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Antibiotic Apocalypse Now

Tamsin Oswald

Consultant Microbiologist

Overview

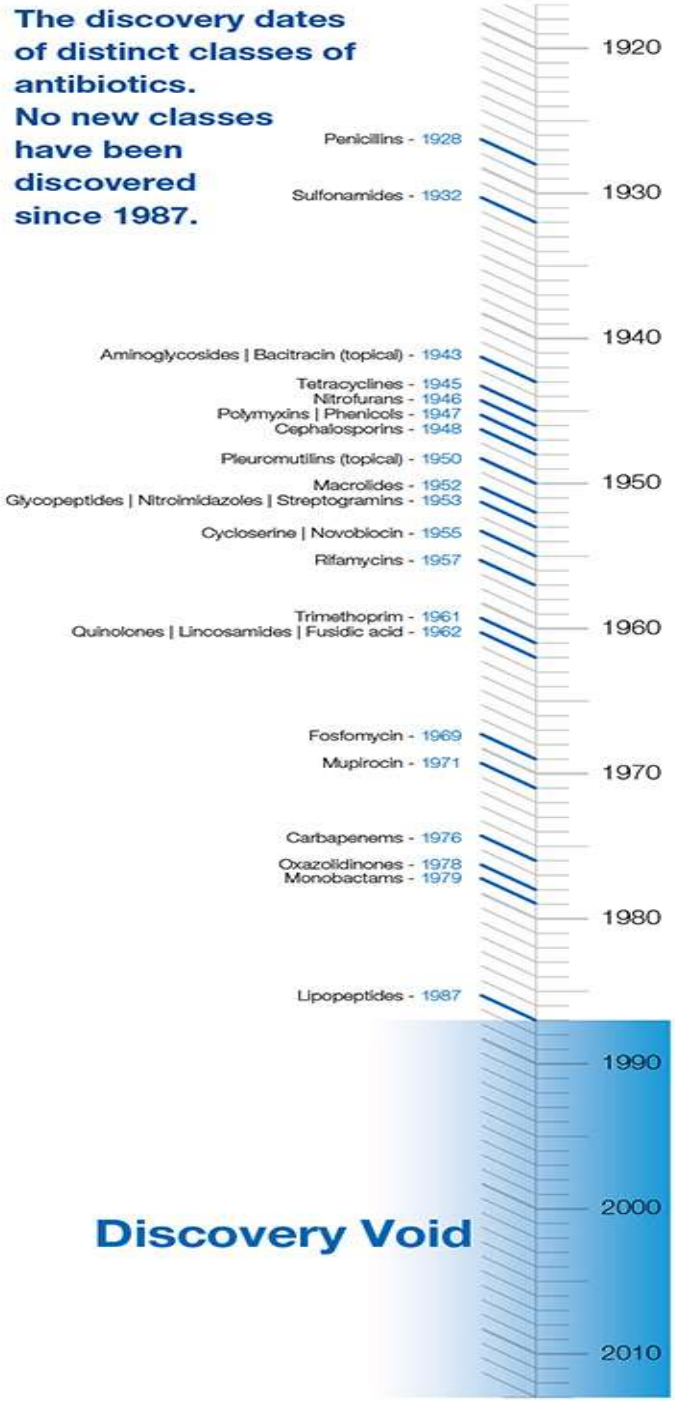
- Antibiotic Development
- Antibiotic Resistance
- Antibiotics in Orthopaedics
- Antibiotic Stewardship
- Summary
- Take Home Messages

Antibiotic

- Disco
  - grea
- Flemi lead to resist
- Resis
- Very f

"The greatest possibility of evil in self-medication is the use of too-small doses, so that, instead of clearing up the infection, the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed on to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save.

"In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted."



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Source: World Economic Forum, adapted from Silver, L.L. Challenges of Antibacterial Discovery. *Clinical Microbiology Reviews*, 2011, 24:71-109.

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Possible Adverse Effects of Antibiotics

- Allergy
- Side effect of antibiotic
- Interaction with other medication
- Effect on normal bacterial flora resulting
  - antibiotic associated diarrhoea
  - oral and vaginal candidiasis
  - colonisation or infection by resistant bacteria (MRSA, ESBL producing Gram negatives, etc)
- Increased antibiotic resistance in community

Patient Harm – prevent and reduce

- CDI rates are rising, fastest in primary care:
  - *+8.2% Q on Q to 29.26 per 100,000 population*
- *E.coli* bacteraemia rates are increasing:
  - *+4.3% Q on Q to 69.77 per 100,000 population*
- Multi drug resistant UTIs
- CA-UTI remain a concern – draft NICE QS UTI
- Carbapenemase-producing Enterobacteriaceae (CPE) surveillance
- Sepsis – National CQUIN for 2015/16

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Beta-lactam allergy

In suspected penicillin allergy, a careful history of the nature of the reaction should be taken:

Vague/minor
(e.g. gastrointestinal disturbance)
→ if appropriate, treatment with a beta-lactam is justified

Non-urticarial rash
(without angio-oedema or anaphylaxis)
→ cephalosporins, carbapenems and monobactam could still be used with caution if appropriate

Urticarial rash/angio-oedema/anaphylaxis
→ all beta-lactams are contraindicated

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Resistance and Allergy

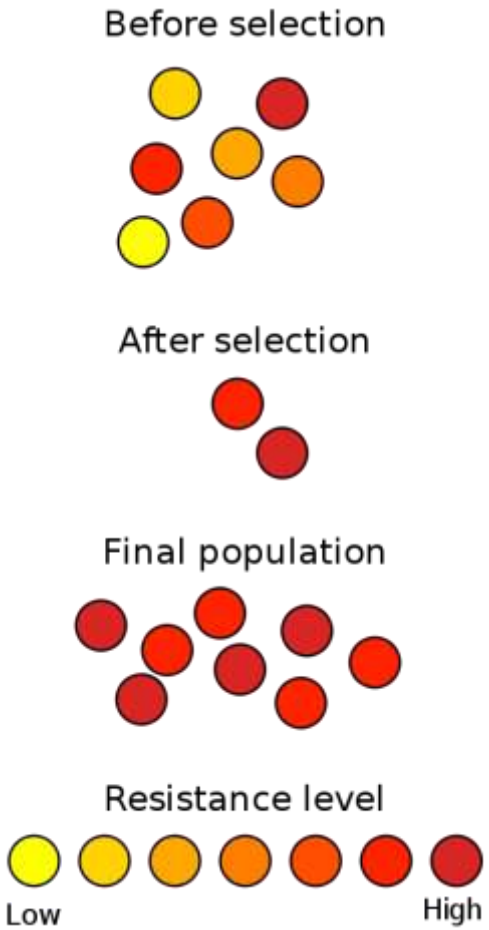
The alternative antibiotics available for treatment:

- May be **less effective**
- May cause **more side effects**
- Are likely to be **more expensive**
- May have to be given in much **larger doses**
- May have to be **iv rather than oral**

Antibiotic Resistance

- Acquired resistance largely absent from bacteria collected pre-1940
- Resistant mutants selected in therapy
- Resistance repeatedly followed introduction of new antibiotics
- Resistance greatest where use heaviest

