



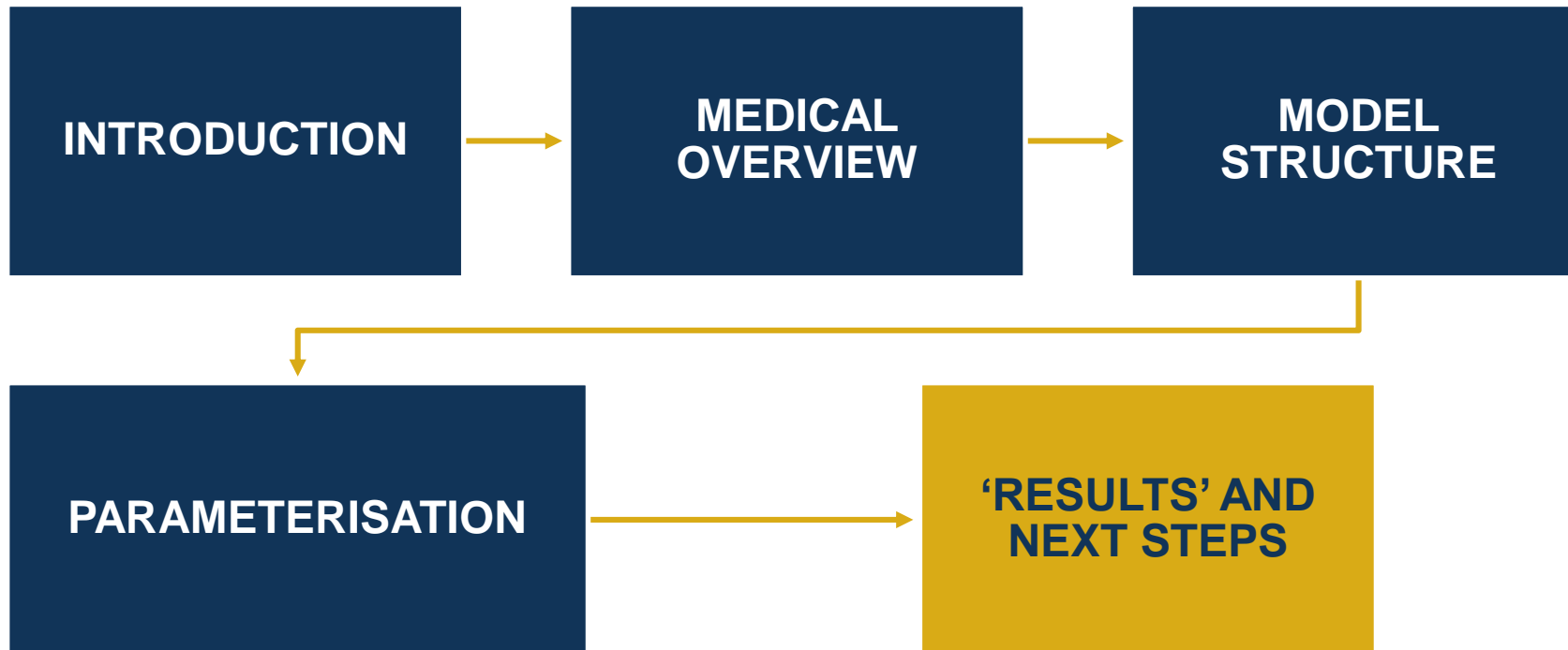
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# When the drugs don't work...

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

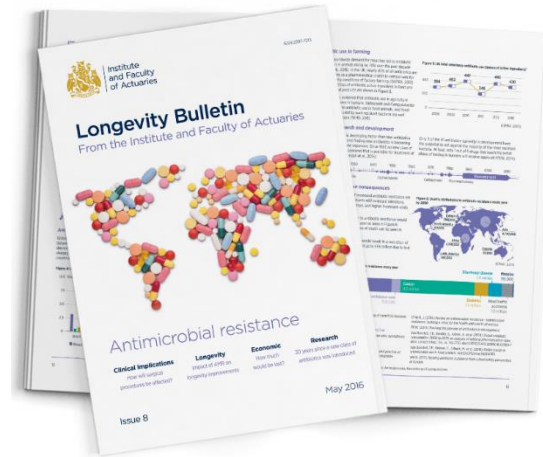


# Agenda



# 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





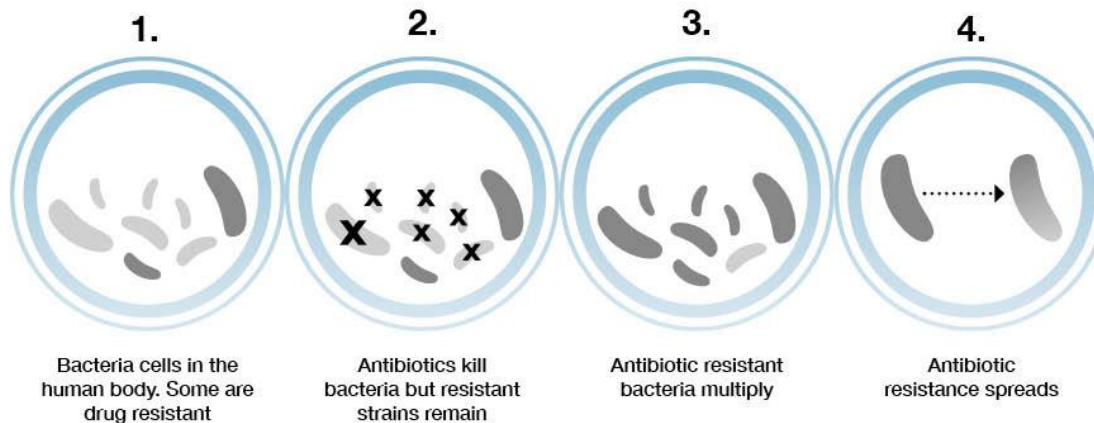
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# Medical overview

