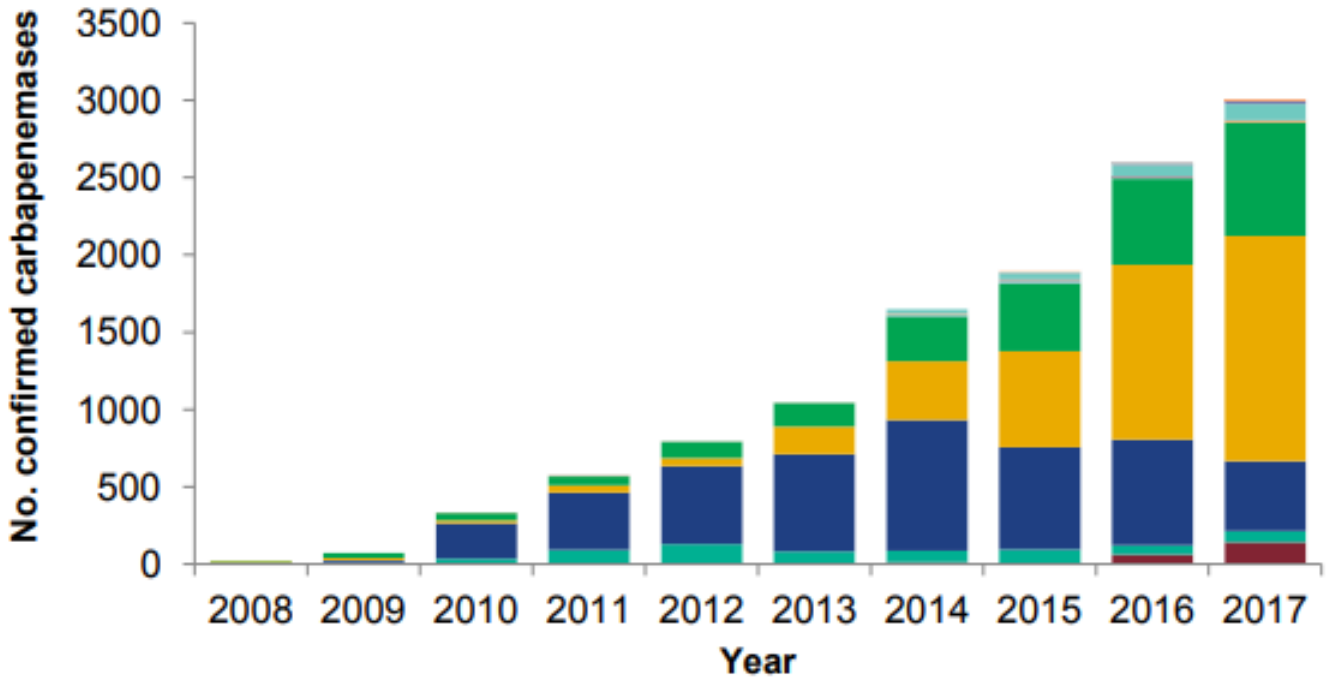
# Gram negative ‘superbugs’

- ESBL – extended spectrum beta lactamase inhibitors
- CPEs – carbapenemase producing enterobacteriales

- **barrier nursing and handwashing**
- **Antibiotic stewardship**

# 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

# 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 *Klebsiella pneumoniae* with the following susceptibility pattern:

*acknowledgement: 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?

- **Very little choice of antibiotic agents?**

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??

