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The O'Neill *Review on Antimicrobial Resistance*

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Background about the Review on AMR

- Established in 2014 as independent arms length group by the UK Prime Minister, co-sponsored by the Wellcome Trust.
- Chaired by Lord Jim O'Neill.
- Tasked to recommend solutions to tackle antimicrobial resistance globally – through the lens of economics and policy-making.
- Mandate to build international consensus for action.
- Published seven interim papers before final report in May 2016 – www.amr-review.org .

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

Recommended actions across ten areas

Special focus on how to increase the supply of drugs and diagnostics

Review on Antimicrobial Resistance

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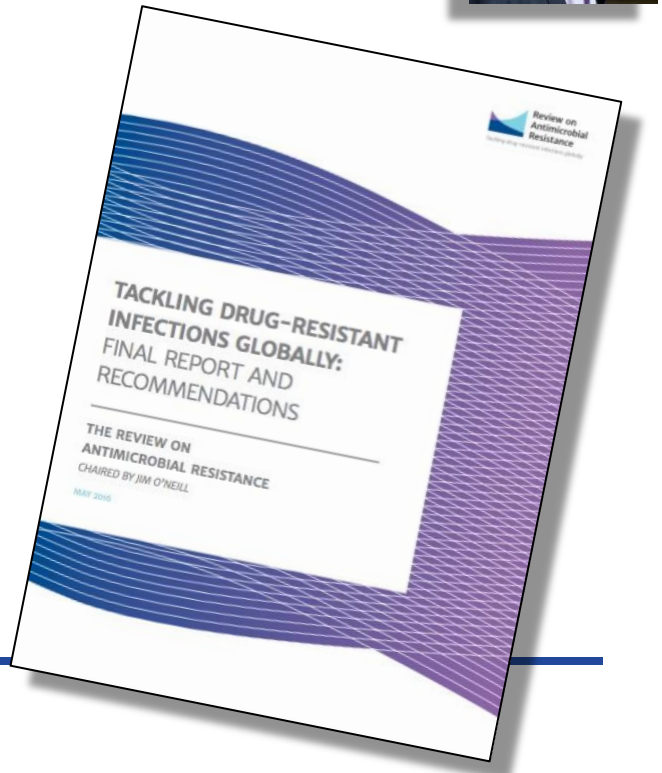
Three strands for surveillance of AMR

1. data on **consumption of antibiotics** in both humans and animals, […] which would help understand the link between antimicrobial use and the development of resistance.
2. data on **resistance rates** for various drug–bug combinations and their impact on patients' health.
3. **molecular biological data** to explain the biological basis of resistance, through characterisation of the types of resistant bacteria and the genetic reasons for their resistance.

- This information should be **gathered within a 'one health' perspective**, covering animals and humans and the environment to provide a complete picture



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Tackling drug-resistant infections globally

