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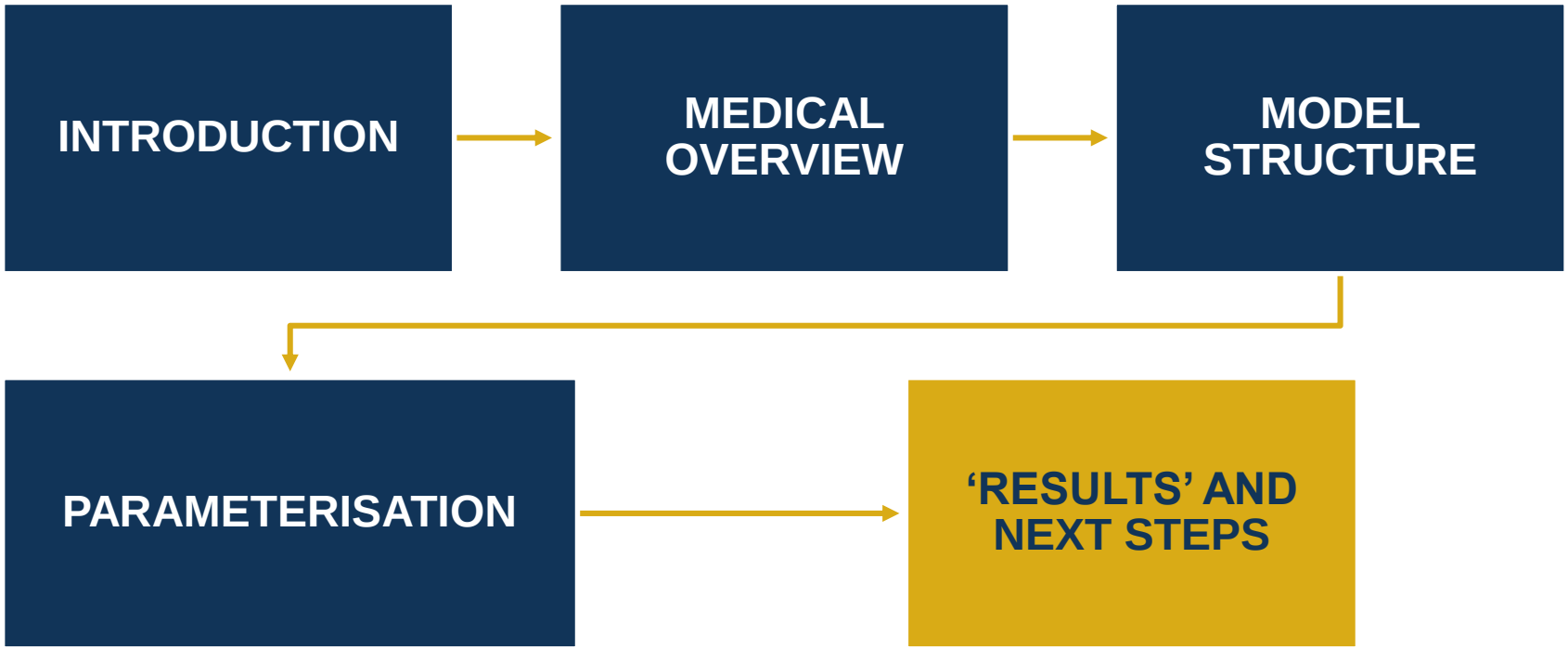
When the drugs don’t work…

Matthew Edwards, Nicola Oliver
and Ross Hamilton
(IFoA Antibiotic Resistance Working Party)

Agenda



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Working party background

ABR Event
Staple Inn
May 2016

- **Develop a simple modelling framework with plausible parameterisation to allow actuaries to develop their own views on likely and stress mortality impacts**
- **This framework would be developed in a UK context but would be expected to be readily transferable to other countries**
- **Working party started in January 2017**

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Working party members

Name	Role	Firm
Matthew Edwards	Chair	Willis Towers Watson
Nicola Oliver	Medical input & Deputy Chair	Medical Intelligence
Sheridan Fitzgibbon	Model structure & parameterisation	Legal & General
Craig Armstrong	Parameterisation (2017)	Aviva
Ross Hamilton	Model development	Lloyds Banking Group
Irene Merk	General	SCOR
Roshane Samarasekera	Model development	GAD
Soumi Sarkar	General	Legal & General
Katherine Fossett	General	Barnett Waddingham

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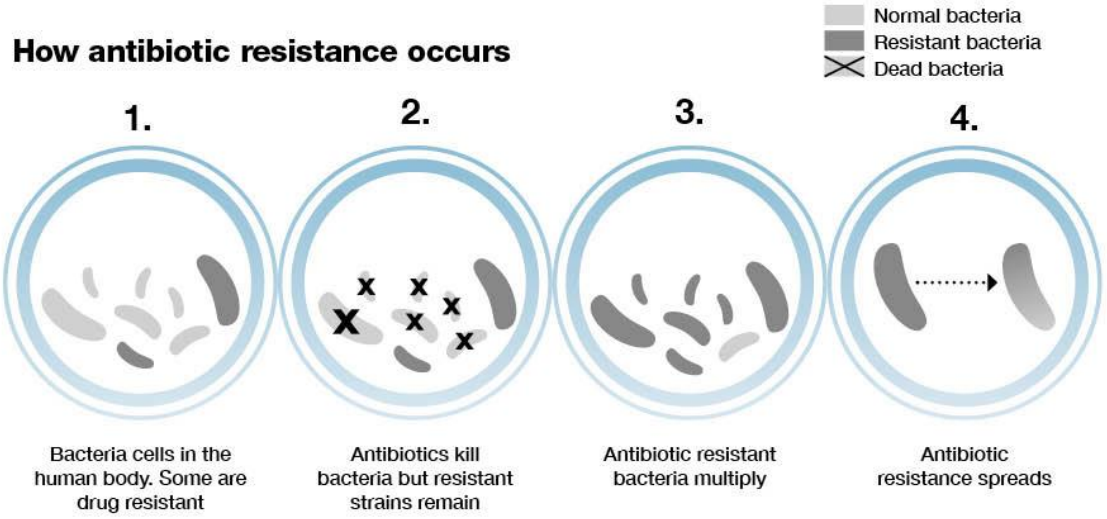
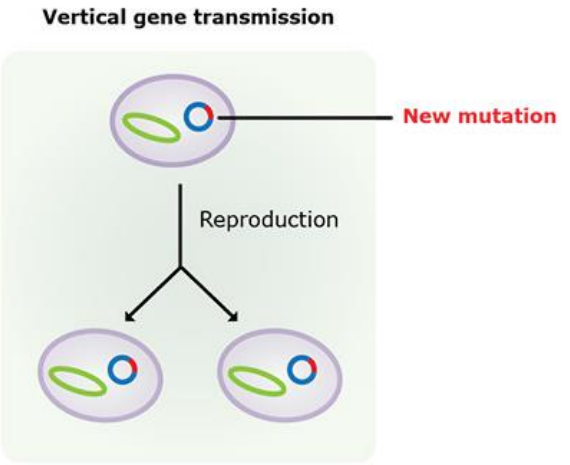
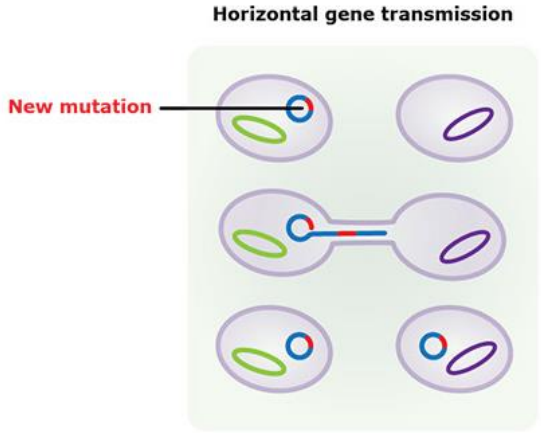
Medical overview