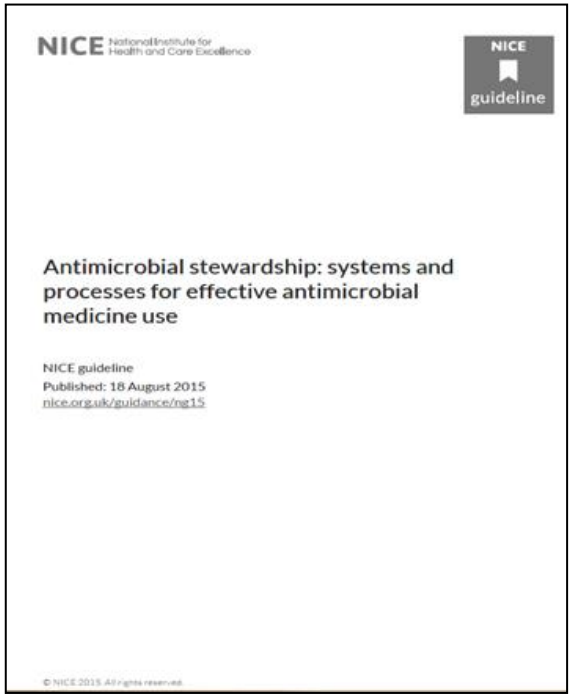
- **What other measures need to be taken?**

Strict patient isolation & use of contact precautions by all HCWs

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