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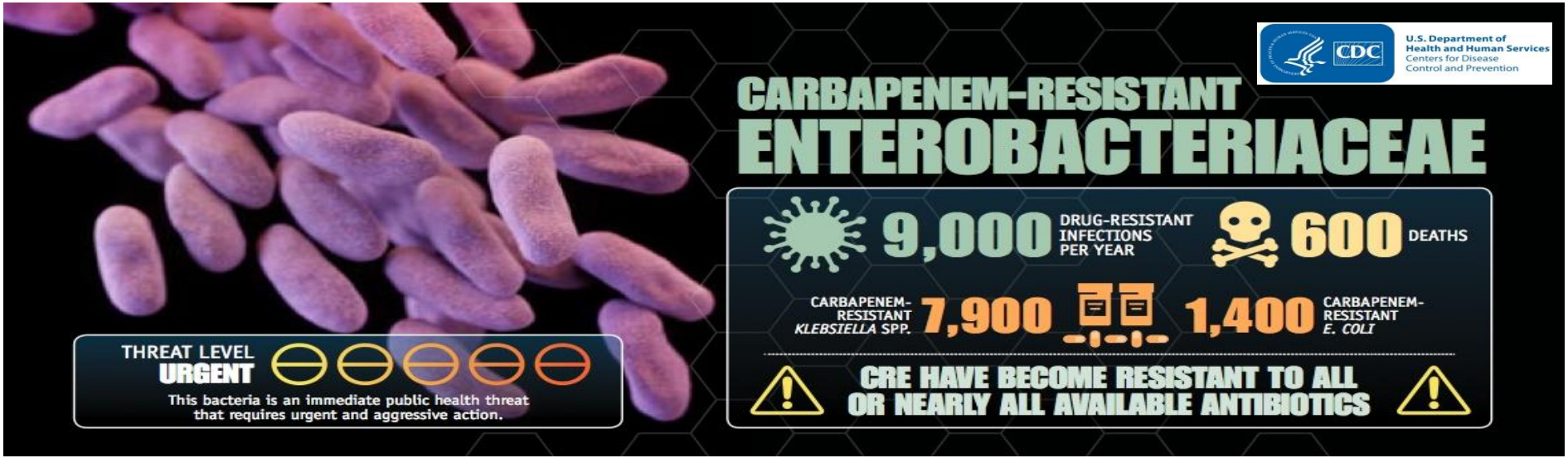
The apex of *current* resistance problems ?



- only colistin is currently active against 90% of CRE (UK data)
- colistin resistance is a growing threat (chromosomal and *mcr* genes)

Which antimicrobials? What are the priorities?

- What our report said:

Urgent need and current funding structures inadequate	Urgent need but current funding structures largely adequate	Need will arise and require future consideration
• TB treatment regimen • Antibiotics • Antifungal medicines	• New malaria treatments	• HIV/AIDS drugs

- Future work needed to set national and global priorities, in particular for antibiotics : public funding should focus on highest needs only.

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WHO Priority Pathogens list for R&D of new antibiotics

- antibiotics specifically active against multidrug- and extensively drug-resistant Gram-negative bacteria.
- antibiotics for the paediatric population and for oral formulations for community diseases with a high morbidity burden such as drug-resistant *Neisseria gonorrhoeae*, *Salmonella typhi* and ESBL-producing *Enterobacteriaeceae.*
- new classes of antibiotics without cross- and co-resistance to existing classes should be supported.
- must also reduce the burden of infections e.g. increased vaccination coverage, improved sanitation or sustained implementation of infection control measures

  www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf

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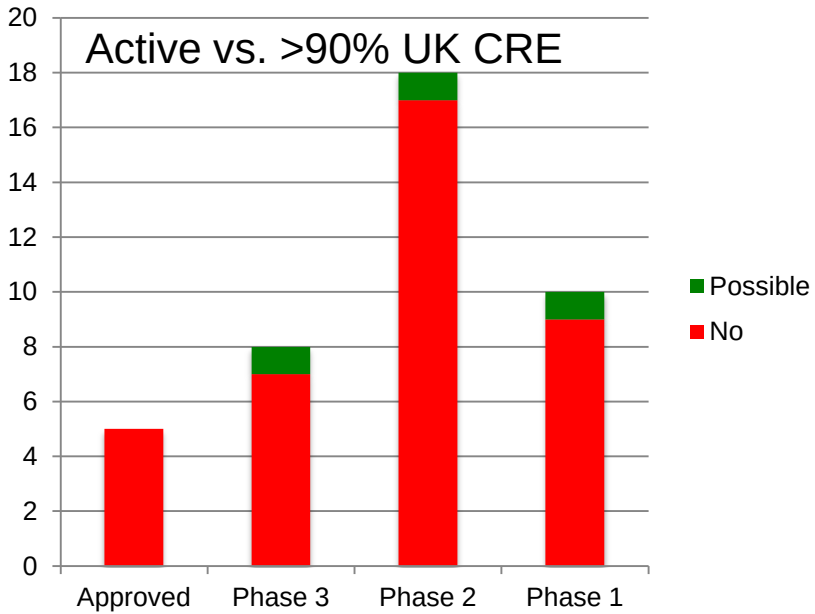
Assessing the potential of the antibiotic pipeline