June 14, 2018

What is antibiotic resistance…







"***The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism***."
Sir Alexander Fleming, 1928

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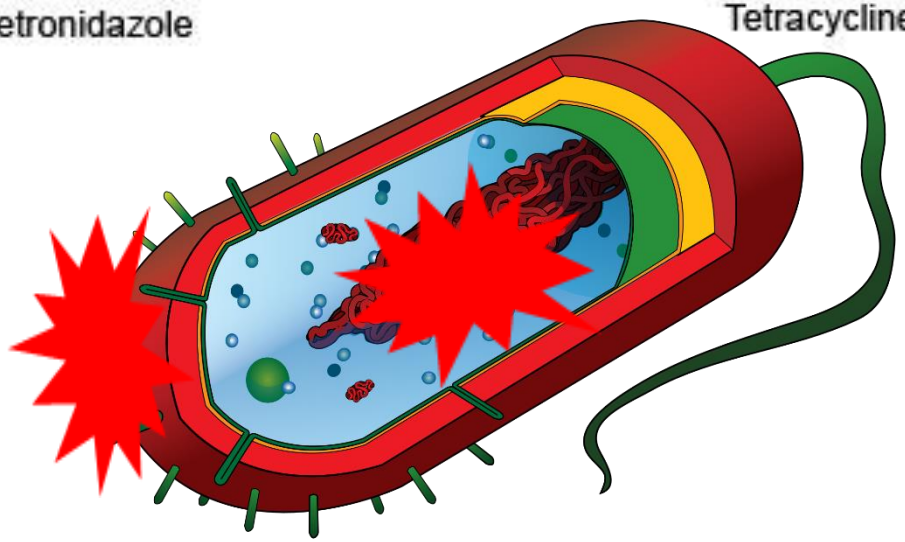
EXAMPLES:
Aminoglycosides
Beta-lactams
Vancomycin
Quinolones
Rifampin
Metronidazole



EXAMPLES:
Chloramphenicol
Erythromycin
Clindamycin
Sulfonamides
Trimethoprim
Tetracyclines

How do antibiotics work? (the science!)

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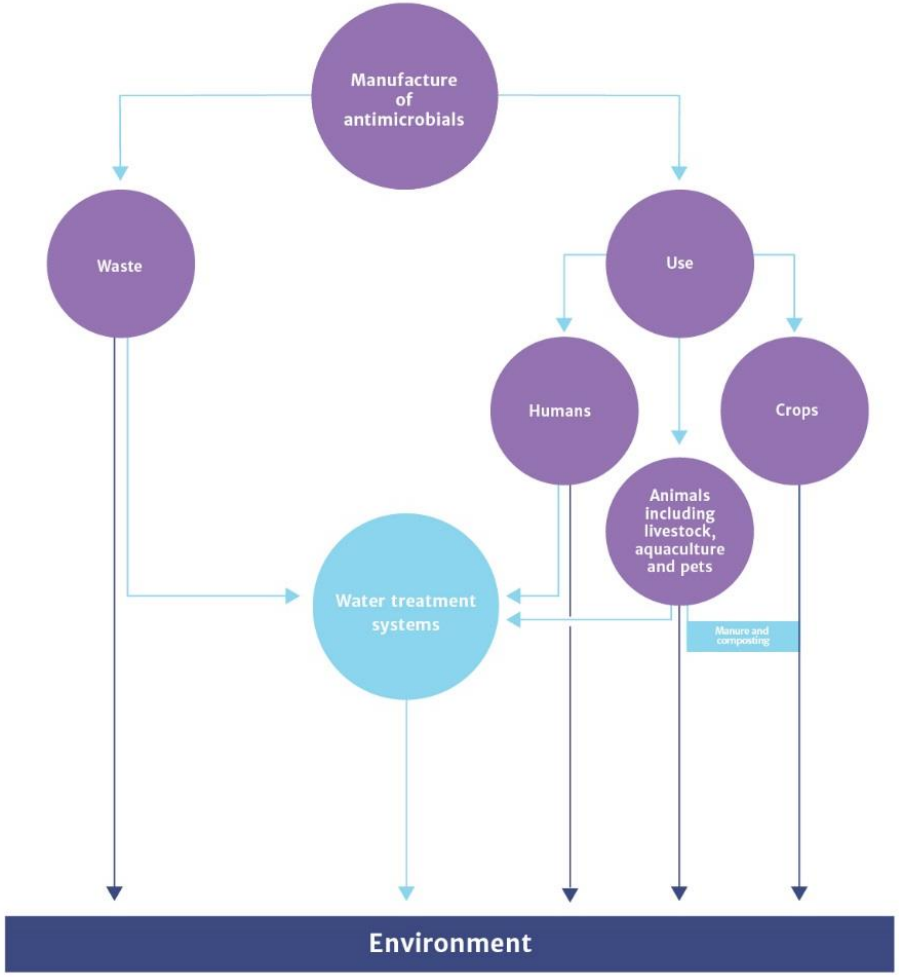
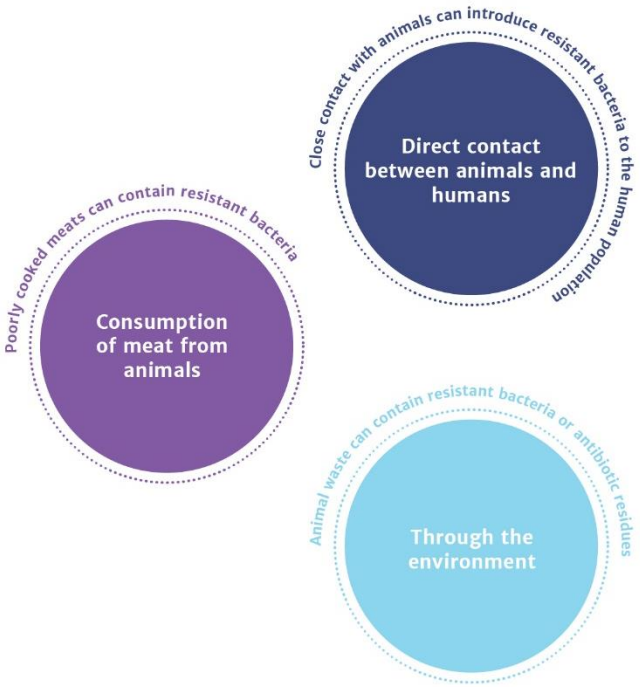
What are the sources of resistance?

