



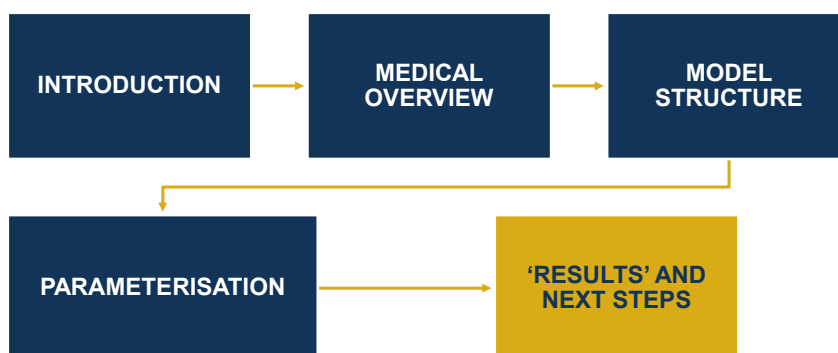
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When the drugs don't work...

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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3

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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4



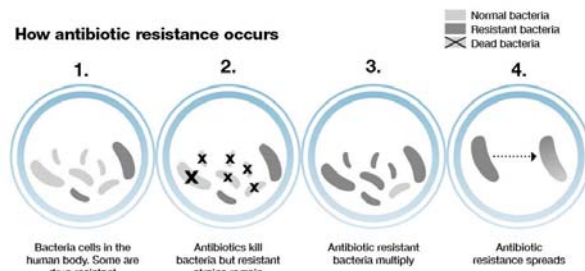
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Medical overview

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What is antibiotic resistance...

How antibiotic resistance occurs



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

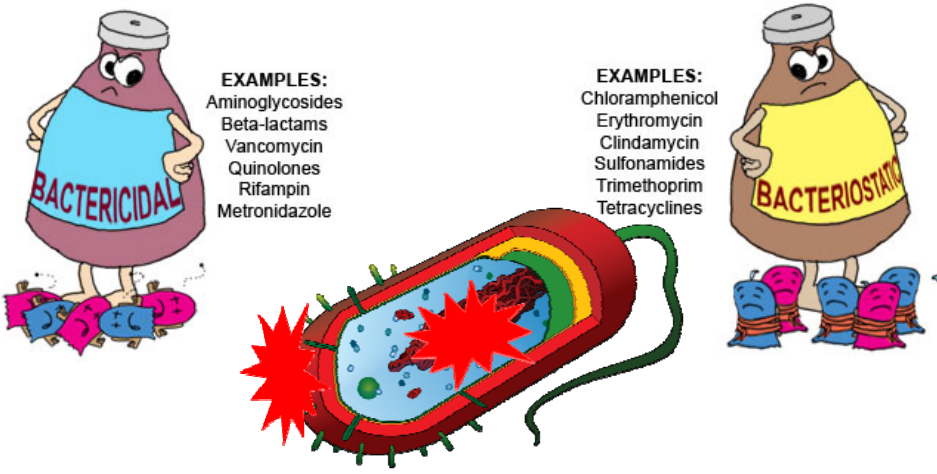
"The thoughtless person playing with penicillin treatment is morally responsible for the death of the man who succumbs to infection with the penicillin-resistant organism." Sir Alexander Fleming, 1928



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6



EXAMPLES:
Aminoglycosides
Beta-lactams
Vancomycin
Quinolones
Rifampin
Metronidazole

EXAMPLES:
Chloramphenicol
Erythromycin
Clindamycin
Sulfonamides
Trimethoprim
Tetracyclines

How does it actually work (the science!)

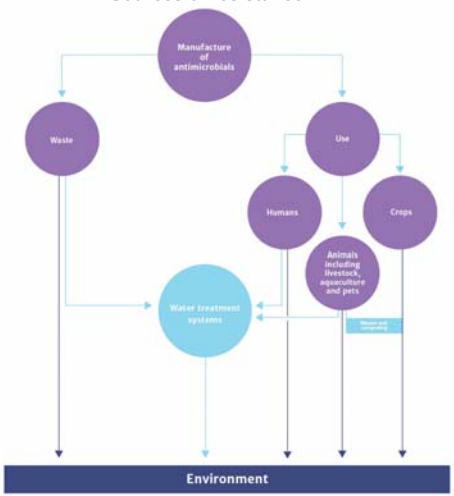
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What are the sources of resistance?