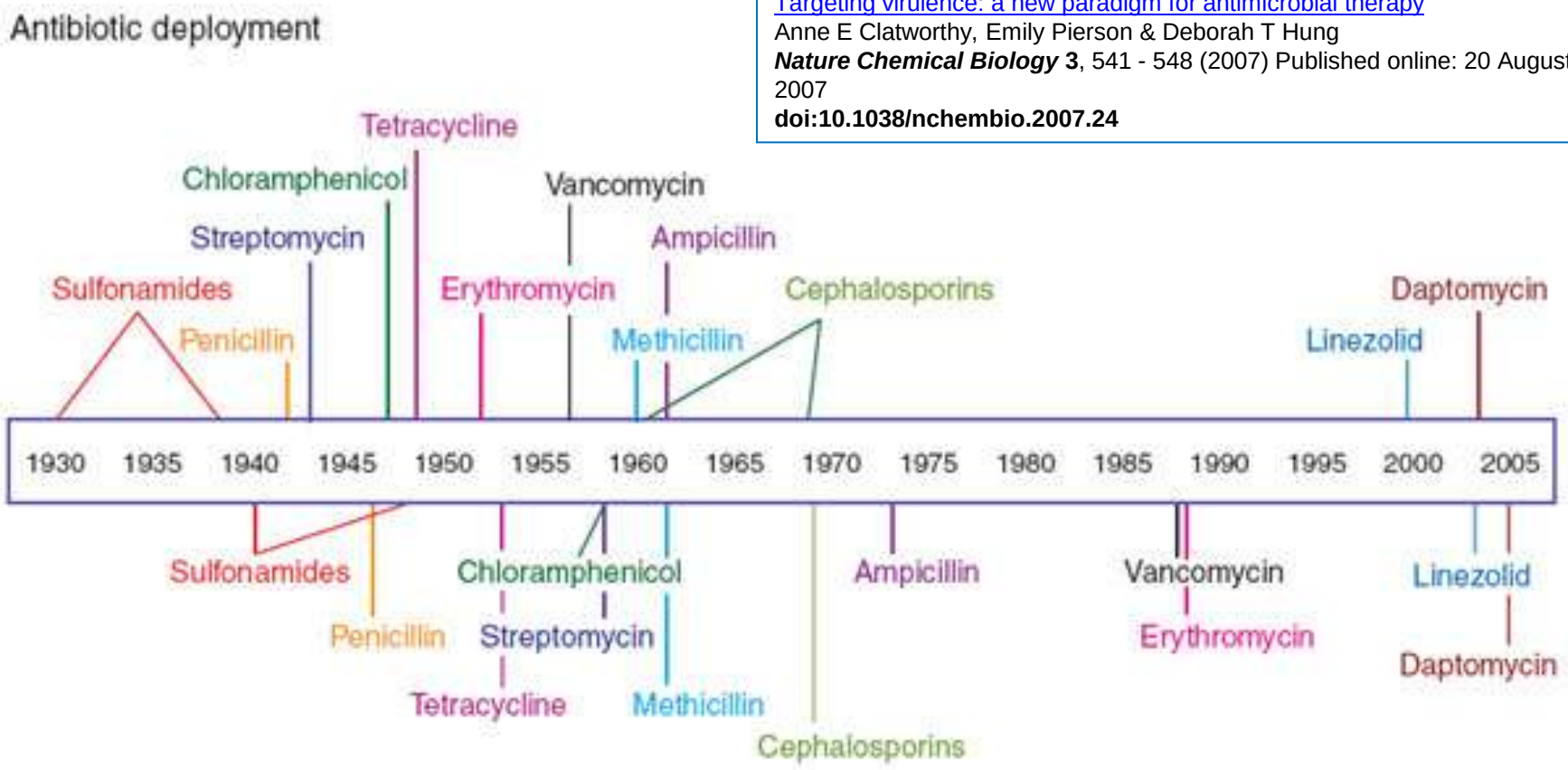
Selection of Resistance



Courtesy of Wikepedia

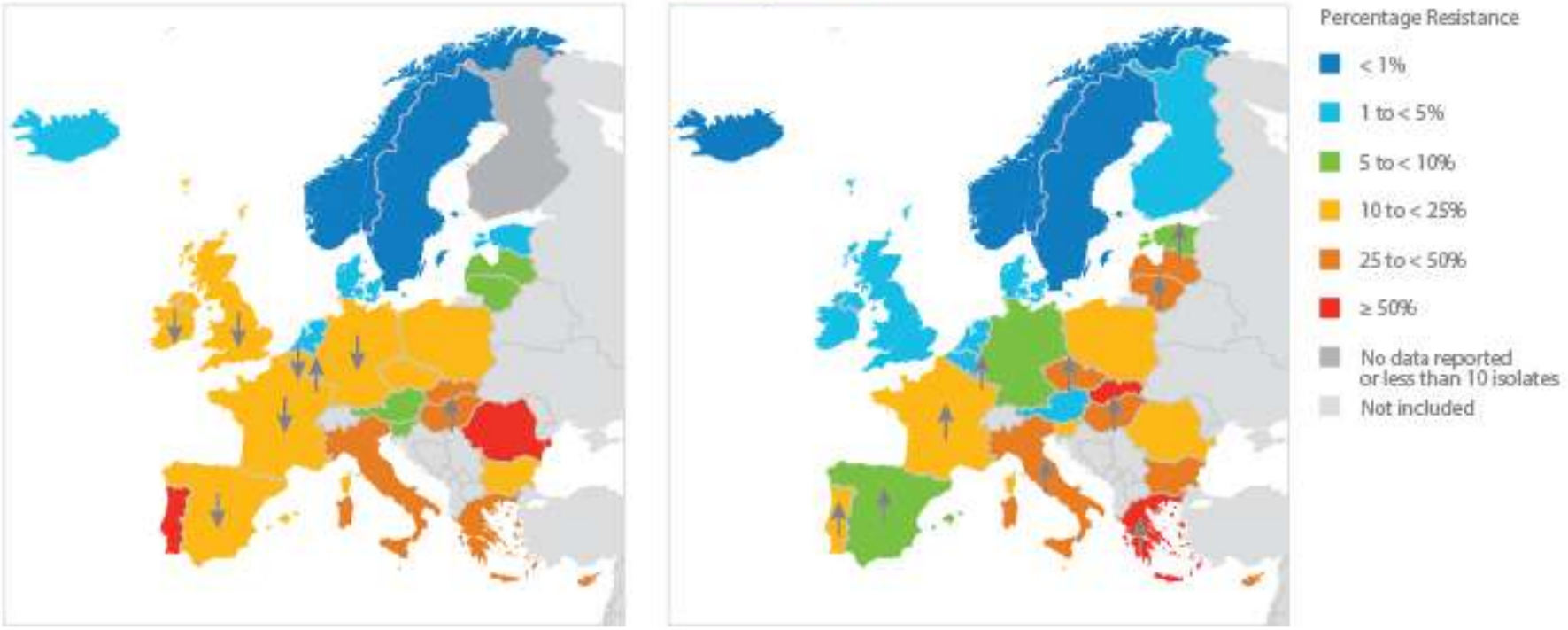
Development of Resistance

Targeting virulence: a new paradigm for antimicrobial therapy
Anne E Clatworthy, Emily Pierson & Deborah T Hung
***Nature Chemical Biology* 3**, 541 - 548 (2007) Published online: 20 August 2007
doi:10.1038/nchembio.2007.24



A. Staphylococcus aureus, resistance to meticillin (MRSA)

B. Klebsiella pneumoniae, combined resistance to three classes of antibiotics (3rd generation cephalosporins, fluoroquinolones and aminoglycosides)



The symbols ↑ and ↓ indicate a significant increasing or decreasing trend for the period 2008-2011, respectively.
These trends were calculated on laboratories that consistently reported during 2008-2011.