Sources of resistance



How animals can pass on resistant bacteria



Infographics sourced from "Review on Antimicrobial Resistance" 2014

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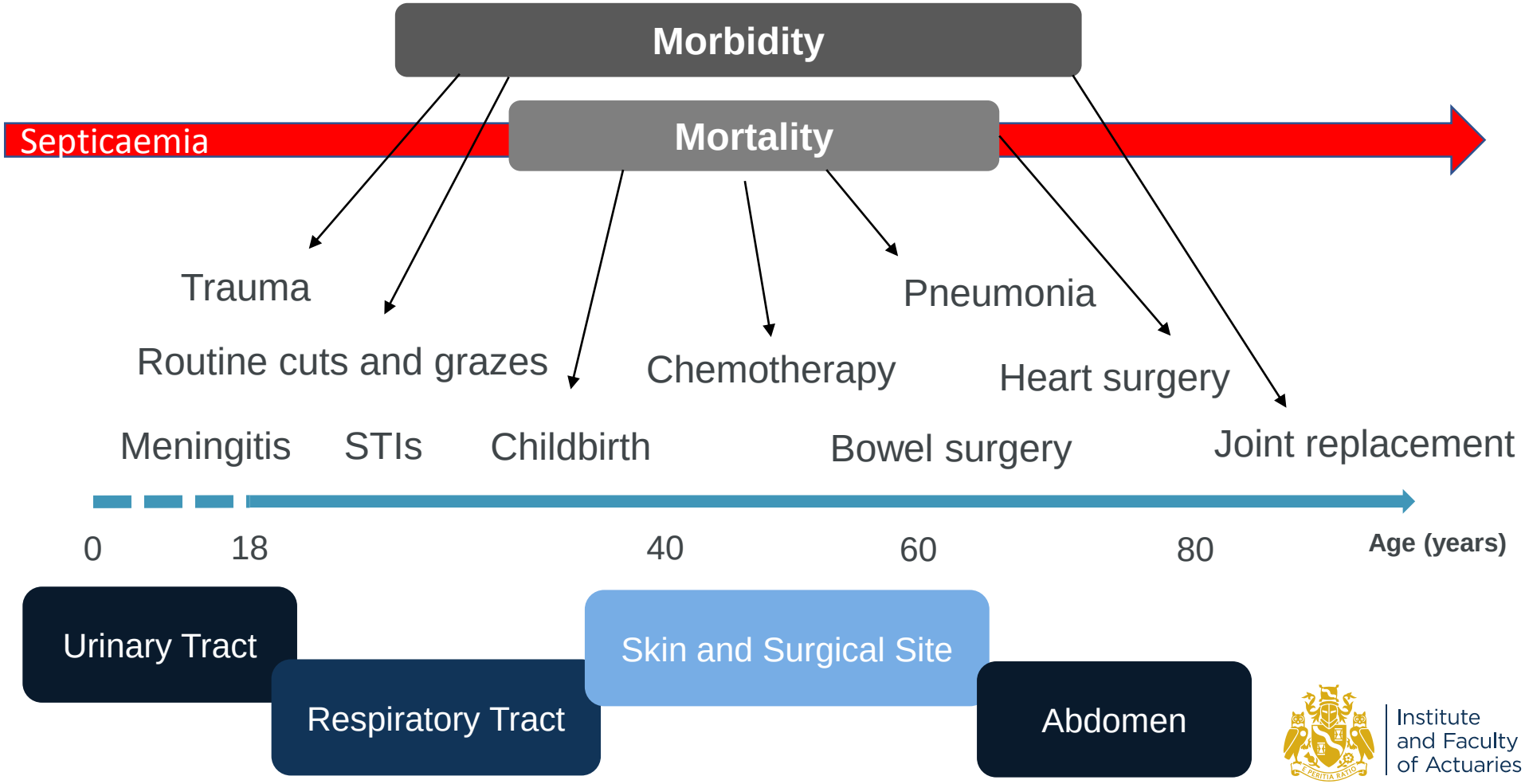
How does ABR affect people and our work?



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Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis

Evelina Tacconelli, Elena Carrara*, Alessia Savoldi*, Stephan Harbarth, Marc Mendelson, Dominique L Monnet, Céline Pulcini, Gunnar Kahlmeter, Jan Kluytmans, Yehuda Carmeli, Marc Ouellette, Kevin Outterson, Jean Patel, Marco Cavaleri, Edward M Cox, Chris R Houchens, M Lindsay Grayson, Paul Hansen, Nalini Singh, Ursula Theuretzbacher, Nicola Magrini, and the WHO Pathogens Priority List Working Group†

Criteria

- Mortality
- Health-care burden
- Community burden
- Prevalence of resistance
- 10-year trend of resistance
- Transmissibility
- Preventability in the community
- Preventability in health-care setting
- Treatability
- Pipeline

"The major objective of the global priority pathogens list (global PPL) is to guide the prioritization of incentives and funding, help align R&D priorities with public health needs and support global coordination in the fight against antibiotic-resistant bacteria"

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Priority 1: CRITICAL

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella spp., fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella spp., fluoroquinolone-resistant