Sources of resistance



How animals can pass on resistant bacteria



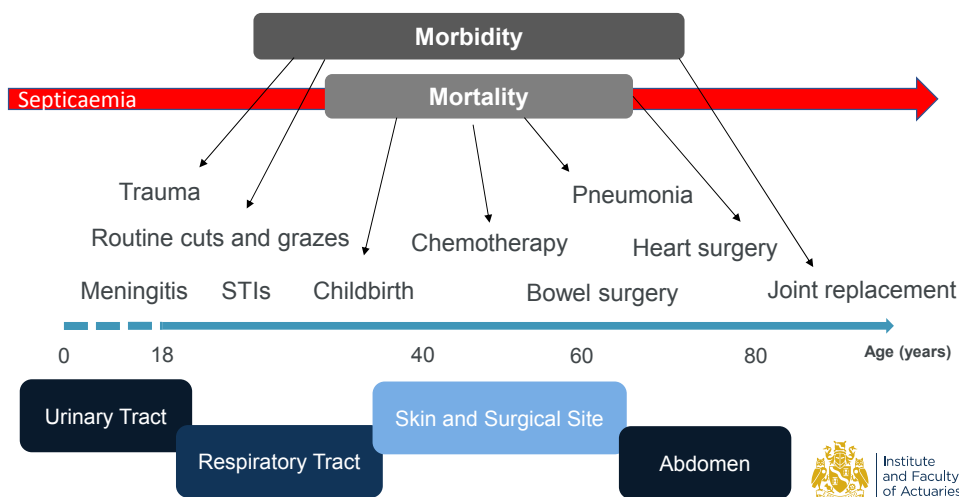
Infographics sourced from "Review on Antimicrobial Resistance" 2014

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8

How does ABR affect people and our work?



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9



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

Evellina Tizzoni, Elena Carrara*, Alessia Savelli*, Stephan Harbarth, Marc Mendelson, Dominique L. Monnet, Céline Pulcini, Gunera Kahlmet, Jan Kuyumcu, Yehuda Carmeli, Marc Ouellet, Kevin Otterson, Jean-Paul, Marco Cavallari, Edward M Cox, Christl Haasch, M. Lindsay Grayson, Paul Hansen, Nalin Singh, Ursula Thewissen, Nicole Magnin, 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**