Source: European Centre for Disease Prevention and Control, EARS-Net, 2012

The 2014 WHO Antimicrobial Resistance Global Report on Surveillance reported an alarming incidence of resistance

Bacteria commonly causing infections in hospitals and in the community

Name of bacterium/ resistance	Examples of typical diseases	No. out of 194 Member States providing data	No. of WHO regions with national reports of 50% resistance or more
Escherichia coli/	Urinary tract infections, blood stream infections		
- vs 3rd gen. cephalosporins		86	5/6
- vs fluoroquinolones		92	5/6
Klebsiella pneumoniae/	Pneumonia, blood stream infections, urinary tract infections		
- vs 3rd gen. cephalosporins		87	6/6
- vs 3rd carbapenems		71	2/6
Staphylococcus aureus/	Wound infections, blood stream infections		
- vs methicillin "MRSA"		85	5/6

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Antibiotic resistance

What is responsible for the emergence and spread of resistance?

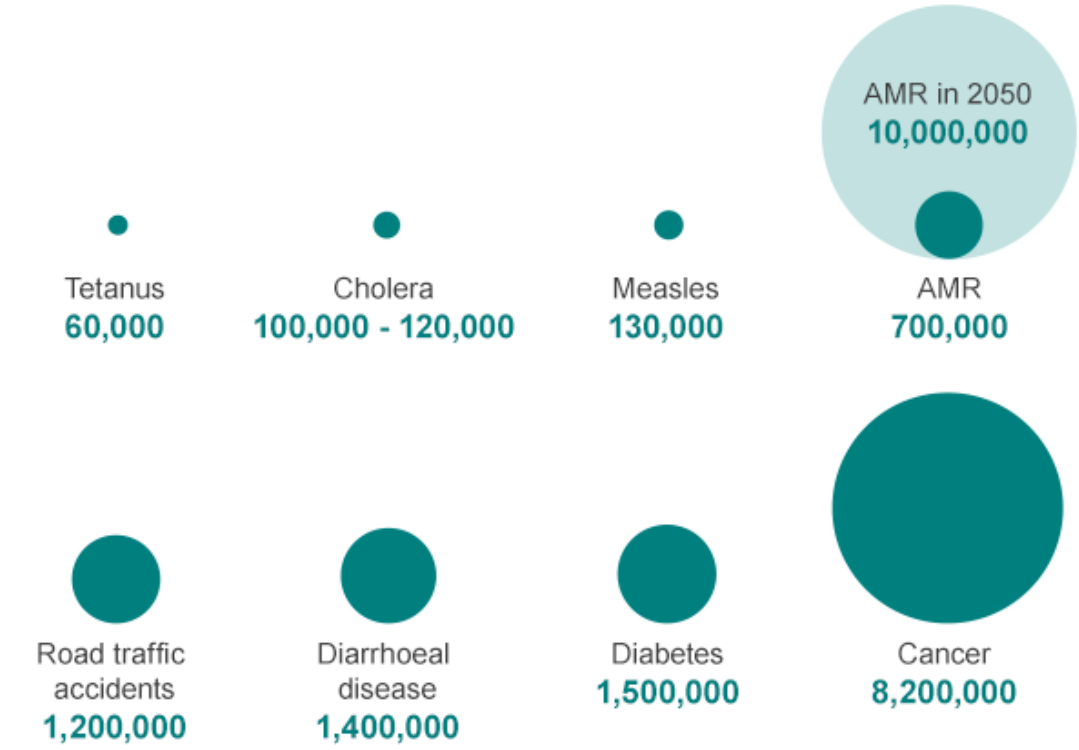
1. The overuse and misuse of antibiotics
2. Poor infection prevention and control

Misuse of antibiotics includes:

- Unnecessary prescription
- Delayed administration in critically ill patients
- Broad-spectrum antibiotics being used too generously, or narrow-spectrum antibiotics used incorrectly
- Incorrect dose
- Incorrect duration
- Not changing antibiotics according to culture results

Superbugs to kill 'more than cancer' by 2050

Deaths attributable to antimicrobial resistance every year compared to other major causes of death



Source: Review on Antimicrobial Resistance 2014

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"Superbugs"

- ***E****nterococcus faecium*
- ***S****taph.aureus* (MRSA/VRSA)
- ***C****.difficile*
- ***A****cinetobacter baumanii*
- ***P****seudomonas aeruginosa*
- **E**nterobacteriaceae (ESBLs/CPEs)

- MDR-TB
- MDR-GC

The Antibiotic Apocolypse is looming….

Imagine modern healthcare without antibiotics…

- Healthcare has become increasingly technological and invasive, improving mortality and morbidity significantly, and antimicrobials have become integrated in many aspects of such care
  - E.g. Surgical prophylaxis, to women delivering by c-section, and to those having cancer treatment.
  - From cradle to grave, antimicrobials have become pivotal in safeguarding the overall health of human societies
- The costs of resistance are not limited to those associated with additional treatment for a primary infection.
  - They must also encompass the costs that might relate to the loss of modern healthcare.
  - In the same way that health systems need adequate and effective health workers to function, they also require effective antimicrobials.
- **Resistance is not just an infectious disease issue; it is a surgical issue, a cancer issue, a health system issue.**
- In the future we may need to rethink how the health system is developed—for instance, redesigning many facilities or reintroducing sanatoriums if effective antibiotic treatments are no longer available

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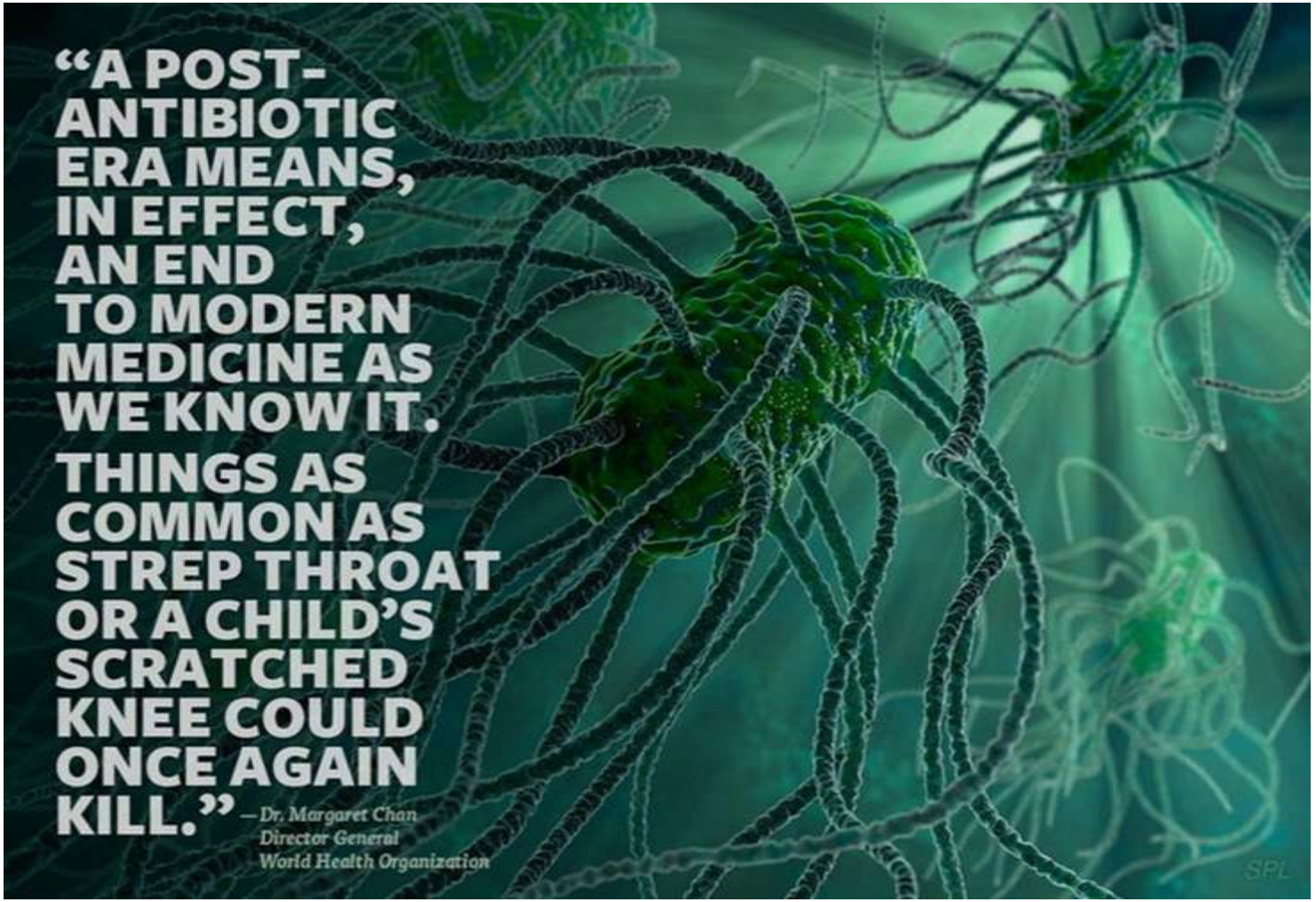
R Smith, J Coast. The true cost of antimicrobial resistance. BMJ. doi: http://dx.doi.org/10.1136/bmj.f1493 - See more at: http://www.lshtm.ac.uk/newsevents/news/2013/antibiotic_apocalypse.html#sthash.5t7Hijb5.dpuf