A. baumannii

Pseudomonas

Enterobacteriaceae

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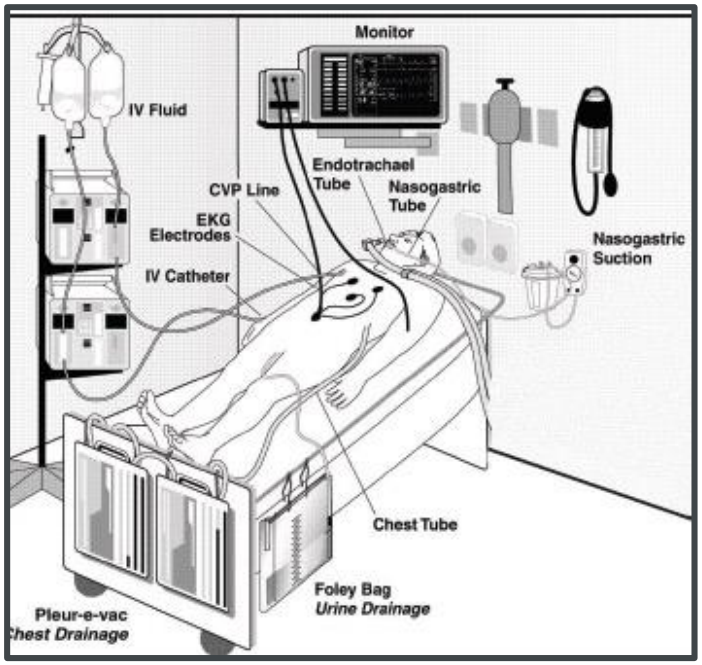
A. baumannii

Driven by AB use and poor infection control

Healthcare Setting

Resistant to colistin in 4% of cases

Resilient



- Pneumonia
- Wound Infection
- Bloodstream Infection
- Urinary Tract

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Pseudomonas

- Found widely in the environment
- Common cause of mild and serious infections
- Risk profile similar to A. Baumannii

Pneumonia

Wound Infection

Bloodstream Infection

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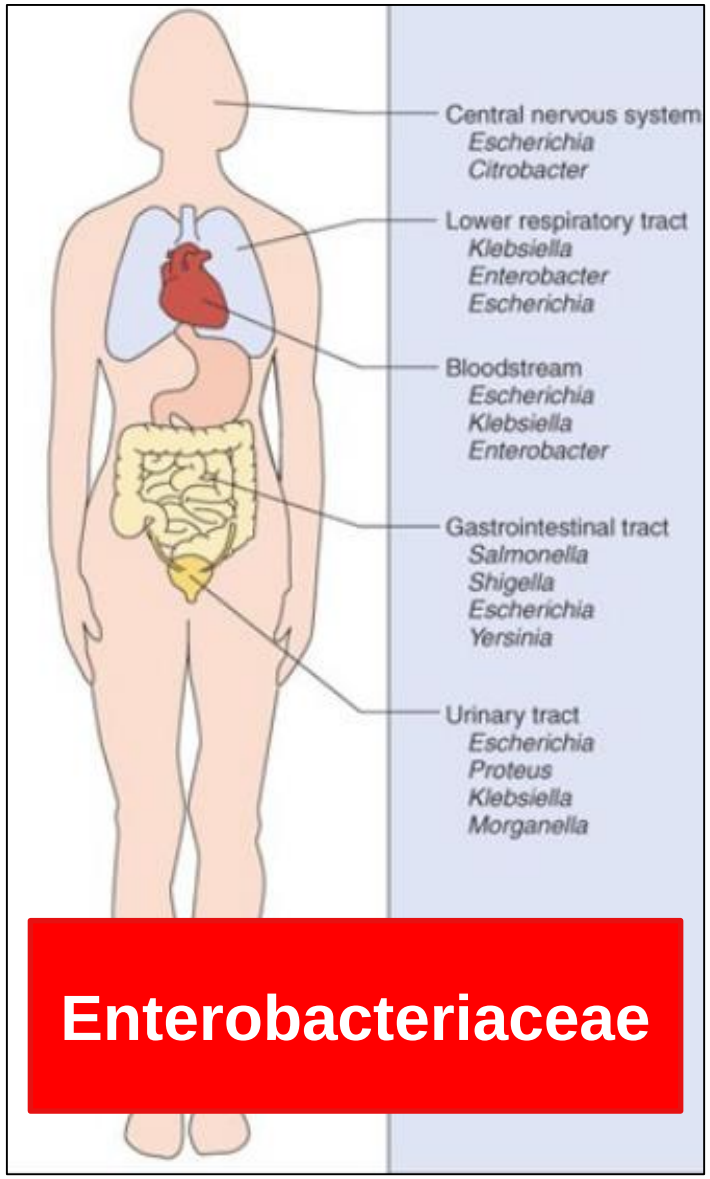
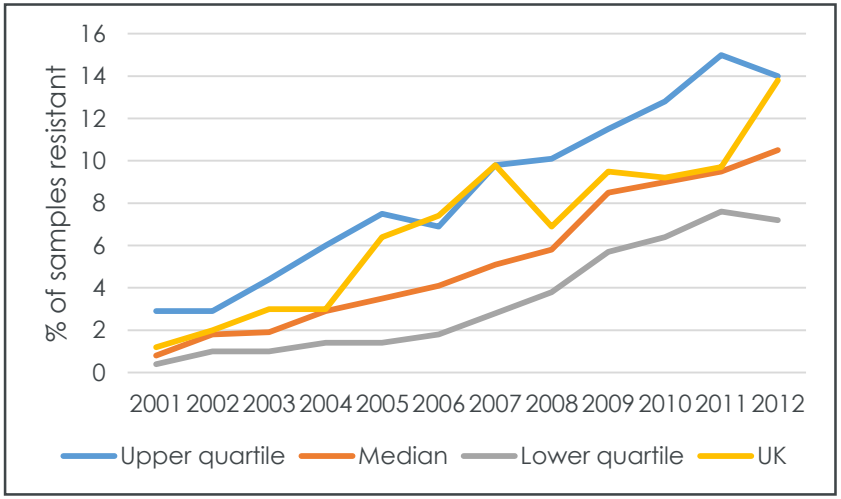


These bacteria are associated with higher frequency of inappropriate antimicrobial therapy, poorer clinical response, and longer length of hospital stay



Third-generation cephalosporin resistance rates in *E. coli* across Europe, showing the UK, 1999 to 2012 (Department of Health, 2015)

