What if there are no new antibiotics?

Highlights of a Wellcome Trust & Department of Health (England) initiated & sponsored review & report into

“Alternatives to Antibiotics”

STOA EuCheMS
28 April 2016
European Parliament, Brussels
Dr Lloyd Czapelewski FRSC
Alternatives to Antibiotics (A2As)

- Review scope
  - Non-compound approaches that target bacteria
  - Approaches that target the host
  - Suitable to treat systemic or invasive infection
  - Administered intravenously, orally or by inhalation
  - Mono-therapy, combination therapy and/or prophylactic use
  - External topical administration excluded

- Formation of a Working Group to consider and to provide a consensus on A2As to inform development of policy in the AMR area
The Working Group (24)

Generalists
- Jared Silverman
- Mike Dawson
- David Payne
- John Rex
- Lloyd Czaplewski

A2A Specialists
- Steve Projan
- David Knowles
- Sigga Olafsdottir
- Peter Warn
- Trevor Trust
- Richard Bax
- Martha Clokie
- Heather Fairhead
- Simon Foster
- Vince Fischetti
- Ian Henderson
- David Harper
- Bob Hancock
- Kai Hilpert
- Chris Thomas
- Brian Jones
- Aras Kadioglu
- Brendan Gilmore
- Sunil Shaunak
Review process

- 50-page technical report on 19 A2A approaches
- Meeting at the Wellcome Trust 10 December 2014
- Collective email “debate” & iterative maturation of the technical report
- Transformation of the report into a consensus Lancet ID manuscript
- Publication of the review in Lancet ID online Jan 12 2016

Alternatives to antibiotics—a pipeline portfolio review

Lloyd Czaplewski, Richard Bax, Martha Clokie, Mike Dawson, Heather Fairhead, Vincent A Fischetti, Simon Foster, Brendan F Gilmore, Robert E W Hancock, David Harper, Ian R Henderson, Kai Hilpert, Brian V Jones, Aras Kadioqiu, David Knowles, Sigriður Ólafsdóttir, David Payne, Steve Projan, Sunil Shaunak, Jared Silverman, Christopher M Thomas, Trevor J Trust, Peter Warn, John H Rex

A2A Review/Lancet ID Article Impact

- O’Neill AMR Team
  - Article informed the Vaccine & Alternatives report (11th Feb 2016)
  - A2A’s to be treated on par with antibiotics with access to the proposed Global Innovation Fund

- Elsevier Atlas Award for research impact
Alternatives to Antibiotics

- Widely adopted
- Mature market

A2As
- Discovered
- Efficacy in an animal model
- Patented
- Published
- Almost a therapy

Where are A2As?

Led by innovators/visionaries

A2As
- Unproven
- Don’t understand the risks
- Needs wider evidence base
- Only 6 published PK studies and 2 safety studies
- Commercially unattractive
- Clinical trials largely negative
Given the current A2A portfolio we cannot expect a new *therapeutic* to treat systemic or invasive bacterial infection within the next 10 years

<table>
<thead>
<tr>
<th>Approach</th>
<th>Probability of registration by 2025 %</th>
<th>First in man use</th>
<th>Target bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibodies</td>
<td>170</td>
<td>Prevent</td>
<td><em>P. aeruginosa, S. aureus, C. difficile</em></td>
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<tr>
<td>Probiotics</td>
<td>124</td>
<td>Treat or Prevent</td>
<td><em>C. difficile</em></td>
</tr>
<tr>
<td>Lysins</td>
<td>26</td>
<td>Treat</td>
<td><em>Gram-positive &amp; Gram-negative?</em></td>
</tr>
<tr>
<td>Bacteriophages</td>
<td>9</td>
<td>Treat</td>
<td><em>P. aeruginosa, C. difficile</em></td>
</tr>
<tr>
<td>Immune Stimulation</td>
<td>43</td>
<td>Prevent or Adjunct</td>
<td><em>C. difficile, Broad-spectrum</em></td>
</tr>
<tr>
<td>Vaccines</td>
<td>188</td>
<td>Prevent</td>
<td><em>C. difficile, P. aeruginosa, S. aureus</em></td>
</tr>
<tr>
<td>Peptides</td>
<td>&lt;20</td>
<td>Treat or Adjunct</td>
<td><em>P. aeruginosa, C. difficile, S. aureus</em></td>
</tr>
</tbody>
</table>

With adequate funding into antibodies, probiotics and vaccines, we expect registration of:

- 2 new medicines for *C. difficile* (probiotic and antibody or vaccine) by 2019
- 1 for *P. aeruginosa* (antibody or vaccine) by 2021
- 1 for *S. aureus* (antibody or vaccine) by 2022
The A2A experiment

• Antibiotics have provided multiple medicines over 70 years & a huge investment
• A2As have not had the same investment
• Insufficient experience and literature of preclinical to clinical transition
• Clinical potential unproven
• Challenging investment argument

• BUT potentially a new source of medicines

• Identify which approaches are most attractive;
• Develop diagnostics to enable use of targeted therapies
• Refocus healthcare from treatment to prophylaxis
• Multiple products will be required to replace a single antibiotic
• Funding should focus on market pull rather than research push
• Invest in experimental clinical medicine not just drug discovery
• Develop A2A networks and a more collegiate approach
• Without adequate funding we cannot act as if there will be replacements for antibiotics
Opportunity – just not enough activity?

Alternatives to Antibiotics

- Antibodies
- Probiotics
- Lysins
- Bacteriophage
- Immune stimulation
- Vaccines
- Peptides
- Immune suppression
- Anti-resistance nucleic acids
- Antibacterial nucleic acids
- Toxin sequestration
- Antibiotic-degrading enzymes
- Transcriptional regulation
- Alphamers
- Metal chelation
- Apheresis of protective antibodies

£1.5 bn
€1.9 bn

Approaches

- Natural products
- Alternatives to antibiotics
- Next Gen Scaffolds
- Novel compounds vs known targets
- Combinations of antibiotics
- Efflux Pump Inhibitors
- Resistance breakers
- Novel targets & compounds

>£10 bn
>€13 bn
Solving the problem of antibiotic resistance

- Partnerships
  - experience, skills and insights
- International
- Coordinated
- Sustained
- Generational challenge
- Big science budgets

>£10 bn
>€13 bn

LHC £6 bn
€8 bn

ISS £96 bn
€123 bn