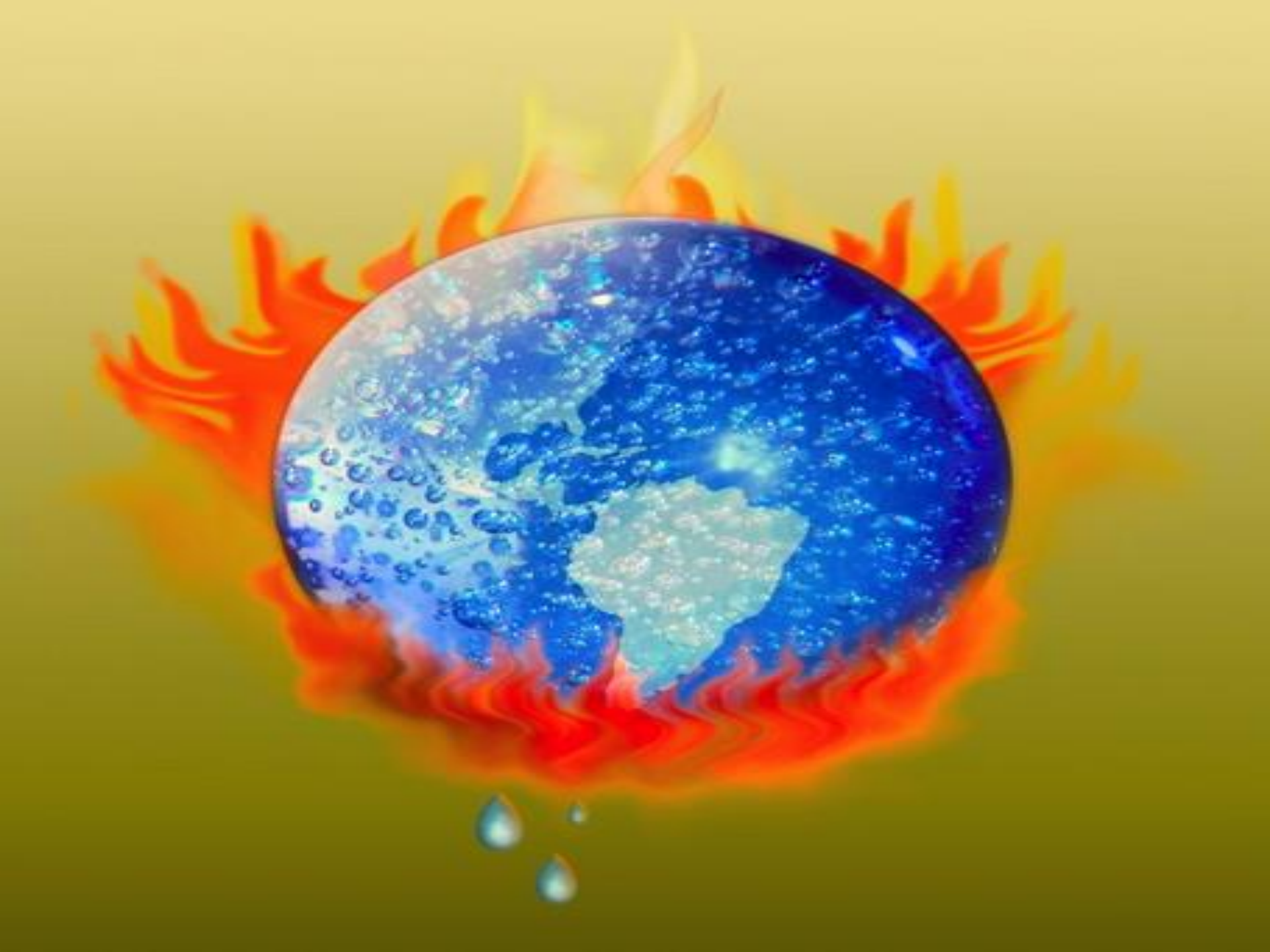
Use of antibiotics – how can we avert catastrophe?

Dr Neil Todd
Clinical Microbiologist
York Teaching Hospital



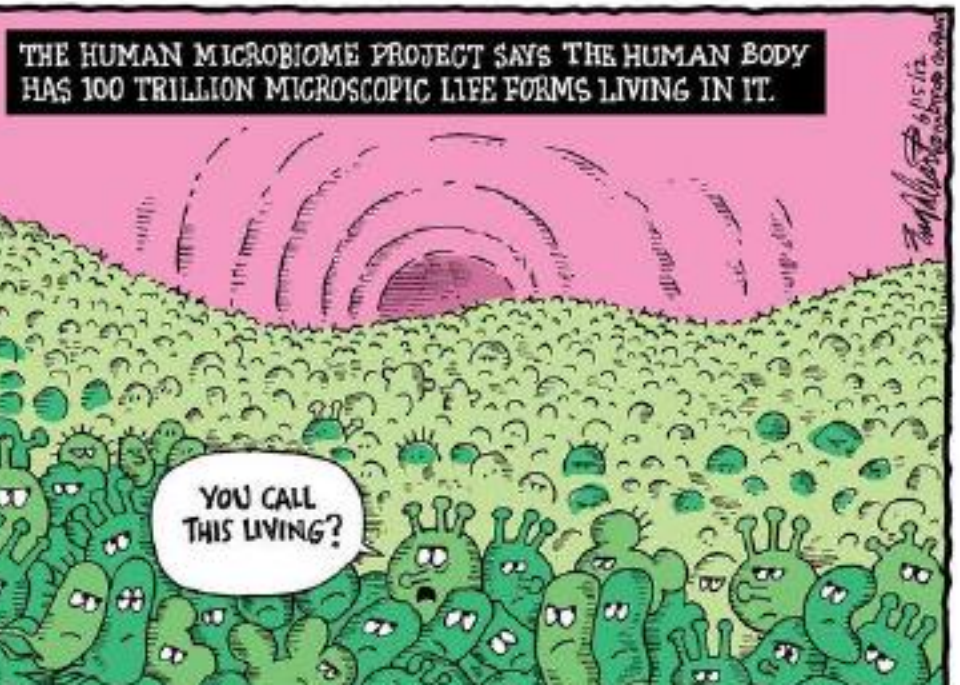
Problems in using antibiotics.

- Side effects.
- Changes microbiome.
- Superinfection.
- Promote cross infection.
- Bacterial resistance.

- Must balance risk and benefit.

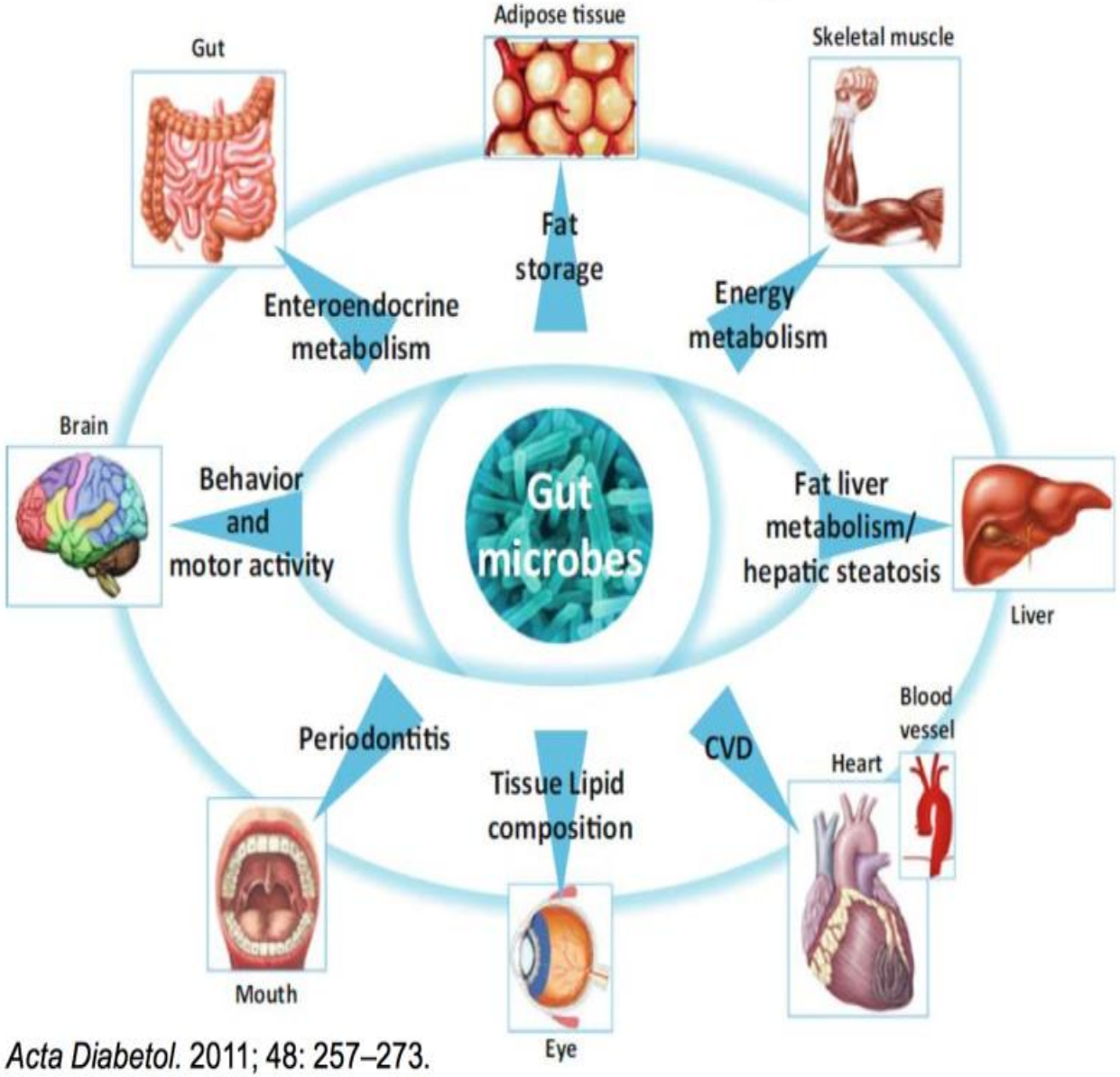
Human Microbiome "Gut Flora"

- 10 times more cells than human cells. ~200g of symbiotic bacteria
- Protective effect against auto-immune diseases like diabetes, rheumatoid arthritis, muscular dystrophy, multiple sclerosis, fibromyalgia, and perhaps some cancers.



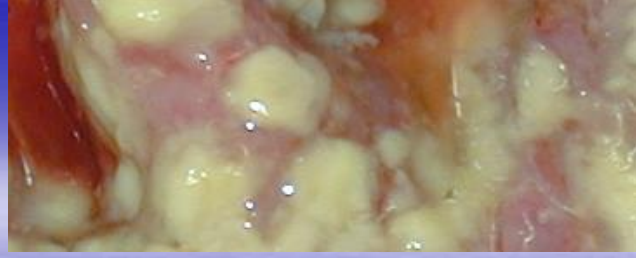
- Protect against invading pathogenic bacteria
- Microbiota are very similar in healthy people
- Chemotherapy and antibiotics can destabilise it

