



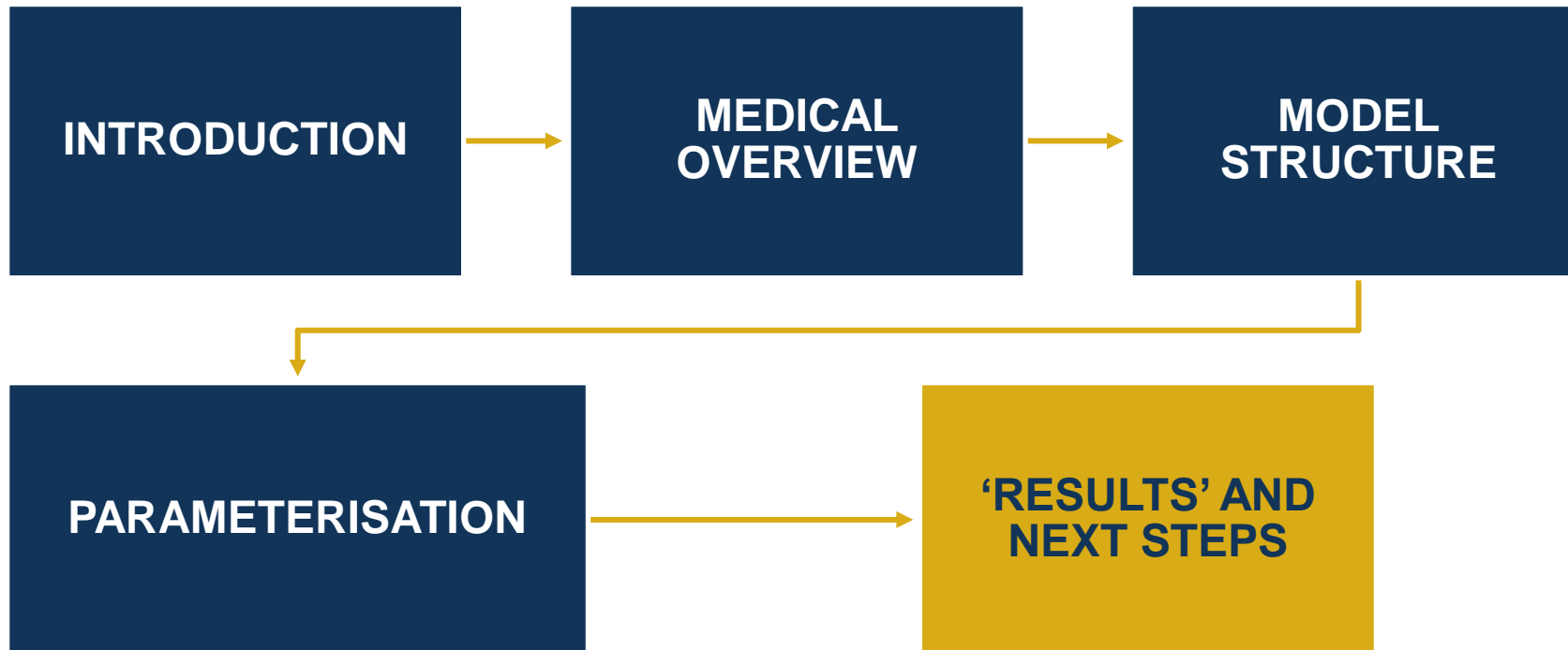
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When the drugs don't work...

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

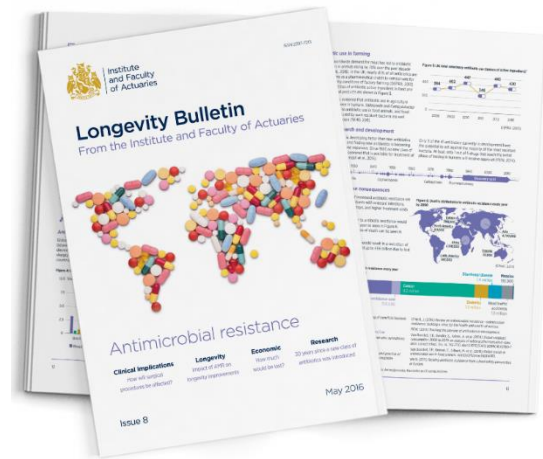


Agenda



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



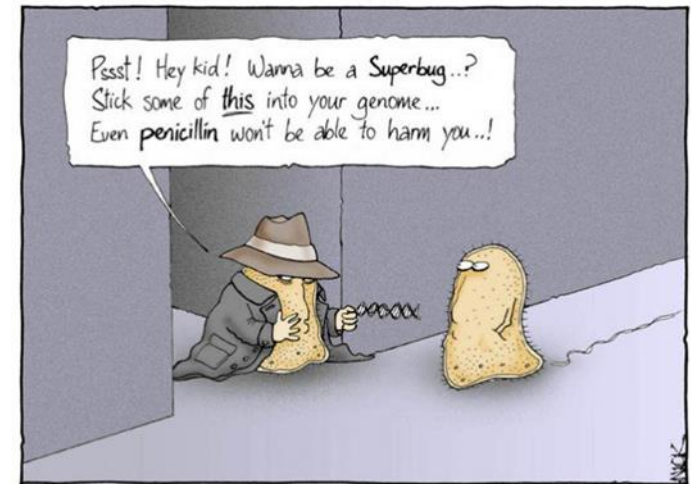
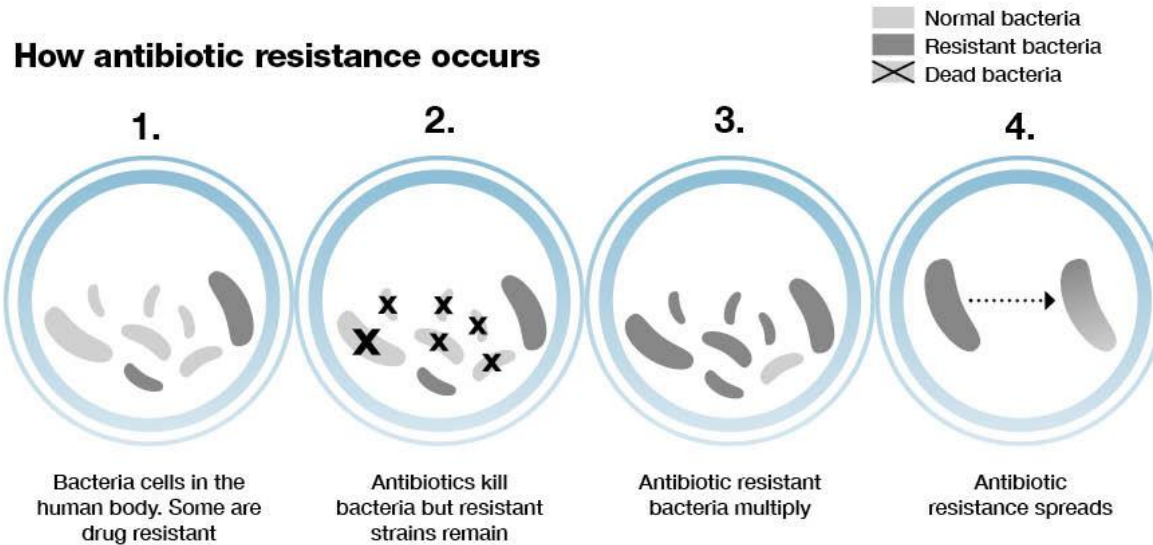