We don't have enough antibiotics in development to tackle the resistance issues we face *now*

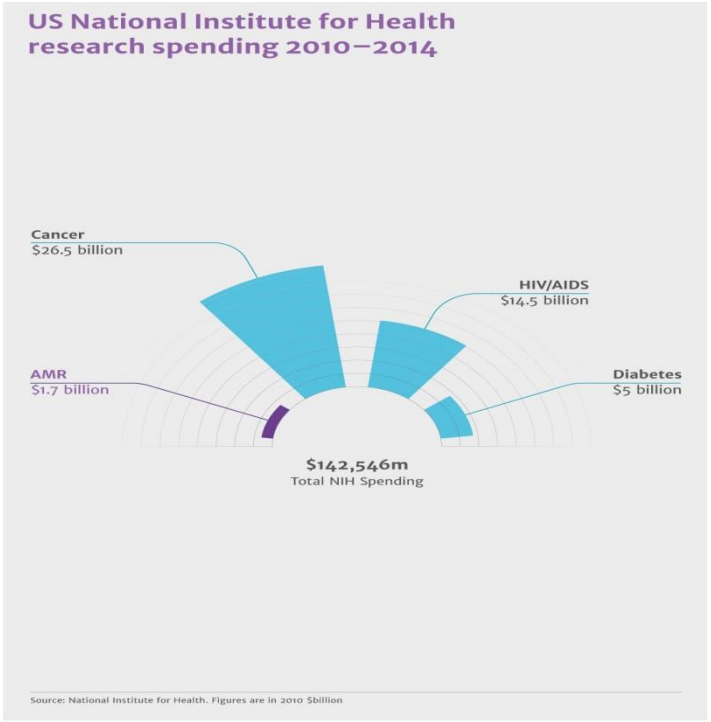
…and the success of those in development is not guaranteed

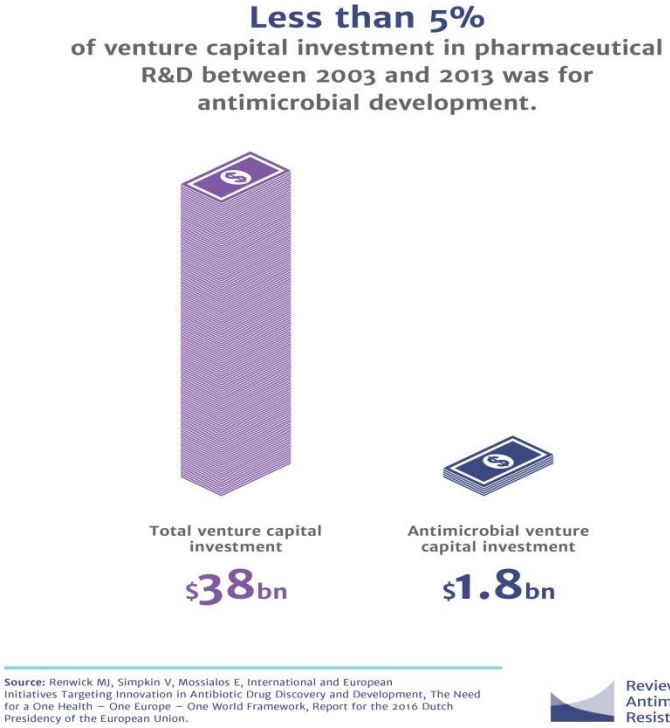
Analysis in 2015 of data from www.pewtrusts.org

Securing new drugs

- **More predictable market to make antibiotics R&D commercially sustainable**
  - lump-sum payments for ‘successful’ drugs
  - ‘de-link’ profitability from sales
- **jump-start a new innovation cycle in antibiotics**
  - Global AMR Innovation Fund
  - boost early-stage R&D into drugs and diagnostics
- **reduce barriers to drug development**
  - lower costs
  - improve the efficiency of research
  - lower global regulatory barriers