# 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

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NICE Guideline August 2015

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

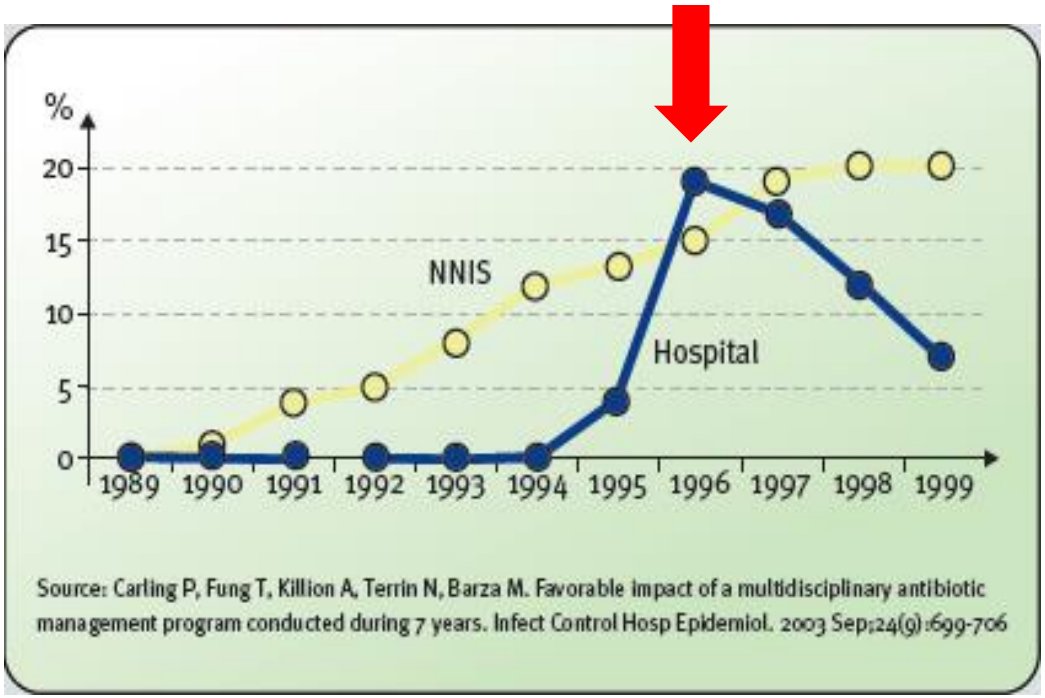
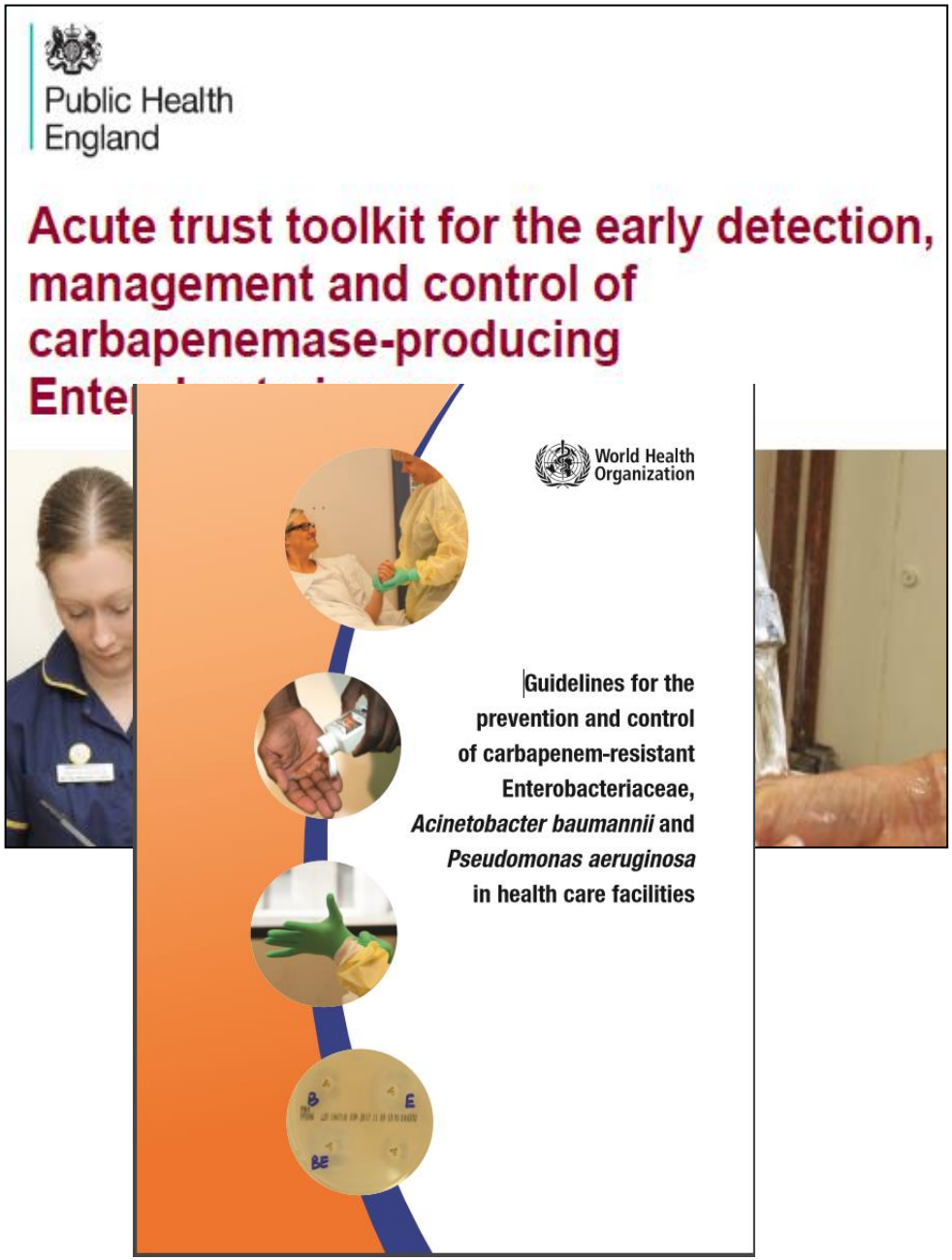