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Medical overview

June 11, 2024

What is antibiotic resistance...



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

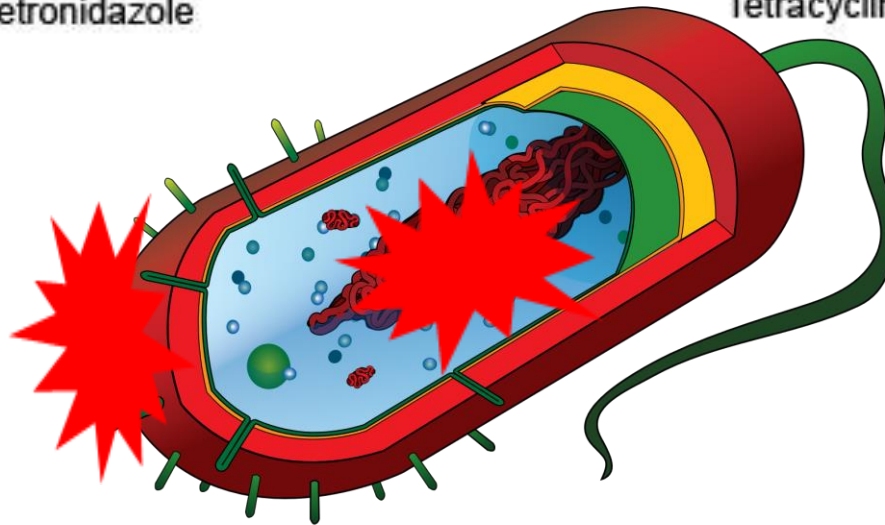
"The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism." Sir Alexander Fleming, 1928



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EXAMPLES:
Aminoglycosides
Beta-lactams
Vancomycin
Quinolones
Rifampin
Metronidazole



EXAMPLES:
Chloramphenicol
Erythromycin
Clindamycin
Sulfonamides
Trimethoprim
Tetracyclines



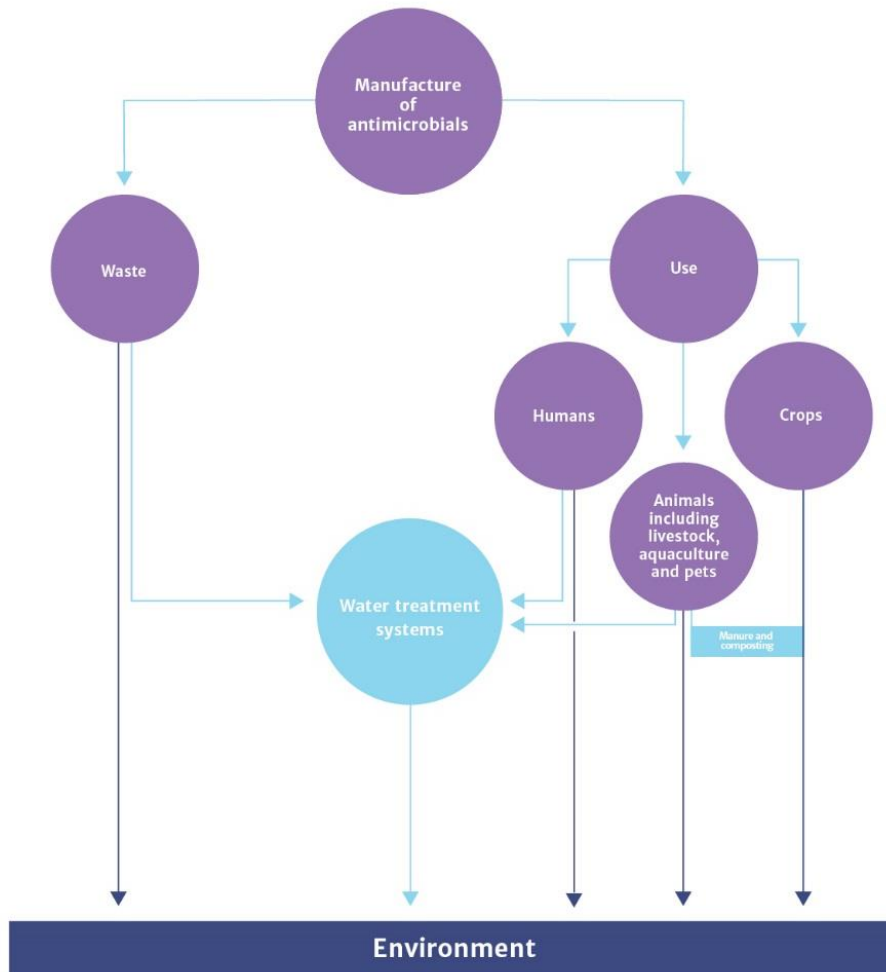
How does it actually work (the science!)



