When the drugs don’t work…
Nicola Oliver and Ross Hamilton
IFoA Antibiotic Resistance Working Party

Agenda

INTRODUCTION  MEDICAL OVERVIEW  MODEL STRUCTURE

PARAMETERISATION  ‘RESULTS’ AND NEXT STEPS
**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**

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
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<tr>
<td>Matthew Edwards</td>
<td>Chair</td>
<td>Willis Towers Watson</td>
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<td>Nicola Oliver</td>
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<td>Model structure &amp; parameterisation</td>
<td>Legal &amp; General</td>
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<td>Craig Armstrong</td>
<td>Parameterisation (2017)</td>
<td>Aviva</td>
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<td>Ross Hamilton</td>
<td>Model development</td>
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<td>Irene Merk</td>
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<td>Model development</td>
<td>GAD</td>
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<td>Soumi Sarkar</td>
<td>General</td>
<td>Legal &amp; General</td>
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<td>Katherine Fossett</td>
<td>General</td>
<td>Barnett Waddingham</td>
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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
How does it actually work (the science!)

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What are the sources of resistance?

Sources of resistance
- Water
- Soil
- Residues
- Animal waste
- Food residues
- Human excreta
- Direct contact between animals and humans

How animals can pass on resistant bacteria
- Direct contact between animals and humans
- Through the environment

Infographics sourced from “Review on Antimicrobial Resistance” 2014

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How does ABR affect people and our work?

- Septicaemia
- Trauma
- Routine cuts and grazes
- Chemotherapy
- Pneumonia
- Heart surgery
- Mortality

- Age (years)
  - 0
  - 18
  - 40
  - 60
  - 80

- Morbidity
  - Meningitis
  - STIs
  - Childbirth
  - Bowel surgery
  - Joint replacement

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

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

- Acinetobacter baumannii, carbapenem-resistant
- Pseudomonas aeruginosa, carbapenem-resistant
- Enterobacteriaceae, carbapenem-resistant, 3rd generation cephalosporin-resistant
Acinetobacter baumannii, carbapenem-resistant

Driven by AB use and poor infection control

Healthcare Setting

Resilient

Resistant to colistin in 4% of cases

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Pseudomonas aeruginosa, carbapenem-resistant

Found widely in the environment

Common cause of mild and serious infections

Risk profile similar to A. Baumannii

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

**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.

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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

<table>
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<tr>
<th>Region</th>
<th>Deaths</th>
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<tr>
<td>North America</td>
<td>317,000</td>
</tr>
<tr>
<td>Latin America</td>
<td>392,000</td>
</tr>
<tr>
<td>Europe</td>
<td>390,000</td>
</tr>
<tr>
<td>Africa</td>
<td>4,150,000</td>
</tr>
<tr>
<td>Asia</td>
<td>4,730,000</td>
</tr>
<tr>
<td>Oceania</td>
<td>22,000</td>
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Source: Review on Antimicrobial Resistance 2014

Tackling resistance takes a long time...

- Changing behaviours
- Developing new antibiotics
Global increase and geographic convergence in antibiotic consumption between 2000 and 2015

Antibiotic-resistant gonorrhoea cases expected to emerge worldwide

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

- 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?
Data sources – what is available?

- Incidence rates for bacteraemias.


- Limited evidence for how resistance interacts with incidence.

- Bias? Monitoring is of HCAIs.
Data sources – what is available?

• Death rates for bacteraemias.

Public Health England

ecdc

Office for National Statistics

PLOS | Open for Discovery

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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.
Trends in resistance can be observed...

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

...and extrapolated forwards

This data can be used to inform projections of the future position
...and extrapolated forwards

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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
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
Working party – next steps

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

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

Questions

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.