Figure 6: Rates of Vancomycin-resistant *Enterococci* in hospital before and after implementation of the antibiotic management program compared with rates in National Nosocomial Infections Surveillance (NNIS) System* hospitals of similar size. *NNIS is now the National Healthcare Safety Network (NHSN).


**Infection Prevention & Control Standard Operating Protocol**

# Preventing the Spread of Carbapenem Resistant Gram negative Bacteria



# Antimicrobial Stewardship:

- is an **inter-professional** effort, across the continuum of care
- involves timely and **optimal** selection, dose and duration of an antimicrobial
- for the **best clinical outcome** for the treatment or prevention of infection
- with **minimal toxicity** to the patient
- and **minimal impact** on **resistance** and other ecological adverse events such as ***C. difficile***"

*[Nathwani et al., 2012]*

# 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

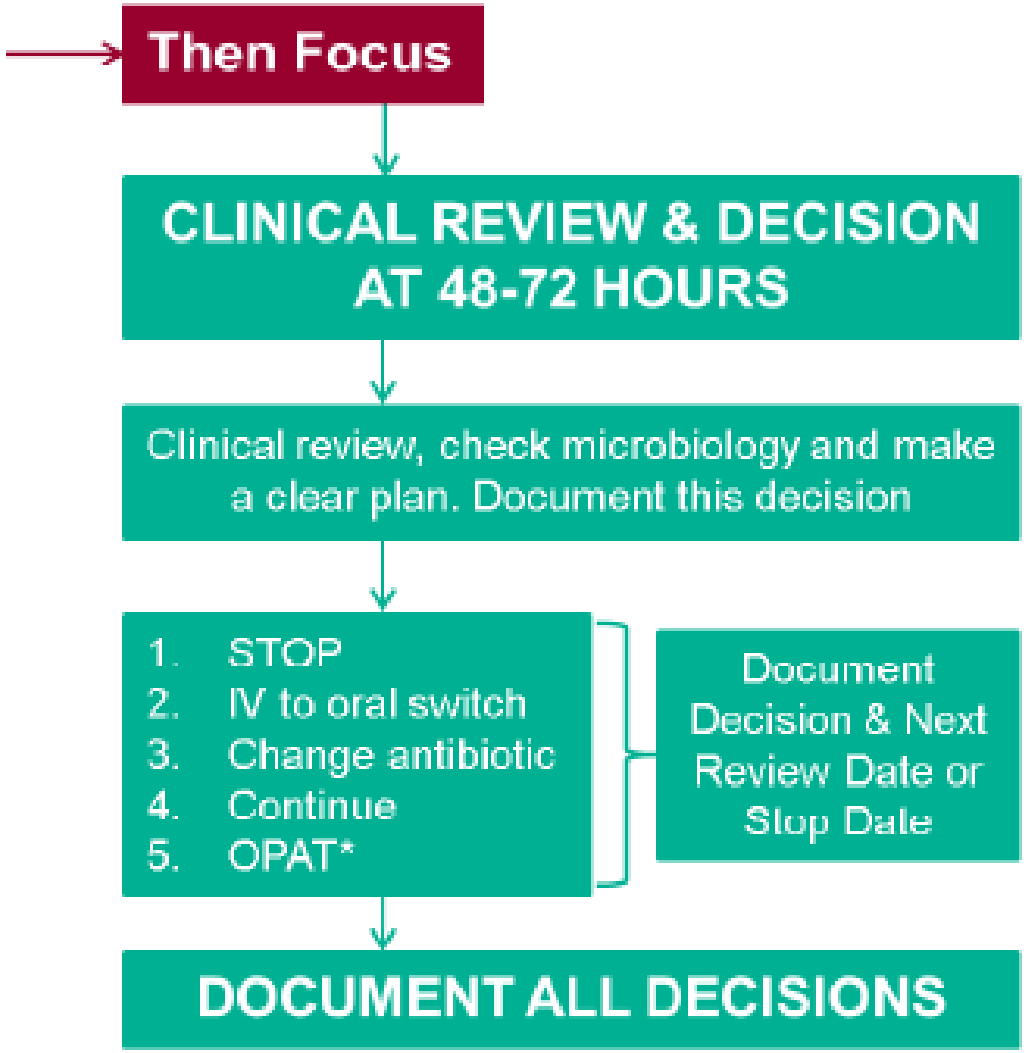
Updated March 2015

# “Start Smart.....”

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