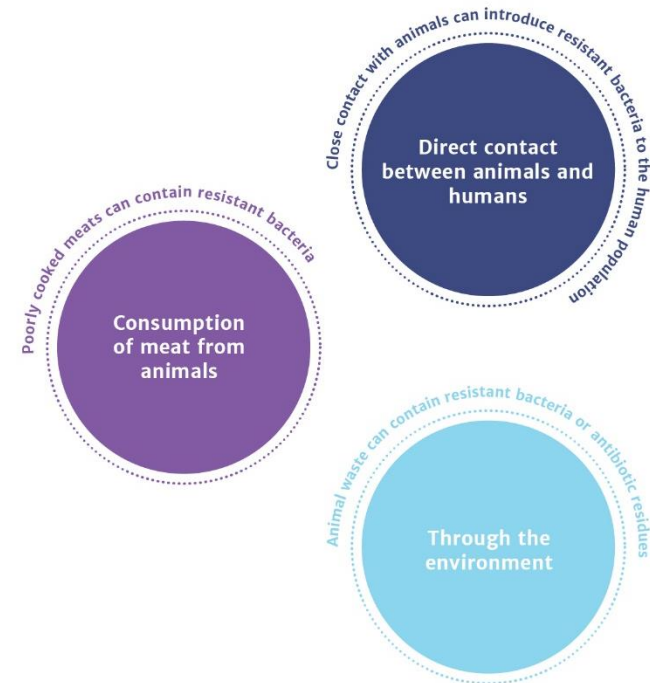
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What are the sources of resistance?

Sources of resistance



How animals can pass on resistant bacteria

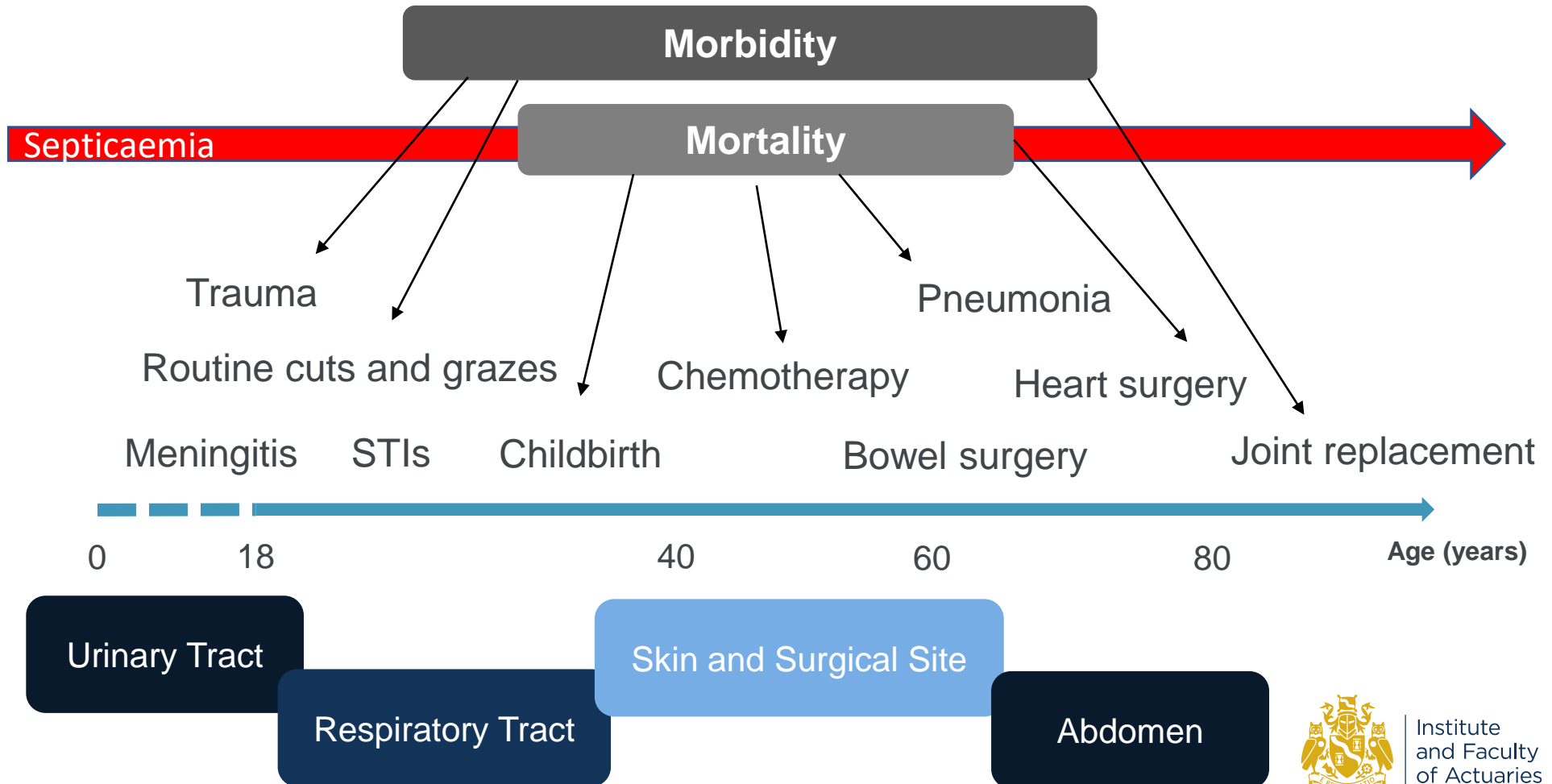


Infographics sourced from "Review on Antimicrobial Resistance" 2014



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How does ABR affect people and our work?





