Tackling the need for new antibacterial drugs

Wendy Lawson
Lead Pharmacist, Infectious Diseases
Imperial College Healthcare NHS Trust, London
& Antibiotic Action Champion
Timeline of Antibiotic Discovery and Development

14 classes of antibiotics for human use introduced 1935-1968
5 since then

1928 discovery of penicillin
Antibiotic Use Benefits Individuals and Society

- HIV/AIDS related infection
- Tuberculosis
- Cystic fibrosis
- HIV/AIDS related infection
- Tuberculosis
- Inherited disorders:
  - Cystic fibrosis
- STDs: Chlamydia
- Gonorrhea
- Neonatal infection
- Puerperal fever
- Otitis media
- Tonsillitis
- Diarrhoea
- Pneumonia
- Surgery:
  - essential, elective, cosmetic
- Trauma: war, wound, accidents
- Animals: pets, food
- Crops: food
- Cancers
- Cardiovascular Transplants
- Hips, prostheses
- Pneumonia
- Chronic obstructive airways disease
- Bronchitis

Adapted from White, A: Boston, 2006
Timeline of Antibiotic Deployment and the Evolution of Antibiotic Resistance

Only now are we understanding the biology and transmission of resistance allowing the design of evidence based strategies to minimise the risk of selecting and spreading antibiotic resistant bacteria

World Health Organisation

• WHO statistics show that:
  – Infections are rated 2-5 of the top 10 causes of death and impact upon the other 5-8 causes
• WHO 2009 stated: “Antibiotic resistance - one of the three greatest threats to human health”
• WHO World Health Day 2011: themed Antimicrobial Resistance
  
  Slogan: No action today, No cure tomorrow
Proportion of multiple resistant *Staphylococcus aureus* (MRSA) among invasive Gr +ve S. aureus isolates in Europe 2003
Proportion of MRSA among invasive *Staphylococcus aureus* isolates Europe 2010
Proportion of *Gr* –ve *Escherichia coli* resistant to 3\(^{rd}\) generation cephalosporins Europe 2010
Proportion of Gr –ve *Klebsiella spp* resistant to 3rd generation cephalosporins in Europe 2010.
Bacteria and People Move Around

J Antimicrob Chemother 2012; 67: 2090-2100
There Are ~200 Antibiotics
Why Are More Needed?

Many of these drugs are not effective against some infections seen today:
  e.g. 3\textsuperscript{rd} November 2011 in a UK hospital
  \item 7/27 patients confirmed gram -ve *E. coli* infections
  \item 6/7 patients had severe, life-threatening infection
  \item 2/6 very limited treatment options (i.e. 3 antibiotics injections from 2 different classes no oral agents available)
What is Cost of Resistance?

- In 2007 across Europe\(^1\) 400,000 infections were caused by multidrug-resistant bacteria with 25,000 attributable deaths
  - resulted in 2.5 million extra hospital days per year
  - additional health care costs and productivity losses of at least €1.5 billion per year
- In 2000 in USA\(^2\) it was shown antibiotic-resistant infections responsible for
  - 8 million additional hospital days per year
  - $20 billion per year in excess health care costs
  - $35 billion per year in society costs

What Was The Response?

Boucher et al., Infectious Diseases Society of America. Report on development pipeline. *Clinical Infectious Diseases* 2009; **48**:1-12

The Global Need for Effective Antibiotics
- moving towards concerted action

September 6-8, 2010 Uppsala, Sweden

In UK: The Urgent Need (TUN) Initiative 2009-10

• The pivotal role of drug licensing & regulation led the British Society of Antimicrobial Chemotherapy (BSAC) working party on ‘The Urgent Need: Regenerating Antibacterial Drug Discovery and Development’ to:
  - Take ‘evidence’ from leaders in industry, academia and regulatory agencies in UK and internationally (chaired by Professor Wise)
  - Identify current obstacles and new approaches that may facilitate new development without compromising patient safety
BSAC The Urgent Need made 10 Recommendations

Discovery research: the scientific challenge of finding new antibiotics

Regulatory opportunities to encourage technology solutions to antibacterial drug resistance

Effective antibacterials: at what cost? The economics of antibacterial resistance and its control

www.bsac.org.uk
Some of the Issues

- An anti-infective is unlike other drugs because it
- Has multiple targets (bacterial species)
- Needs activity for many different infections
- Be effective in various and several body sites
- Genuine rarity of agents for Gram-negative bacteria
- Need to permeate and then evade innate efflux
- Over-optimism in the 1990s for what genomics could deliver led to disappointment
- Reduction in research capacity
  - Mergers among Big Pharma, which reduced the number and diversity of discovery teams
  - Reduced funding to academia
Why Are There No New Antibiotics?