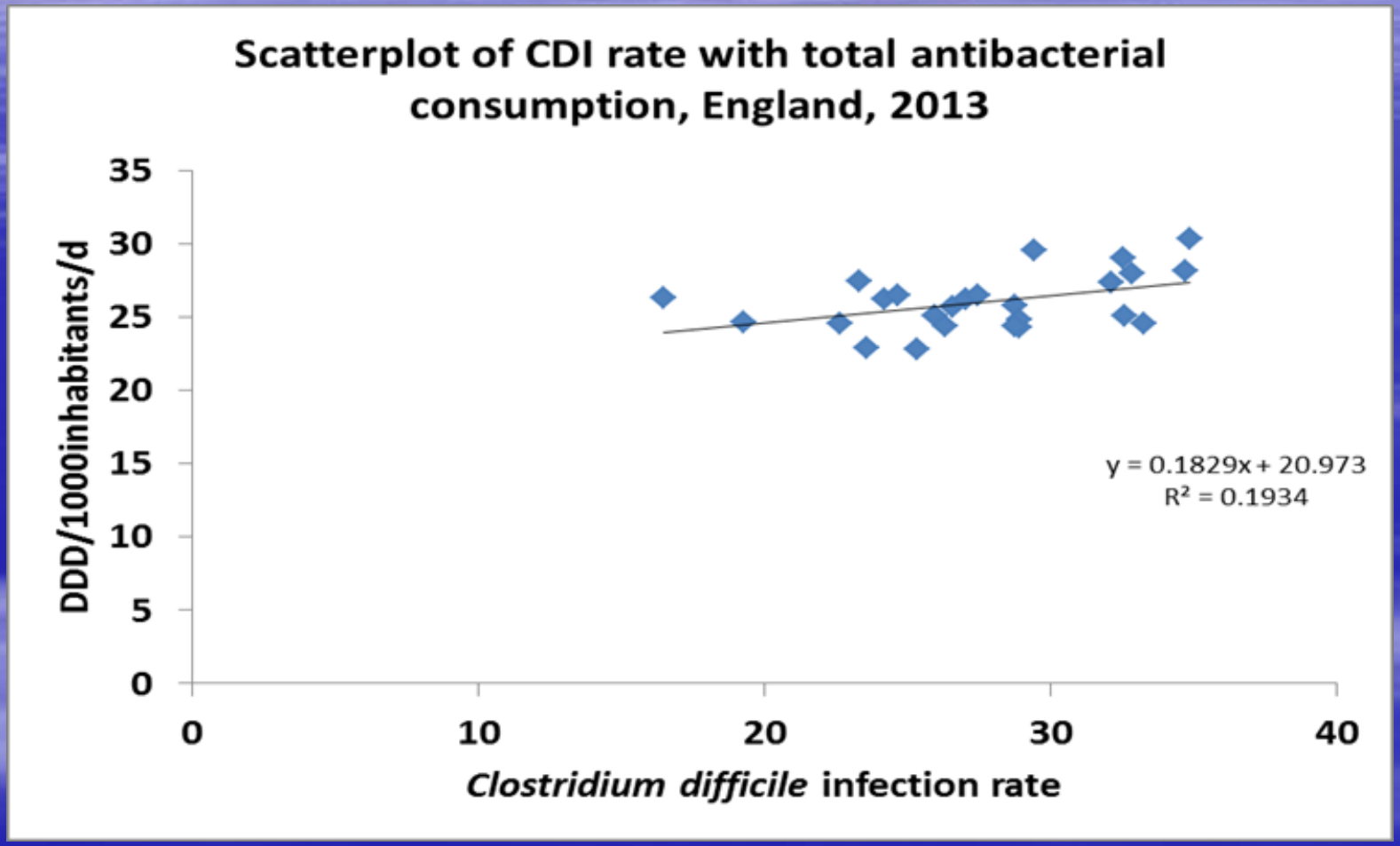
Microbiota – Far Reaching Effects



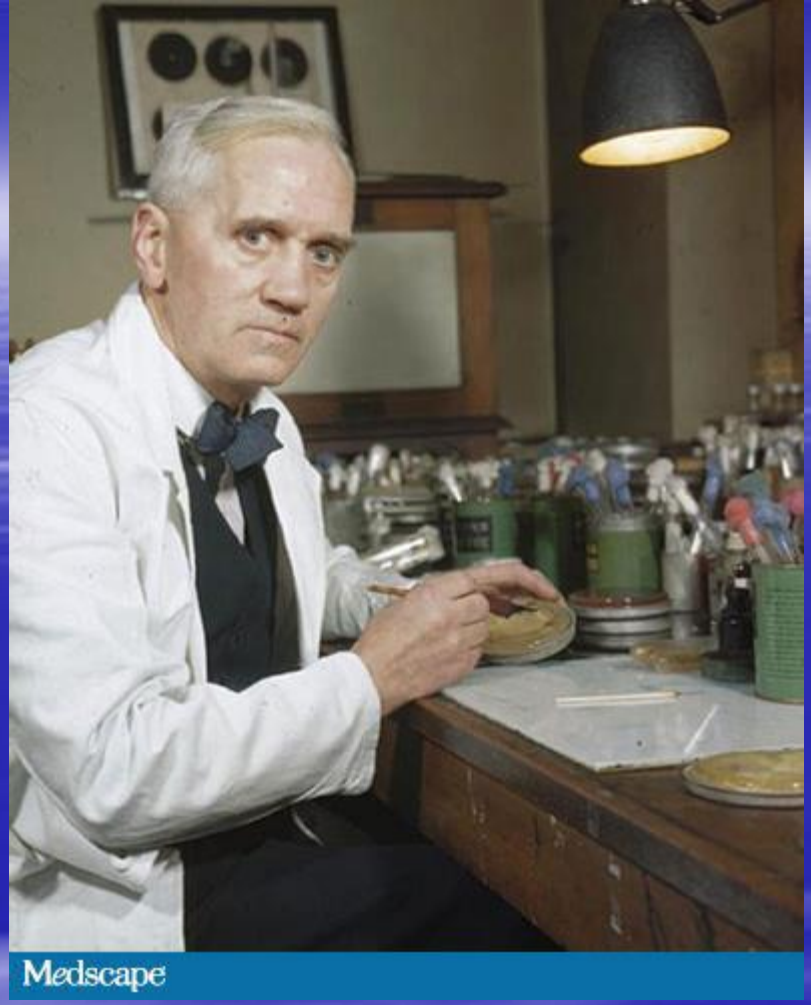
Burcelin R et al. *Acta Diabetol.* 2011; 48: 257–273.

Evidence: Antibiotic use and *Clostridium difficile* vary by area





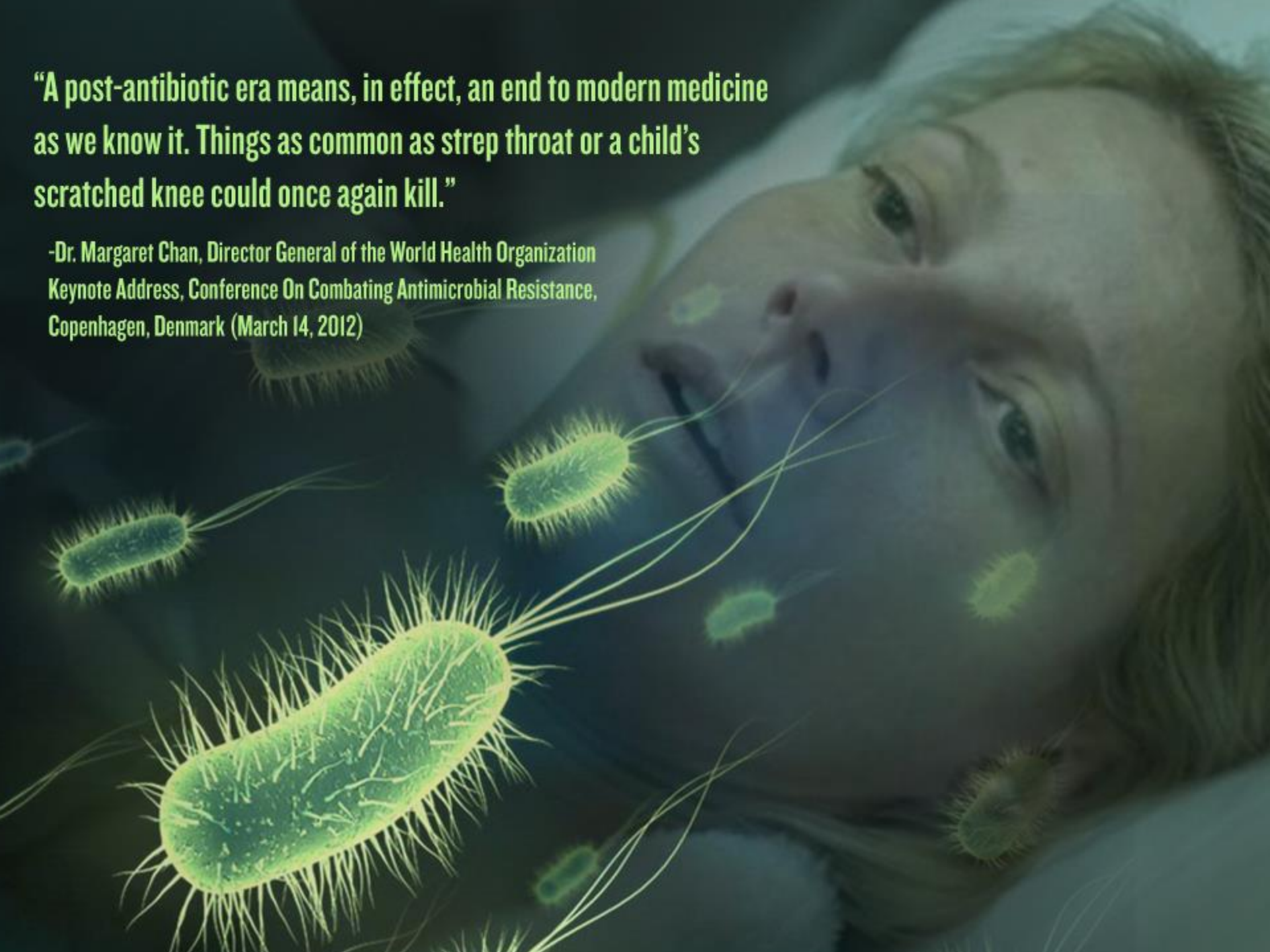
PHE surveillance data, Susan Hopkins 2014.

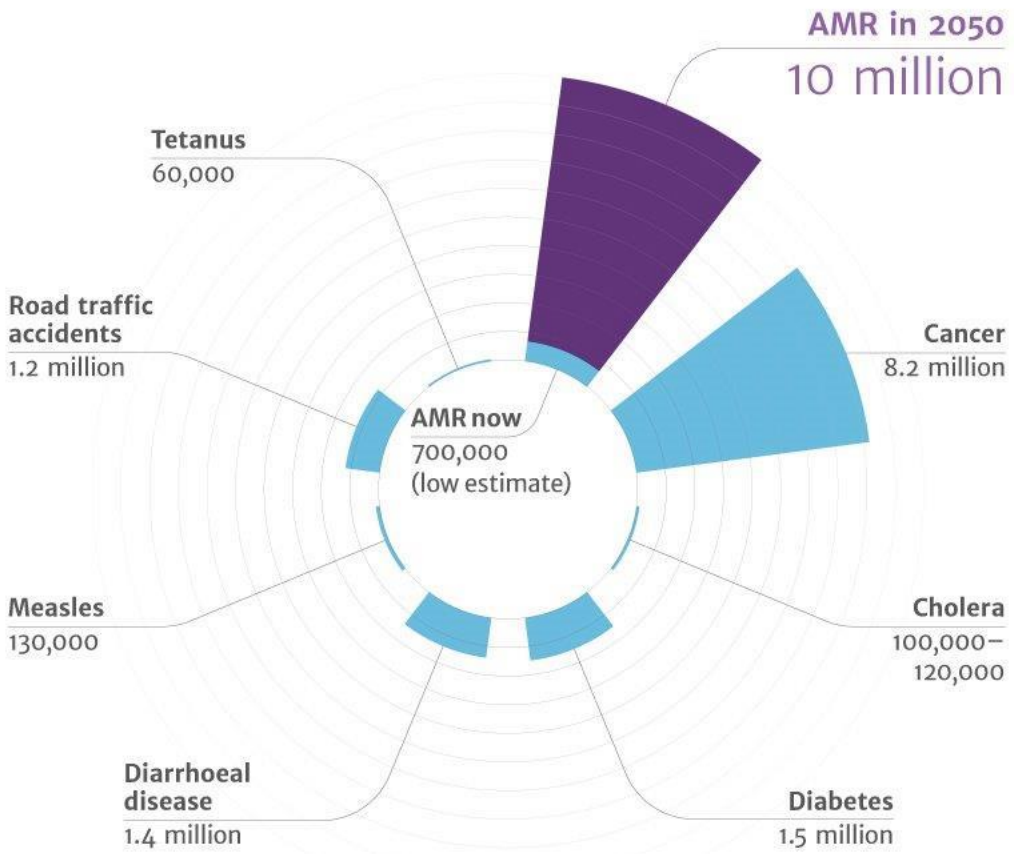


Overuse Them, and Lose Them

"In such cases, the thoughtless person playing with penicillin 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.“ Sir Alexander Fleming - 1945