Triumph of Death by Pieter Bruegel c1562

Courtesy of the National Geographic



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World Health Organisation

- WHO statistics
  - Infections are 2-5 of the top 10 causes of death
  - Infections impact upon the other 5-8 causes
- WHO 2009: Antibiotic resistance

  - one of the three greatest threats to human health
- WHO World Health Day. 7 April 2011
  - Antimicrobial resistance:

no action today, no cure tomorrow

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The Department of Health

- Chief Medical Officer Dame Sally Davies: **“Resistance to antibiotics risks health, it is a catastrophe to rank with terrorism and climate change”**

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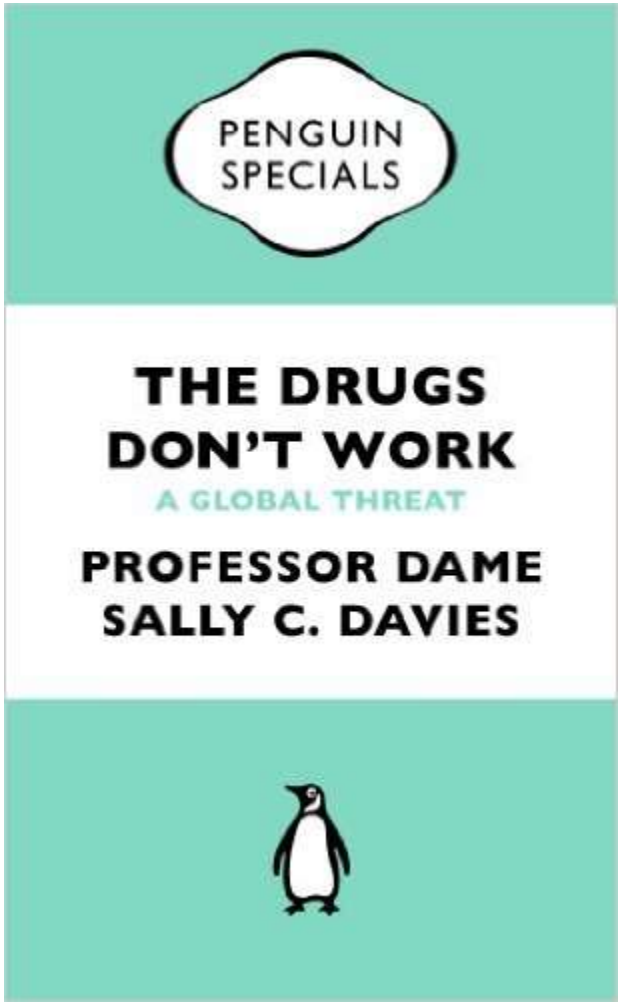

TEDx

The drugs don't work: Sally Davies at TEDxAlbertopolis: https://www.youtube.com/watch?v=7evvWt8XN7o

Life in the post-antibiotic era is going to suck | Kevin Judice | TEDxSMU https://www.youtube.com/watch?v=YHiMsoj3XHk

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Department of Health

Department for Environment Food & Rural Affairs

UK Five Year Antimicrobial Resistance Strategy 2013 to 2018

Northern Ireland Executive

Llywodraeth Cymru Welsh Government

The Scottish Government Riaghaltas na h-Alba

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7 Key Areas

- Improving infection prevention and control practices
- Optimising prescribing practice
- Improving professional education, training and public engagement
- Developing new drugs, treatments and diagnostics
- Better access to and use of surveillance data
- Better identification and prioritisation of AMR research needs
- Strengthened international collaboration

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Public Health England

NHS

Patient Safety Alert

Stage Two: Resources

Addressing antimicrobial resistance through implementation of an antimicrobial stewardship programme

18 August 2015

Alert reference number: NHS/PSA/Re/2015/007

Alert stage: Two - Resources

Antimicrobial resistance (AMR) has risen alarmingly over the last 40 years and inappropriate use of antimicrobials is a key driver[1]. From 2010 to 2013, total antibiotic prescribing in England increased by 6%, comprised of a 4% rise in general practice and a 12% increase in hospital inpatient prescribing[2].

The consequences of AMR include increased treatment failure for common infections and decreased treatment options where antibiotics are vital, such as during certain cancer treatments[3]. Antimicrobial stewardship is key to combating AMR and is an important element of the UK Five Year Antimicrobial Resistance Strategy[4].

Antimicrobial stewardship embodies an organisational and system-wide approach to promoting and monitoring the judicious use of antimicrobials by:

- optimising therapy for individual patients;
- preventing overuse and misuse; and
- minimising the development of resistance at patient and community levels.

This alert has been jointly issued by Health Education England, NHS England and Public Health England (PHE) to highlight the challenge of AMR and to signpost the toolkits developed by PHE to support the NHS in improving antimicrobial stewardship in both primary and secondary care.

Primary care resource (including out-of-hours, urgent care centres and walk-in centres)

- TARGET (Treat Antibiotics Responsibly, Guidance, Education, Tools) (http://www.rcgp.org.uk/clinical-and-research/target-antibiotics-toolkit.aspx) is designed to be used by the whole primary care team within the GP practice or out-of-hours setting, as well as being relevant to mental health care settings. The toolkit aims to help influence prescribers' and patients' attitudes, beliefs and perceived barriers to optimal antibiotic prescribing.

Secondary care resource

- Start Smart then Focus (https://www.gov.uk/government/publications/antimicrobial-stewardship-start-smart-then-focus) provides an outline of evidence-based antimicrobial stewardship practice for use in secondary care settings. The toolkit provides information on strategies to improve antibiotic use within secondary care as well as suggested audits to improve practice.

The actions in this alert will also support the current national work on sepsis to ensure both appropriate antibiotic prescribing and review (https://www.england.nhs.uk/2014/09/02/psa-sepsis/).

These toolkits should be read alongside, "*Clostridium difficile*: how to deal with the problem"[5], "*Clostridium difficile* infection: risk with broad-spectrum antibiotics"[6], and the recently published "Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use"[7].