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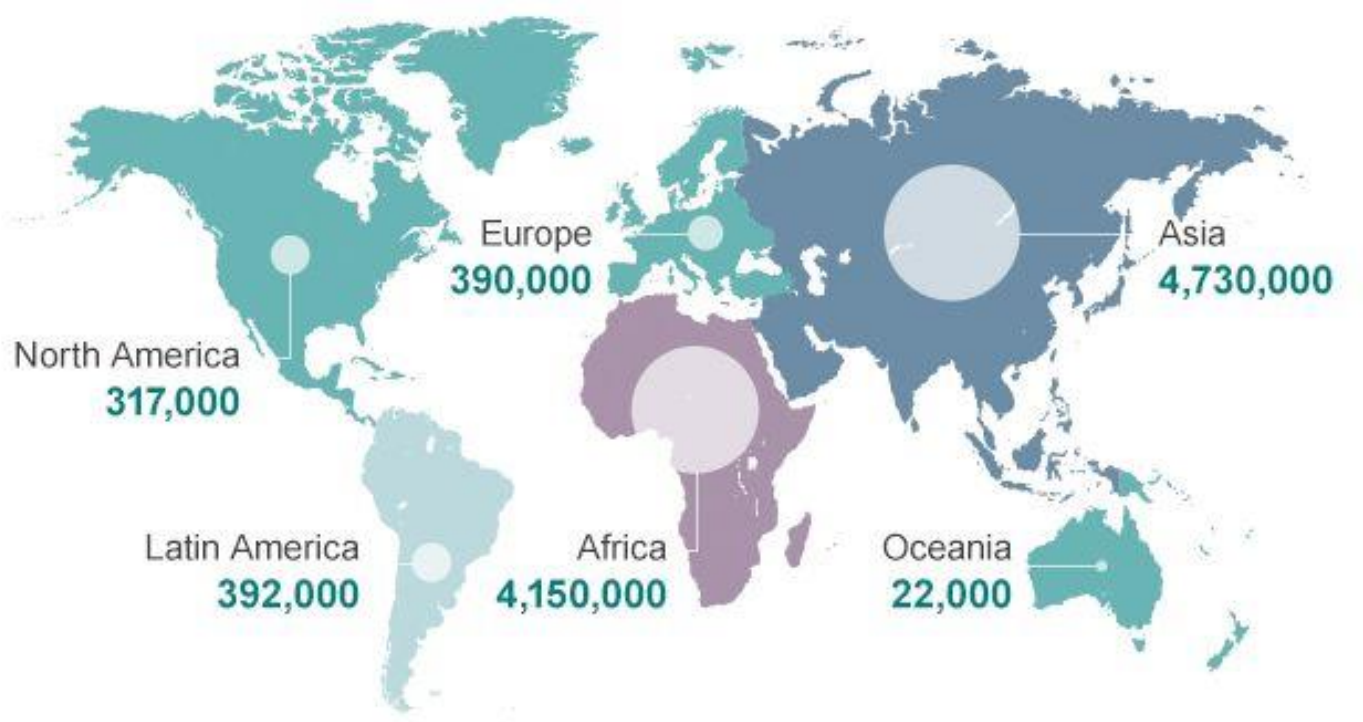
…and why it is important?

"We have reached a critical point and must act now on a global scale to slow down antimicrobial resistance" – Professor Dame Sally Davies, UK Chief Medical Officer

Deaths attributable to antimicrobial resistance every year by 2050



Source: Review on Antimicrobial Resistance 2014

Tackling resistance takes a long time…

Changing behaviours

Developing new antibiotics

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nature microbiology

LETTERS

https://doi.org/10.1038/s41564-018-0110-1

OPEN

Culture-independent discovery of the malacidins as calcium-dependent antibiotics with activity against multidrug-resistant Gram-posi

Bradley M. Hover[1], Seong-Hwan Kim[1], Micah Katz[1], Zachary
Melinda A. T
and Sean F. E

Berglund *et al. Microbiome* (2017) 5:134
DOI 10.1186/s40168-017-0353-8

Microbiome

RCH

Open Access

CrossMark

ification of 76 novel B1 metallo-β-mases through large-scale screening nomic and metagenomic data

und[1,2], Nachiket P. Marathe[2,3], Tobias Österlund[1,2], Johan Bengtsson-Palme[2,3], Stathis Kotsakis[2,3], Flach[2,3], D G Joakim Larsson[2,3] and Erik Kristiansson[1,2*]

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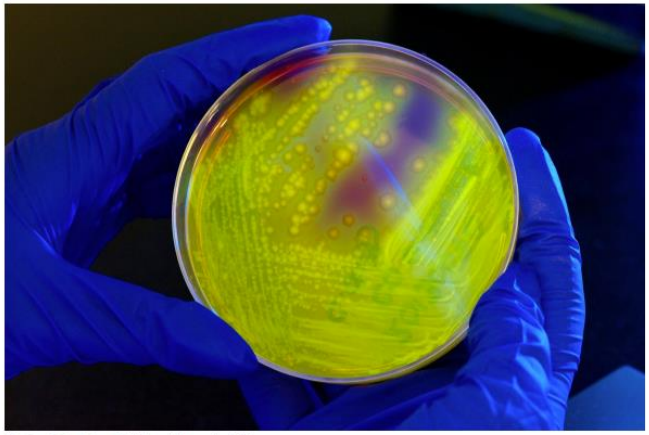

Clostridium difficile bacteria in a petri dish, glowing under long-wave ultraviolet light.

Rewriting Life

Edible CRISPR Could Replace Antibiotics

Researchers are developing a probiotic to make disease-causing bacteria self-destruct.

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Model structure and parameterisation

Ross Hamilton

June 14, 2018

Objectives & Research

Define Objectives	• Model ABR impact on: • Mortality • Morbidity
Literature Review	• KPMG / RAND model • Research papers
Model Structure	• Complex enough to model scenario • Not overly complex • Capable of being adapted by users

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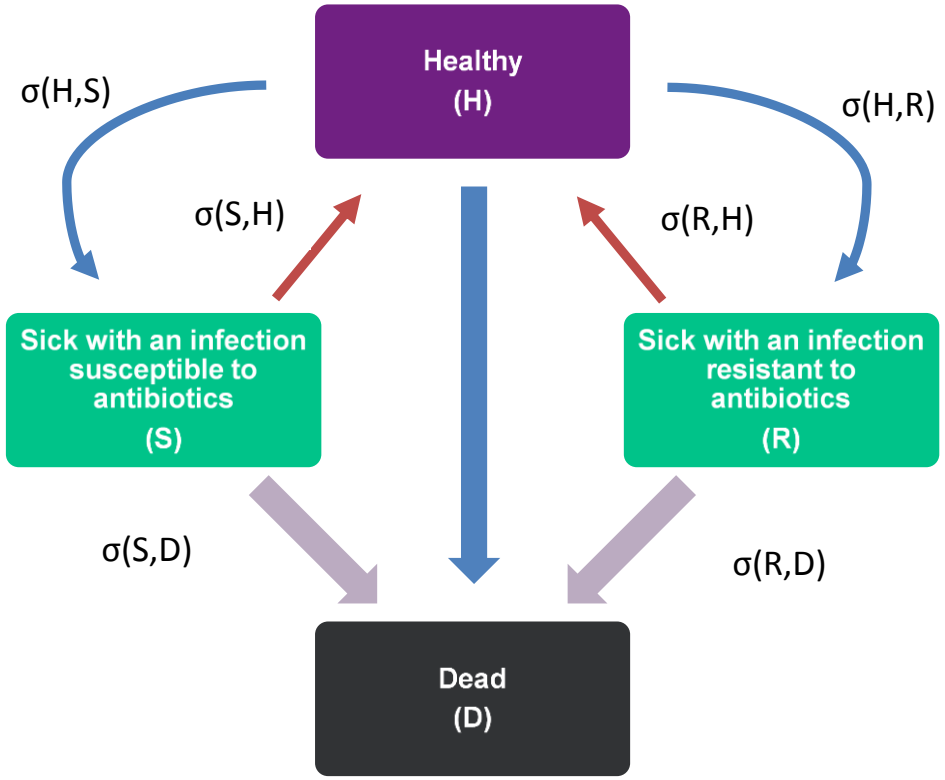
Chosen model structure