“Push” incentives have been insufficient





Now there are new “Push” incentives

- History of under-investment in AMR but course correction has started, eg:
  - NIH, BARDA
  - CARB-X partnership with AMR Centre in Alderley Park and Wellcome Trust
  - EU IMI programme.
  - GARDP in Geneva, a new product development partnership focused on antibiotic R&D.
  - UK global AMR innovation fund

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New ‘Push’ incentives: CARB-X (March ‘17)

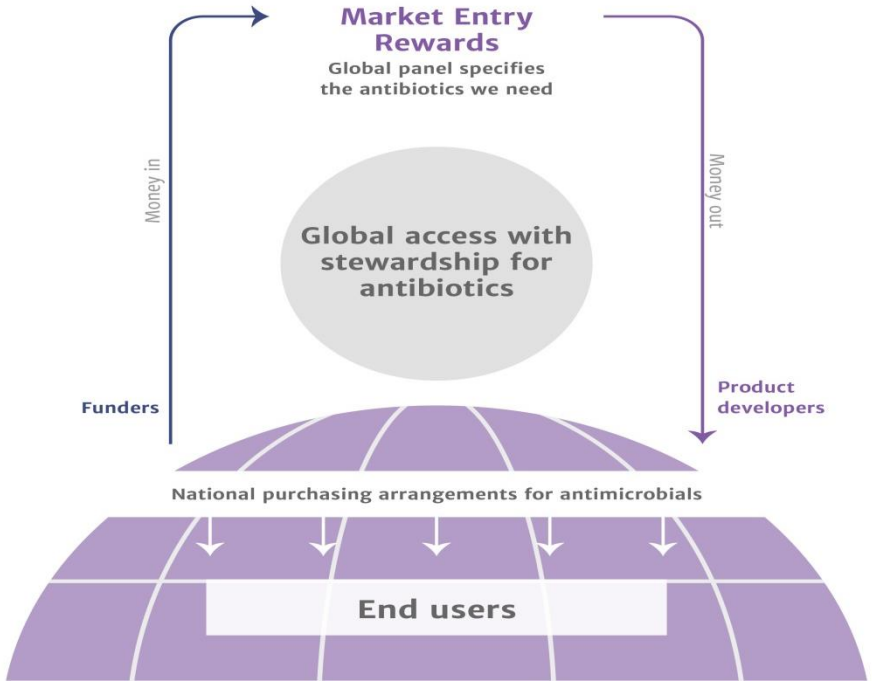
CARB-X Antibacterial Treatment and Prevention Product Portfolio - Novelty Screen

Sponsor	Product	Novelty			Description	Priority		Development Stage			
		New Abx Class?	New Non-traditional Product?	New Target?		CDC	WHO	Hit to Lead	Lead Optimization	Pre-Clinical	Phase I
Tetraphase Pharmaceuticals	TP-6076				Next-generation tetracycline	✓	✓	*Acinetobacter + Enterobacteriaceae*			
Cidara Therapeutics	CD201		✓	✓	Bifunctional immunotherapy	✓	✓	*Acinetobacter + P. aeruginosa. + Enterobacteriaceae*			
Microbiotix	T3SS Inhibitor		✓	✓	Virulence modifier	✓	✓	*P. aeruginosa*			
Spero Therapeutics	SPR741			✓	Potentiator	✓	✓	Gram-negative activity			
Entasis Therapeutics	ETX000				Oral Gram-negative combination	✓	✓	Gram-negative activity			
Forge Therapeutics	FG-LpxC	✓		✓	Inhibitor of LpxC	✓	✓	Gram-negative activity			
Oppilotech	LPS	✓		✓	Targets synthesis of LPS	✓	✓	Gram-negative activity			
ContraFect	Gram-negative lysins		✓	✓	Recombinant lysin protein	✓	✓	*P. aeruginosa*			
Redx Pharma	NBTI	✓			Dual-acting topoisomerase inhibitor	✓	✓	*Acinetobacter + P. aeruginosa. + Enterobacteriaceae*			
Visterra	VIS705		✓	✓	Antibody-drug conjugate	✓	✓	*P. aeruginosa*			

The above projects are Powered by CARB-X utilizing non-dilutive funding from BARDA, Wellcome Trust, & NIAID. The stage of development is approximate as of March 2017 (please refer to each company's website for updated information). Characterizations of new Abx Class and New Target by CARB-X, following Pew pipeline analysis. Other characterizations by CARB-X experts and external expert opinion. Abx = traditional small molecule antibiotic. Non-traditional Product = not a traditional small molecule antibiotic.