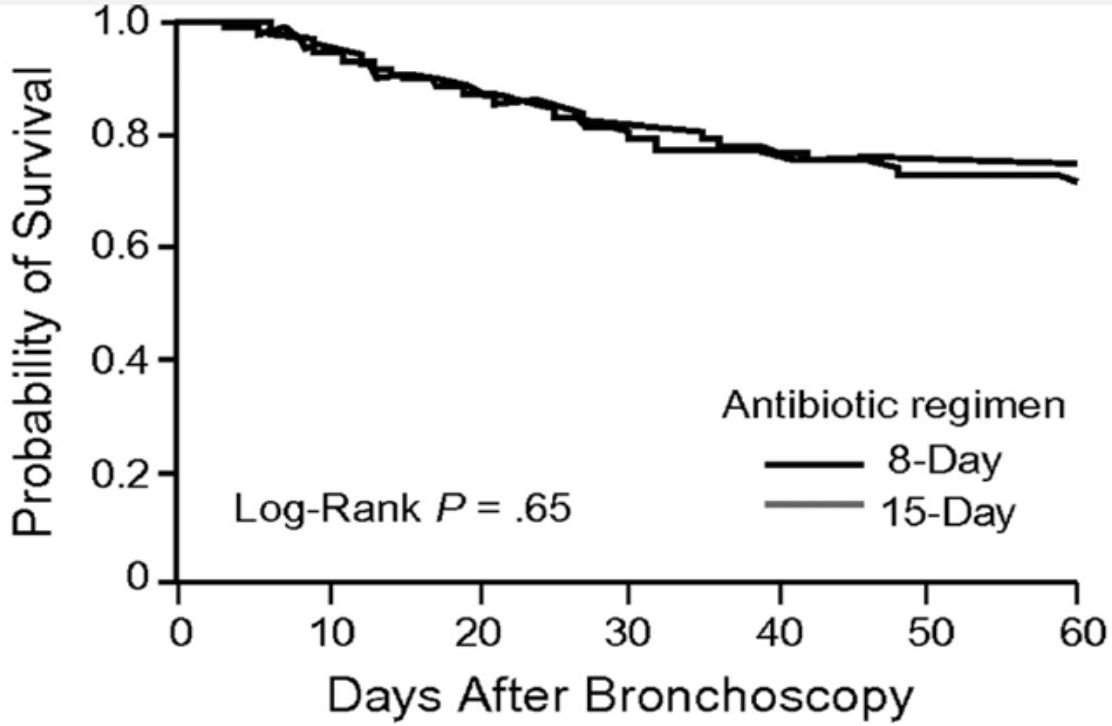
1. Take thorough drug allergy history
2. Initiate prompt effective antibiotic treatment within one hour of diagnosis (or as soon as possible) in patients with severe sepsis or life-threatening infections[α]
3. Comply with local antimicrobial prescribing guidance
4. Document clinical indication (and disease 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)

# ....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

# 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

# Prescribing Antibiotics

# Empirical selection of antibiotics

What is empirical treatment?

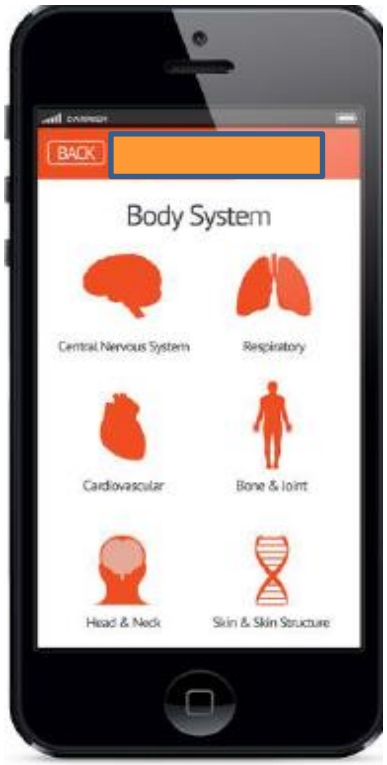
- When pathogen and/or antibiotic sensitivities are uncertain (**best guess**)
- Narrow spectrum wherever possible
- Broad-spectrum reserved for severe infections

How to choose empirical treatment?

- Local pathogen epidemiology and sensitivity data is important and is the basis of local antibiotic guidelines
- Streamline to narrow-spectrum antibiotic when sensitivities are available
- Don’t use a sledgehammer to crack a nut!!

