When the drugs don’t work...
Matthew Edwards, Nicola Oliver and Ross Hamilton
(IFoA Antibiotic Resistance Working Party)
Agenda

INTRODUCTION → MEDICAL OVERVIEW → MODEL STRUCTURE

PARAMETERISATION → ‘RESULTS’ AND NEXT STEPS
Working party background

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 members

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<tr>
<th>Name</th>
<th>Role</th>
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Medical overview
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 do antibiotics work? (the science!)
What are the sources of resistance?

Sources of resistance

- Manufacture of antimicrobials
- Waste
- Use
- Humans
- Crops
- Animals including livestock, aquaculture and pets
- Water treatment systems
- Environment

How animals can pass on resistant bacteria

- Direct contact between animals and humans
- Consumption of meat from animals
- Through the environment

Infographics sourced from “Review on Antimicrobial Resistance” 2014
How does ABR affect people and our work?

Septicaemia

Mortality

Morbidity

Trauma
Routine cuts and grazes
Pneumonia
Heart surgery

Meningitis
Chemotherapy

Respiratory Tract

STIs
Childbirth
Bowel surgery

Abdomen

Skin and Surgical Site

Urinary Tract

Age (years)

0 18 40 60 80

June 14, 2018
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”
A. baumannii

Pseudomonas

Enterobacteriaceae

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

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

June 14, 2018
Pseudomonas

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

Pneumonia  Wound Infection  Bloodstream Infection
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)
“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

Changing behaviours
Developing new antibiotics

Deaths attributable to antimicrobial resistance every year by 2050

North America: 317,000
Latin America: 392,000
Europe: 390,000
Africa: 4,150,000
Asia: 4,730,000
Oceania: 22,000

Source: Review on Antimicrobial Resistance 2014
Global increase and geographic convergence in antibiotic consumption between 2000 and 2015

Eili Y. Klein1,3,4, Thomas P. Van Boeckel1, Elena M. Martinez2, Suraj Pant1, Sumanth Gandra3, Simon A. Levin3,4,5,6, Herman Goossens7, and Ramanan Laxminarayan8

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Contributed by Simon A. Levin, February 23, 2018; sent for review October 3, 2017; accepted December 21, 2017


INDEPENDENT

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
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. T. Tzanetos1, and Sean F. B. Egan1

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

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

Berglund1, Nachiket P. Marathe2,1, Tobias Österlund1,2, Johan Bengtsson-Palme2,3, Stathis Korsakis2,3, Flach2,3, D G Joakim Larsson2,3 and Erik Kristiansson1,2

Edible CRISPR Could Replace Antibiotics

Researchers are developing a synthetic biotechnology to reduce the use of disease-causing bacteria in self-destruct.
Model structure and parameterisation

Ross Hamilton
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

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.
Data sources – mortality

Death rates for bacteraemia

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.
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

Projected growth in % E. coli resistance

- Continued resistance
- Tapered resistance
- Decreasing resistance
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
‘Results’ and next steps
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)
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
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.