It is proposed that antimicrobial stewardship management teams/committees, or equivalent, use evidence of implementation of the recommendations in these resources to demonstrate compliance with the Code of Practice on the prevention and control of infections[8].

Actions

Who: All organisations providing NHS funded care where antibiotics are prescribed, dispensed or administered

When: To commence immediately and be completed by 31 March 2016

1. Bring this Alert to the attention of those holding leadership roles for antimicrobial stewardship in your organisation (e.g. Directors of Infection Prevention in acute and ambulance trusts, Heads of Medicines Optimisation in acute and mental health trusts, lead GPs and lead pharmacists in primary care).
2. Review the resources signposted in this Alert and through linking with organisational or cross-system antimicrobial stewardship teams/committees, or equivalent, identify how the resources can be used to support your local antimicrobial stewardship programme.
3. By either circulating this Alert or through local alternatives (such as newsletters, local awareness campaigns etc.) ensure that staff are aware of the key antimicrobial stewardship messages and resources relevant to their clinical practice.

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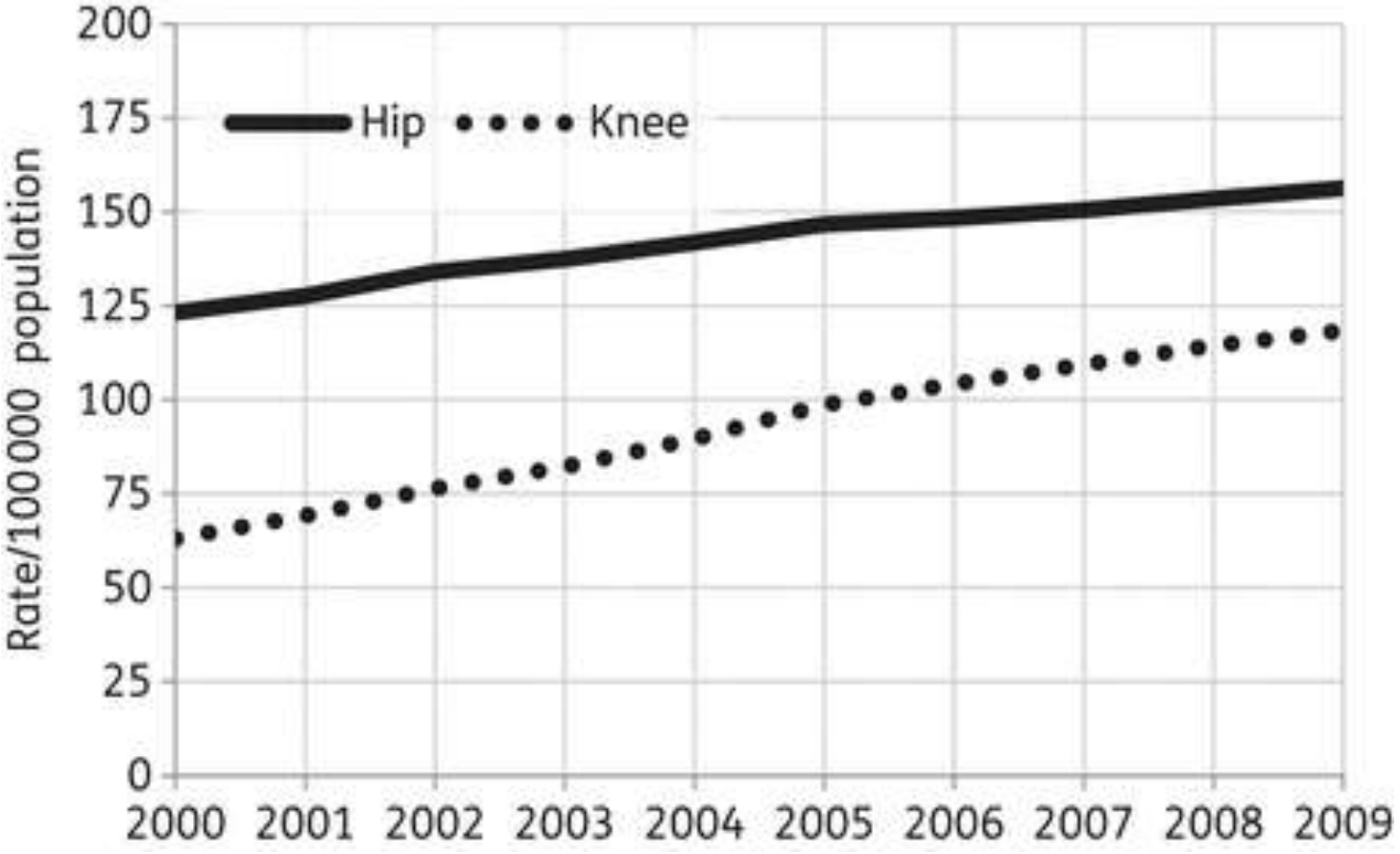

Trends in hip and knee replacement surgery across OECD countries. Data extracted from Figures 4.7.3 and 4.7.4, Health at a Glance 2011: OECD Indicators (http://www.oecd.org/els/health-systems/49105858.pdf). Hip data for 25 OECD countries; knee data for 21 OECD countries.

Figure 3: Trends in the annual cumulative incidence of SSI (%) in the orthopaedic surveillance categories, with lower and upper 95% CIs, NHS hospitals in England