# Antimicrobial Guidelines

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



# 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

# 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' if they were not indicated in the first place**

# 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

# Sources of Information & Advice

- Antimicrobial guidelines (use Rx app)
- British National Formulary
- Antimicrobial pharmacist/ward pharmacist
- Clinical Microbiologist
- Medicines Information Department

# ANTIBIOTIC GUARDIAN


https://antibioticguardian.com/

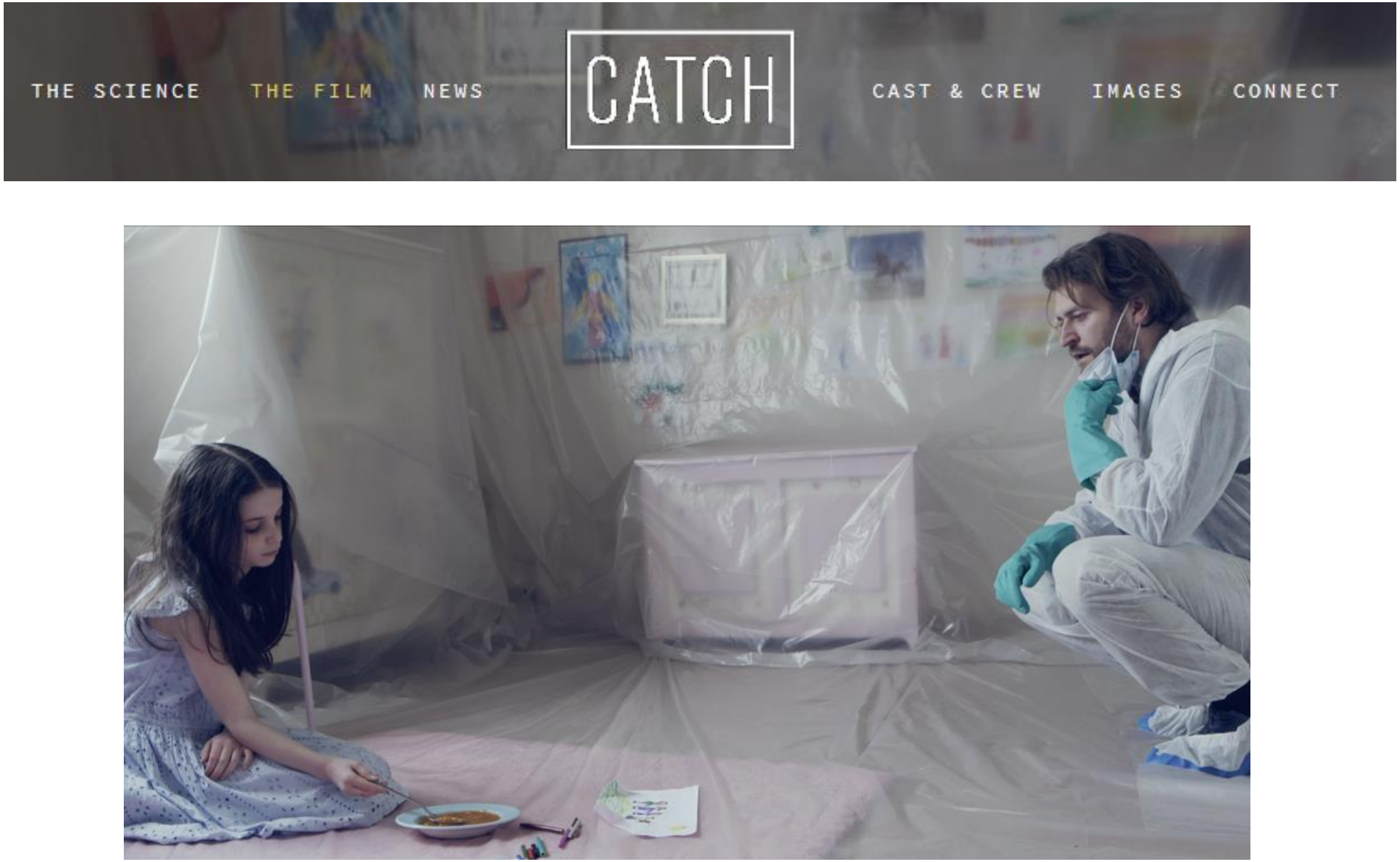
**CURRENT PLEDGES: 32061**

## 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




http://www.catchshortfilm.com/the-science-behind-catch

# www.antibioticaware.com