ANTIBIOTIC ACTION

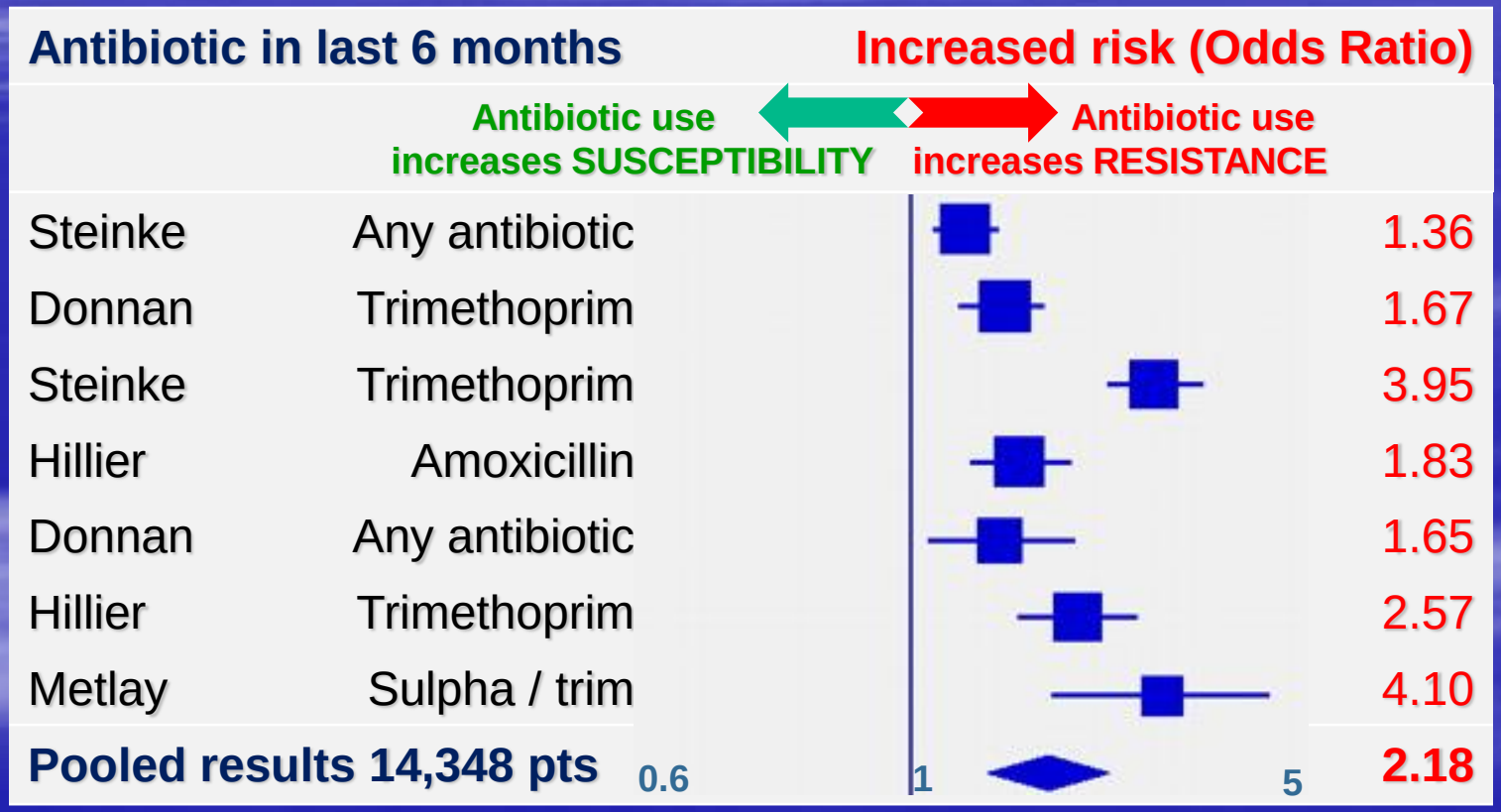

"A post-antibiotic era means, in effect, an end to modern medicine as we know it. Things as common as strep throat or a child's scratched knee could once again kill."
-Dr. Margaret Chan, Director General of the World Health Organization
Keynote Address, Conference On Combating Antimicrobial Resistance,
Copenhagen, Denmark (March 14, 2012)


AMR in 2050
10 million
Tetanus
60,000
Road traffic accidents
1.2 million
Cancer
8.2 million
AMR now
700,000
(low estimate)
Measles
130,000
Cholera
100,000–120,000
Diarrhoeal disease
1.4 million
Diabetes
1.5 million

Evidence:
Does our antibiotic use increase resistance?

Costelloe: Examined previous antibiotic use and subsequent resistance
5 studies of UTI with 14,348 patients in general practice

This Forest plots shows individual study and pooled odds ratio of increased risk



Longer duration and multiple courses associated with greater resistance

Costelloe C et al. BMJ 2010;340:bmj.c2096

Evidence: Risk of resistance persists for at least 12 months after your prescribing

	Increased risk of resistant organism	
	Antibiotic in past 2 months	**Antibiotic in past 12 months**
UTI 5 studies: n = 14,348	**2.5 times**	1.33 times
RTI 7 studies: n = 2,605	**2.4 times**	2.4 times

A meta analysis of English Primary Care

Costello *et al. BMJ. (*2010) 340:c2096.

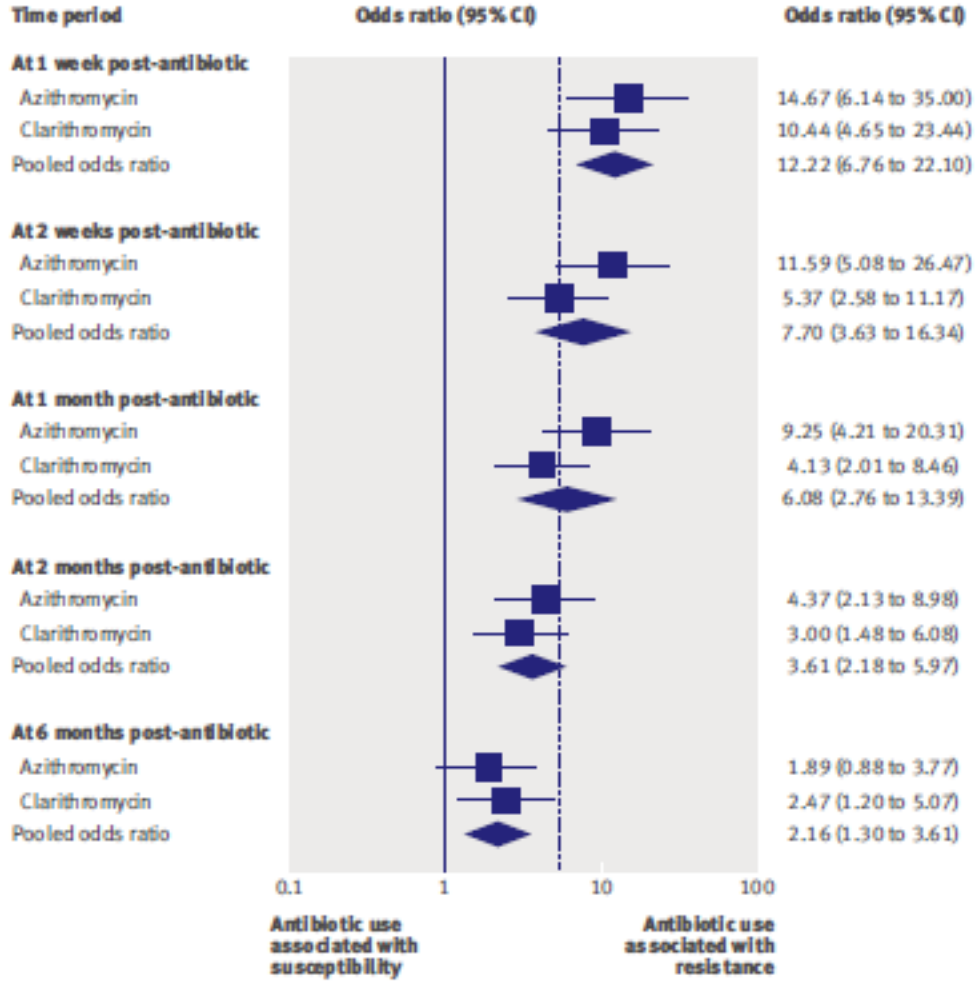


Fig 4| Forest plot showing individual analytic and pooled ORs (log scale) for resistance in respiratory tract streptococci of healthy volunteers from the Malhotra-Kumar study[85] and previous antibiotic prescribing

HAZARD LEVEL
URGENT

These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

Clostridium difficile (C. difficile), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

HAZARD LEVEL
SERIOUS

These are significant antibiotic-resistant threats. For varying reasons (e.g., low or declining domestic incidence or reasonable availability of therapeutic agents), they are not considered urgent, but these threats will worsen and may become urgent without ongoing public health monitoring and prevention activities.

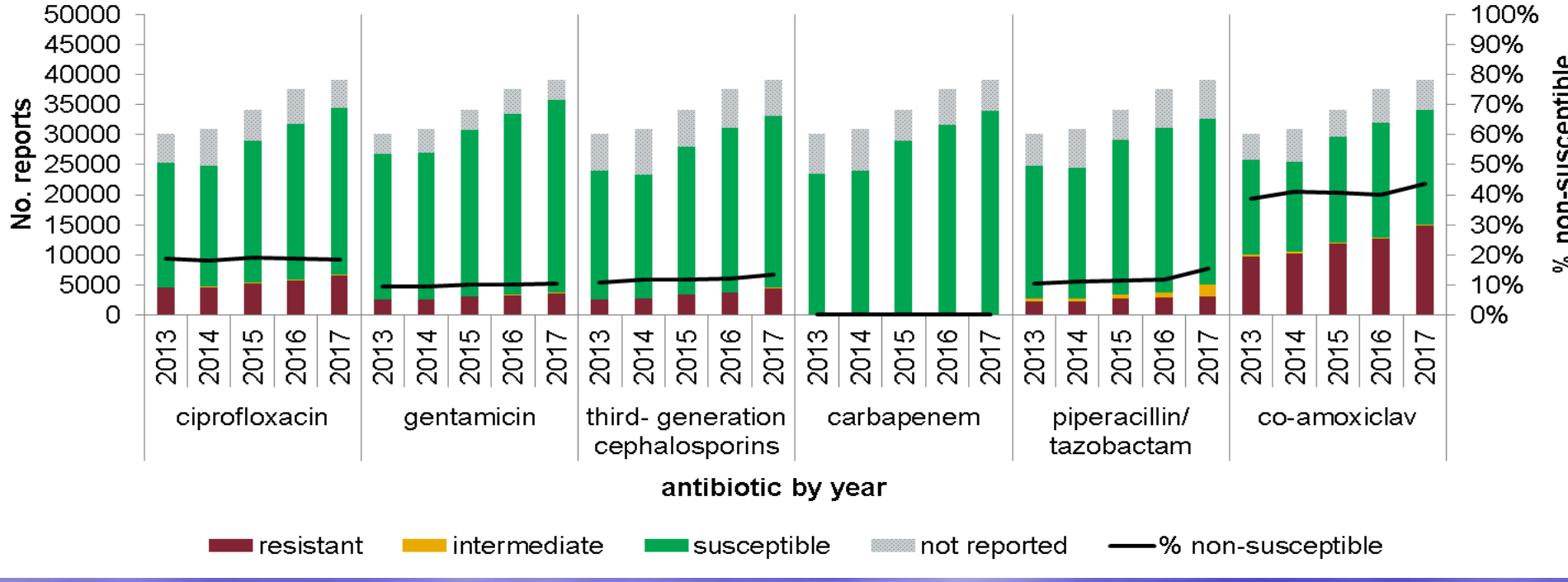
Multidrug-resistant *Acinetobacter*, Drug-resistant *Campylobacter*, Fluconazole-resistant *Candida* (a fungus), Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs), Vancomycin-resistant *Enterococcus* (VRE), Multidrug-resistant *Pseudomonas aeruginosa*, Drug-resistant Non-typhoidal *Salmonella*, Drug-resistant *Salmonella* Typhi, Drug-resistant *Shigella*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Drug-resistant *Streptococcus pneumonia*, Drug-resistant tuberculosis (MDR and XDR)

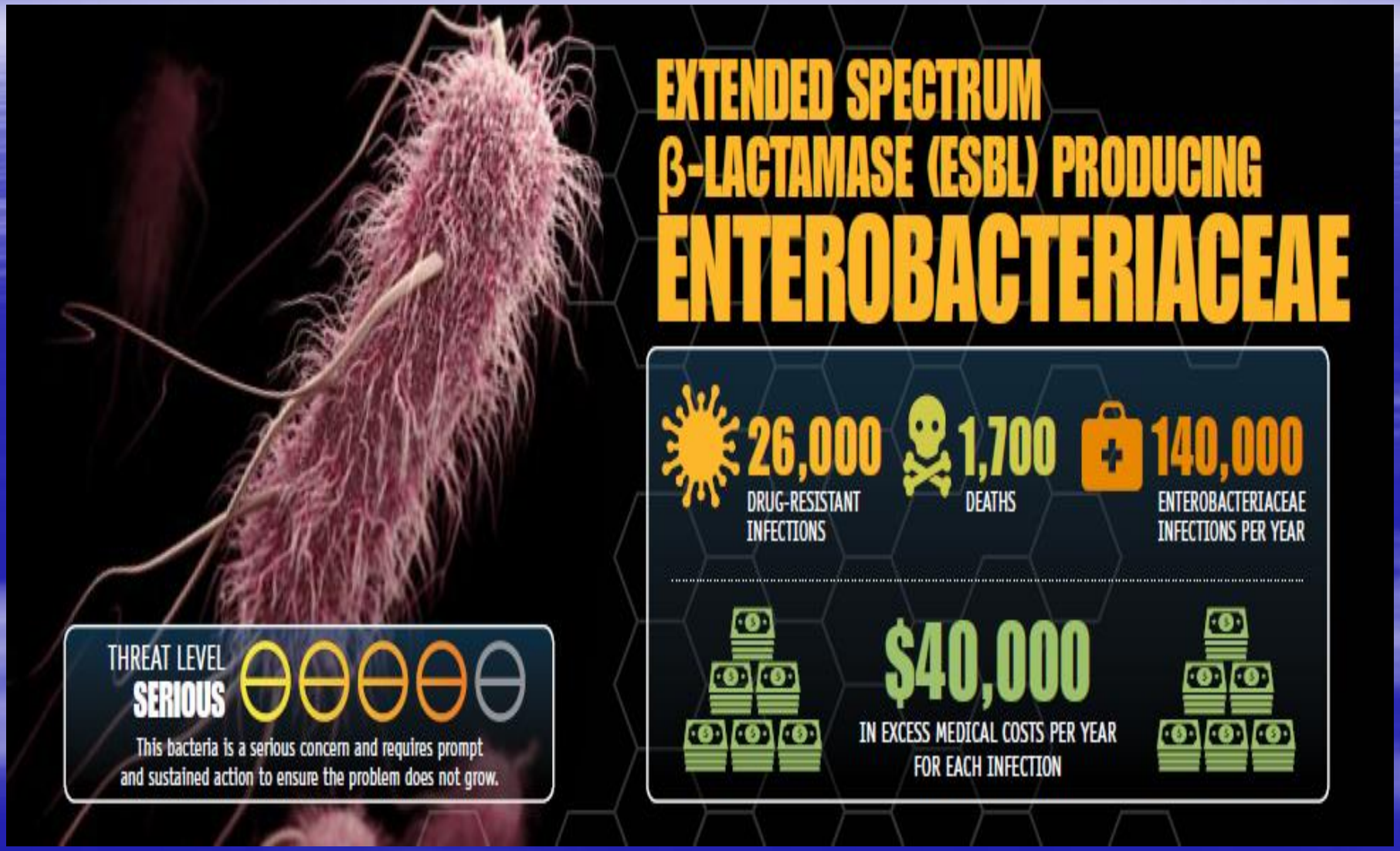
HAZARD LEVEL
CONCERNING

These are bacteria for which the threat of antibiotic resistance is low, and/or there are multiple therapeutic options for resistant infections. These bacterial pathogens cause severe illness. Threats in this category require monitoring and in some cases rapid incident or outbreak response.