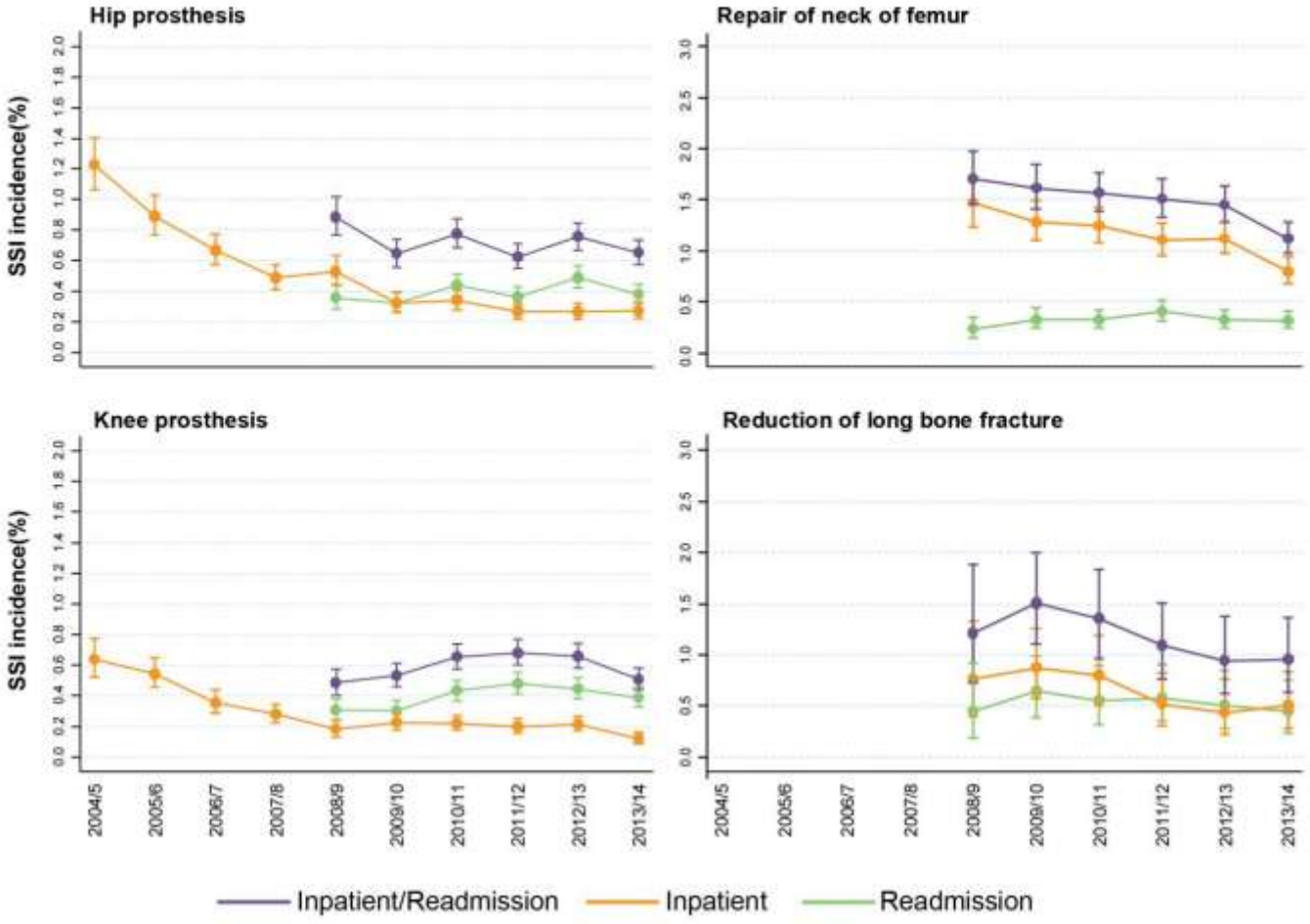

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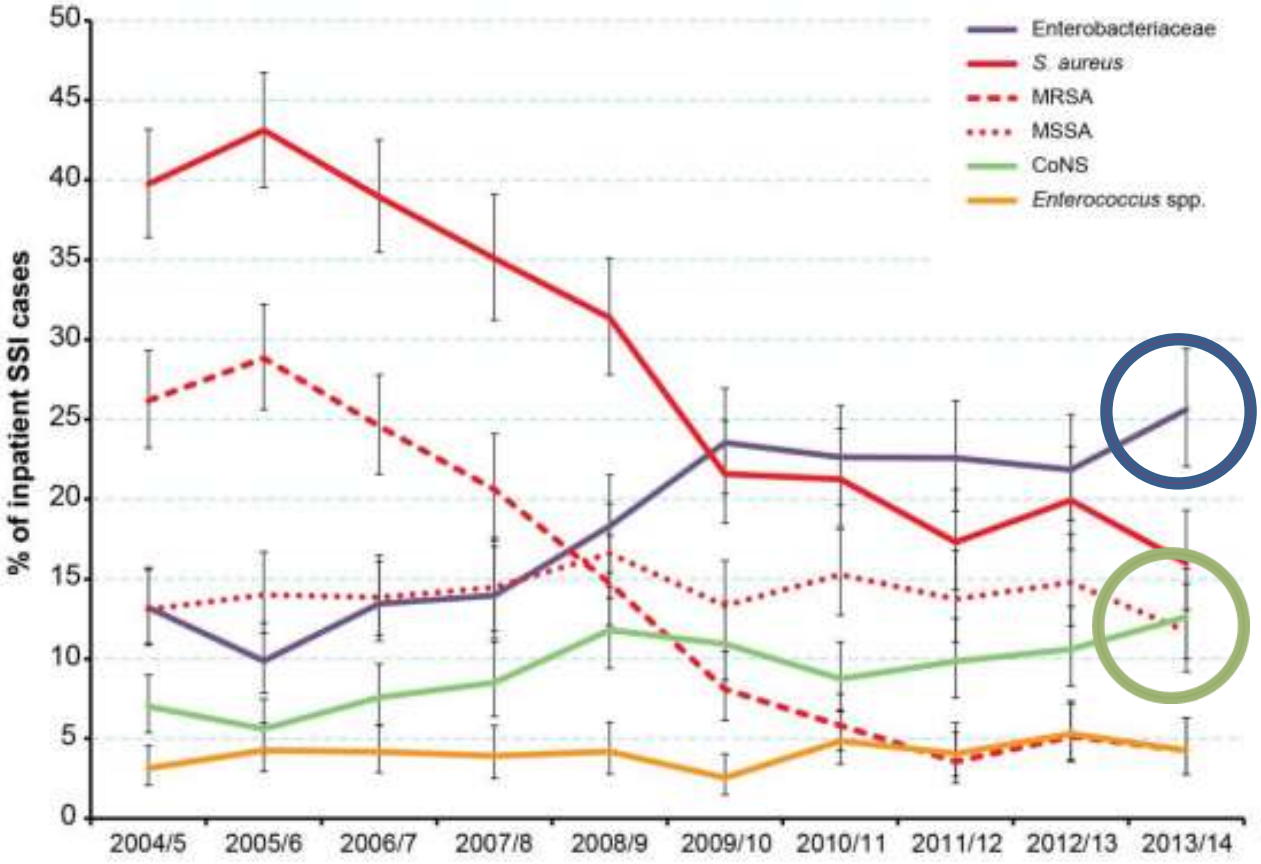
Figure 8: Trends in key micro-organisms reported as causing SSI (inpatient), all surgical categories*, NHS hospitals in England



*excludes breast, cranial, cardiac (non-CABG) and cranial surgery

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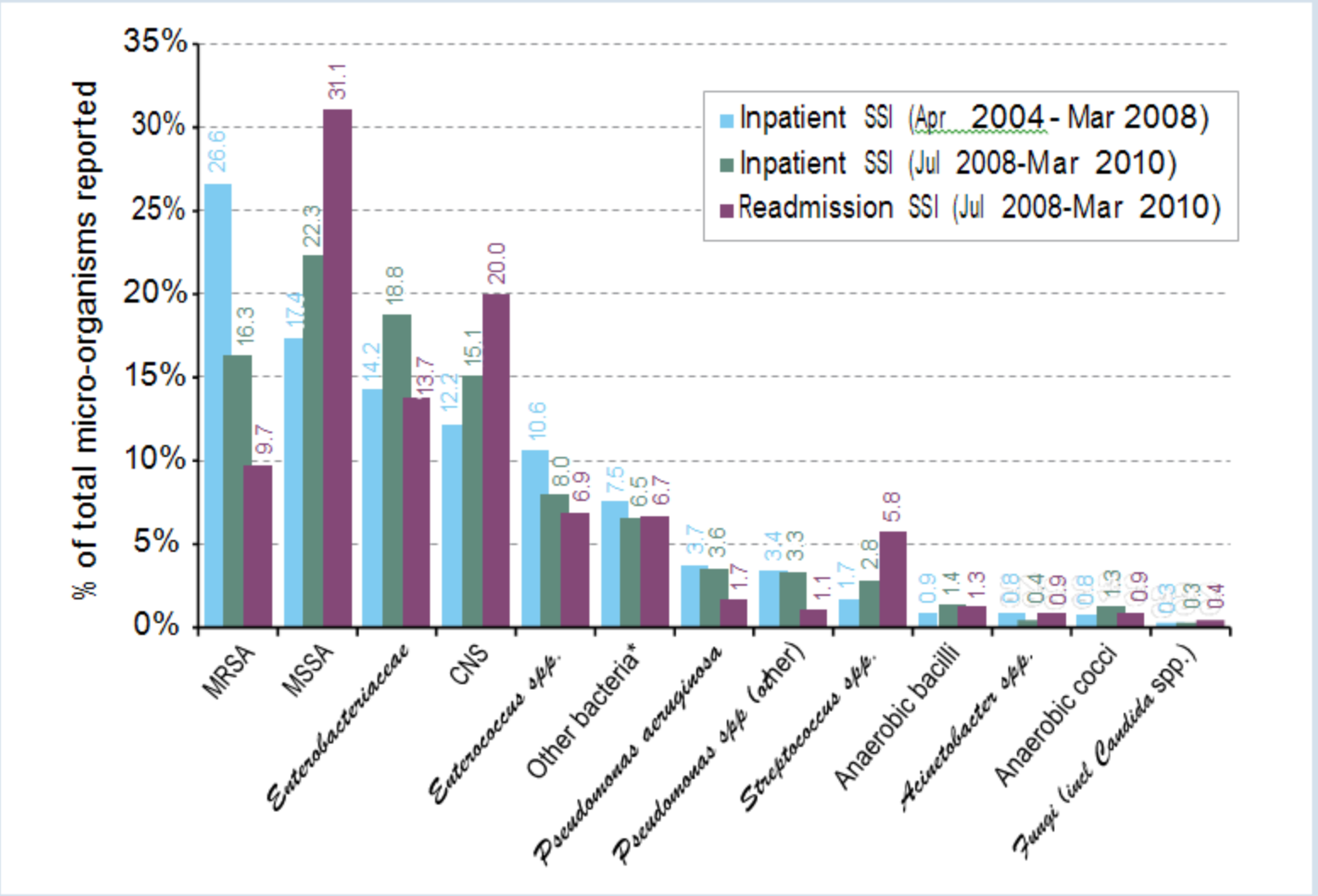
Figure 10: Micro-organisms reported as causing SSI (all orthopaedic categories), England