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 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

**Acinetobacter baumannii,
carbapenem-resistant**

**Pseudomonas aeruginosa,
carbapenem-resistant**

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



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Acinetobacter baumannii, carbapenem-resistant

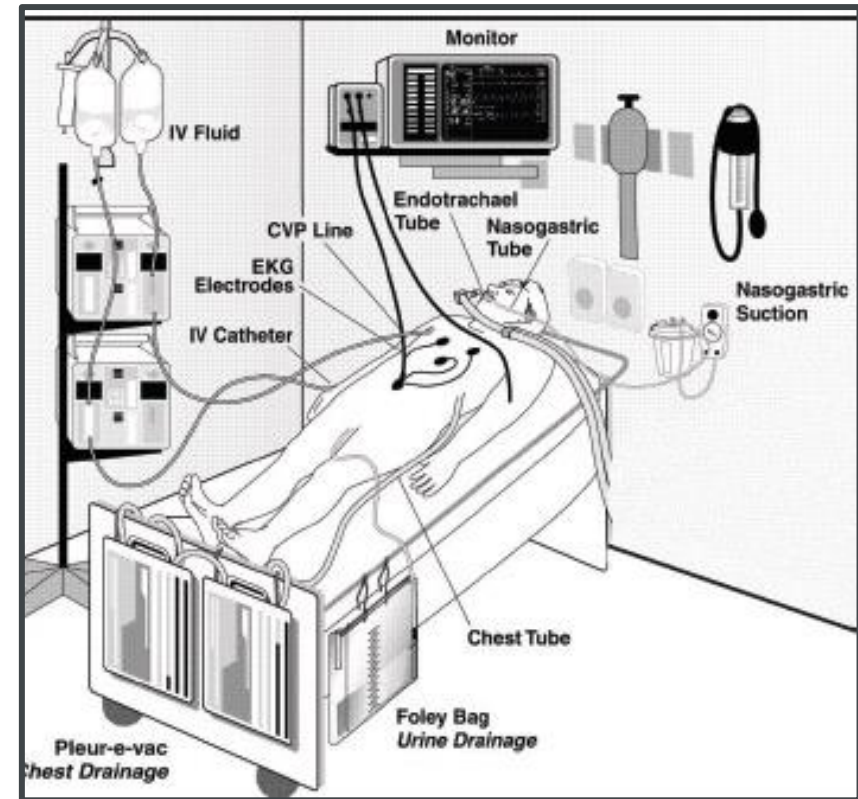
Driven by AB
use and poor
infection
control



Healthcare
Setting

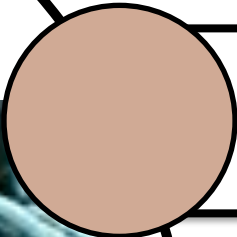
Resistant to
colistin in 4%
of cases

Resilient

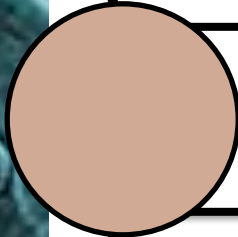




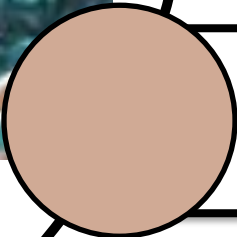
Pseudomonas aeruginosa,
carbapenem-resistant



Found widely in the environment



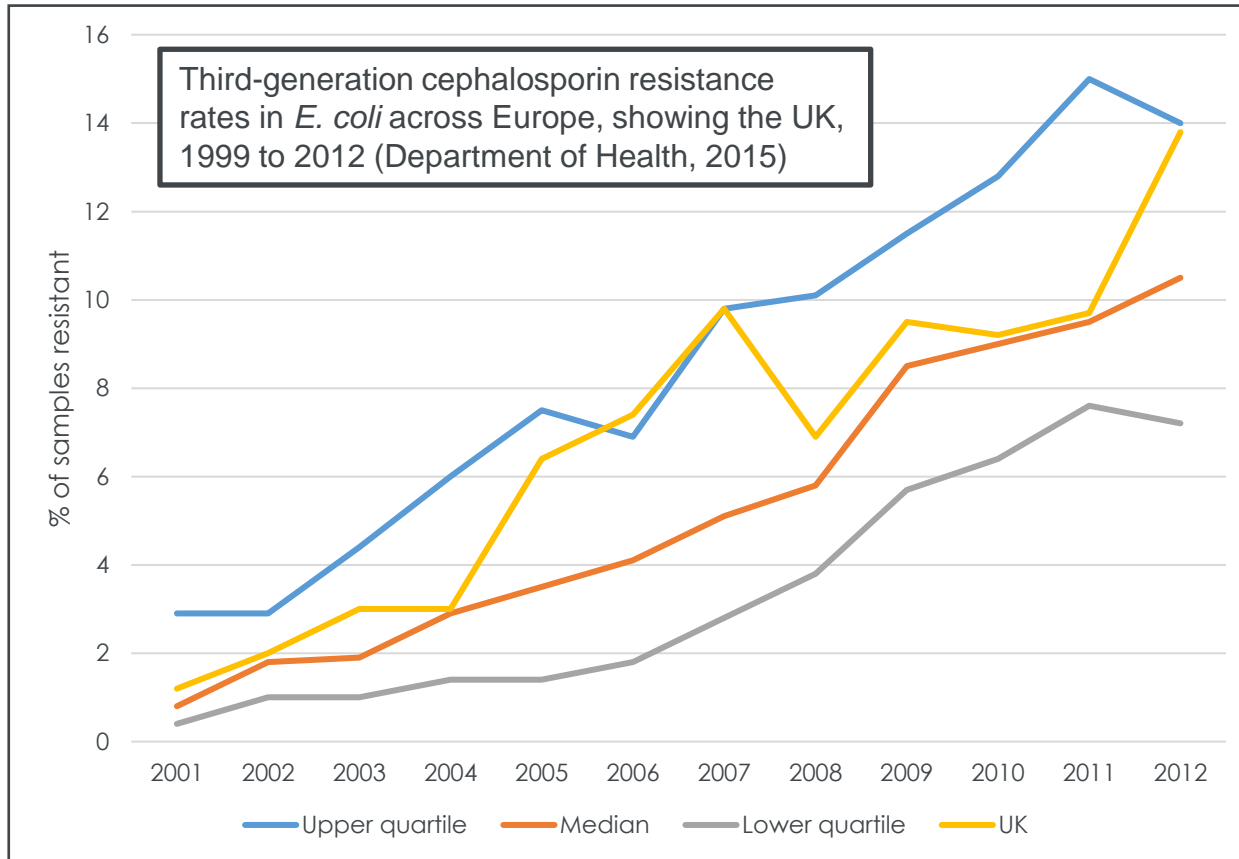
Common cause of mild and serious infections