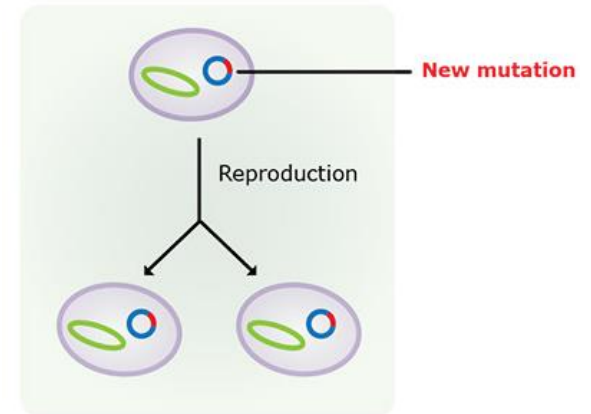
June 14, 2018

# What is antibiotic resistance...

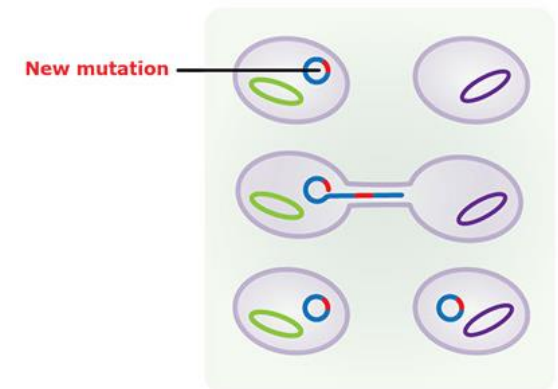
## How antibiotic resistance occurs



## Vertical gene transmission



## Horizontal gene transmission



***"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

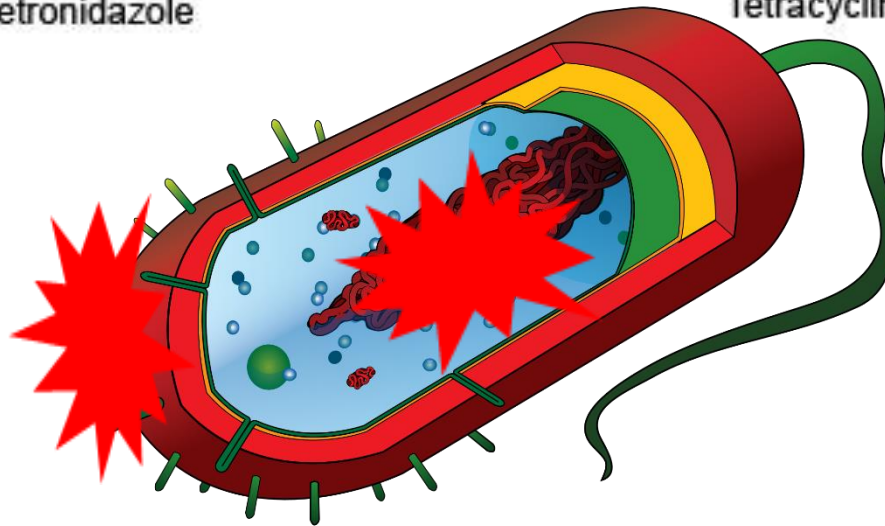


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**EXAMPLES:**  
Aminoglycosides  
Beta-lactams  
Vancomycin  
Quinolones  
Rifampin  
Metronidazole