*Other bacteria includes mainly: Diptheroids (unspecified); *Bacillus* spp, *Corynebacterium* spp.

(Sixth Report of the Mandatory Surveillance of Surgical Site Infection in Orthopaedic Surgery)

Organisms isolated from 55 patients with PJI Nov 2007-May 2009

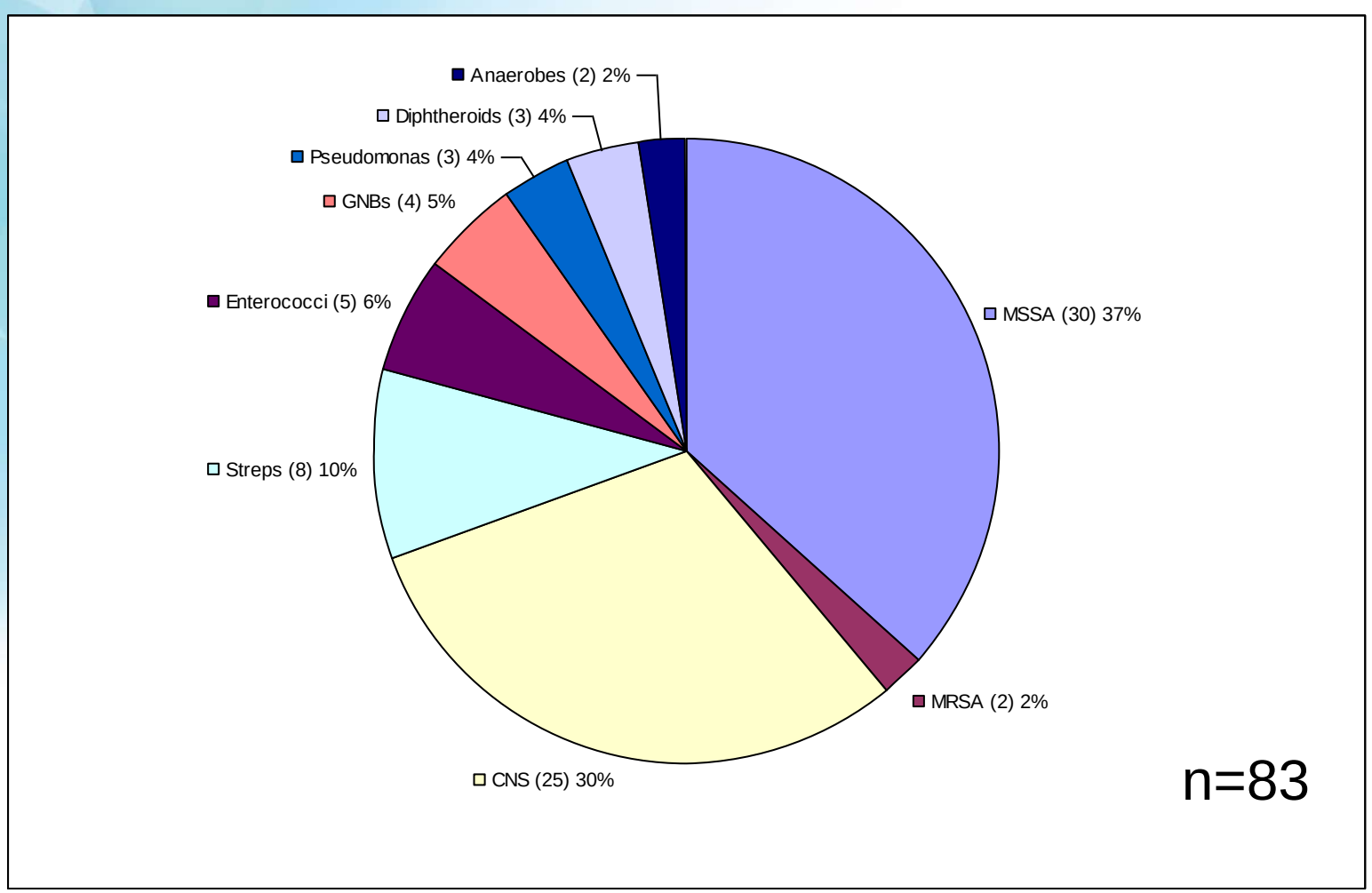


Table I. Micro-organisms reported as causing surgical site infection (SSI) following hip or knee prosthesis surgery (Apr 2010 to Mar 2013)

		London		Midland and East of England		North of England		South of England		England (total)	
No.	%	n	%	n	%	n	%	n	%	n	%
All SSI isolates	MSSA	25	*20.2*	88	*27.2*	87	*26.9*	91	*29.2*	291	*26.9*
	MRSA	3	*2.4*	24	*7.4*	8	*2.5*	10	*3.2*	45	*4.2*
	CoNS	39	*31.5*	73	*22.5*	85	*26.3*	79	*25.3*	276	*25.5*
	Enterobacteriaceae	20	*16.1*	52	*16.0*	58	*18.0*	39	*12.5*	169	*15.6*
	Other bacteria*	10	*8.1*	35	*10.8*	26	*8.0*	40	*12.8*	111	*10.2*
	Enterococcus spp.	11	*8.9*	20	*6.2*	31	*9.6*	17	*5.4*	79	*7.3*
	Streptococcus spp.	5	*4.0*	24	*7.4*	17	*5.3*	21	*6.7*	67	*6.2*
	Pseudomonas spp.	11	*8.9*	6	*1.9*	11	*3.4*	14	*4.5*	42	*3.9*
	Fungi	0	*0.0*	2	*0.6*	0	*0.0*	1	*0.3*	3	*0.3*
	Total	124	*100*	324	*100*	323	*100*	312	*100*	1,083	*100*
Deep or organ-space SSI isolates	CoNS*	23	*31.5*	51	*24.6*	71	*30.5*	64	*27.2*	209	*27.9*
	MSSA	18	*24.7*	50	*24.2*	62	*26.6*	54	*23.0*	184	*24.6*
	MRSA	1	*1.4*	13	*6.3*	3	*1.3*	8	*3.4*	25	*3.3*
	Enterobacteriaceae	12	*16.4*	34	*16.4*	40	*17.2*	35	*14.9*	121	*16.2*
	Other bacteria†	5	*6.8*	20	*9.7*	19	*8.2*	32	*13.6*	76	*10.2*
	Enterococcus spp.	5	*6.8*	18	*8.7*	18	*7.7*	13	*5.5*	54	*7.2*
	Streptococcus spp.	3	*4.1*	18	*8.7*	12	*5.2*	19	*8.1*	52	*7.0*
	Pseudomonas spp.	6	*8.2*	2	*1.0*	8	*3.4*	9	*3.8*	25	*3.3*
	Fungi	0	*0.0*	1	*0.5*	0	*0.0*	1	*0.4*	2	*0.3*
	Total	73	*100*	207	*100*	233	*100*	235	*100*	748	*100*