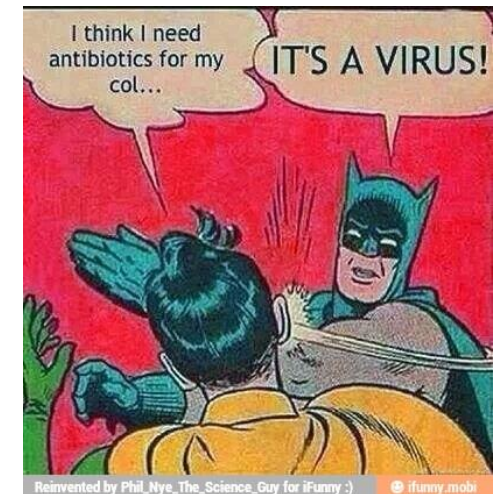
Risk profile similar to A. Baumannii



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



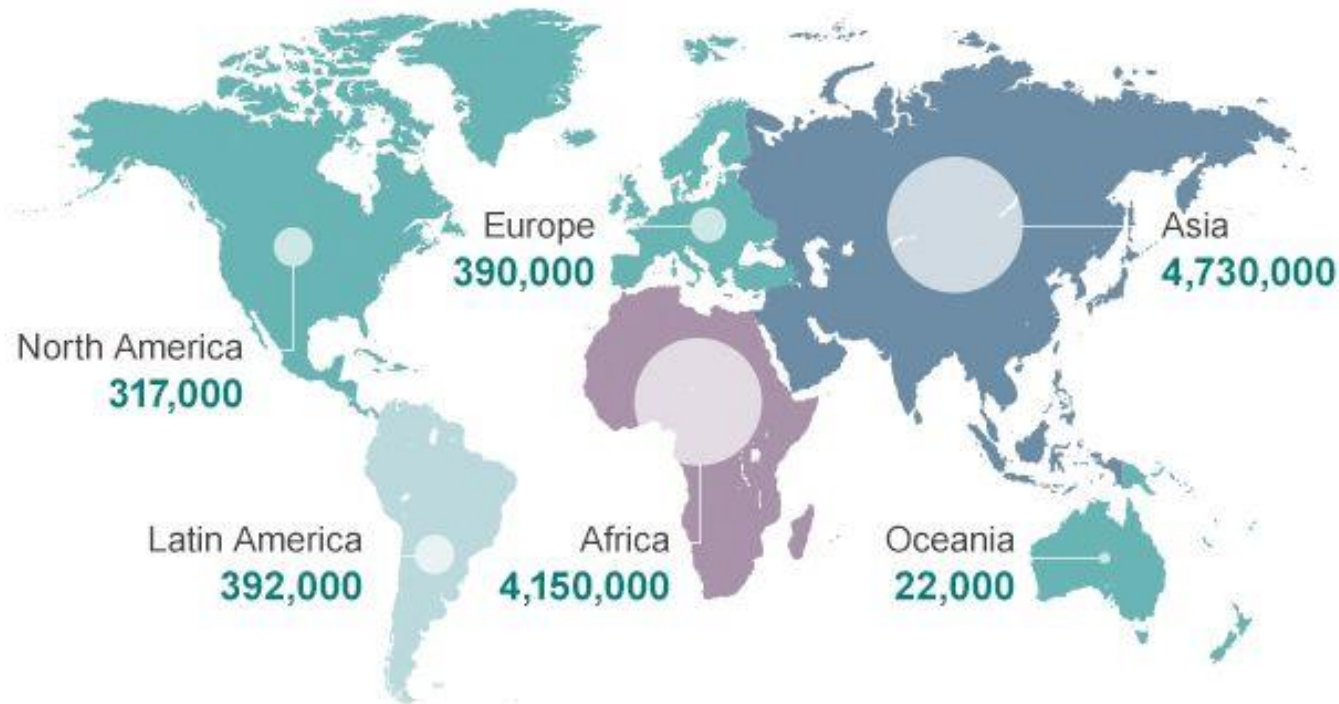
These bacteria are associated with higher frequency of inappropriate antimicrobial therapy, poorer clinical response, and longer length of hospital stay



...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^{a,b,c,1}, Thomas P. Van Boeckel^d, Elena M. Martinez^a, Suraj Pant^a, Sumanth Gandra^a, Simon A. Levin^{e,f,g,1}, Herman Goossens^h, and Ramanan Laxminarayan^{a,f,i}

^aCenter for Disease Dynamics, Economics & Policy, Washington, DC 20005; ^bDepartment of Emergency Medicine, Johns Hopkins School of Medicine, Baltimore, MD 21209; ^cDepartment of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205; ^dInstitute of Integrative Biology, ETH Zürich, CH-8006 Zürich, Switzerland; ^eDepartment of Ecology and Environmental Science, Princeton University, Princeton, NJ 08544; ^fBeijing Institute of Microbiology and Infectious Diseases Institute, University of Antwerp, Antwerp, Belgium; ^gDepartment of Biology, University of Washington, Seattle, WA 98104; ^hDepartment of Microbiology, University of Antwerp, Antwerp, Belgium; ⁱDepartment 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

News InFact Politics Voices



Combinations thwart efforts to curb antibiotic-resistant gonorrhoea researchers

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



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

Bradley M. Hover¹, Seong-Hwan Kim¹, Micah Katz¹, Zachary Melinda A. ...
and Sean F. E.

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

Microbiome

MIT Technology Review

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

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Edible CRISPR Could Replace Antibiotics

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

RESEARCH

Open Access



Identification of 76 novel B1 metallo- β -lactamases through large-scale screening of metagenomic and metagenomic data

Berglund^{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*}

"...m bad to worse, but we're
we're doing badly again."



