THE ANTIBIOTIC WEBINARS: 2
SMALL AND MEDIUM SCALE ANTIBIOTIC DEVELOPERS
Challenges they face and the way forward

At a time when existing antibiotics are becoming ineffective, major pharma companies have vacated the new antibiotic R&D space. Small and medium antibiotic developers have taken up the responsibility instead.

August 24, 2023
We are currently facing **three key crisis**

- **Crisis 1**: Antibiotics are becoming ineffective
- **Crisis 2**: The antibiotic development crisis
- **Crisis 3**: The issue of access
Stagnant years!
of antibiotic pipeline for priority pathogens

Priority pathogens = unmet need = most are Gram-negatives

- 12 pathogens categorized into critical, high and medium priority by the WHO in 2017 to guide global antibiotic research

As per World Health Organization’s priority pathogen list, 2017;
^Number of antibiotic candidates; Source: World Health Organization
Global antibiotic pipeline: weak, fragile, dry, anemic!

297 (anti-bacterial candidates)
- 217 (preclinical)
- 77 (clinical)
- 3 (pre-registration)

32 (non-traditional)

45 (traditional)

28 (target WHO priority pathogens)

Priority pathogens, M. tuberculosis and C. difficile

In comparison:
- >10,000 medicines under active clinical development for cancer
- >1,800 for neuropsychiatric conditions
- ~1,500 for endocrine, blood and immune disorders*

Agents that lack intrinsic antibacterial activity and work through other means; May not substitute traditional

Agents that act by directly targeting components necessary for bacterial growth or to kill the pathogen

Source: WHO database updated till late 2021; *WHO’s Global Health Observatory on Health Research and Development
## Clinical development pipeline

<table>
<thead>
<tr>
<th>TRADITIONAL ANTIBIOTIC CANDIDATES: 46</th>
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<tbody>
<tr>
<td><strong>Phase 1: 22</strong></td>
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<tr>
<td>Targeting WHO priority pathogens</td>
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<tr>
<td>Developers in Phase 1: Bugworks Research, Juvabio, Entasis Therapeutics, Pfizer/Aria Pharmaceutical, KBP BioSciences Pharmaceutical Technical, MicRX, Meiji Seika, Gpex Biopharma, Roche, Spero Therapeutics, TAINS Pharmaceutical, Venatorx, Sinoven, Woodard</td>
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<tr>
<td>Developers in Phase 2: Debiopharm International, TenNor Therapeutics</td>
</tr>
<tr>
<td>Developers in Phase 3: Sichuan Pharmaceutical Holding Group, Glaxo SmithKline (GSK), Entasis Therapeutics, Allecra Therapeutics, Woodard, Iterum Therapeutics, Venatorx Pharmaceuticals/Global Antimicrobial Research and Development Partnership (GARDP), Entasis Therapeutics/GARDP, Developers in Pre-registration: Fujifilm Toyama</td>
</tr>
<tr>
<td>Targeting <em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Developers in Phase 1: GSK-TB drug accelerator/Bill &amp; Melinda Gates Foundation, Innovative Medicines for Tuberculosis Foundation, TB Alliance, Institute of Mediria Medica, Institute of Mediria Medica/TB Alliance</td>
</tr>
<tr>
<td>Developers in Phase 2: GSK, University of Munich, LegoChem Biosciences/Haihe Biopharm, Otsuka Pharmaceutical, TB Alliance/Sequella, TB Alliance/Bill and Melinda Gates Foundation, Querient</td>
</tr>
<tr>
<td>Targeting <em>Clostridioides difficile</em></td>
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<tr>
<td>Developers in Phase 2: Crestone, Deinove, Acurx Pharmaceutical, MGB Biopharma; Developers in Phase 3: Summit Therapeutics</td>
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### Near-future scenario bleak

- **Only nine** in phase 3
- **None for** *M. tuberculosis*
- **Only two** for critical priority pathogens
- **Solithromycin** is the only one in pre-registration stage
Small firms, big task – Non-traditional candidates