- initial investment of $24 million in 11 projects, chosen from among 168 applications by an advisory board of antibiotic experts.
- CARB-X will also be awarding an additional $24 million in milestone-based payments to the companies to advance the projects beyond the early stages of development.
- The companies are matching the money with private funds to bring the total investment to $75 million

Our proposal for a global ‘pull’ incentive that co-exists with diverse national arrangements



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Market entry rewards would have a powerful impact on antibiotic R&D given the size and shape of the current yearly global market

Patented antibiotics form a small percentage of the total $40 billion per year antibiotics market, so $1.6 billion a year would have a material impact.

$4.7 bn

Patented antibiotics market

$1.6 bn

Market entry reward

Data and analysis by IMS Health, in the countries they had patent data for only 12.3% ($3.8bn) of sales were on patent while $26.9bn were off patent. We then presumed that this ratio remained the same in the 20% of countries they did not have patent data for, even though these countries tend to buy less patented drugs, making the above figures a high estimate of the patented market.

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New drug development …and antibiotic stewardship

- Not mutually exclusive
- In the future, new antibiotics must be viewed differently
  - not regarded as ‘cure more’ replacements by prescribers
  - not regarded as market blockbusters by manufacturers
- Changes in behaviour and expectation are essential
- *****This must be underpinned by better and faster diagnostics*****
  - old drugs should be used for ‘susceptible infections’
  - new drugs must be held in reserve for ‘resistant infections’

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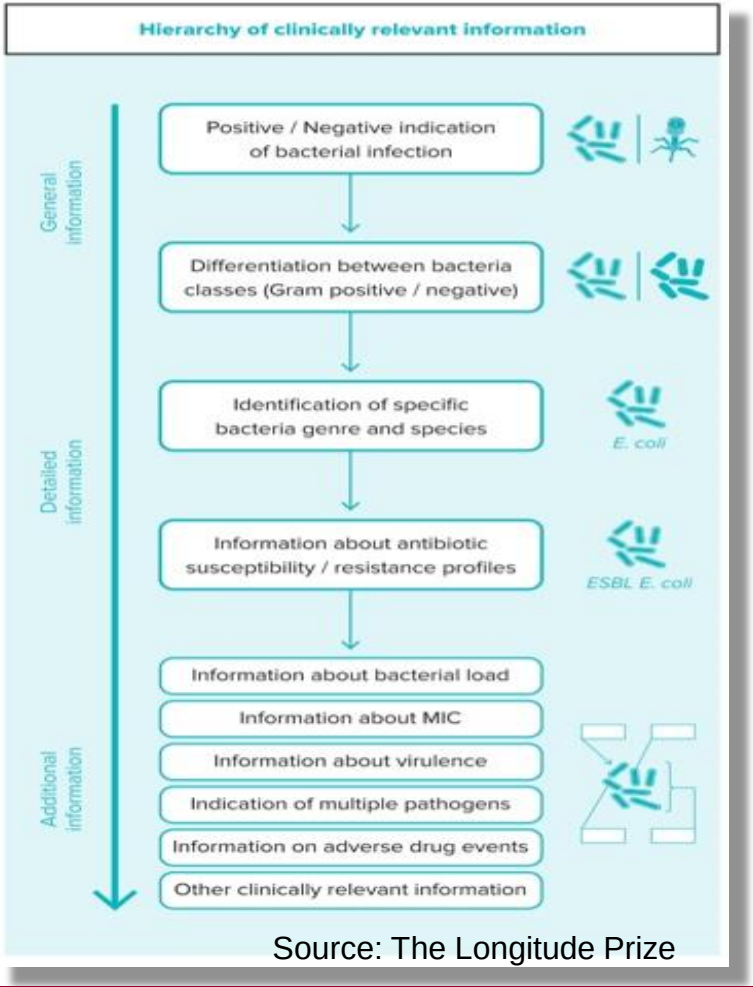
What might new tests do ?