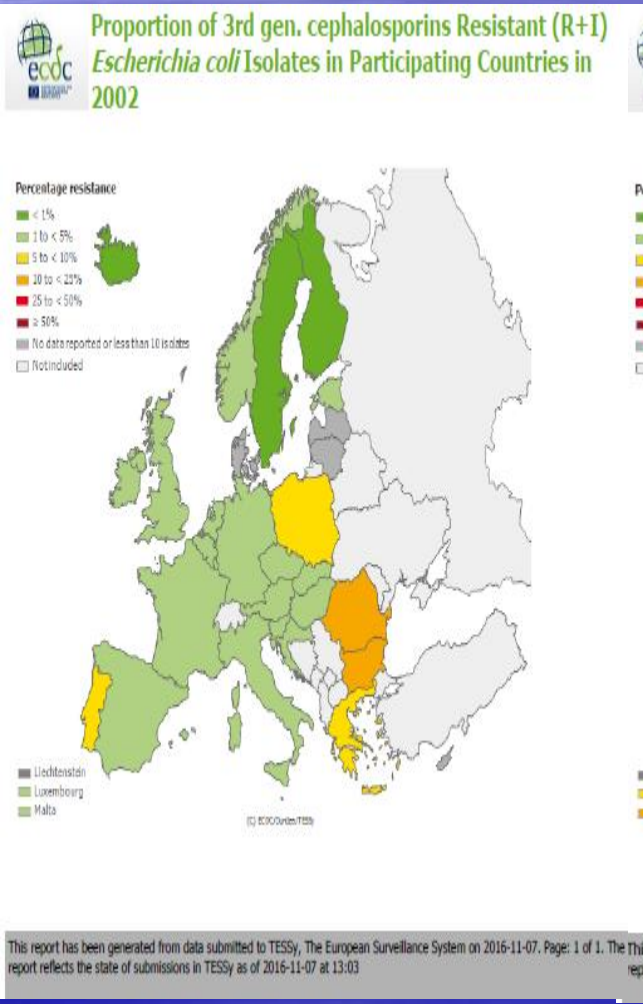
Vancomycin-resistant *Staphylococcus aureus* (VRSA), Erythromycin-resistant *Streptococcus* Group A, Clindamycin-resistant *Streptococcus* Group B

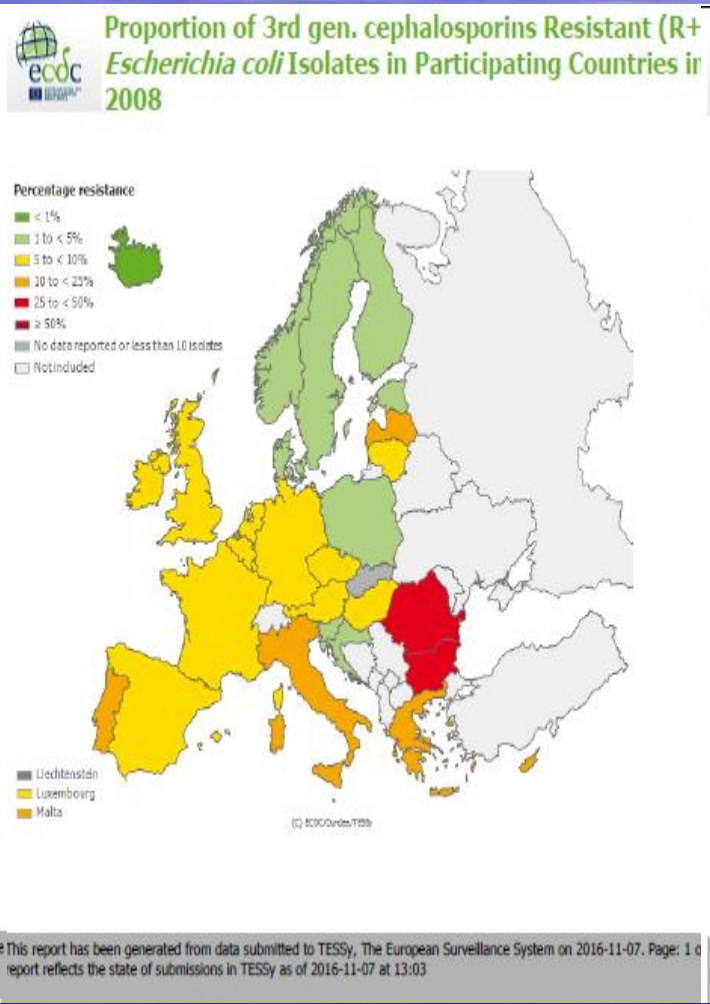
E. coli – ESPAUR 2018 Blood Cultures

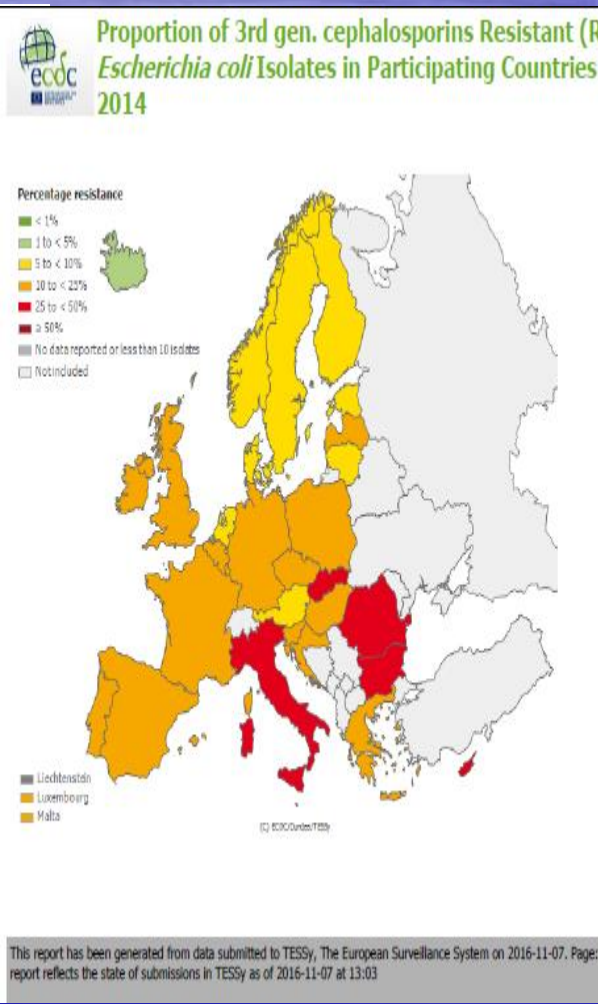



EXTENDED SPECTRUM
β-LACTAMASE (ESBL) PRODUCING
ENTEROBACTERIACEAE
26,000
DRUG-RESISTANT INFECTIONS
1,700
DEATHS
140,000
ENTEROBACTERIACEAE INFECTIONS PER YEAR
$40,000
IN EXCESS MEDICAL COSTS PER YEAR FOR EACH INFECTION
THREAT LEVEL
SERIOUS
This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

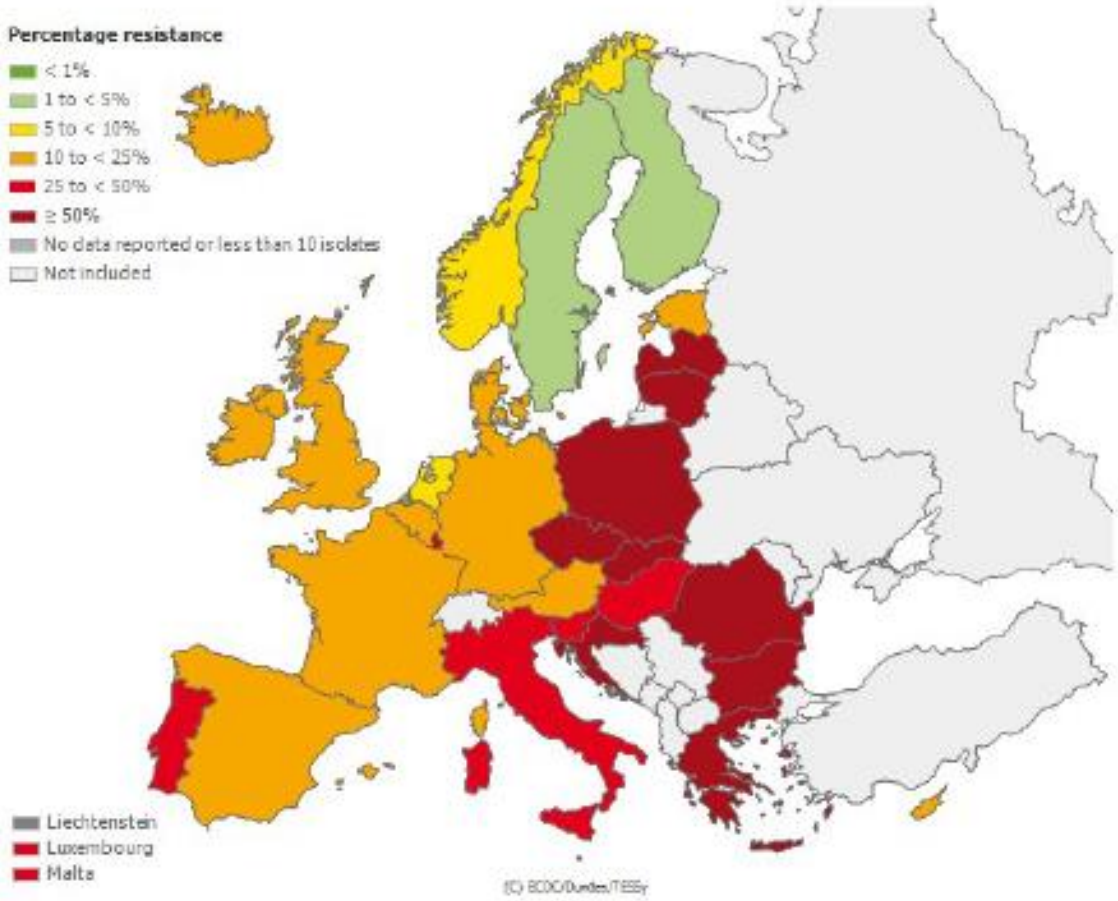
E coli resistant to 3rd gen cephalosporins from blood cultures - ESBLs