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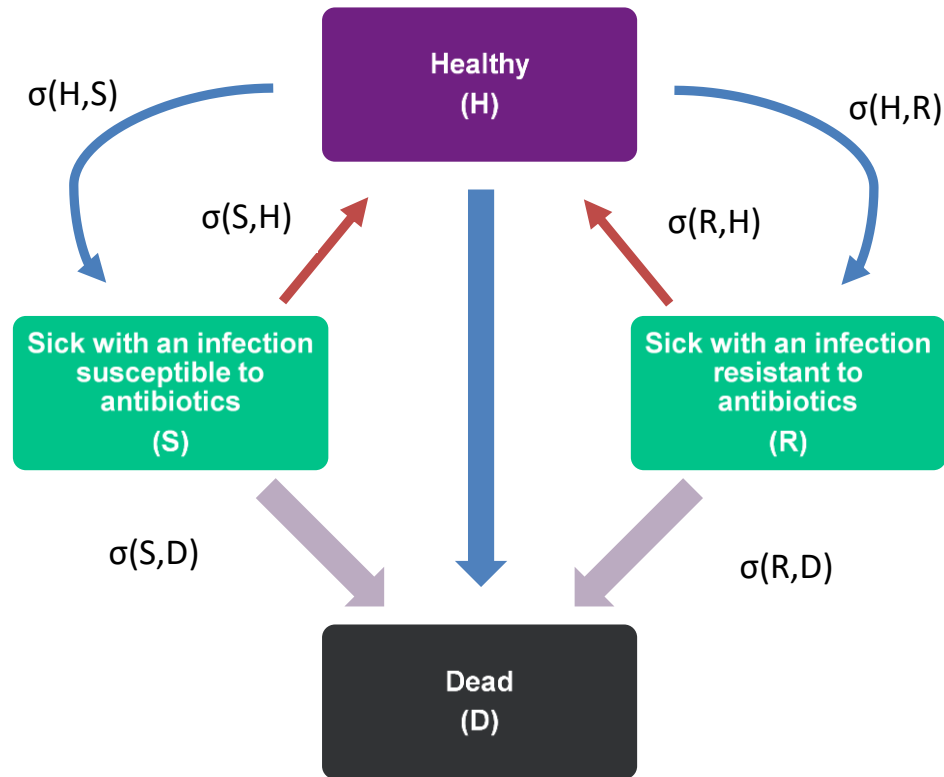
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Model structure and parameterisation

Ross Hamilton

June 11, 2024

How can we model this impact?



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 – what is available?



Public Health
England

- Current and historical resistance profiles for *S. aureus*, *E. coli* and selected other infections vs various antibiotics



Office for
National Statistics

 **PLOS** | Open for
Discovery



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Data sources – what is available?



Public Health
England



Office for
National Statistics

 **PLOS** | **Open for
Discovery**

- Current and historical resistance profiles for *S. aureus*, *E. coli* and selected other infections vs various antibiotics.
- Resistance is not absolute. Resistance can be to a single antibiotic, or multidrug resistance.
- Bias? Are samples more likely to be taken from the very ill? Will resistant strains be over-represented because of this?



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Data sources – what is available?



Public Health
England

- Incidence rates for bacteraemias.



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Data sources – what is available?



Public Health
England



Office for
National Statistics



- Incidence rates for bacteraemias.
- 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 – what is available?



Public Health
England

- Death rates for bacteraemias.



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Data sources – what is available?



Public Health
England



Office for
National Statistics



- Death rates for bacteraemias.
- Limited data. *E. coli* monitoring in England goes back to 2013.
- 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.



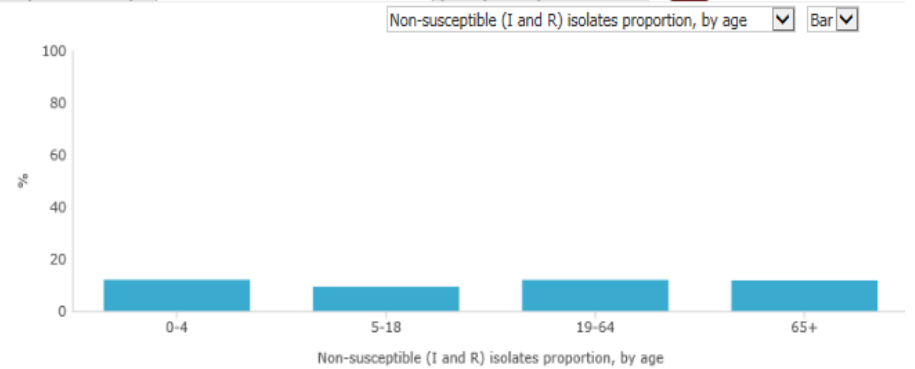
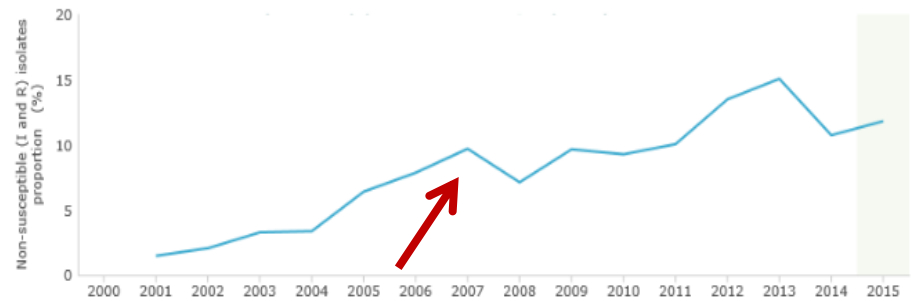
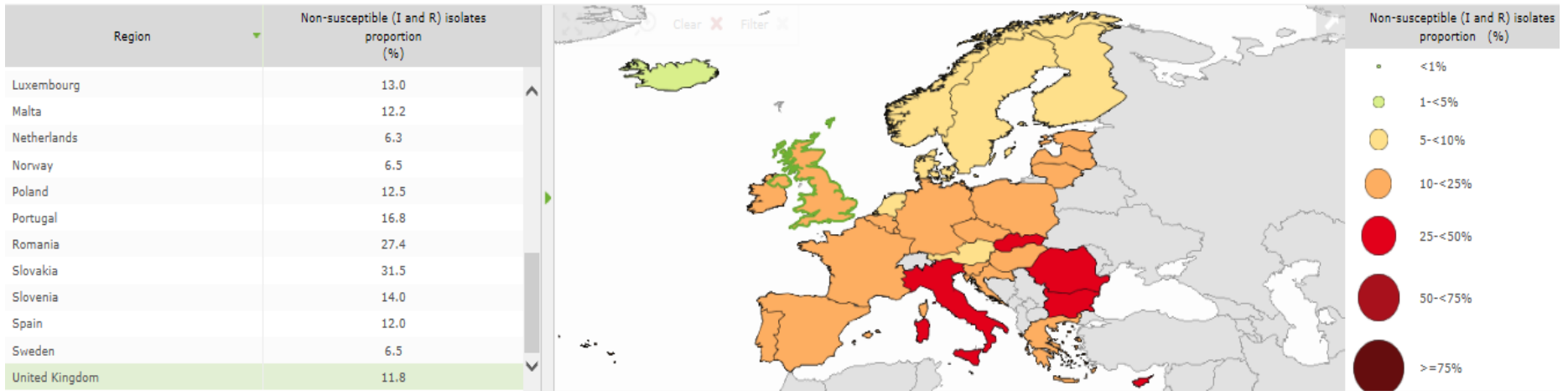
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Trends in resistance can be observed...