Modelling criteria

- Simplicity
- Availability of data
- Appropriate outputs

Basic structure decided on:

- Multi-state Markov model
- Calibrate to current observed levels of mortality and morbidity
- Project varying resistance over time and calculate the change in mortality and morbidity

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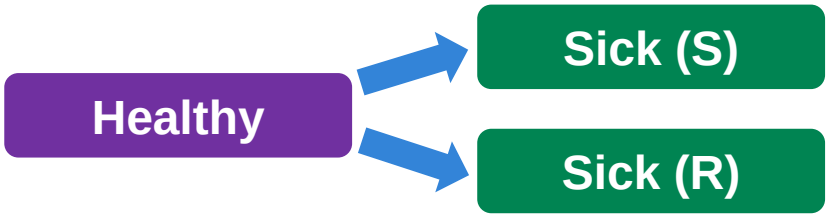
Data sources – incidence

Incidence rates for bacteraemia



Public Health England

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

Limitations

- Limited data. *E. coli* monitoring in England goes back to 2013.
- Limited evidence for how resistance interacts with incidence.
- Bias? Monitoring is of HCAIs.

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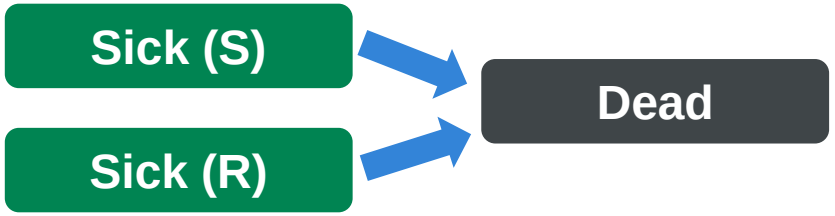
Data sources – mortality

Death rates for bacteraemia



Public Health England

PLOS Open for Discovery

Limitations

- Granularity of data:
  - Confounding causes of death?
  - Academic literature is helpful here.
- Large error bounds around estimates of the relative virulence of resistant and susceptible strains.
- Bias? The most ill are more likely to be sampled.