**EXAMPLES:**  
Chloramphenicol  
Erythromycin  
Clindamycin  
Sulfonamides  
Trimethoprim  
Tetracyclines

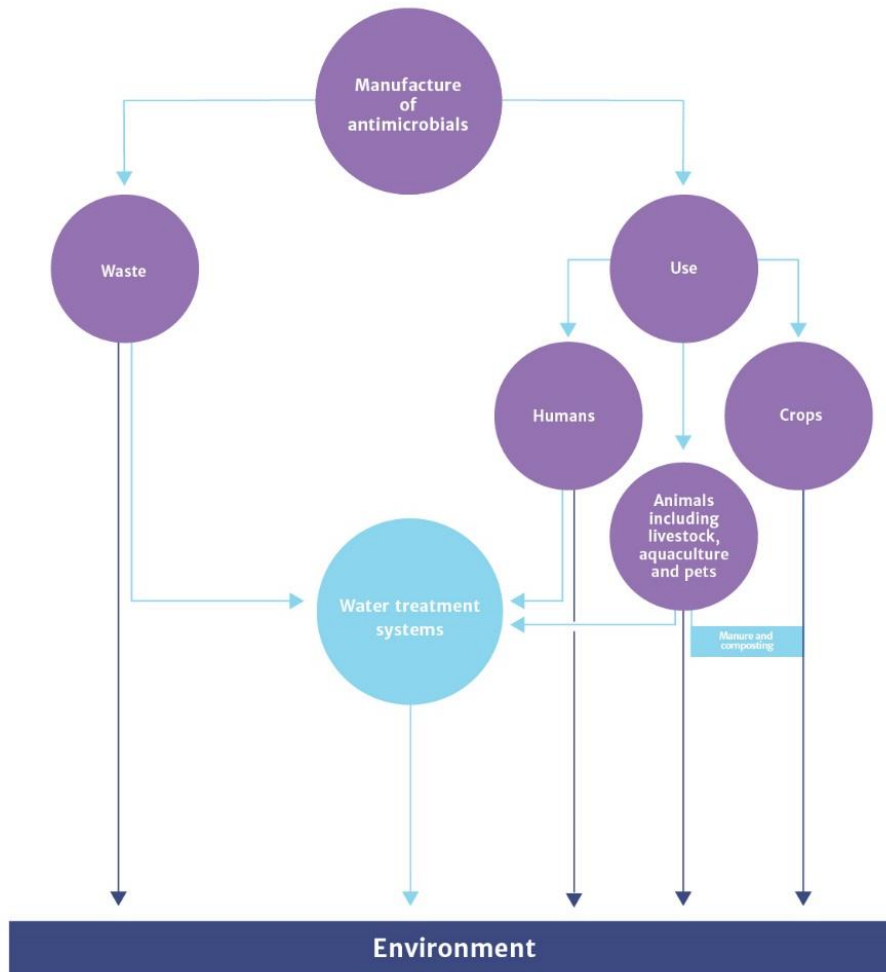


## How do antibiotics work? (the science!)

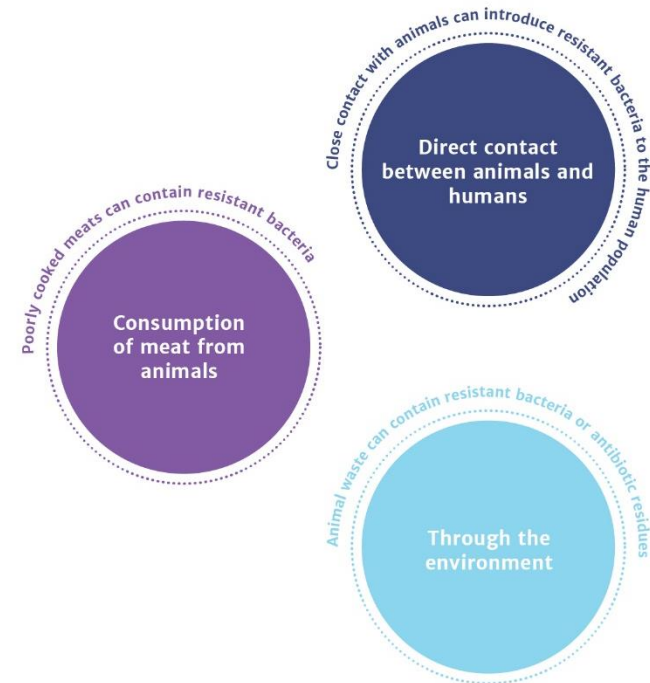


# What are the sources of resistance?

## Sources of resistance



## How animals can pass on resistant bacteria



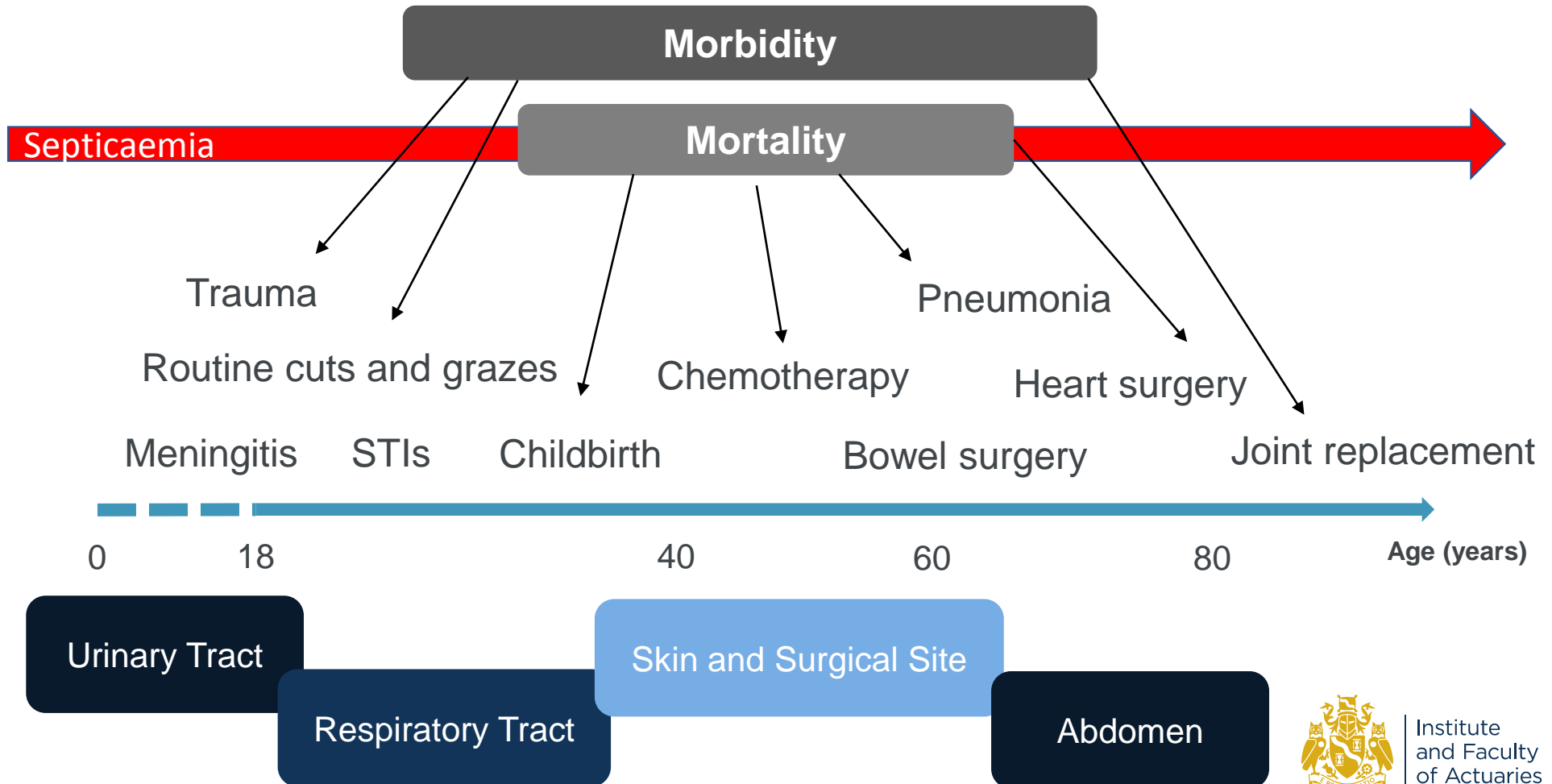
Infographics sourced from "Review on Antimicrobial Resistance" 2014



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# How does ABR affect people and our work?