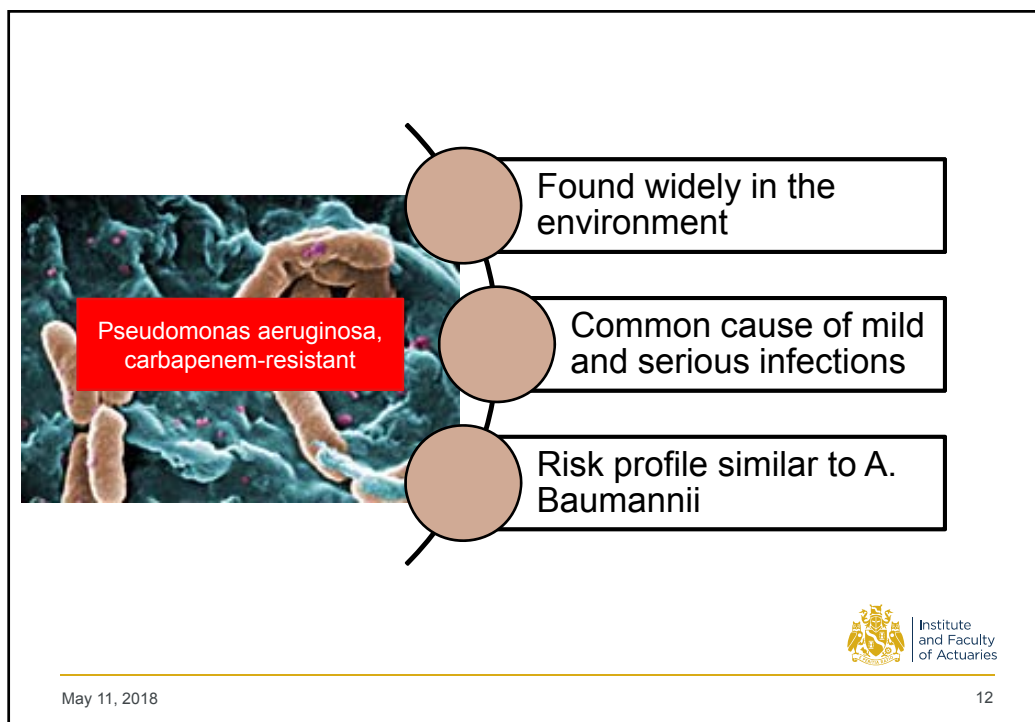
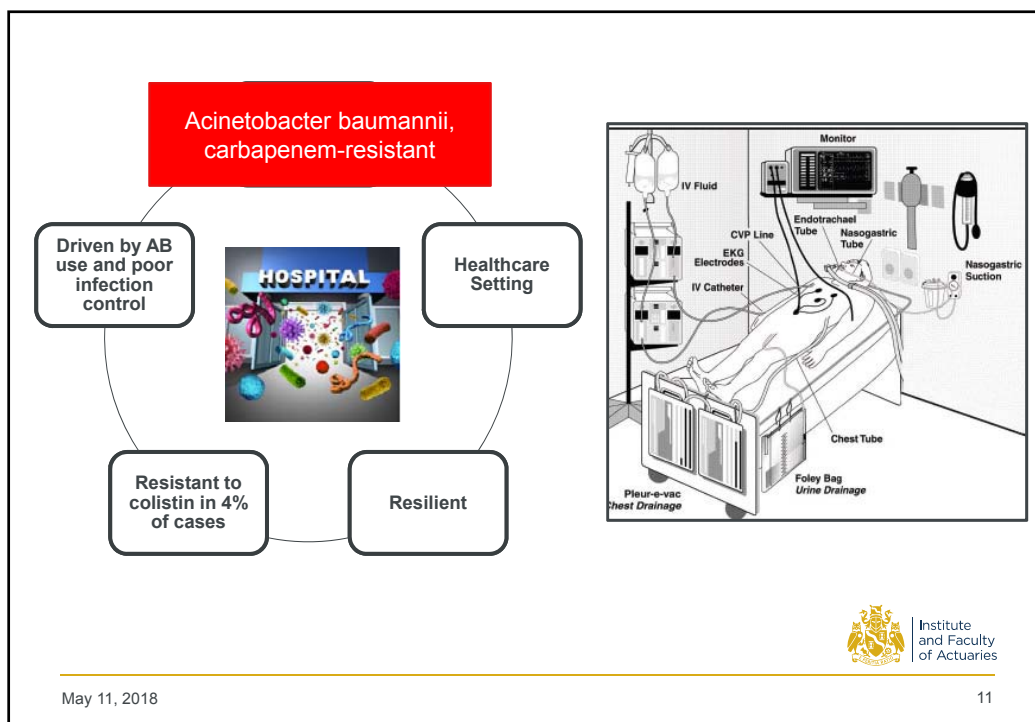
**Enterobacteriaceae,
carbapenem-resistant, 3rd
generation
cephalosporin-resistant**



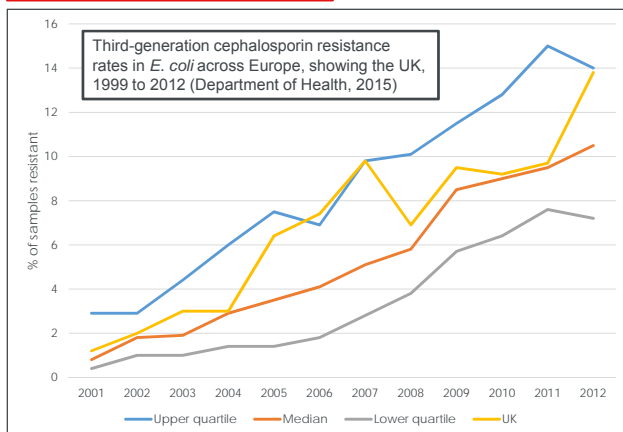
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10



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



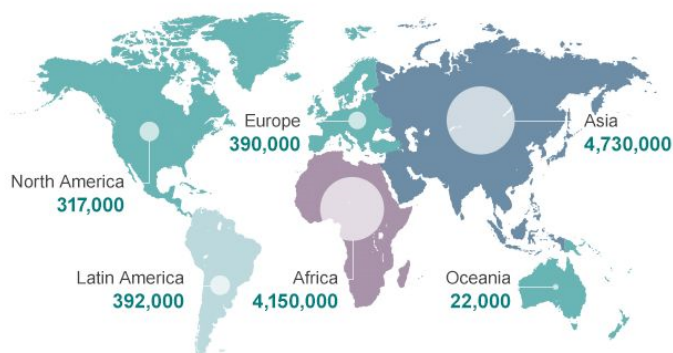
These bacteria are associated with higher frequency of inappropriate antimicrobial therapy, poorer clinical response, and longer length of hospital stay



...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



Tackling resistance takes a long time...