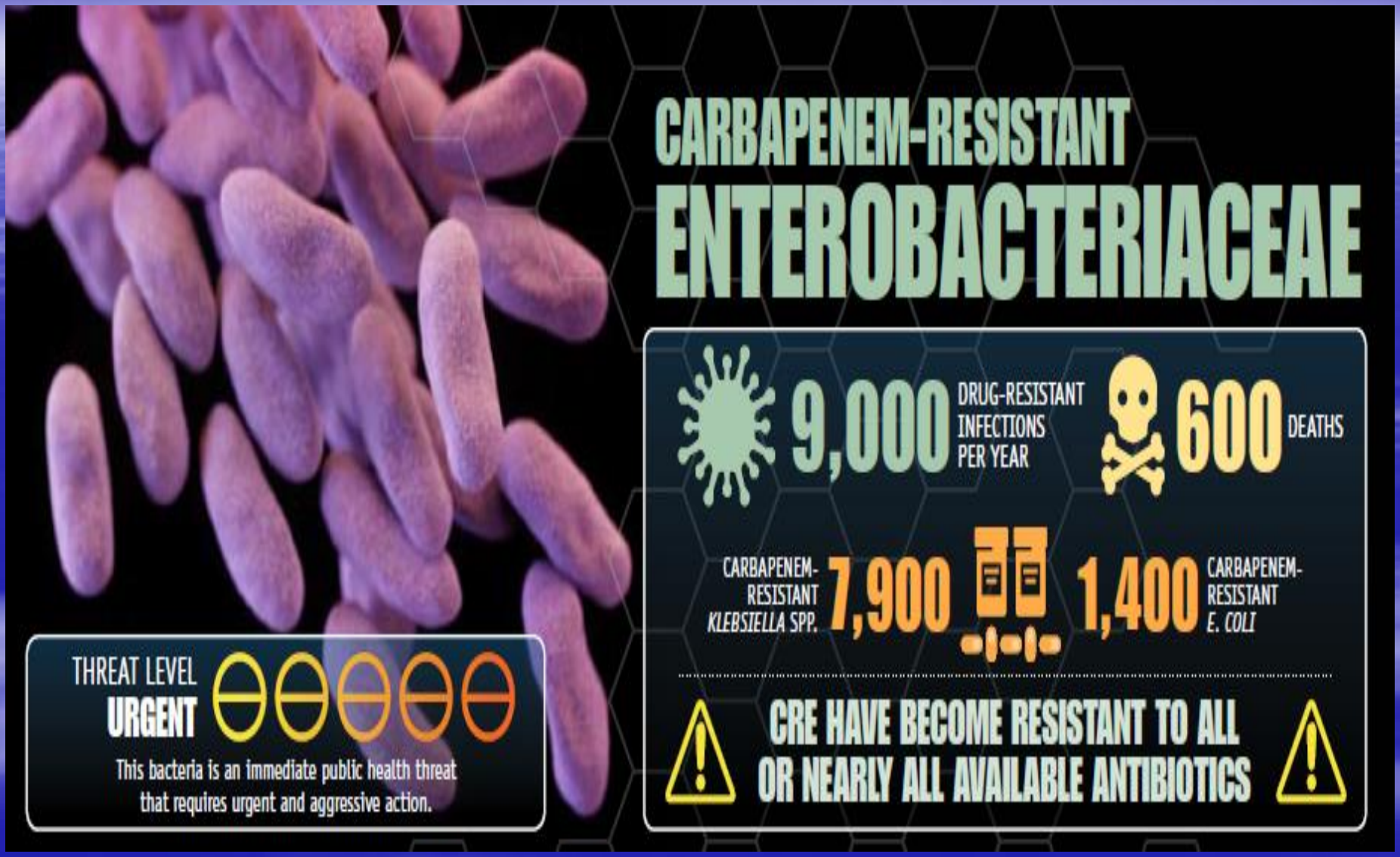






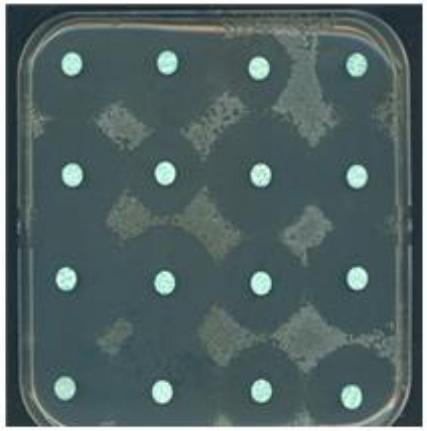
Proportion of 3rd gen. cephalosporins Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2012



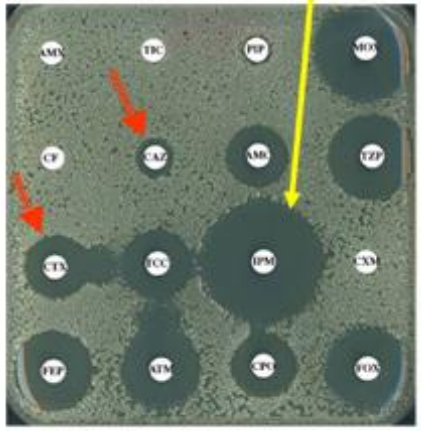

CARBAPENEM-RESISTANT
ENTEROBACTERIACEAE
9,000 DRUG-RESISTANT INFECTIONS PER YEAR
600 DEATHS
CARBAPENEM-RESISTANT KLEBSIELLA SPP. 7,900
1,400 CARBAPENEM-RESISTANT E. COLI
CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS
THREAT LEVEL
URGENT
This bacteria is an immediate public health threat that requires urgent and aggressive action.

Multidrug-resistance and therapeutic dead-ends
Escherichia coli, our best friend and our worst enemy

E. coli
of our youth



E. coli
of modern days



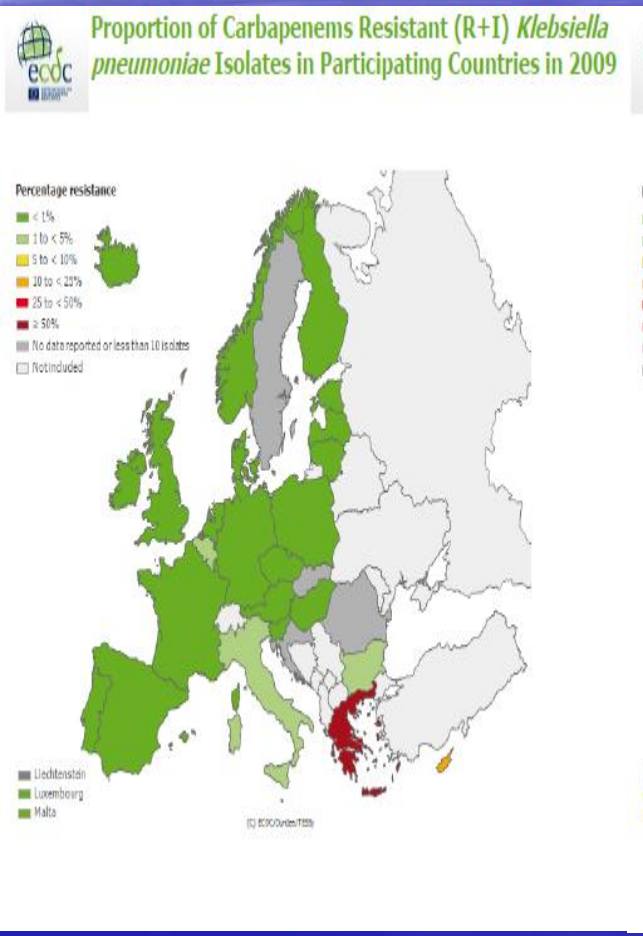
ESBL (CTX-M-15)

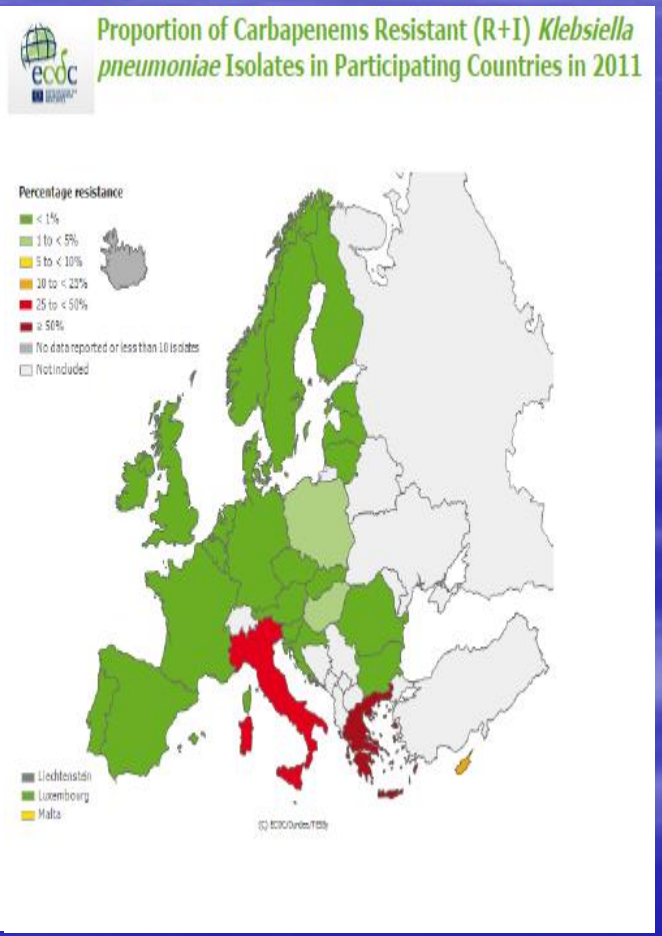
E. coli
of tomorrow

Carbapenemases
KPC, OXA-48, NDM, VIM, and IMP

CNR : Résistance aux antibiotiques

Carbapenem resistant Klebsiella from blood cultures





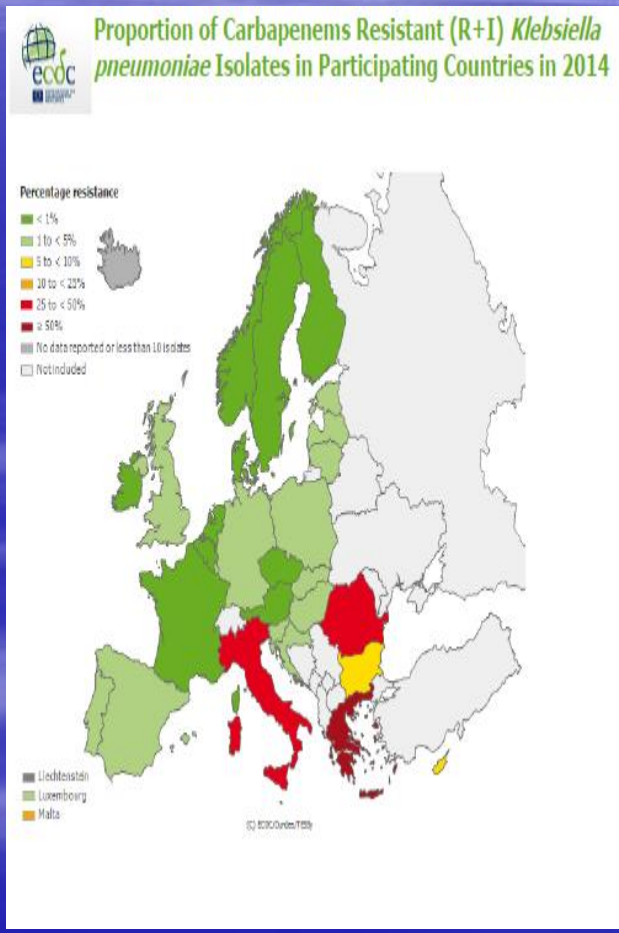


Figure 2.4 Number of confirmed CPE isolates referred to PHE's AMRHAI Reference Unit, 2008 – 2017