## 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 Cavalieri, Edward M Cox, Chris R Houchens,  
M Lindsay Grayson, Paul Hansen, Nalini Singh, Ursula Theuretzbacher, Nicola Magrinj, 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, 3<sup>rd</sup> 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*, 3<sup>rd</sup> 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

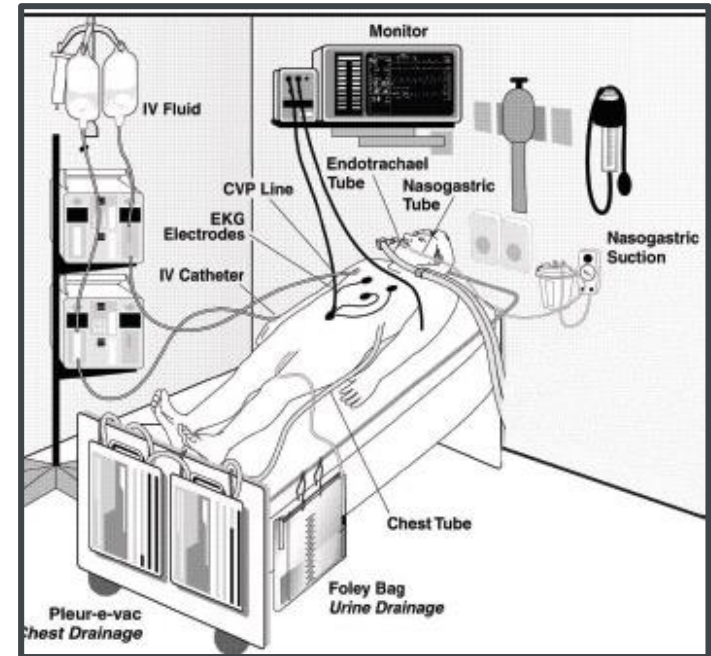
Driven by AB use and poor infection control



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*

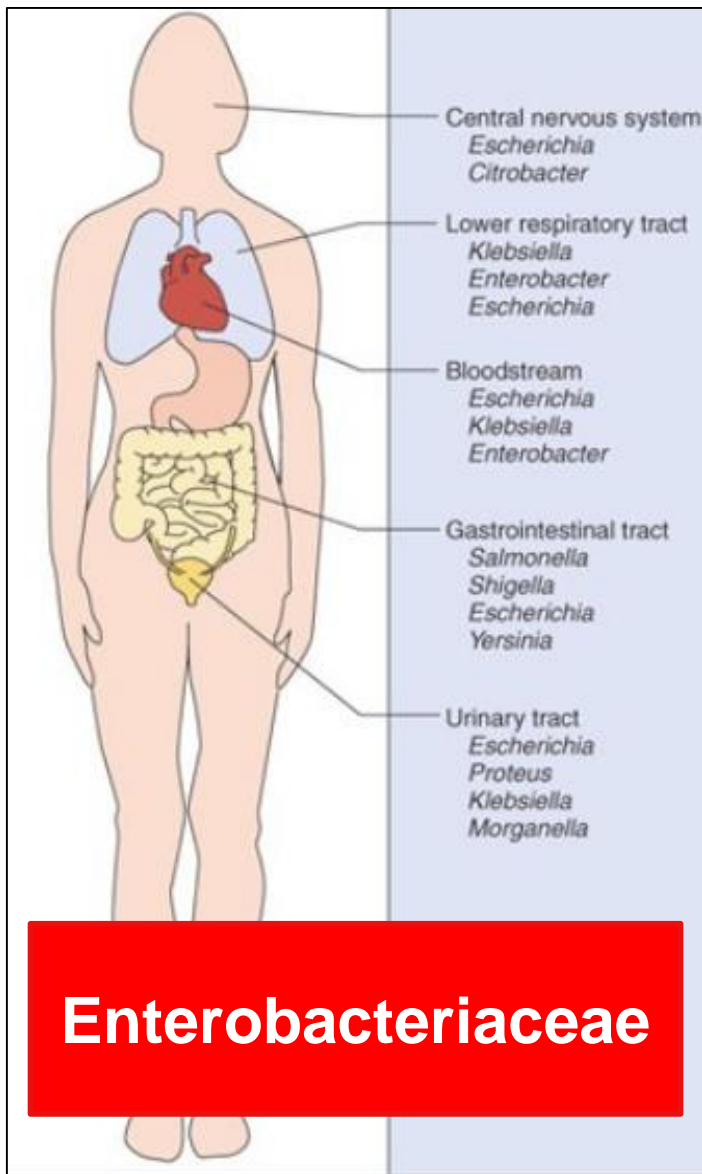
Pneumonia

Wound  
Infection

Bloodstream  
Infection

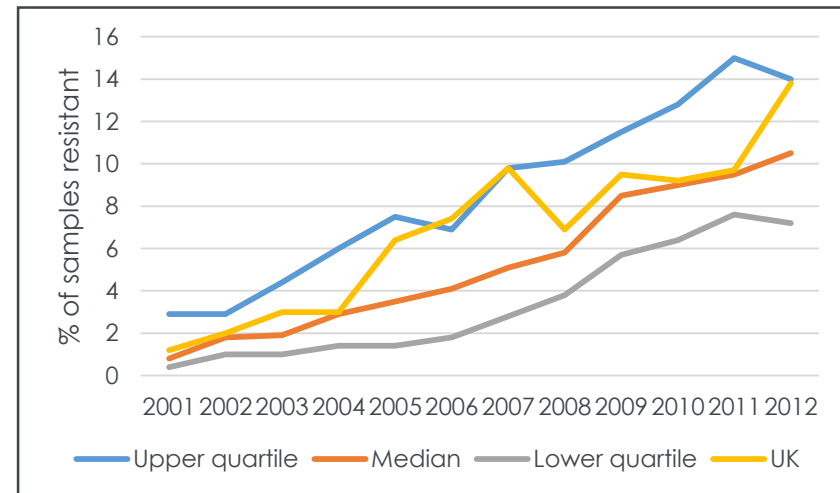


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## Enterobacteriaceae

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)