AMR diagnostics might tell the prescriber:

1. that there is / is not evidence of bacterial infection

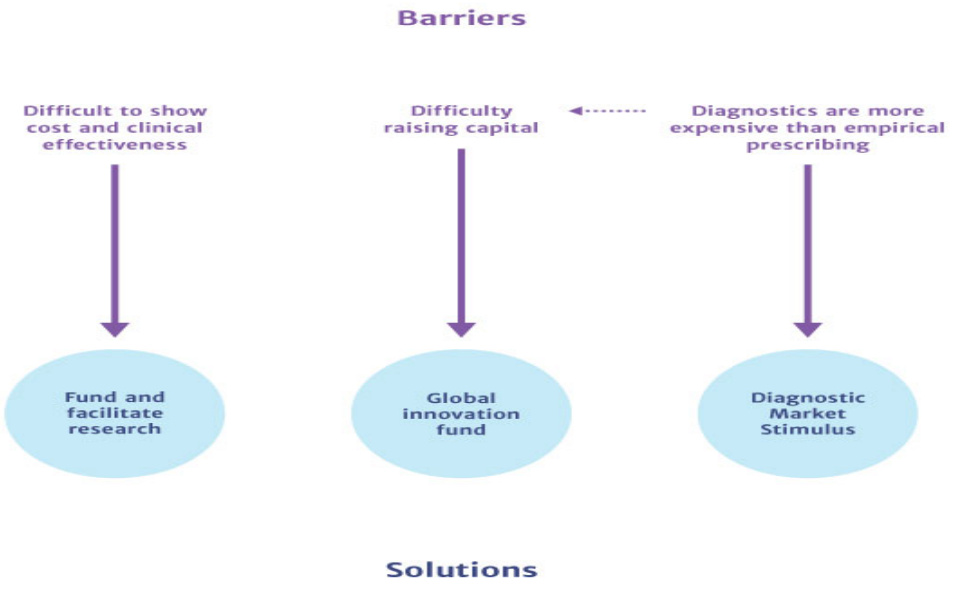
2. that a pathogen is potentially resistant to particular drugs (molecular)

3. that an infecting organism *is susceptible* to particular drugs (rapid AST)



Source: The Longitude Prize

A PLAN TO OVERHAUL DIAGNOSTIC DEVELOPMENT



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New ‘Push’ incentives: CARB-X (March ‘17)

CARB-X Antibacterial Devices and Diagnostic Product Portfolio

Sponsor	Type	Technology	Development Stage			
			Feasibility Demonstration	Optimization and Preparation for Development	Product Development	System Integration and Testing
Proteus	Rapid POC Dx	Optical bacterial imaging	POC Diagnostic			

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- 1/11 funded projects is for a novel diagnostic

  http://www.carb-x.org/

UK Response to O'Neill

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Published the formal response in September 2016, setting out proposed action including:

- Halving the inappropriate prescription of antibiotics in human health by 2020;
- Halving the number of healthcare associated bloodstream infections that pose the biggest risk – such as *E. coli* - by 2020;
- antibiotic use in livestock and fish farmed for food to 50mg/kg, by 2018.
- Working with the global finance and health community to develop a global system that rewards companies that develop new, successful antibiotics and make them available to all who need them.

Specific focus of the UK AMR Strategy

- **PREVENT** (people from being infected – infection prevention and control)
- **PRESERVE** (the antibiotics we have – good stewardship)
- **PROMOTE** (development of new antimicrobials, new approaches, better diagnostics – the independent review by Lord Jim O'Neill)

Underpinned by:

– Surveillance
– R&D
– One Health approach
– International collaboration