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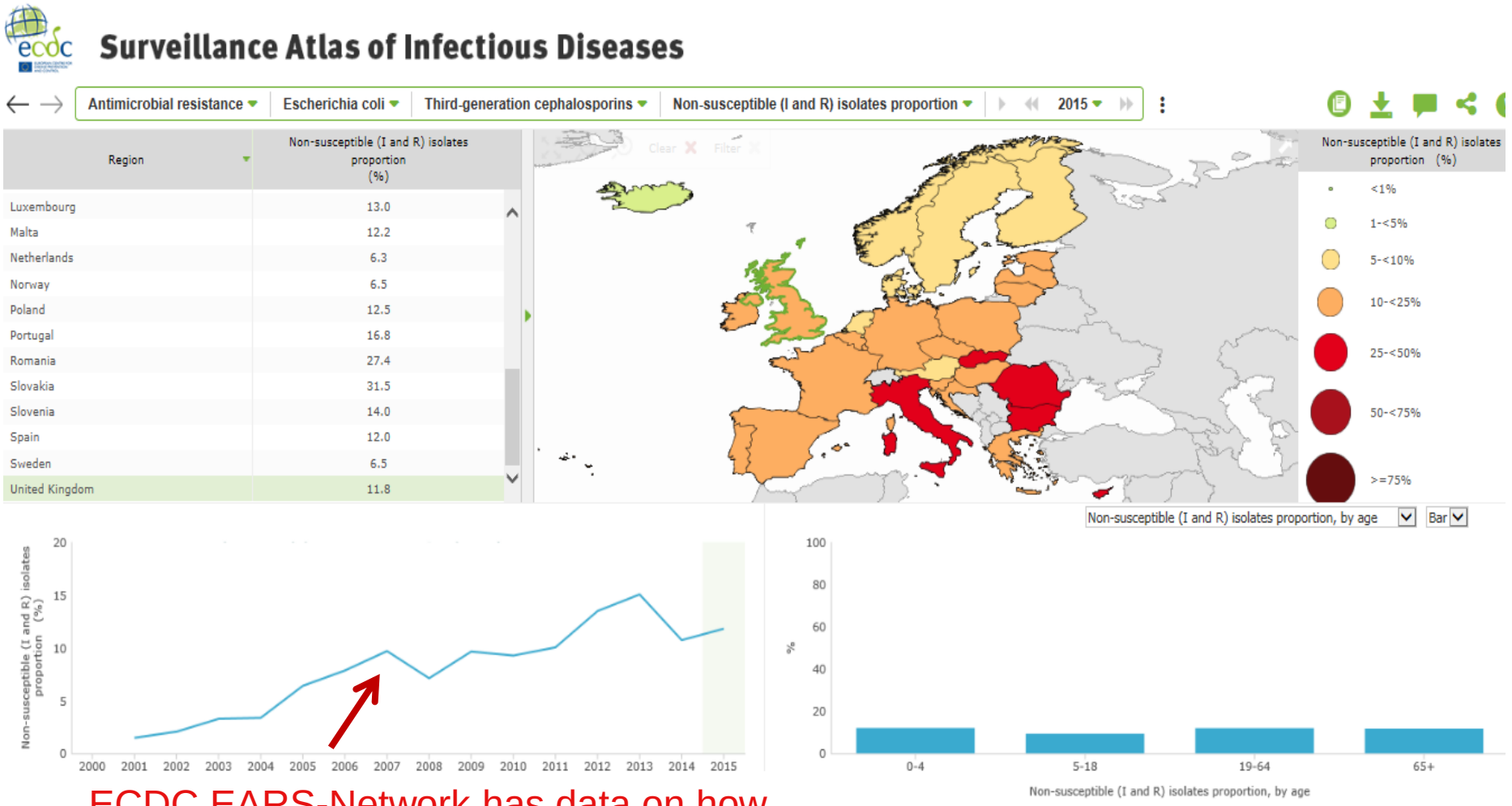
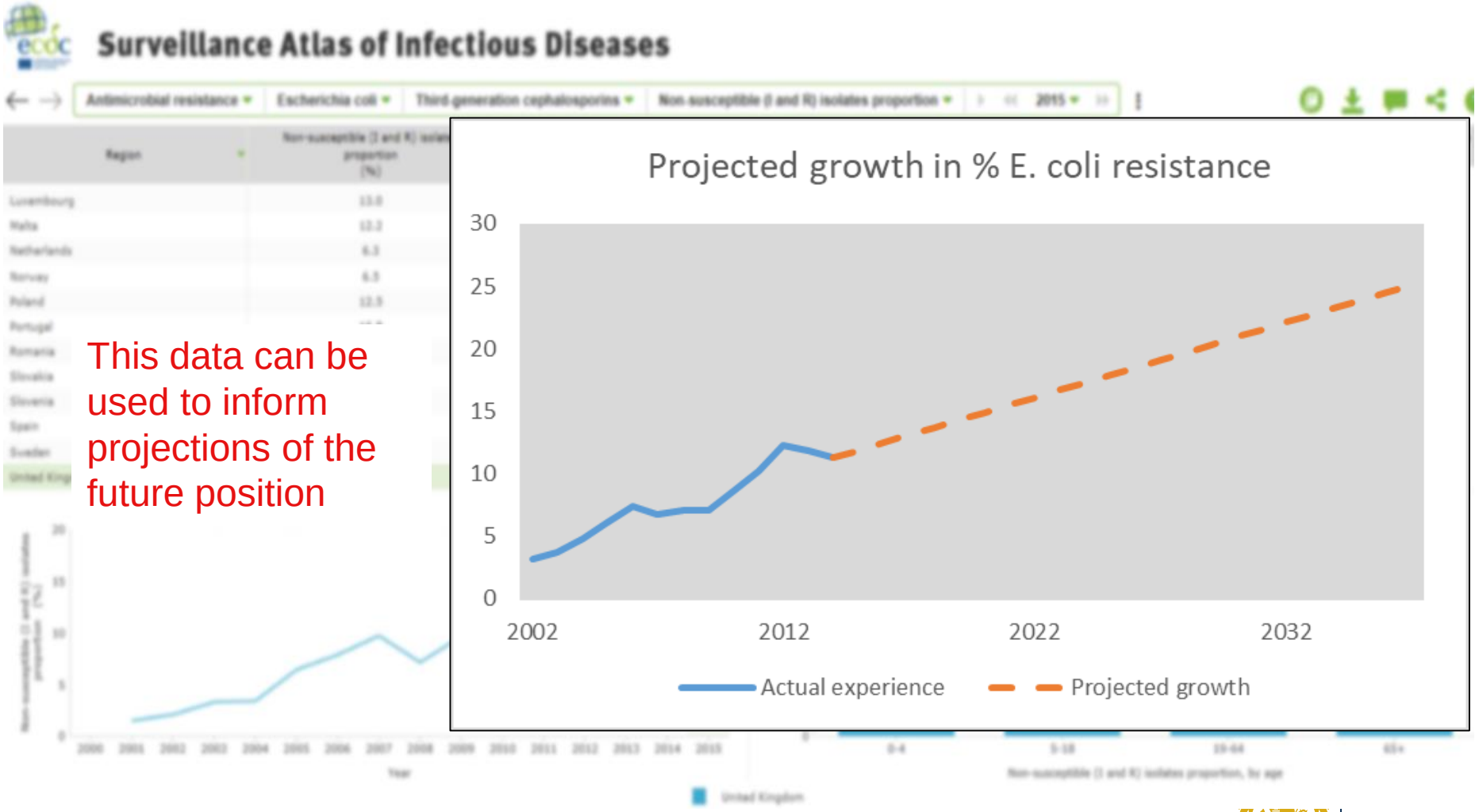
Trends in resistance can be observed…



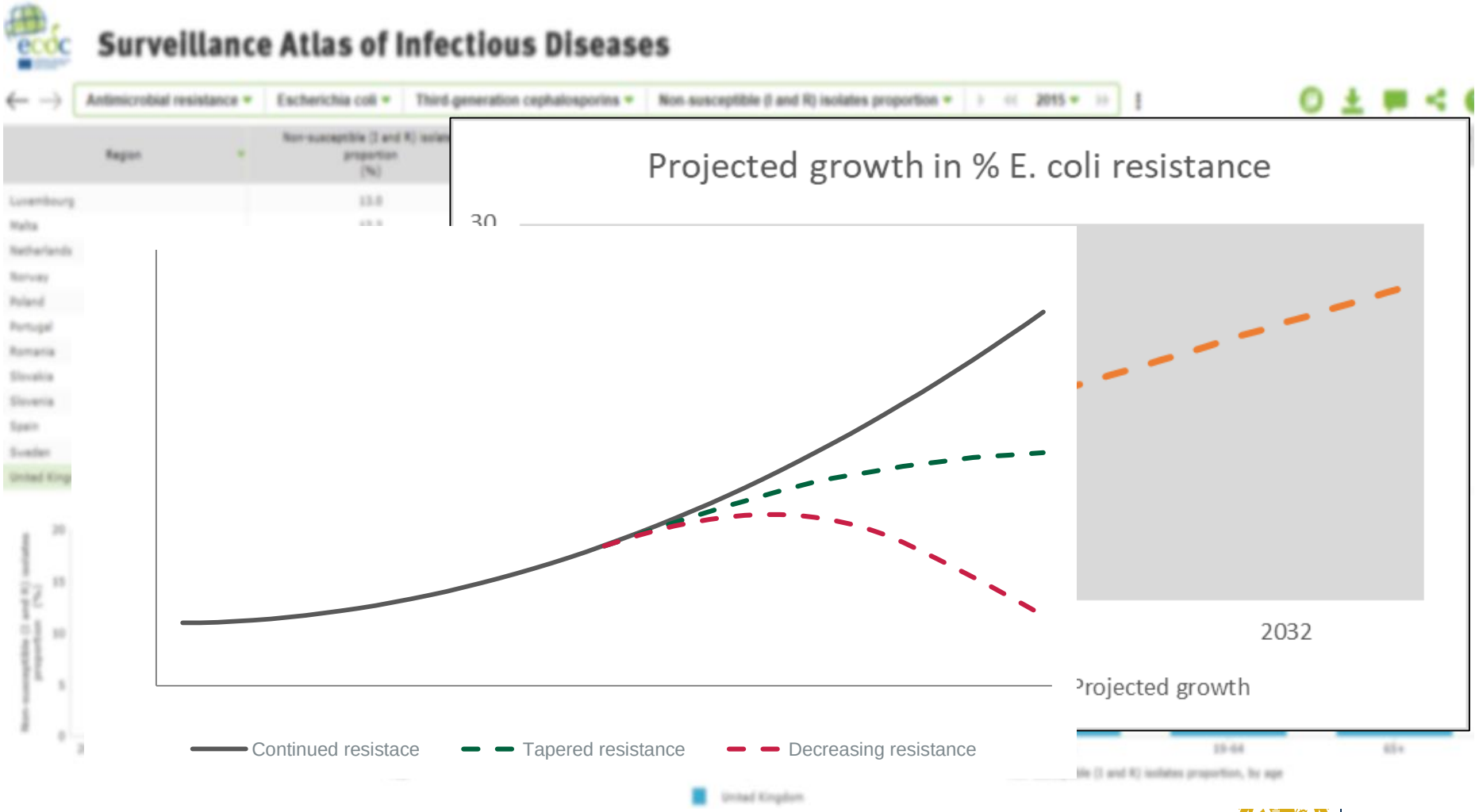
ECDC EARS-Network has data on how resistance has increased over time