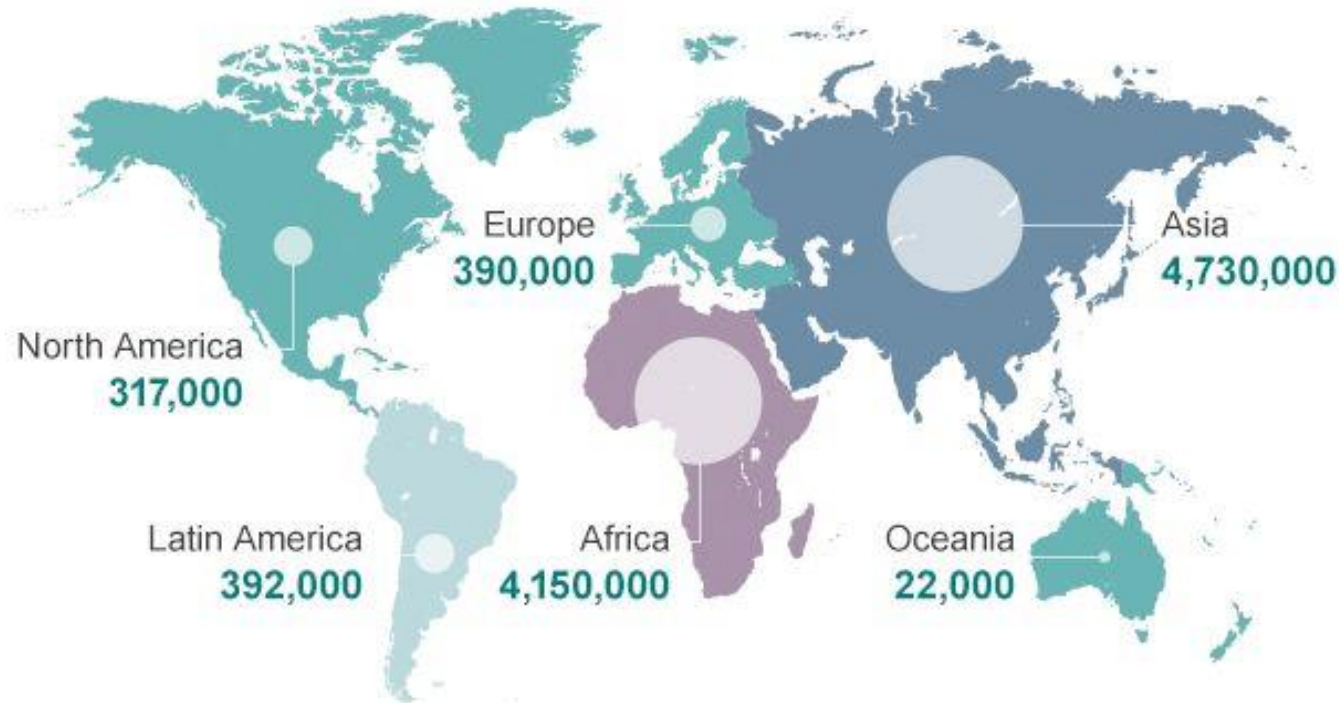




# ...and why it is important?

*“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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# Global increase and geographic convergence in antibiotic consumption between 2000 and 2015

Eili Y. Klein<sup>a,b,c,1</sup>, Thomas P. Van Boeckel<sup>d</sup>, Elena M. Martinez<sup>a</sup>, Suraj Pant<sup>a</sup>, Sumanth Gandra<sup>a</sup>, Simon A. Levin<sup>e,f,g,1</sup>, Herman Goossens<sup>h</sup>, and Ramanan Laxminarayan<sup>a,f,i</sup>

<sup>a</sup>Center for Disease Dynamics, Economics & Policy, Washington, DC 20005; <sup>b</sup>Department of Emergency Medicine, Johns Hopkins School of Medicine, Baltimore, MD 21209; <sup>c</sup>Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205; <sup>d</sup>Institute of Integrative Biology, ETH Zürich, CH-8006 Zürich, Switzerland; <sup>e</sup>Department of Ecology and Environmental Science, Princeton University, Princeton, NJ 08544; <sup>f</sup>Beijing Institute of Microbiology and Infectious Diseases Institute, University of Antwerp, Antwerp, Belgium; <sup>g</sup>Department of Biology, University of Washington, Seattle, WA 98104; <sup>h</sup>Department of Microbiology and Infectious Diseases, University of Antwerp, Antwerp, Belgium; <sup>i</sup>Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08544

Contributed by Simon A. Levin, February 23, 2018 (sent for review October 3, 2017)



NEWS



INDEPENDENT

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## Antibiotic-resistant gonorrhoea cases expected to emerge worldwide

News > Health

# Antibiotic-resistant gonorrhoea cases expected to emerge worldwide

Warnings after UK man and two Australians suffer STI untreatable with usual drugs

Sally Wardle | Friday 20 April 2018 18:39 BST | 10 comments



218 shares

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

Bradley M. Hover<sup>1</sup>, Seong-Hwan Kim<sup>1</sup>, Micah Katz<sup>1</sup>, Zachary Melinda A. ...  
and Sean F. E.

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

Microbiome

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*Quasidominant* bacteria in a petri dish glowing under long wave ultraviolet light.

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RESEARCH

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# Identification of 76 novel B1 metallo- $\beta$ -lactamases through large-scale screening of metagenomic and metagenomic data

Berglund<sup>1,2</sup>, Nachiket P. Marathe<sup>2,3</sup>, Tobias Österlund<sup>1,2</sup>, Johan Bengtsson-Palme<sup>2,3</sup>, Stathis Kotsakis<sup>2,3</sup>, Florian Flach<sup>2,3</sup>, D G Joakim Larsson<sup>2,3</sup> and Erik Kristiansson<sup>1,2\*</sup>



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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