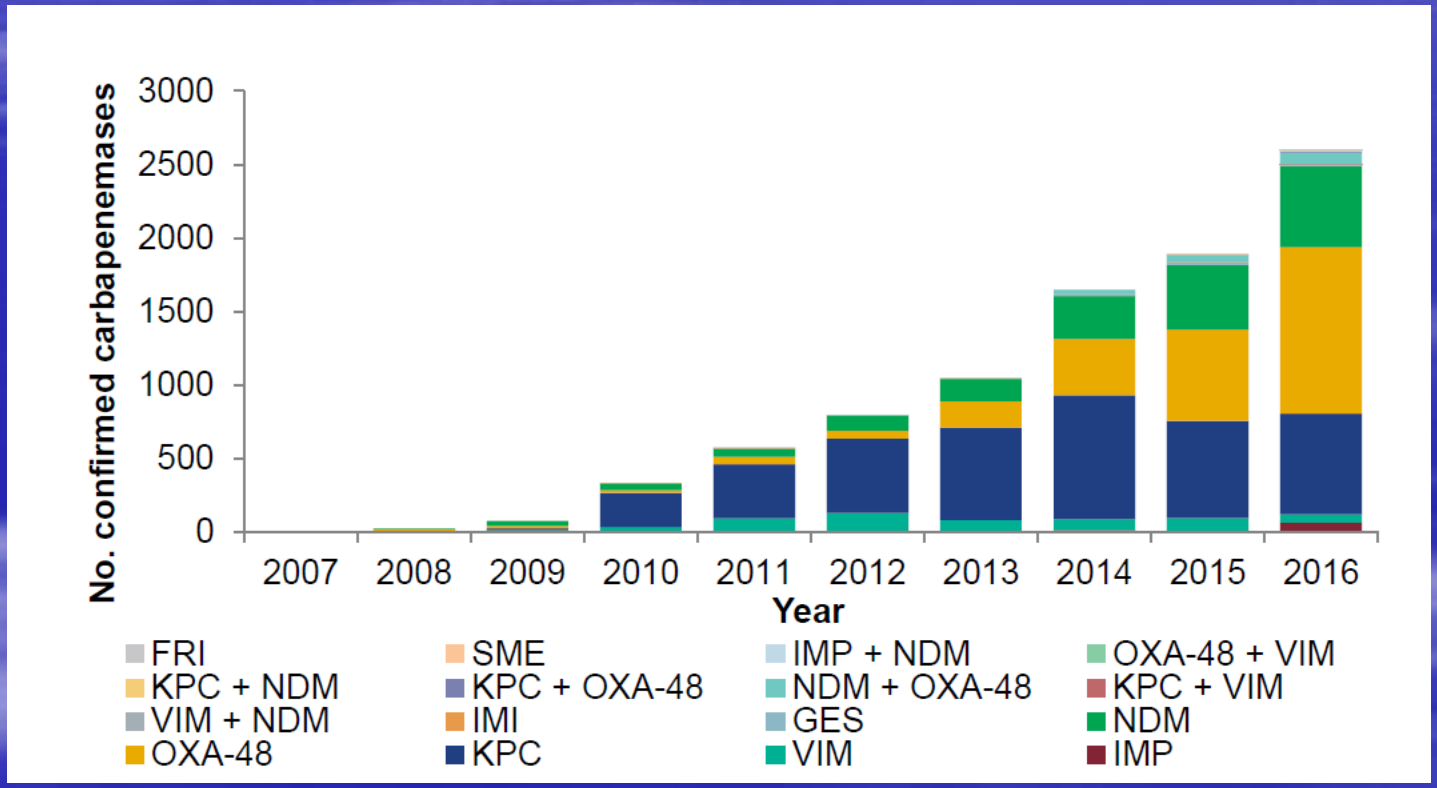
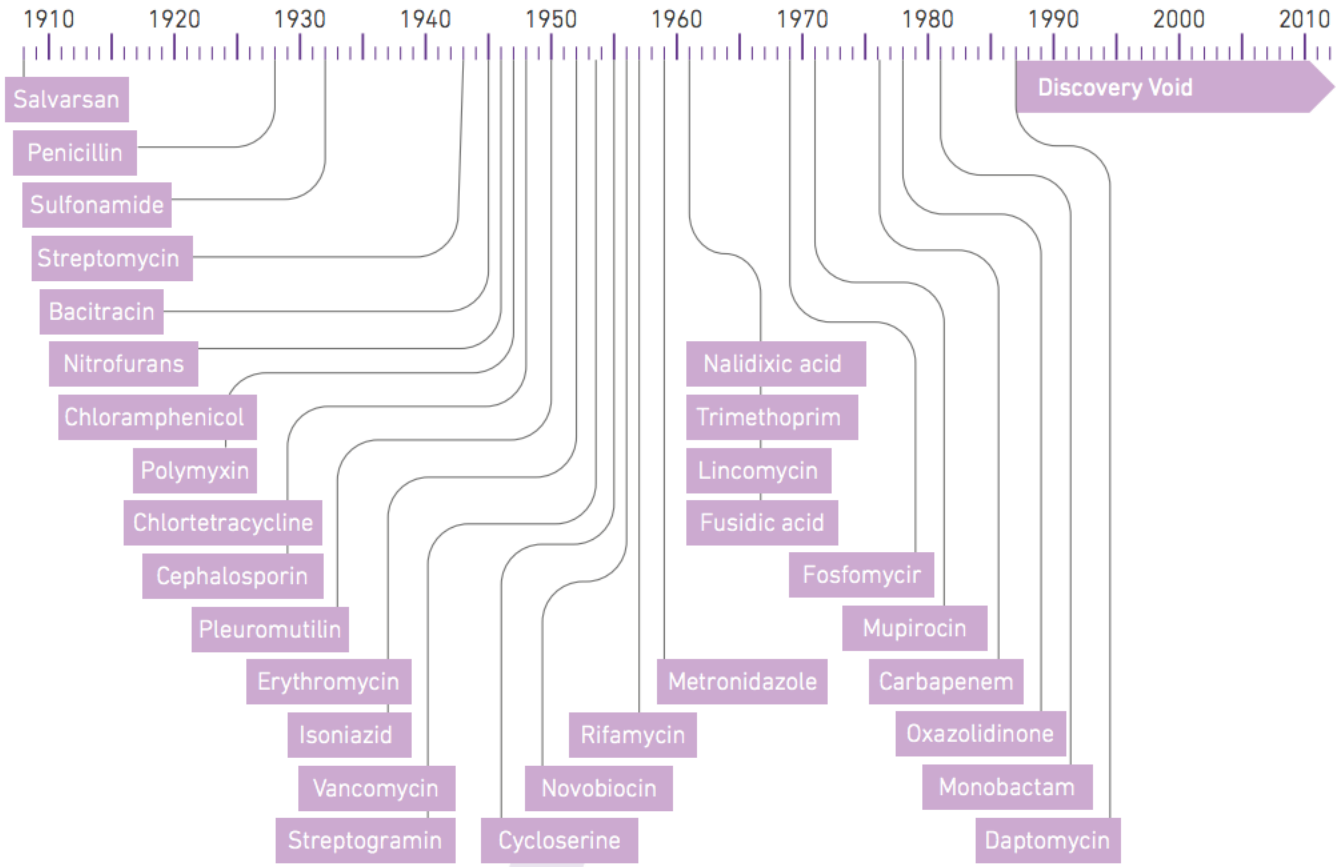


Figure 1 **Dates of discovery of distinct classes of antibacterial drugs**

Illustration of the "discovery void." Dates indicated are those of reported initial discovery or patent.



Adapted from Silver 2011 (1) with permission of the American Society of Microbiology Journals Department.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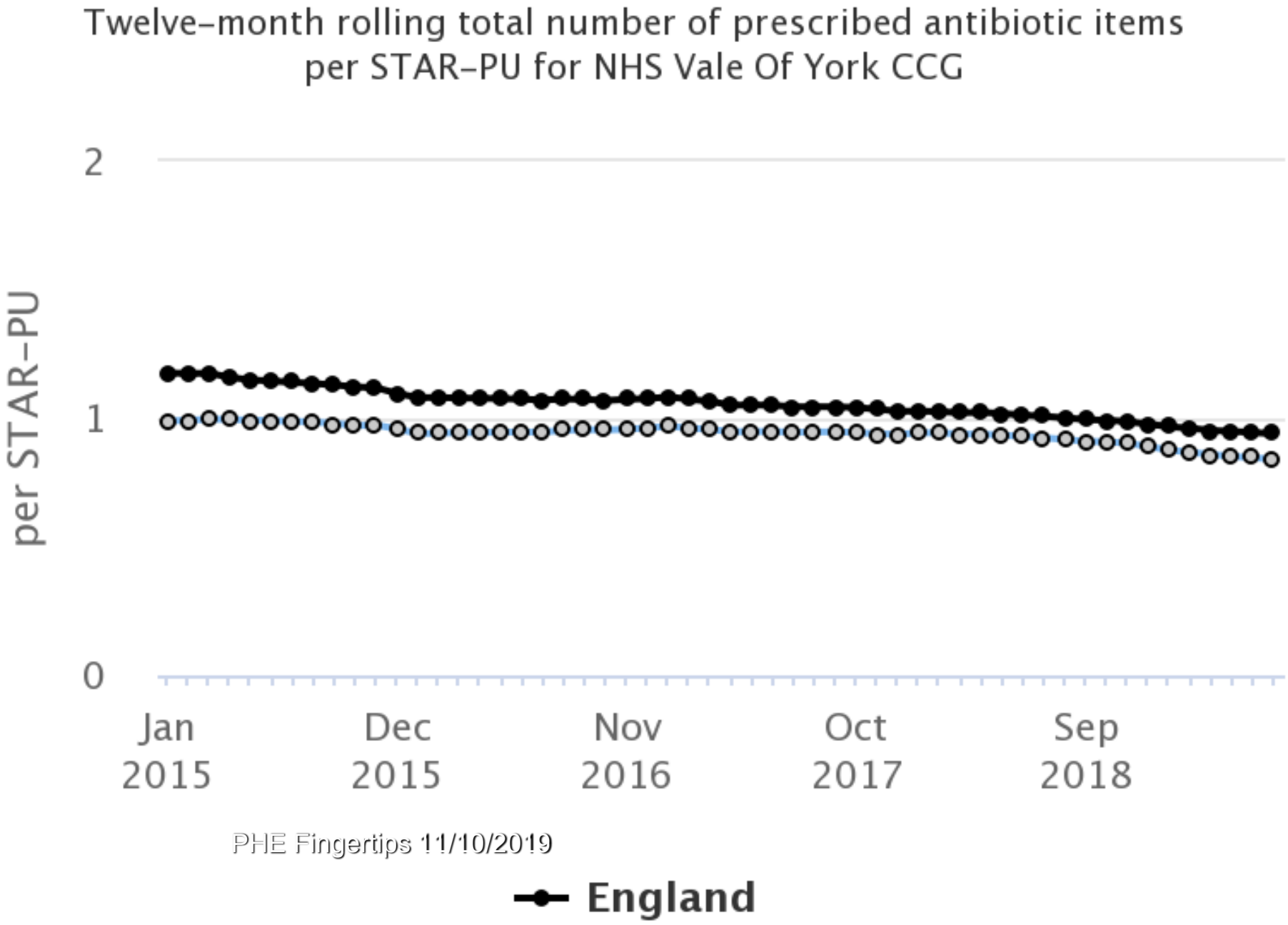
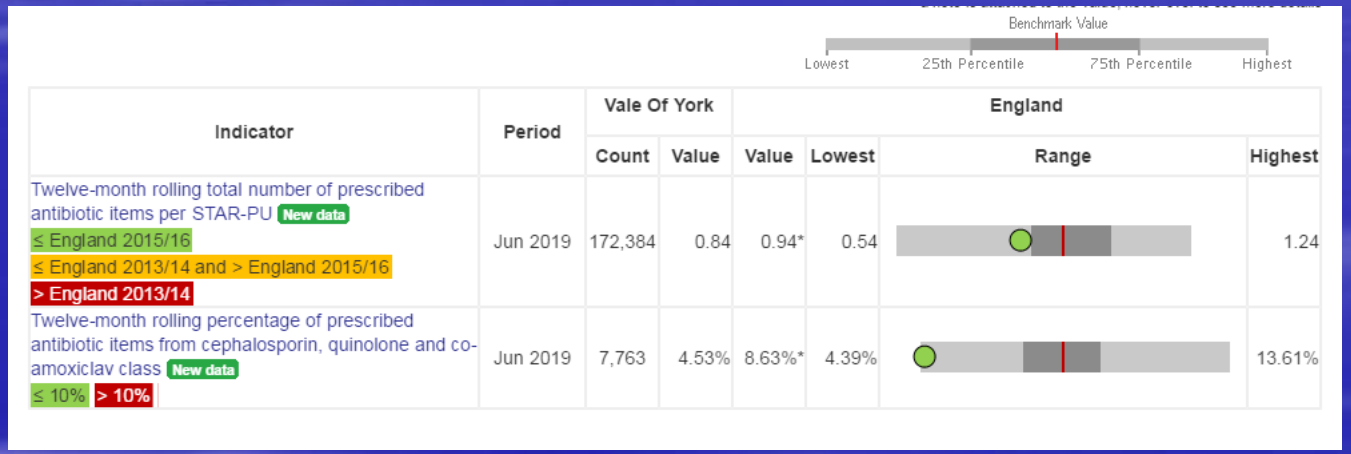
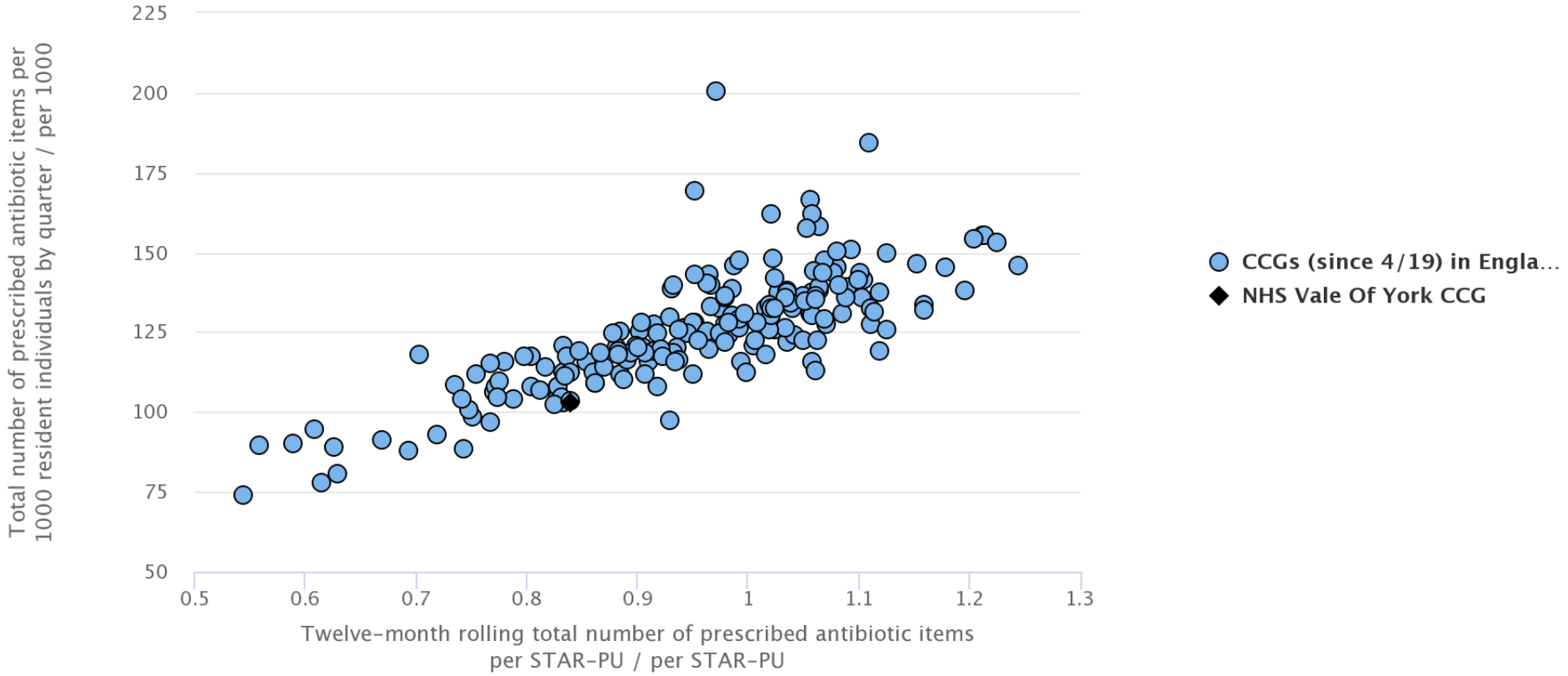