* The majority in this group comprised diptheroids/Corynebacterium spp. (40%) followed by unidentified organisms (31%)
† The majority in this group comprised diptheroids/Corynebacterium spp. (42%) followed by unidentified organisms (28%)
MSSA, met(h)icillin-sensitive *S. aureus*; MRSA, met(h)icillin-resistant *S. aureus*; CoNs,coagulase-negative staphylococci

What is Antibiotic Stewardship?

- It is an inter-professional effort, across the continuum of care
- It 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 otherecological adverse events such as C. difficile”

[Nathwani et al., 2012]

All it is essentially is:

- **right antibiotic**
- **right patient**
- **right time**
- **right dose**
- **right route**
- **every time**
- **causing the least harm to the patient and future patients**

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What Can We Do?

- Educate and raise awareness among healthcare workers and the general public
- Restrict/improve the use of the antibiotics we have now
- Improve infection control

Teamwork

- SSI Steering Group
- Robust surveillance
  - SSI Surveillance nurses/co-ordinators
- Training and education
- Rigorous examination of published literature
  - pre-, peri- and post-op interventions
- Improved surgical discipline & standardisation
- Regular review of infecting organisms and sensitivities
- Collaboration in development of antibiotic guidelines
- Action planning
- RCAs of all deep infections
- Audits
- Real-time feedback
- Open sharing and dissemination of information
- Publication of our work and research
- Training events open to other organisations
- Patient involvement

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But most importantly

- **All potentially infected orthopaedic patients should be discussed by and MDT**

- Members may include:
  - Orthopaedic surgeons
  - Trainees
  - Surgical assistants
  - Microbiologists
  - Infectious Disease Physicians
  - Research nurses
  - Surveillance nurses

- Consider:
  - Teleconferencing
  - Virtual MDTs via email

Summary

- Antibiotics are a powerful tool in the prevention and treatment of infection

- But, they must be used appropriately to reduce the risk of adverse effects for the individual and to slow down the development of resistance and preserve their usefulness for the next generation and beyond

- This will require working together as a team locally, nationally and globally.

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Take Home Messages

- Antibiotic resistance is rapidly increasing globally
- There are not likely to be any new classes of antibiotics in the next 10-20 years
- We need to look after the antibiotics we have
- Regular review of local orthopaedic infections to identify resistance trends and update antibiotic guidelines accordingly
- Always follow the local antibiotic guidelines or phone a friend

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Antibiotic Action

Securing the future of antibiotic development …. determined to make a difference

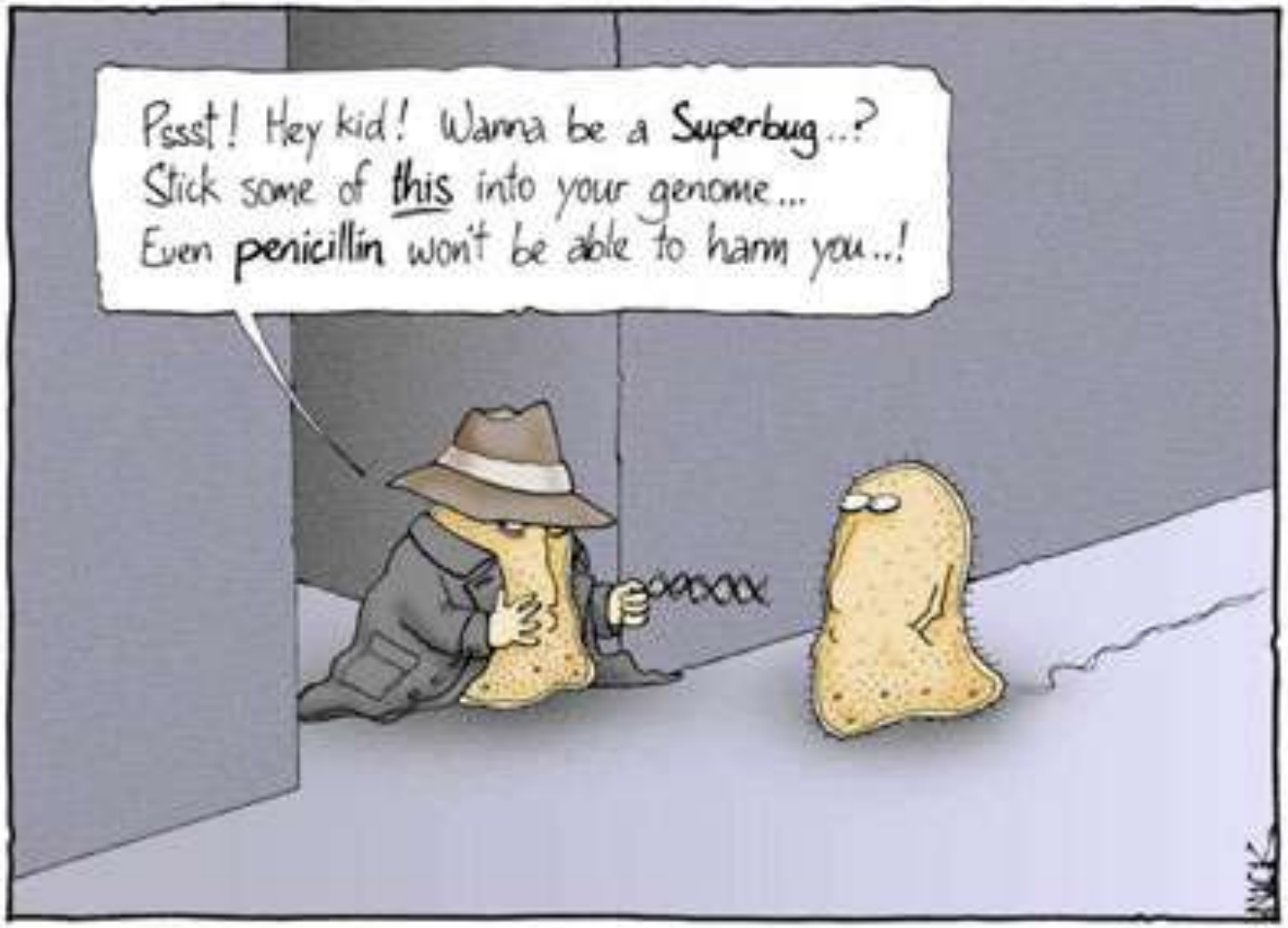
www.antibiotic-action.com

New antibiotics are urgently needed for use now and in the future

No antibiotics – no chemotherapy | No antibiotics – no transplant surgery | No antibiotics – no hip/knee replacements | No antibiotics – no treatment for infectious diseases | No antibiotics – no heart surgery | No antibiotics – no cystic fibrosis treatment | No antibiotics – no kidney transplants

NO ANTIBIOTICS – NO CURE – NO CHANCE

The simple truth



It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

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The End
Any Questions?

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Thank you