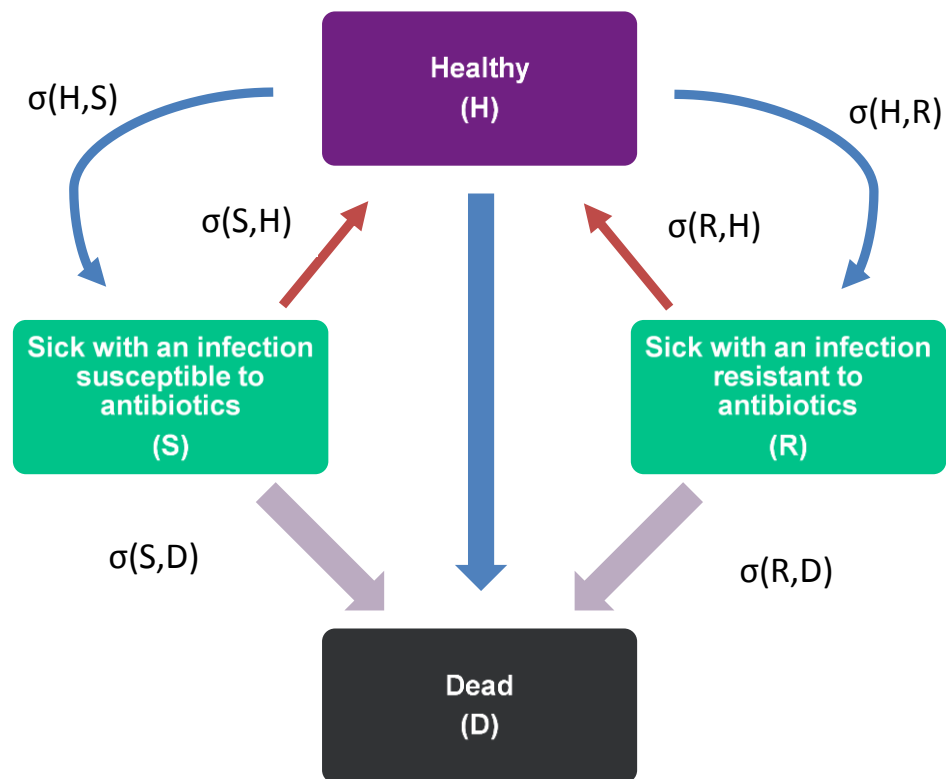
- KPMG / RAND model
- Research papers

## Model Structure

- Complex enough to model scenario
- Not overly complex
- Capable of being adapted by users



# Chosen model structure



## Modelling criteria

- Simplicity
- Availability of data
- Appropriate outputs

## Basic structure decided on:

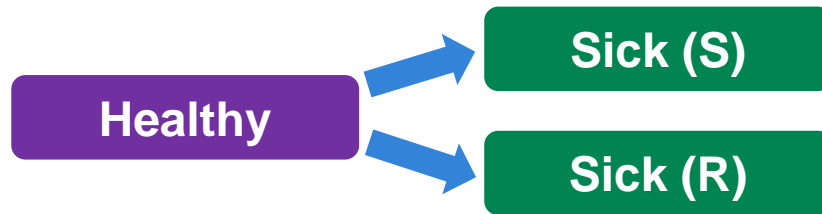
- Multi-state Markov model
- Calibrate to current observed levels of mortality and morbidity
- Project varying resistance over time and calculate the change in mortality and morbidity





# Data sources – incidence

## Incidence rates for bacteraemia



Public Health  
England



## Limitations

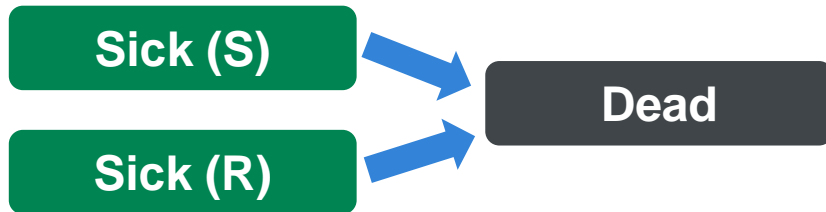
- Limited data. *E. coli* monitoring in England goes back to 2013.
- Limited evidence for how resistance interacts with incidence.
- Bias? Monitoring is of HCAs.



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# Data sources – mortality

## Death rates for bacteraemia



Public Health  
England



## 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.



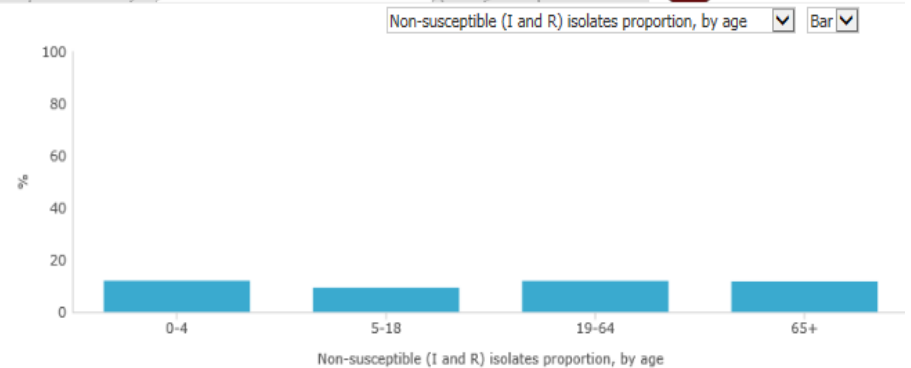
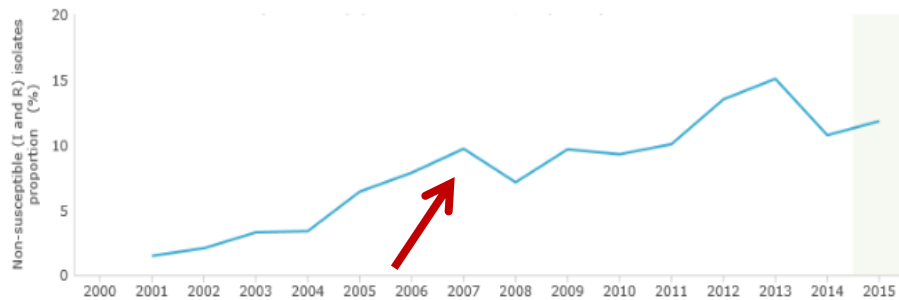
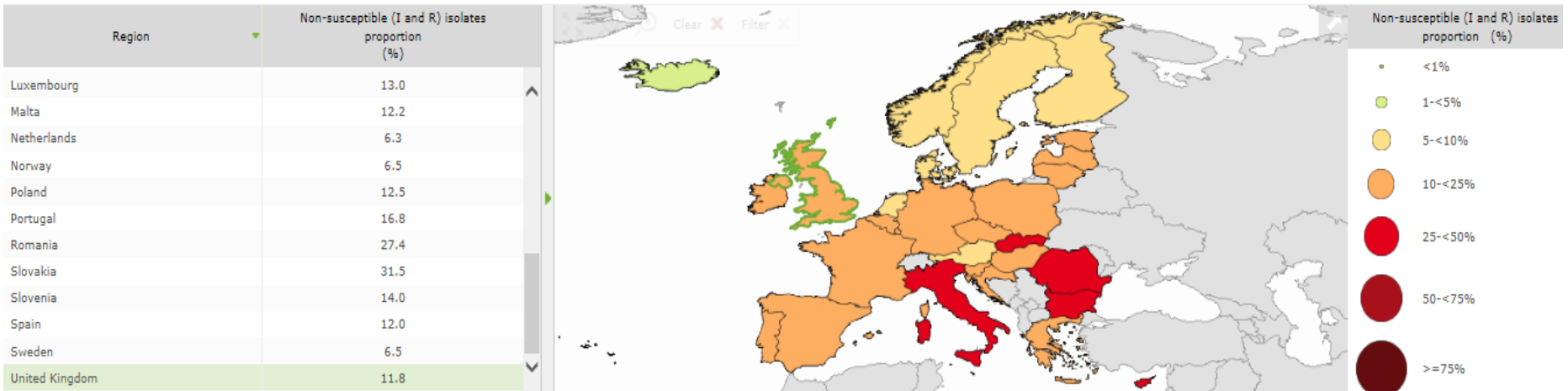
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# Trends in resistance can be observed...