Twelve-month rolling total number of prescribed antibiotic items per STAR-PU for NHS Vale Of York CCG
2
1
0
per STAR-PU
Jan 2015
Dec 2015
Nov 2016
Oct 2017
Sep 2018
PHE Fingertips 11/10/2019
England



Indicator	Period	Vale Of York		England			
		Count	Value	Value	Lowest	Range	Highest
Twelve-month rolling total number of prescribed antibiotic items per STAR-PU New data ≤ England 2015/16 ≤ England 2013/14 and > England 2015/16 > England 2013/14	Jun 2019	172,384	0.84	0.94*	0.54		1.24
Twelve-month rolling percentage of prescribed antibiotic items from cephalosporin, quinolone and co-amoxiclav class New data ≤ 10% > 10%	Jun 2019	7,763	4.53%	8.63%*	4.39%		13.61%

Vale of York Antibiotic Prescribing

PHE Fingertips 11/10/2019

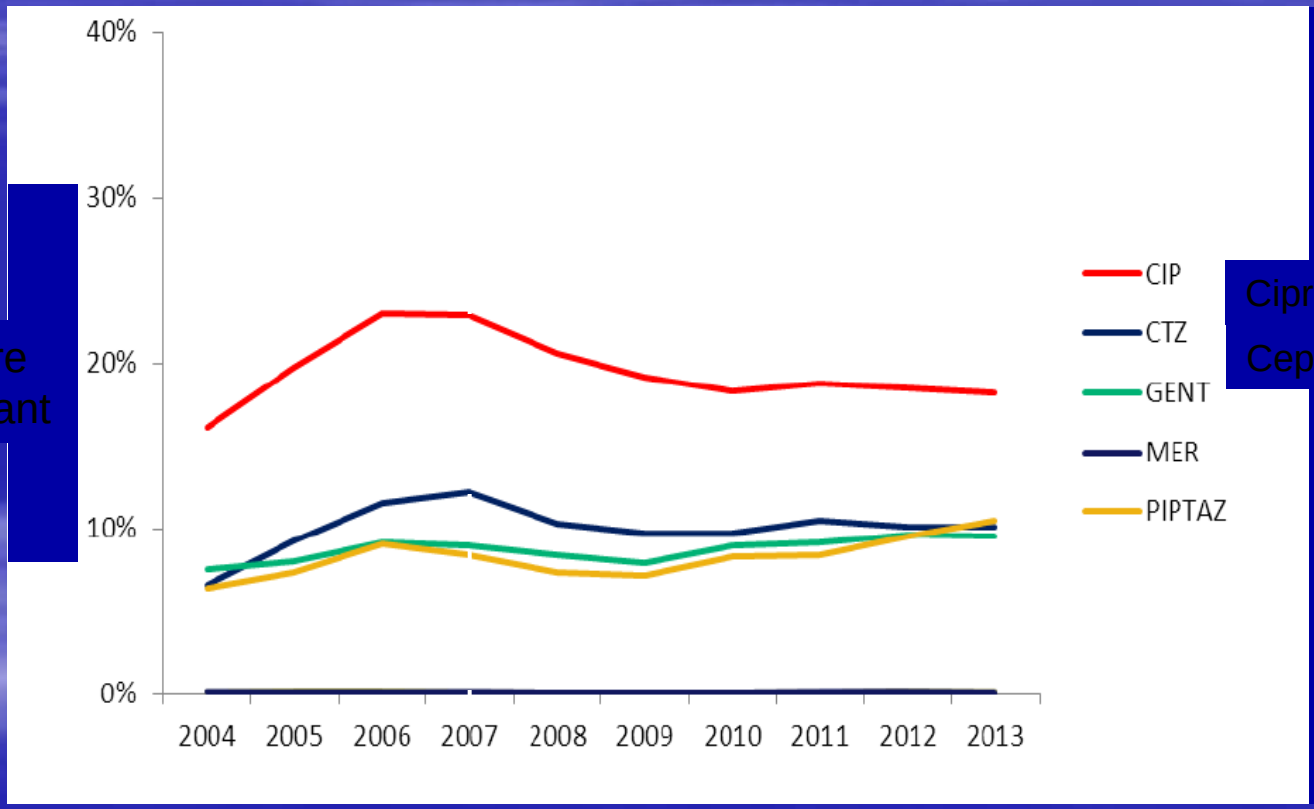


Vale of York Antibiotic Prescribing

PHE Fingertips 11/10/2019

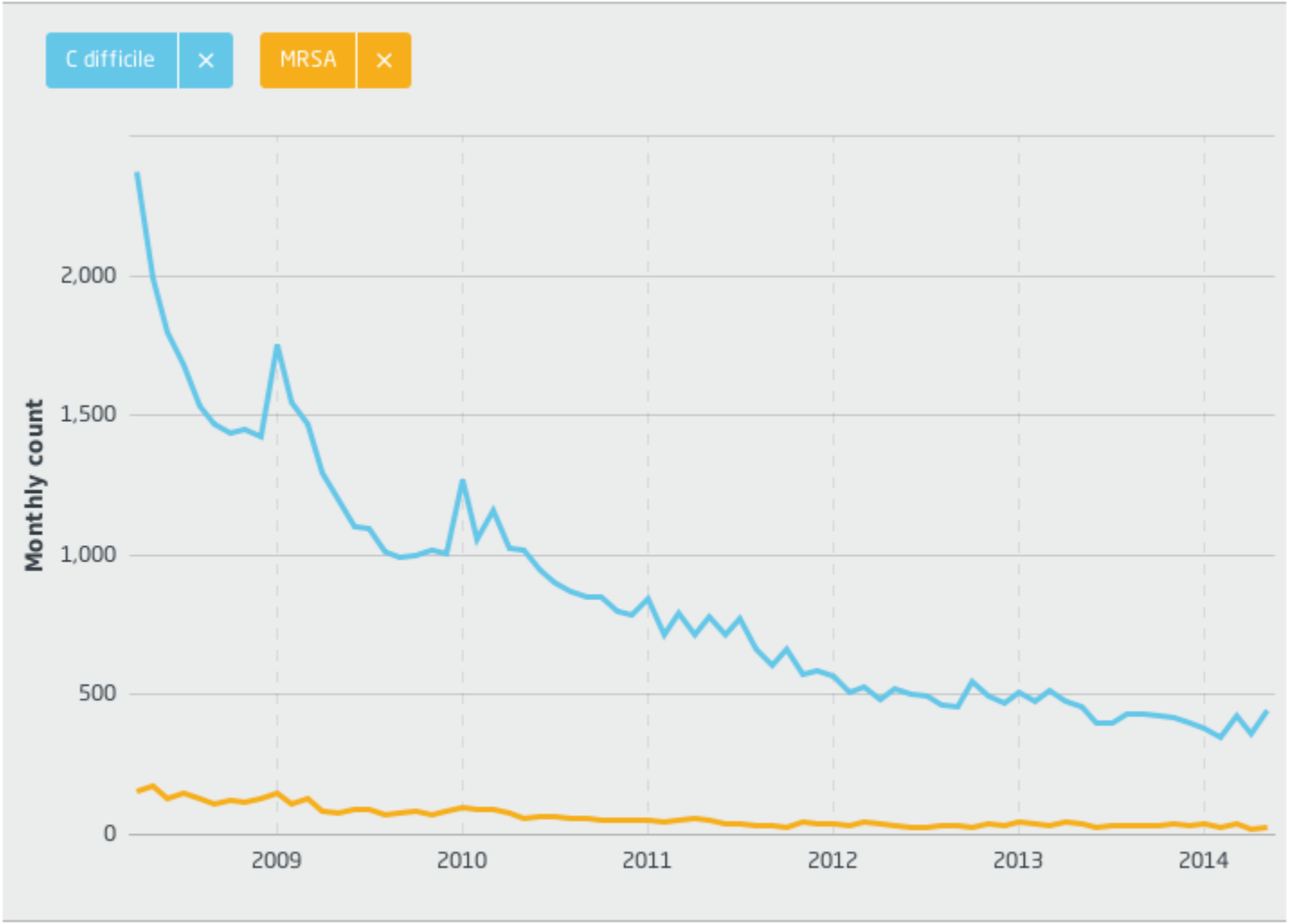
Prescribing: As ciprofloxacin & cephalosporin use has decreased so has resistance

Antibiotic resistance data from *E.coli* in blood cultures 2004 – 2013



Livermore et al Lancet Infectious Diseases 2013

Figure 32: Monthly counts of C difficile and MRSA



Data source: Trust-apportioned monthly counts of C difficile infection http://www.hpa.org.uk.

Post-infection review assigned monthly counts of methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia www.hpa.org.uk.

Strategies to improve use

- Better diagnosis – reduce uncertainty
- Appropriate use of Microbiology Lab
- Clinical scoring systems – eg centor
- POCT – eg CRP testing, pH test vaginal secretions
- Follow evidence based guidance – NY policy, NICE
- Delayed prescriptions/stop orders
- Improved patient education

Effective use of microbiology laboratory

- Only send samples which will influence management
- Obtain good quality samples before antibiotic therapy
- Provide clear clinical details
- Ensure samples transported promptly to lab
- Await culture results whenever possible
- Phone lab for interim results if patient deteriorates

Rejection of samples

- Must meet Minimum labelling standards
- Inadequate sample volume for test
- Wrong container used
- Clinical criteria for testing not indicated e.g. urinary antigen testing and CURB65 score

Poor quality sampling

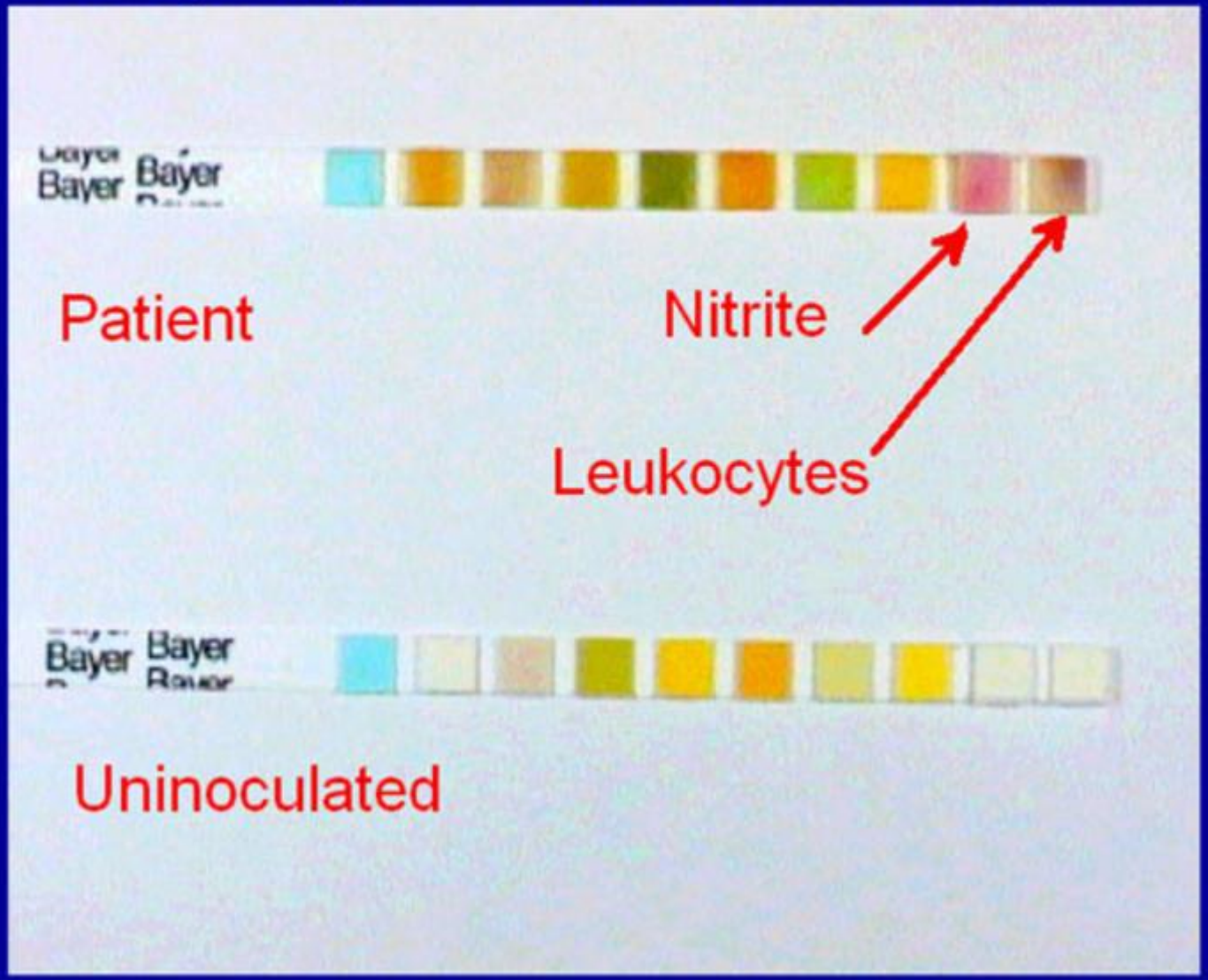
- Sampling in absence of signs and symptoms of infection
- Swabs when pus or fluid available
- Sampling after starting antibiotics
- Leg ulcer swabs
- Multiple swabs from different parts of a wound
- Mucoid/salivary sputum samples
- Duplication of samples

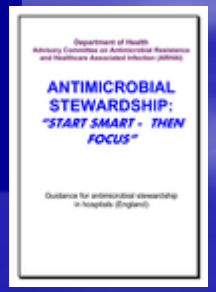
Leads to unneeded antibiotic therapy

Urine sampling

- Bacteriuria vs infection
- Detect bacteriuria in young children, pregnancy, pre-op
- Dip stick alone should not guide testing and therapy
- Catheter samples of limited use

Urine dipstick positive for nitrite and leukocytes





Prevalence of Asymptomatic Bacteriuria

Age (years)	Women	Men
20	1%	1%
70	20%	15%
>70 + long-term care	50%	40%
Spinal cord injury (with intermittent catheterization)	50%	50%
Chronic urinary catheter	100%	100%
Ileal loop conduit	100%	100%

Nicolle LE. *Int J Antimicrob Agents*. 2006 Aug;28 Suppl 1:S42-8.

