Review of the health technology assessment (HTA) process for antibiotics in Europe

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Developing new economic models to incentivise antibiotic discovery and development activities while safeguarding the efficacy of antibiotics by researching and advocating their appropriate use.

October 2014 – September 2017
Astellas Pharma Europe Ltd
AstraZeneca
Cubist Pharmaceuticals
F. Hoffmann-La Roche Ltd
GlaxoSmithKline R&D
Pfizer Ltd
Sanofi-Aventis R&D
DRIVE-AB Work Packages

• WP 1A: Define “responsible” use of antibiotics
• WP 1B: Set, communicate and revise public health priorities
• WP 1C: Develop antibiotic valuation models
• WP 2: Create, test and validate new economic models
• WP 3A: Coordinate and manage the project
• WP 3B: Stakeholder platform and external communication
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HTA connects evidence to policy.

Health technology assessment is the systematic evaluation of properties, effects and/or impacts of health technologies and interventions. It covers both the direct, intended consequences of technologies and interventions and their indirect, unintended consequences. The approach is used to inform policy and decision-making in health care, especially on how best to allocate limited funds to health interventions and technologies.

- World Health Organization
HTA connects regulation to management.

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Assessment</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Clinical effectiveness</td>
<td>Procurement</td>
</tr>
<tr>
<td>Performance</td>
<td>Ethics</td>
<td>Selection</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Social issues</td>
<td>Training</td>
</tr>
</tbody>
</table>

HTA is conducted according to set guidelines.
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There’s no guidelines or methods advice specific to antibiotics.

Antibiotics are treated like any other drug.
Antibiotics are different from other drugs in ways that are important for HTA.

• Transmission benefit: Treating one patient decreases overall incidence.

• Resistance cost: Using an antibiotic selects for resistance.
Antibiotics provide benefits that other drugs do not.

- **Enabling benefit:** Many surgical and medical procedures rely on prophylaxis with antibiotics.
- **Insurance benefit:** We may want to have an antibiotic in reserve before we really need it, so it’s ready if resistance arises or worsens.
- **Diversity/protection benefit:** Having multiple antibiotics may reduce selection pressure and delay resistance.
Case study review: Do HTA agencies take the unique values of antibiotics into account?
We searched HTA reports from the past 10 years in 11 countries.

We included the 10 largest EU economies + Norway. Austria, Belgium, Italy, Poland, and Sweden do not have HTA reports on antibiotics.

<table>
<thead>
<tr>
<th>Country</th>
<th>Agency</th>
<th>Full Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>HAS</td>
<td>French National Authority for Health/Haute Autorité de Santé</td>
</tr>
<tr>
<td>Germany</td>
<td>IQWiG</td>
<td>Institute for Quality and Efficiency in Healthcare/Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (GBA and DIMDI also searched)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>ZI</td>
<td>National Health Care Institute/Zorginstituut Nederland</td>
</tr>
<tr>
<td>Norway</td>
<td>NOKC</td>
<td>Norwegian Knowledge Center for the Health Services</td>
</tr>
<tr>
<td>Scotland</td>
<td>SMC</td>
<td>Scottish Medicines Consortium</td>
</tr>
<tr>
<td>Spain</td>
<td>AETS</td>
<td>National Health Technologies Assessment Agency/Agencia de Evaluación de Tecnologías Sanitarias</td>
</tr>
<tr>
<td>UK</td>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>Wales</td>
<td>AWMSG</td>
<td>All Wales Medicines Strategy Group</td>
</tr>
</tbody>
</table>
We selected 5 antibiotics for review, based on the number of available reports.

1. Aztreonam
2. Ceftaroline fosfamil
3. Colistimethate sodium
4. Fidaxomicin
5. Tigecycline

• Includes a mix of new technologies and reformulations of older products.
• All were reviewed in multiple countries.
• We reviewed public reports available in Dutch, English, German, and Spanish.
We examined 17 HTA reports.

<table>
<thead>
<tr>
<th>Name</th>
<th>France</th>
<th>Ger</th>
<th>Neth</th>
<th>Nor</th>
<th>Scot</th>
<th>Spain</th>
<th>UK</th>
<th>Wales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Ceftaroline fosfamil</td>
<td>X</td>
<td>E</td>
<td></td>
<td>X</td>
<td>A</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Colistimethate sodium</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>A</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tigecycline</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

A = NICE Advice, not a health technology appraisal guidance

E = Exemption from benefit-assessment report
The antibiotics

1. Aztreonam (solution for inhalation)
   • Class: monobactam
   • Spectrum: Narrow-spectrum against Gram-negative pathogens including *Pseudomonas aeruginosa*
   • Justification: Need for drug for patients with cystic fibrosis and *Pseudomonas aeruginosa* who cannot tolerate other available treatments

2. Ceftaroline fosamil (powder for infusion with solution)
   • Class: cephalosporin (advanced generation)
   • Spectrum: Broad-spectrum against Gram-positive and Gram-negative pathogens
   • Justification: Active against MRSA, VRE, and many other resistant pathogens
   • NOT active against ESBLs, *Pseudomonas aeruginosa* or *Acinetobacter*
The antibiotics

3. Colistimethate sodium (dry powder for inhalation)
   • Class: polymixin
   • Spectrum: Aerobic Gram-negative organisms including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*
   • Justification: Need for fast and effective drug (especially against *P. aeruginosa*) for patients with cystic fibrosis

4. Fidaxomicin (tablet)
   • Class: macrocyclic (first in class)
   • Spectrum: Narrow-spectrum against Gram-positive aerobes and *Clostridium difficile*
   • Justification: Need for an oral drug with low resistance that is active against *C. difficile*
5. Tigecycline (powder for infusion with solution)
   - Class: glycylcycline, a tetracycline derivative (first in class)
   - Spectrum: Broad-spectrum, with activity against Gram-positive, Gram-negative, and anaerobic organisms
   - Justification: Need for more treatment options against MRSA and VRE
## Results

The HTA reports raised related issues, but did not explicitly include these values in their recommendations.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Resistance cost</th>
<th>Enabling value</th>
<th>Diversity value</th>
<th>Insurance value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftaroline fosfamil</td>
<td>Mentioned; Informally factored into a rejection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistimethate sodium</td>
<td>Implied</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>Mentioned</td>
<td>Mentioned</td>
<td>Mentioned</td>
<td>Implied</td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
<td>Implied</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• The unique value of new antibiotics are not being systematically considered in current HTA practice.

• This impacts approval and reimbursement decisions, which in turn impacts pharmaceutical companies’ willingness to engage in antibiotics R&D.

• We need:
  • Methods for incorporating these values in the decision process.
  • To strengthen the role of HTA recommendations (so budget holders are willing to pay for more expensive antibiotics when they add value).
This research has received support from the Innovative Medicines Initiative Joint Undertaking under grant agreement n°115618 [Driving re-investment in R&D and responsible antibiotic use – DRIVE-AB – www.drive-ab.eu], resources of which are composed of financial contribution from the European Union’s Seventh Framework Programme (FP7/2007-2013) and EFPIA companies’ in kind contribution.