## Surveillance Atlas of Infectious Diseases

← → Antimicrobial resistance ▾ Escherichia coli ▾ Third-generation cephalosporins ▾ Non-susceptible (I and R) isolates proportion ▾ ▶ ◀◀ 2015 ▶▶ ⋮



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



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# ...and extrapolated forwards

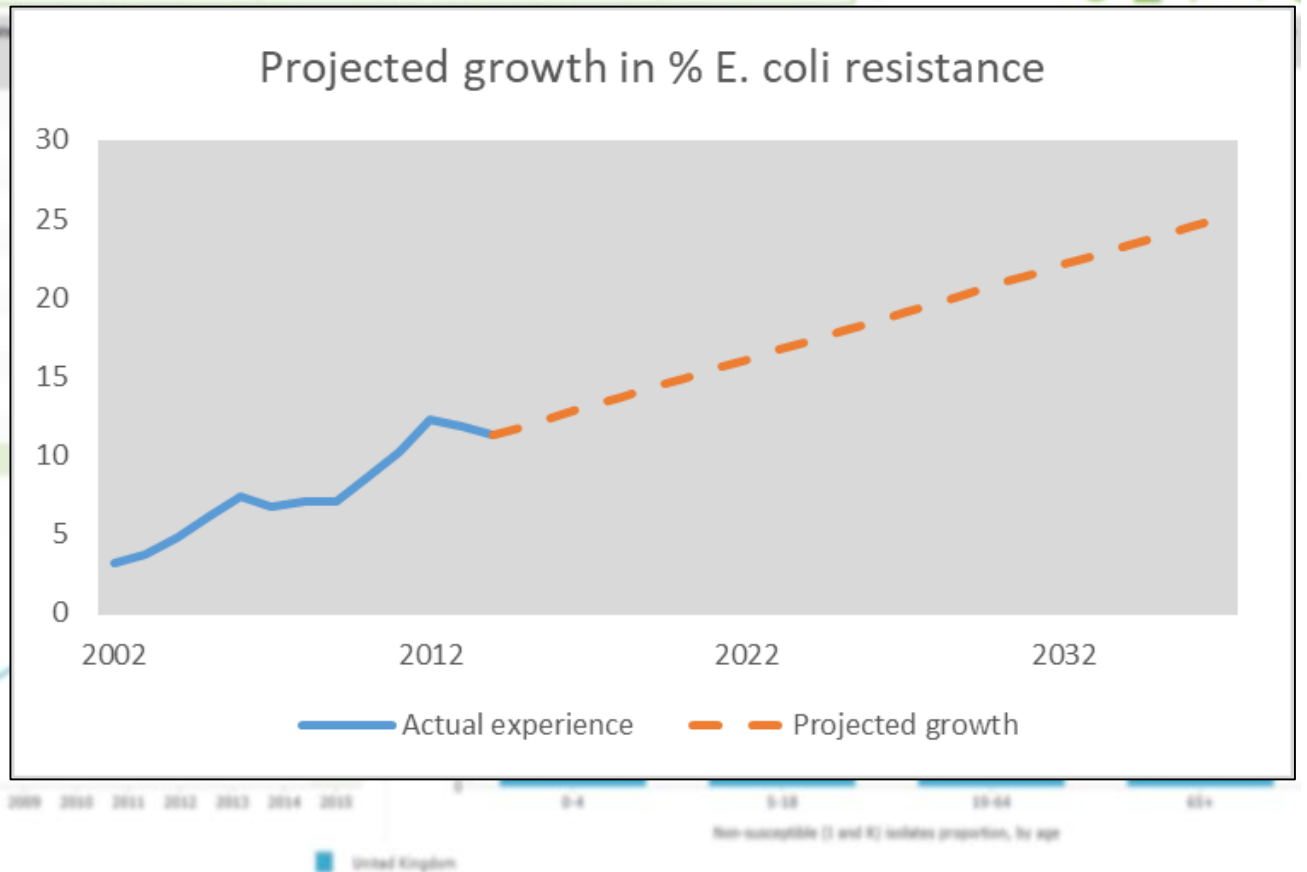


## Surveillance Atlas of Infectious Diseases

← → Antimicrobial resistance Escherichia coli Third generation cephalosporins Non-susceptible (I and R) isolates proportion 2015

Region	Non-susceptible (I and R) isolates proportion (%)
Luxembourg	13.0
Malta	12.2
Netherlands	6.3
Norway	6.0
Poland	12.5
Portugal	---
Romania	---
Slovakia	---
Slovenia	---
Spain	---
Sweden	---
United Kingdom	---