Early ideas to improve management of asymptomatic bacteriuria

- Changes to dip stick testing methods to avoid nitrite and leucocyte esterase testing
- Sampling limited to patients with symptoms of urinary tract infection
- Clinical algorithm defining when to test and when to treat
- Look for systemic inflammation and absence of other sites of infection before bacteriuria identified as cause of acute delirium
- Default reporting of urine cultures without sensitivities

North Yorkshire antibiotic prescribing guideline for primary care

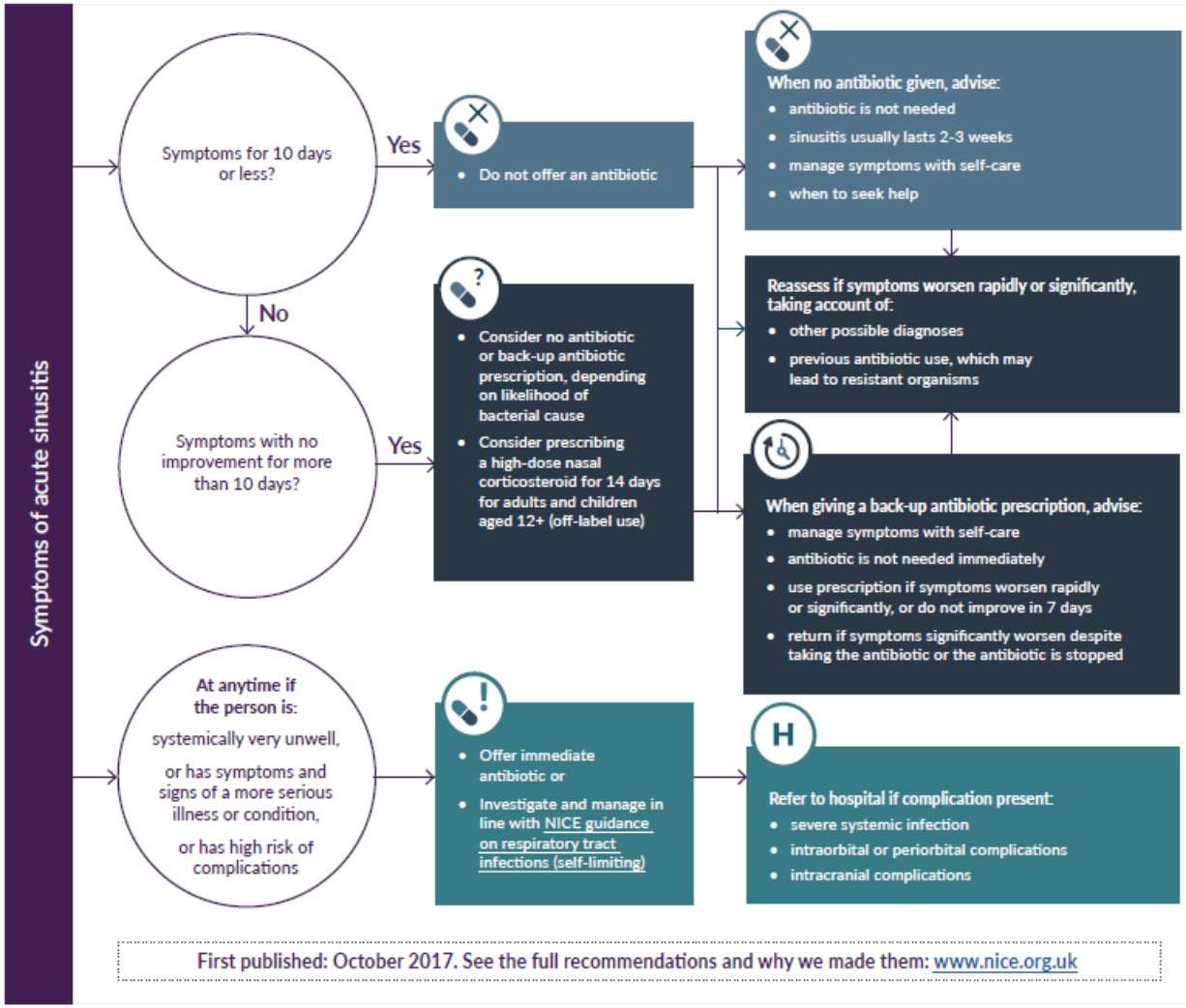
This prescribing guide has been produced to provide primary care clinicians with clear advice on the empirical antibiotic treatment of common infections, to promote the judicious use of antibiotics and to minimise the emergence of bacterial resistance.

Treatment guidelines contained in this guide have been adapted from the Public Health England (formerly HPA) Management of Infection for Primary Care guidelines.

Version 3.2 October 2015, Review date: September 2017

Sinusitis (acute): antimicrobial prescribing

NICE National Institute for Health and Care Excellence



First published: October 2017. See the full recommendations and why we made them: www.nice.org.uk

Self-care

- Consider paracetamol or ibuprofen for pain or fever (for under 5s, see the NICE guideline on fever in under 5s: assessment and initial management)
- Little evidence that nasal saline or nasal decongestants help, but people may want to try them
- No evidence for oral decongestants, antihistamines, mucolytics, steam inhalation, or warm face packs

Evidence on antibiotics

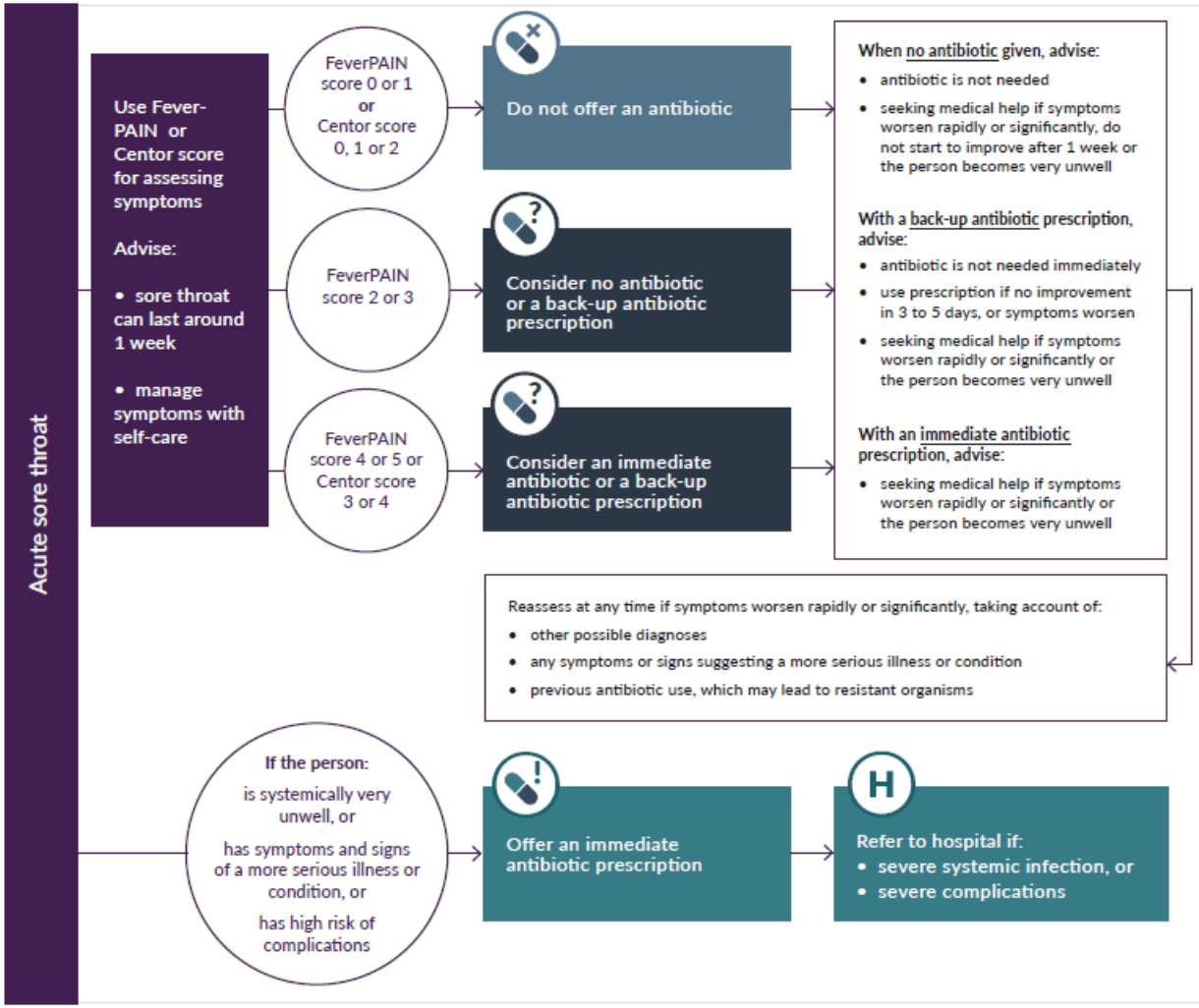
- Antibiotics make little difference to how long symptoms last or the number of people whose symptoms improve
- Possible adverse effects include diarrhoea and nausea

Bacterial cause may be more likely if several of the following are present:

- Symptoms for more than 10 days
- Discoloured or purulent nasal discharge
- Severe localised unilateral pain (particularly pain over teeth and jaw)
- Fever
- Marked deterioration after an initial milder phase

Sore throat (acute): antimicrobial prescribing

NICE National Institute for Health and Care Excellence



Self-care

- Consider paracetamol for pain or fever, or if preferred and suitable, ibuprofen
- Drink adequate fluids
- Some evidence that medicated lozenges can help reduce pain in adults
- No evidence was found for non-medicated lozenges, mouthwashes, or local anaesthetic mouth spray on its own

Evidence on antibiotics

- Antibiotics make little difference to how long symptoms last or the number of people whose symptoms improve
- Withholding antibiotics is unlikely to lead to complications
- Possible adverse effects include diarrhoea and nausea

FeverPAIN score

- Fever, Purulence, Attend within 3 days or less, Severely Inflamed tonsils, No cough or coryza

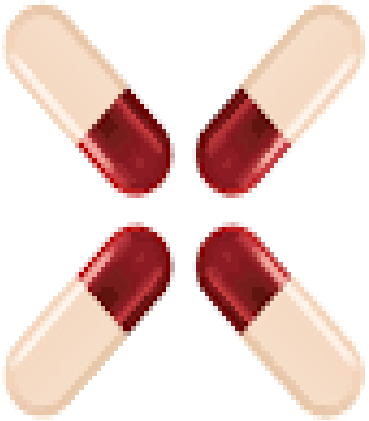
1 point for each

Centor score

- Tonsillar exudate, Tender anterior cervical lymphadenopathy or lymphadenitis, History of fever (>38°C), No cough

1 point for each

First published: January 2018



TARGET

Keep Antibiotics Working

Antimicrobial Stewardship

for all our sakes!

To the non expert, what really is AMS?

"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]

4 goals of AMS

1. Improve patient outcomes
2. Improve patient safety (eg *C.difficile*)
3. Reduce resistance
4. Reduce healthcare costs

Public Health England

Healthmatters Tackling antimicrobial resistance

ANTIBIOTIC GUARDIAN CERTIFICATE

I have pledged to be an

ANTIBIOTIC GUARDIAN

You can become an Antibiotic Guardian too

www.antibioticguardian.com

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UK SUPPORT FOR EUROPEAN ANTIBIOTIC AWARENESS DAY

Public Health England