Changing
behaviours

Developing
new
antibiotics

Source: Review on Antimicrobial Resistance 2014

PNAS

Global increase and geographic convergence in antibiotic consumption between 2000 and 2015

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

^aCenter for Disease Dynamics, Economics & Policy, Washington, DC 20005; ^bDepartment of Emergency Medicine, Johns Hopkins School of Medicine, Baltimore, MD 21205; ^cDepartment of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205; ^dInstitute of Integrative Biology, ETH Zurich, CH-8092 Zurich, Switzerland; ^eDepartment of Ecology and Environmental Science, Princeton University, Princeton, NJ 08542; ^fTemple Medical Microbiology, Vaccine & Infectious Diseases Institute, University of Antwerp of Washington, Seattle, WA 98104

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

NEWS

INDEPENDENT News Infect Politics Voices

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 16:19 BST | 18 comments

218 shares

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ER

Combinations thwart efforts to curb researchers

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nature microbiology LETTERS

<https://doi.org/10.1038/s41564-018-0160-1>

OPEN

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

Bradley M. Hoyer¹, 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

Think Big. Take Risks. INNOVATE!

Edible CRISPR Could Replace Antibiotics

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

Emtech

Open Access

Research

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

and^{1,2}, Nachiket P. Marathe^{2,3}, Tobias Osterlund^{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*}

INDEPENDENT

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

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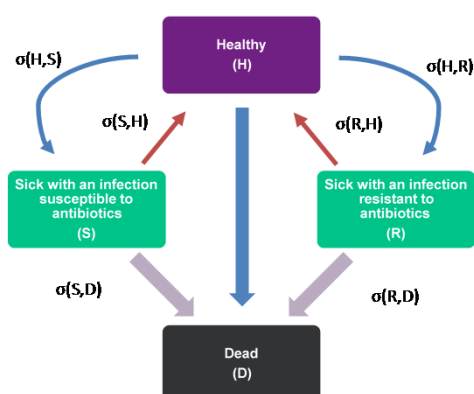
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Model structure and parameterisation

Ross Hamilton

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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



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18

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



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19

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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20

Data sources – what is available?



Public Health
England



Office for
National Statistics

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- Incidence rates for bacteraemias.



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21

Data sources – what is available?



Public Health
England



Office for
National Statistics

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Discovery

- 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 HCAIs.



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22

Data sources – what is available?



Public Health
England



Office for
National Statistics

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- Death rates for bacteraemias.



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23

Data sources – what is available?



Public Health
England



Office for
National Statistics

PLOS | Open for
Discovery

- 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.