This data can be used to inform projections of the future position



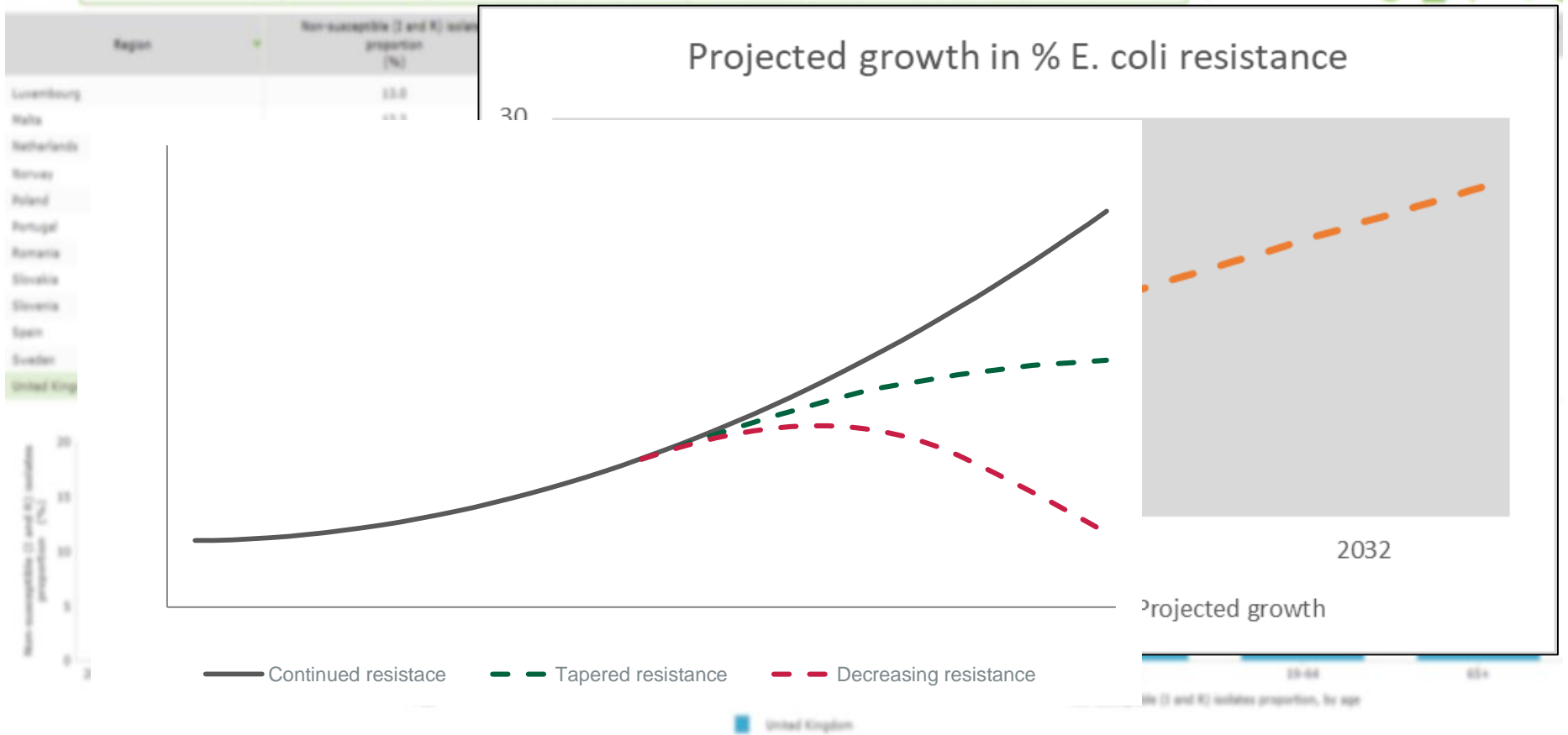
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# ...and extrapolated forwards



## Surveillance Atlas of Infectious Diseases

← → Antimicrobial resistance Escherichia coli Third generation cephalosporins Non-susceptible (I and R) isolates proportion 2015



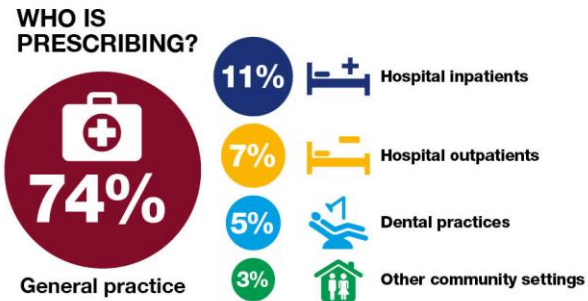
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# Future of resistance?

**TACKLING ANTIMICROBIAL RESISTANCE ON TEN FRONTS**

- Public awareness
- Sanitation and hygiene
- Antibiotics in agriculture and the environment
- Vaccines and alternatives
- Surveillance
- Rapid diagnostics
- Human capital
- Drugs
- Global Innovation Fund
- International coalition for action

Review on Antimicrobial 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

1% increase in mortality rate ( $qx$ ) from one strain

Perhaps ~0.2% / 0.25% pa reduction to CMI model LTR?

Allowing for all main strains of bacteria

**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**

- **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**

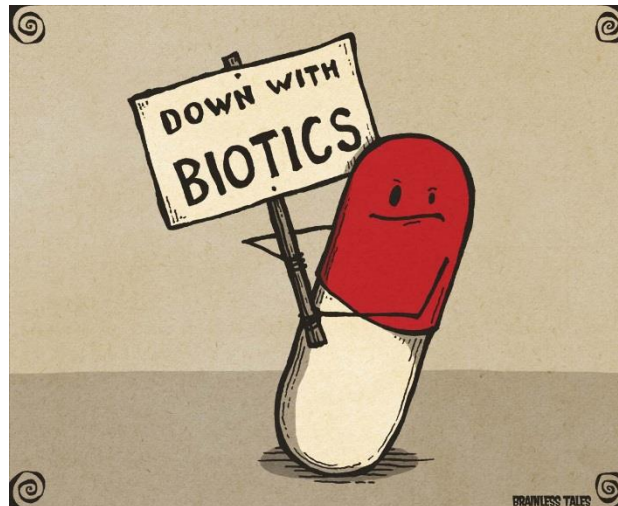
## **Model development**

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



# 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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