…and extrapolated forwards



| of Actuaries

…and extrapolated forwards



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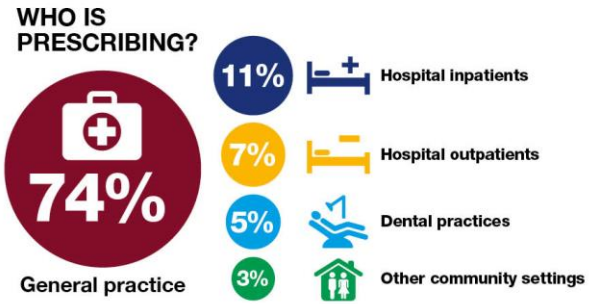
Future of resistance?



30 years since a new class of antibiotics was last introduced….

Barriers to R&D Investment

Cautious optimism in 2 new compounds

Infographics sourced from "Review on Antimicrobial Resistance" 2014

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‘Results’ and next steps

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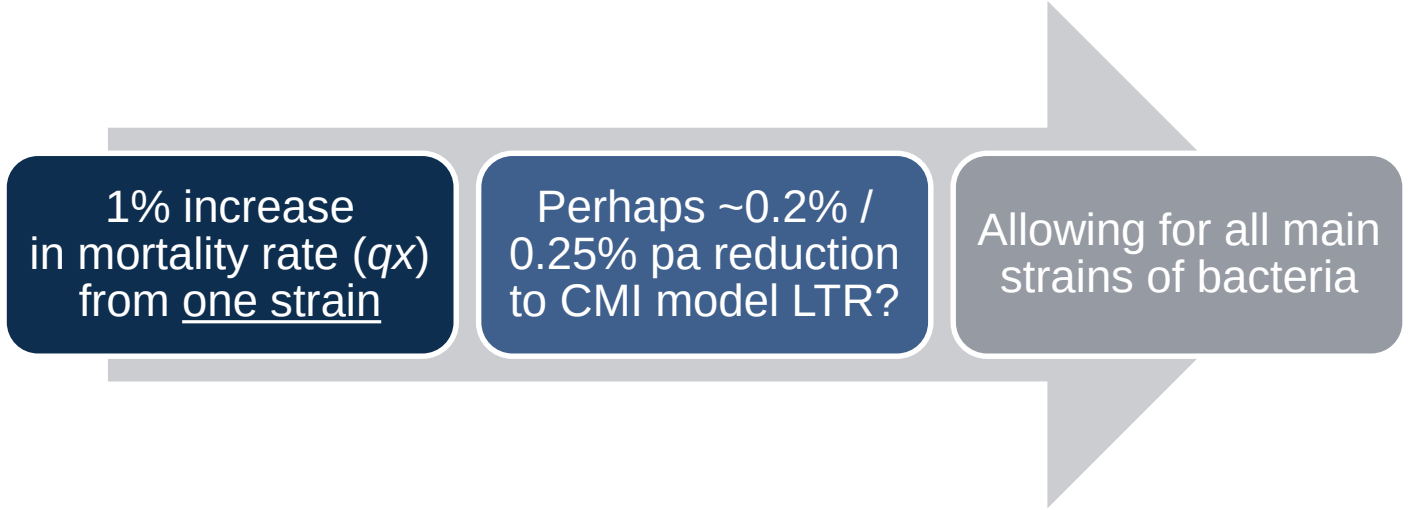
Initial Results: *E. coli* resistance

Parametrisation based on:

- Growth in *E. coli* bacteria resistant to 3rd generation cephalosporin antibiotics
- Ages 19-64, i.e. working age population
- Projected position in 2037, i.e. 20 years' time

Results:

Central scenario



In a bad scenario (95% confidence level not 1-in-200), there could be a 10-20% increase in overall mortality (with all main strains)

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Working party – next steps

Sessional meeting February 2019

Model development

- Parameterisation – other main bacteria (5)
- Interactions between pathogens
- Validation / Documentation

- **Full model release**
- **Suggested parameterisation based on UK data**
- **Associated paper – main issues relating to sources of ABR, mitigation actions, recent trends, other projection results / methodologies, and background to our model and results from the model**

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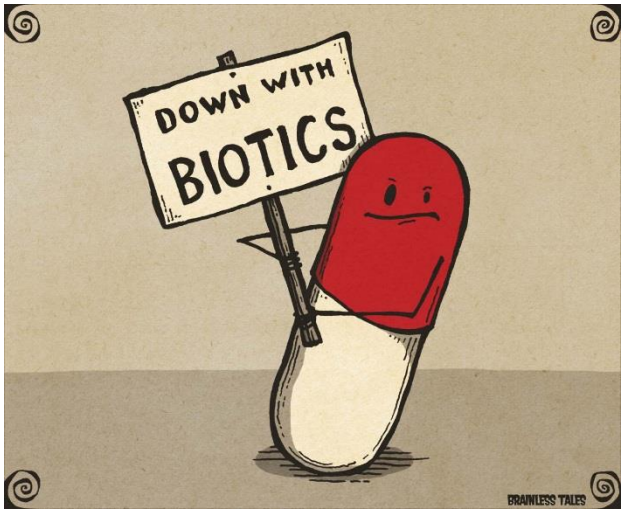
Questions

Comments



Expressions of individual views by members of the Institute and Faculty of Actuaries and its staff are encouraged.

The views expressed in this presentation are those of the presenter.

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