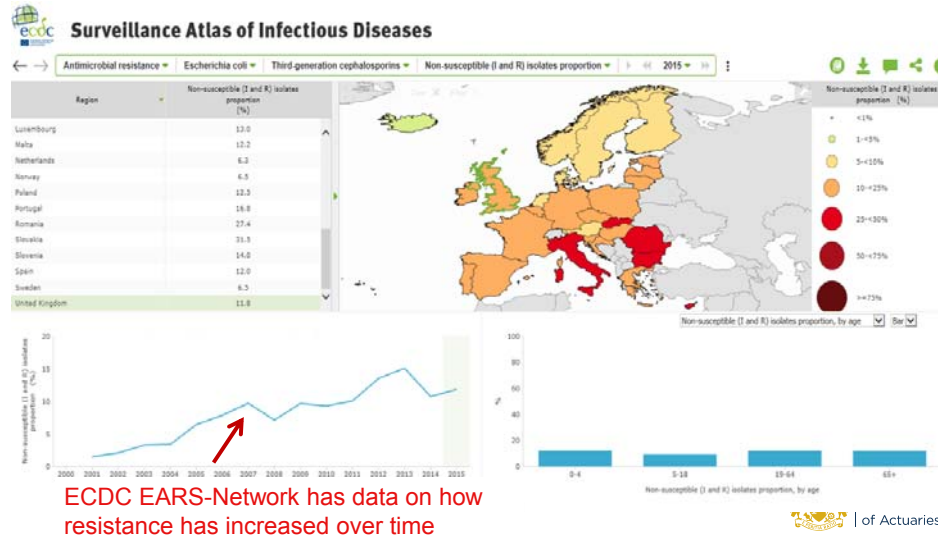


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24

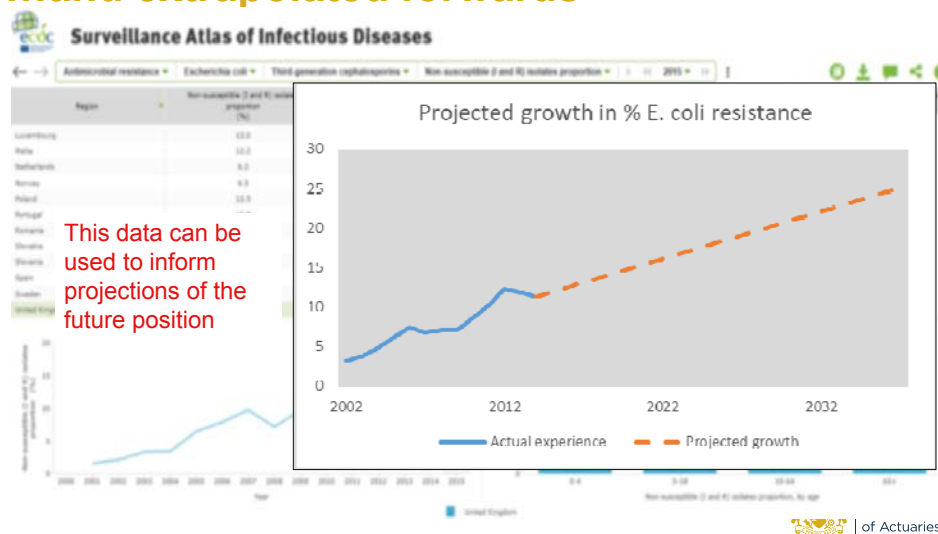
Trends in resistance can be observed...



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25

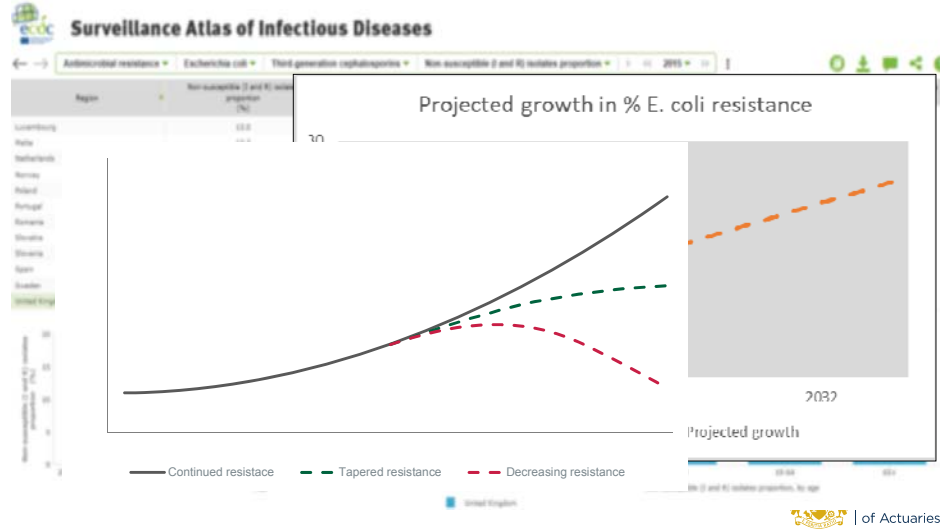
...and extrapolated forwards



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26

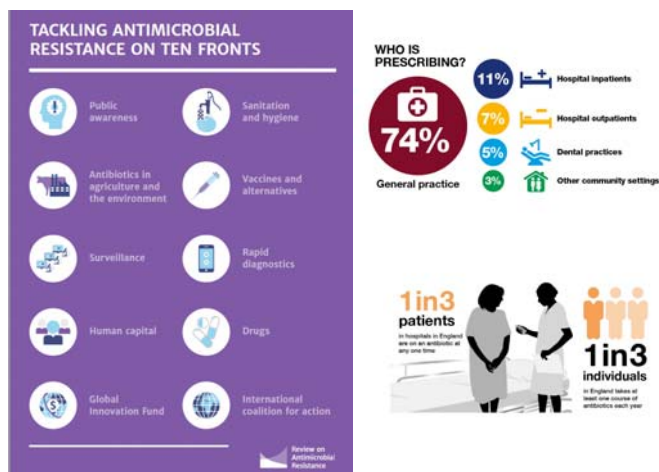
...and extrapolated forwards



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27

Other considerations



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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28



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'Results' and next steps

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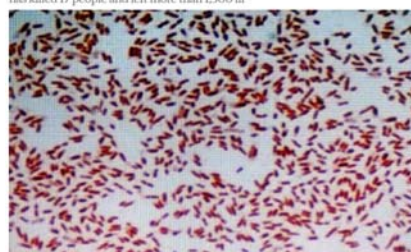
Example Results: *E. coli* resistance

- 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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30

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



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31

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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32