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

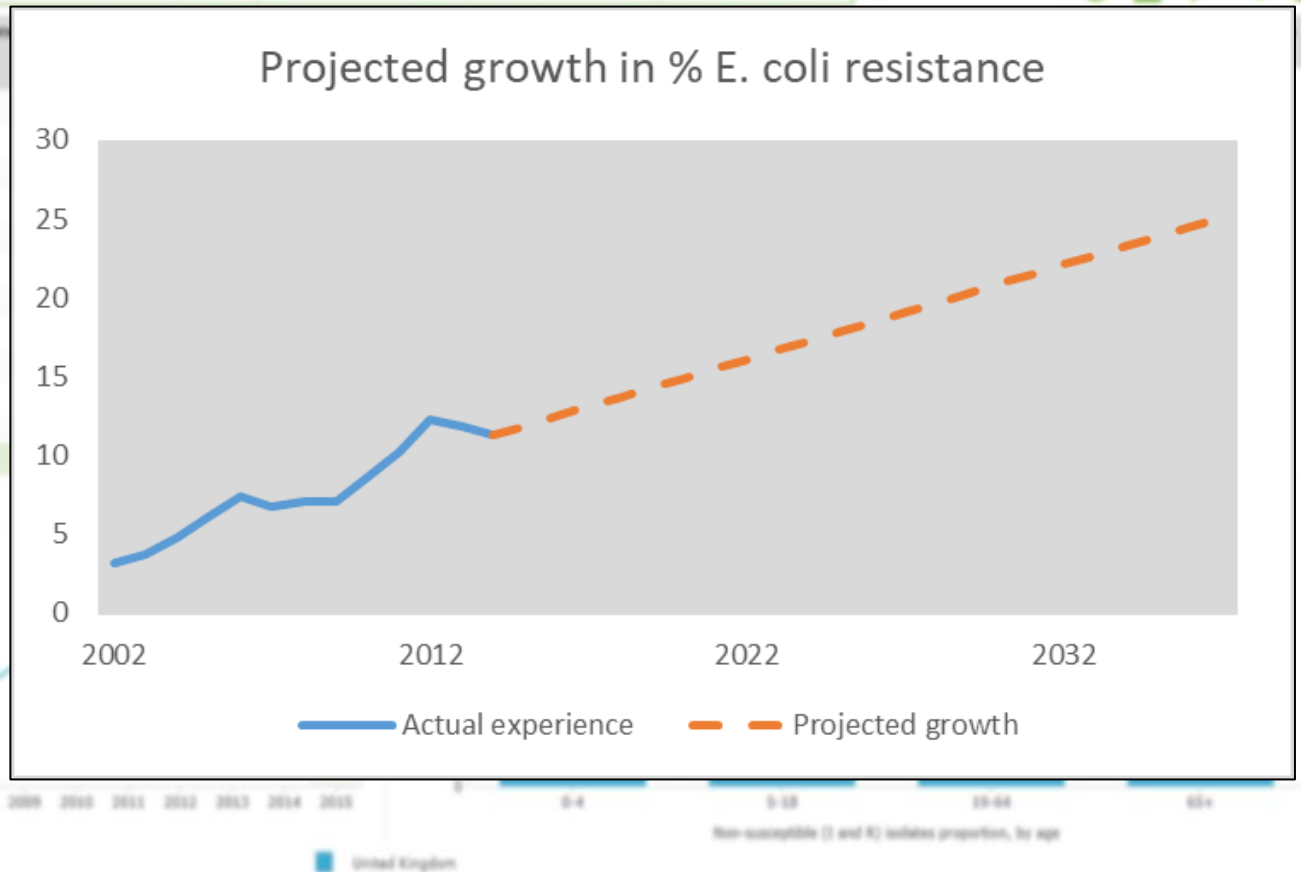


Surveillance Atlas of Infectious Diseases

← → 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

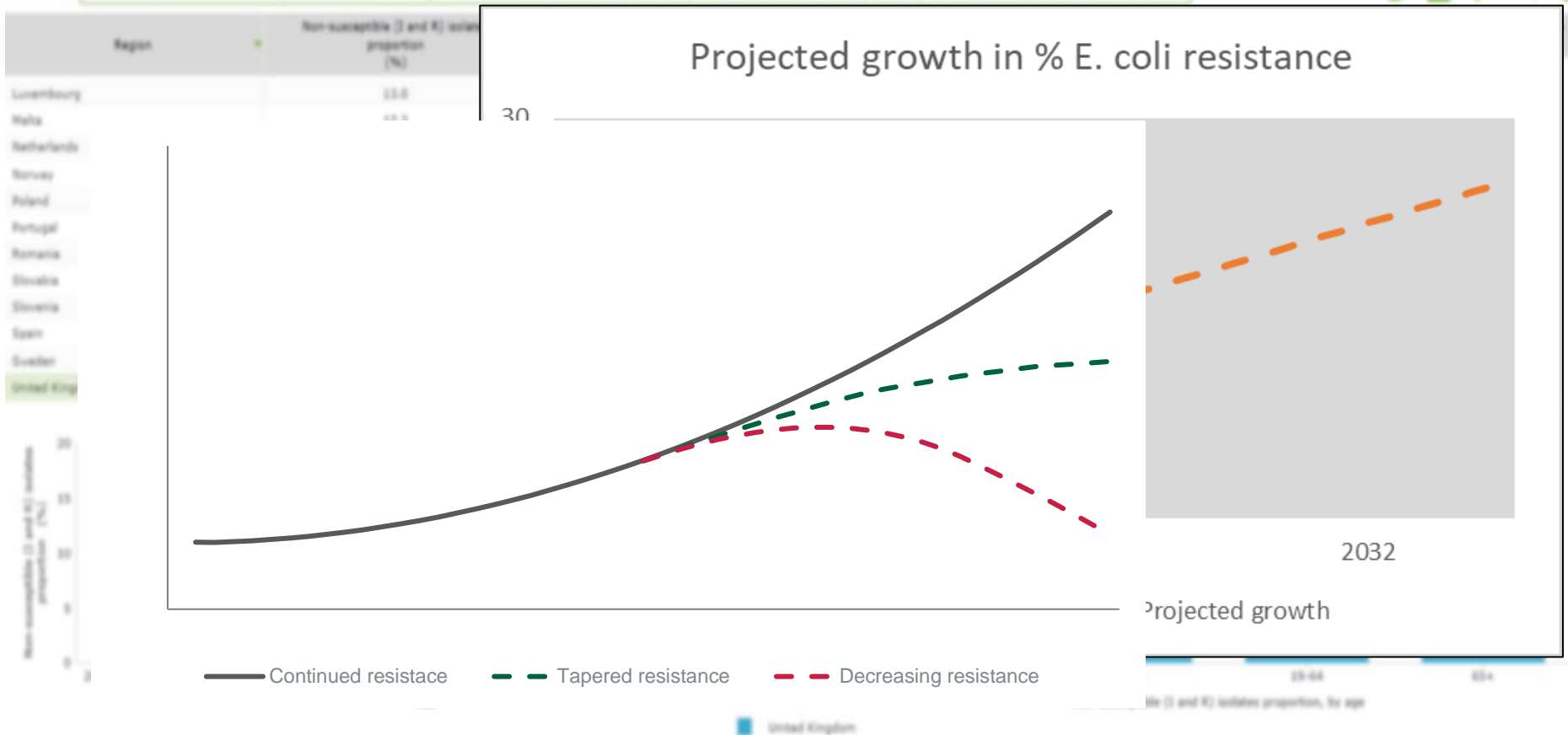


...and extrapolated forwards



Surveillance Atlas of Infectious Diseases

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



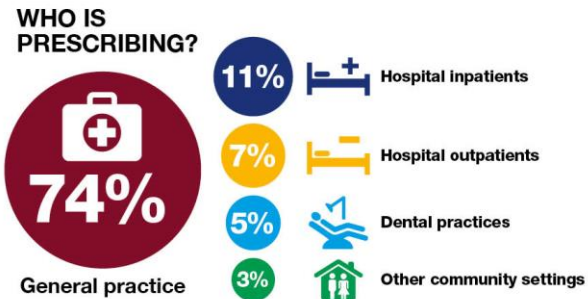
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Other considerations

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

June 11, 2024

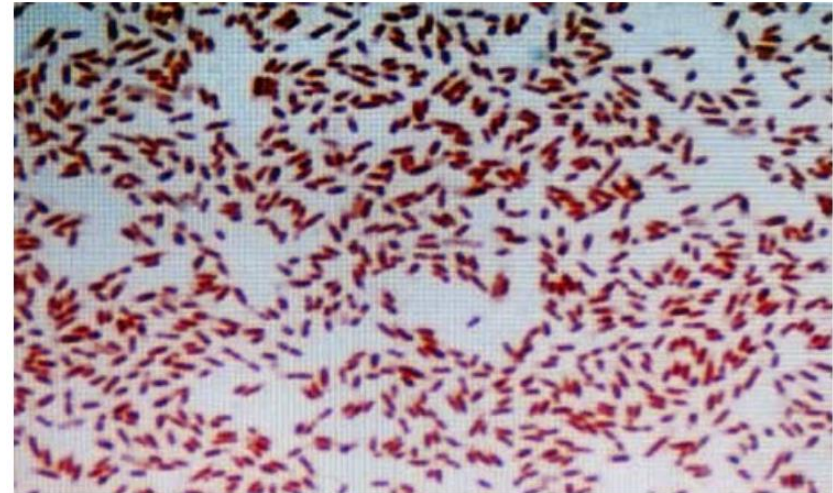
Example Results: *E. coli* resistance

- Initial example parameterisation 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
- Under a plausible central scenario there would be a 1% uplift in overall mortality
