The economics of the antibacterial pipeline and access crisis

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The innovation problem: shortfall of public funding and private investments to support high-impact preclinical R&D projects
The CLINICAL pipeline is insufficient and not focused VS the PRECLINICAL pipeline is innovative but lacks funding

- The AMR Action Fund has struggled to find investment opportunities, with Henry Skinner saying the clinical pipeline is “much thinner” than he had originally realized.
- WHO agrees that “the clinical pipeline and recently approved antibiotics are insufficient.” In contrast, “[t]he preclinical pipeline is innovative and includes a large number of non-traditional approaches.” Yet, “[t]he preclinical antibacterial pipeline continues to rely on micro and small companies and academic institutions,” and the analysis “clearly indicates significant volatility and turnover.”
- It is clear that the problem is limited public and private investments in projects in preclinical development, failing to replenish an insufficient clinical pipeline.
The causes of the problem: lack of incentives for private investments in antibacterial R&D
Why don’t innovative antibiotics enjoy blockbuster sales?

• Initial sales are low because innovative antibiotics are held in reserve to prevent the development of resistance (and diagnostic devices are slow to update to include new antibiotics in susceptibility panels)
  – WHO AWaRe: new innovative antibiotics = RESERVE category

• Prices are low because of multiple reasons:
  – Health technology assessments (HTAs) focus on benefits for individual patients and do not recognize the societal value of antibiotics (see STEDI values, e.g., avoiding transmission and enabling other medical procedures)
  – Comparators in HTAs are low-cost generic antibiotics, and it is difficult/unethical to run superiority trials when existing treatments still save lives
  – Very expensive new antibiotics would block access in poorer countries and would incentivize potential marketing
Global antibiotic markets: decades of generic growth, but $150B decline in the engine behind R&D

Global Antibiotic Revenues (billions 2021US$, IQVIA)

Cumulative revenue gap = $150B

Gap now $13B / year

Recent private R&D investors lost >$3.7b in AMR

<table>
<thead>
<tr>
<th>Company</th>
<th>OOP cash to first antibiotic approval</th>
<th>Current market cap or $ realized for R&amp;D investors</th>
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</thead>
<tbody>
<tr>
<td>AKAO</td>
<td>$637m</td>
<td>$0</td>
</tr>
<tr>
<td>CDTX</td>
<td>$395m (P3)</td>
<td>$118m</td>
</tr>
<tr>
<td>ETTX</td>
<td>$247m (P3)</td>
<td>$113m*</td>
</tr>
<tr>
<td>MLNT</td>
<td>$593m</td>
<td>$0</td>
</tr>
<tr>
<td>NBRV</td>
<td>$507m</td>
<td>$5m</td>
</tr>
<tr>
<td>POLN:SW</td>
<td>$397m (P3)</td>
<td>$18m (SPEX:SW)</td>
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<tr>
<td>PRTK</td>
<td>$624m</td>
<td>$105m</td>
</tr>
<tr>
<td>MCRB</td>
<td>$671m</td>
<td>$650m (microbiome)</td>
</tr>
<tr>
<td>TTPH</td>
<td>$657m</td>
<td>$16m</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>$4.728B</strong></td>
<td><strong>$1.025B</strong></td>
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OOP from Outterson K, Health Affairs 2021 (Supp. Fig. S6) + public filings 2Q22 for Achaogen, Cidara, Entasis, Melinta, Nabriva, Polyphor, Paratek, Seres, & Tetraphase.
* Acquisition price May 2022
Market caps as of 16 May 2023
The magnitude of the problem: the funding gap for push and pull incentives
## 6+ innovative high-impact treatments are needed per decade

<table>
<thead>
<tr>
<th>Report/strategy</th>
<th>Target (therapeutics)</th>
<th>Extrapolation for 10 years</th>
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<tbody>
<tr>
<td><strong>IDSA 10x20</strong></td>
<td>10 “new systemic” over 10 years</td>
<td>10</td>
</tr>
<tr>
<td><strong>AMR Review</strong></td>
<td>15 “new”, of which at least 4 “breakthrough”, over a decade</td>
<td>15 (of which 4 breakthrough)</td>
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<tr>
<td><strong>GUARD</strong></td>
<td>One additional “high-need” per year</td>
<td>10</td>
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<tr>
<td><strong>DRIVE-AB</strong></td>
<td>16-20 “truly innovative” over 30 years</td>
<td>5-7</td>
</tr>
<tr>
<td><strong>U.S. NAP 2020-2025</strong></td>
<td>Three “new” by 2025</td>
<td>6</td>
</tr>
<tr>
<td><strong>BARDA Strategic Plan 2022-2026</strong></td>
<td>Three “novel” by 2026</td>
<td>6</td>
</tr>
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6+ innovative high-impact treatments require a pipeline

Basic Research  
~$3 billion

Early-stage product development  
~$5.6 billion

Advanced development and post-approval  
~$3.3 billion

>6000 basic research projects per decade

~215 projects per decade, from Hit-to-Lead to First-in-Human studies

~12 projects beginning clinical efficacy studies per decade, including regulatory and post-approval costs in HICs only

6 new high-impact treatments per decade

IMPORTANT: These estimates do not account for the costs of regulatory submissions, post approval and access in high-burden low- and middle-income countries. Also, TB is not included.

Preliminary results based on probabilities of success and phase costs from best available data. Validation is underway with upstream and downstream partners, including AMRAF and GARDP.
Magnitude of the funding gap in the PRECLINICAL stages of antibacterial R&D for therapeutics over the next 10 years

Total investment needs

$5.6 billion

Expected investments at current levels

$1.9 billion

Funding gap

$3.7 billion

- 400M CARB-X
- 15M IMI AMR Accelerator
- 300M Other public & philanthropic
- 840M Venture capital
- 180M IPOs
- 90M FOPOs
- 90M Licensing deals

Preliminary results based on data from the Global R&D Hub and BIO, plus expert views.
“There is a broad agreement that push funding should complement the pull models above, acting where the pull models are least efficient: in the early phases of development.”

“There is relative consensus on the need to provide additional push funding, in a range between USD 250 and USD 400 million on an annual basis, and at a global level ... This range corresponds to what is necessary for reinvigorating the pipeline in conjunction with the pull incentives.”

• Best estimate for a global antibacterial subscription = $310M (range: $220M-$480M) per drug annually over 10 years
  • The PASTEUR Act is within this range, as is the global pull incentive implied by the UK pilot
• Both push and pull incentives are necessary for sustainable and robust antibacterial drug development
“Fair share” pull incentive targets within G7+EU27

Fair share of a $3.1B global subscription pull incentive, allocated by relative GDP

Figures are average per drug, per year, paid over 10 years

Payments might be lower at registration, but could increase as stronger evidence is presented

All figures 2022 US$, millions

Swiss “fair share” = US$ 4.4M

Outterson 2023, https://open.bu.edu/handle/2144/42568
How should ideal pull incentives look like?

• Delink revenues from sales
• Be of sufficient magnitude and predictable (see prior slides about global amount and fair share)
• Be rapidly implementable
• Coordinate across countries/regions to select a similar set of products based on a similar balance of novelty and patient utility
• Include sound but realistic guardrails regarding both access and stewardship
Three innovation and financial targets for UNGA 2024

Innovation:
• At least 6 new high-impact antibacterial treatments by 2034

Financial (in order to achieve the innovation target):
• Double existing push incentives focusing on preclinical development, with a minimum of USD 200 million per year globally from governments and philanthropic organizations
• Implement a coordinated set of pull incentives totaling $310M (range: $220M-$480M) per drug per year over 10 years globally, fully delinked