• Withdrawal of ‘Big’ Pharma from this area
  – Lack of return on investment for industry
  – New business models needed
• Funding for basic discovery and research inadequate for the task
  – Depletion of skills (especially natural products)
• Licensing and Regulation model does not fit for antibiotics
  – Many issues with clinical trials - better diagnostics needed
• LESS 5% products in R&D pipeline are antibiotics

Launched September 2011

“Antibiotic resistance - one of the three greatest threats to human health.

World Health Organisation, 2009
What is Antibiotic Action?

Direct outcome of TUN initiative - the forum through which all parties called – government, health professionals, industry and charities – to identify and implement solutions within the research, regulation and economic markets to regenerate the discovery of antibiotic agents of the future.

‘Global Initiative’
Action

– Petition delivered to 10 Downing Street was presented to the House of Commons 4500 signatures
– Early day motion received cross political party support
– All party parliamentary group to identify and advise government

• Memorandum of understanding with the WHO to help the deliver their action plan on antibiotic resistance
• Working with infection organisations across the globe
What else is needed?

1. Identify ways to encourage pharmaceutical companies to start making these drugs again
   - Quicker and easier (cheaper) to regulate and license new antibiotics

2. A new business model - a global alliance of public-private-philanthropic funding
   - Fund discovery, research and development
   - Share the risk and the profit
HOW YOU CAN HELP?

• Sign the Petition on-line (100,000 by 2012)
  • Ask your family, friends and colleagues
• Share information via Facebook, Twitter and other social media
• Display a poster/materials from web at your university, laboratory, office, local shop
• Put a web widget on your website or email address
• Become an Antibiotic Action Champion via website

www.antibiotic-action.com
ACKNOWLEDGE:
Professor Laura Piddock
BSAC Chair in Public Engagement
l.j.v.piddock@bham.ac.uk
Carbapenemase-mediated resistance in the UK (n = 1315)*

Non-fermenters = 312
Enterobacteriaceae = 1003

*excludes A. baumannii with OXA-types

ARMRL, Unpublished data
<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Metallo-enzyme Producers (IMP, NDM or VIM)</th>
<th>Non-metallo-enzyme Producers (KPC or OXA-48 like)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. coli</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>Imipenem</td>
<td>9%</td>
<td>1%</td>
</tr>
<tr>
<td>IPM+EDTA [b]</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>U%</td>
<td>U%</td>
</tr>
<tr>
<td>PIP + tazobactam</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>4%</td>
<td>18%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0%</td>
<td>12%</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Amikacin</td>
<td>17%</td>
<td>32%</td>
</tr>
<tr>
<td>Ceftriaxine</td>
<td>100%</td>
<td>97%</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>100%</td>
<td>47%</td>
</tr>
</tbody>
</table>

a. Susceptibility defined using BSAC v. 10.1 breakpoints [7].

b. Diagnostic test to distinguish metallo- from non-metallo- enzymes; not for therapeutic use.
The Urgent Need (TUN) Initiative 2009-10

- Established in UK to regenerate antibacterial drug discovery & development
- ‘Evidence’ from interested parties in UK and international in 3 areas
- Research, regulation and economics
- Chair: Professor Richard Wise, microbiologist
  - 8 UK members
  - 8 overseas advisors (American Society of Microbiology, Inf Diseases Society of America...)

The Urgent Need (TUN) Initiative 2009-10

- Established in UK to regenerate antibacterial drug discovery, research and development
  - Chair: Professor Richard Wise, microbiologist
    - 8 UK members
    - 8 overseas advisors (American Society of Microbiology, ID Society of America, ReAct)
  - ‘Evidence’ from interested parties in UK and international in 3 areas
  - Research, regulation and economics

A Working Party of the British Society for Antimicrobial Chemotherapy (BSAC)