- In an extreme scenario, based on 95% confidence level upper bound, there would be a 2-3% uplift in overall mortality
- And this is just for one strain of bacteria ...
- Model will help actuaries understand the overall impact on mortality/morbidity and quantify the financial impact, even calibrating their own scenarios

theguardian

E coli: the deadly European outbreak

Questions and answers about the virulent strain of the E coli bacterium, which has killed 17 people and left more than 1,500 ill



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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**

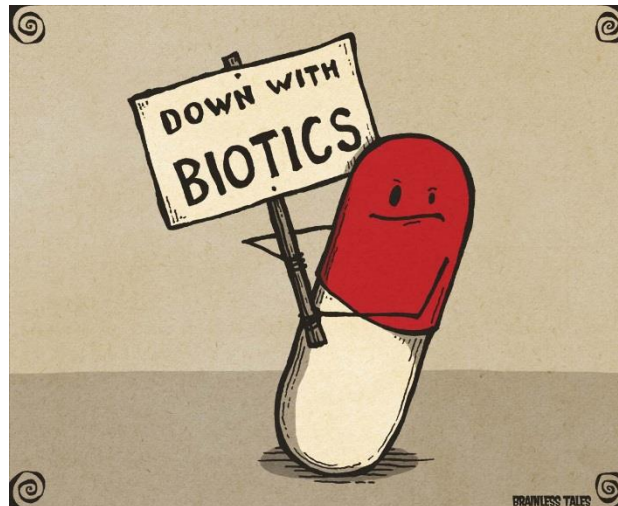
Model development

- **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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