Clinical development pipeline

<table>
<thead>
<tr>
<th>NON-TRADITIONAL ANTIBIOTIC CANDIDATES*: 34</th>
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<tbody>
<tr>
<td><strong>Phase 1: 12</strong></td>
</tr>
<tr>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Targeting WHO priority pathogens</td>
</tr>
<tr>
<td>Developers in Phase 1: Malvern Biosciences, Aptorum Group, Eagle Pharmaceuticals, GSK, Locus Biosciences, Senatus, Trellis Biosciences</td>
</tr>
<tr>
<td>Developers in Phase 2: Amata Pharmaceuticals, Aridis Astra Zeneca/MedImmune, BiomX, Gamaleya Research Institute of Epidemiology and Microbiology, Lumen Bioscience, Roviant Sciences/in Iron BioTechnology, AlgiaPharma AS, Adaptive Phage Therapeutics, BioAegis Therapeutics, Felix Biotechnology/Yale University</td>
</tr>
<tr>
<td>Developers in Phase 3: Tashkent Pediatric Medical Institute, Aridis Pharmaceutical, Contrafect</td>
</tr>
<tr>
<td>Developers in Pre-registration: AtoxBio</td>
</tr>
<tr>
<td>Targeting <em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>Developers in Phase 1: Bioversys/GSK</td>
</tr>
<tr>
<td>Targeting <em>Clostridioides difficile</em></td>
</tr>
<tr>
<td>Developers in Phase 1: Artugen Therapeutics, Lumen Bioscience, Nubiyota/Takeda, Ferring (Ribiotox)</td>
</tr>
<tr>
<td>Developers in Phase 2: Finch Therapeutics, Da Volterra, Immunomed, Synthetic Biologics, Vedanta Biosciences</td>
</tr>
<tr>
<td>Developers in Phase 3: Ferring Pharmaceuticals, Seres Therapeutics</td>
</tr>
<tr>
<td>Developers in Pre-registration: Biome Bank</td>
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</tbody>
</table>

Near-future scenario bleak

- Only five in phase 3
- Only two in pre-registration stage
- None for *M. tuberculosis* (only one in phase 1)

Approximately 80% of new antibiotic discoveries are reported to be from small developers

Source: A 2022 report by biotechnology innovation organisation
Only 3 out of the 217 have their Investigative New Drug (IND) application submitted.

31 are in clinical trial application/IND-enabling studies.

Too less a pool, considering the high failure risk at this stage.

Pre-clinical pipeline as on WHO database updated until late 2021.
84% preclinical candidates developed by micro, small and medium developers

As per WHO, out of 217 antibacterial preclinical candidates,

- Developer institutions of **183 candidates (84%)** are:
  - Micro (≤ 10 employees)
  - Small (11-50 employees)
  - Medium (51-500 employees)
Teething troubles: Examples of some global companies

- Small-medium scale antibiotic developers are **struggling** to develop antibiotics or making money from what they have developed

- **Of the 12** antibiotic companies gone public in the past 10 years, **only five are still active** today*
  
  - **Filed for bankruptcy**: e.g. Melinta Therapeutics (2019; recovered later), Achaogen (2019; after USFDA approved use of its antibiotic in one condition and not in other), Aradigm (2019; while pursuing regulatory approval of its inhaled antibiotic) and Nabriva Therapeutics (announcing closure in 2023)
  
  - **Faced diminished values/exits**: e.g. Tetraphase Pharmaceuticals (from $1.8 billion to $43 million), Spero Therapeutics (halted its commercialisation activities of its late stage UTI drug and laid off 75% of its staff in 2022)

- When these pharmaceuticals collapsed, it took **out of circulation**—or sharply reduced the availability of—**five of the 15 antibiotics** approved by the US FDA since 2010**

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*A 2022 report by biotechnology innovation organisation; ** 2020 article of Nature
Most of the world’s 15 big pharmaceutical companies* do not have antibiotics in their clinical pipeline.

Many who were developing earlier have exited. Some many years ago; some recently. Only GSK, Roche, Pfizer and AbbVie are currently developing.

Collectively, the 2022 revenue of these 15 companies was about $711 billion, 17.5% of which ($124 billion) was total investment in research and development.

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**Big Exodus by high-earning companies**

<table>
<thead>
<tr>
<th>Company and Annual Revenue (2022)</th>
<th>R&amp;D expenditure in 2022 (per cent of overall revenue)</th>
<th>Total number of molecules</th>
<th>Clinical pipeline focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca $44.4 billion</td>
<td>$9.7 billion (21.8%)</td>
<td>170</td>
<td>Oncology [95], cardiovascular, renal and metabolism [24], respiratory and immunology [28], rare disease [15], vaccine and immune therapies [3], others [5]</td>
</tr>
<tr>
<td>F Hoffmann-La Roche CHF 63.2 billion</td>
<td>CHF 14 billion (22.1%)</td>
<td>104</td>
<td>Immunology [11], infectious diseases [5: bacterial 2], metabolic [1], neuroscience [24], oncology, hematology [51], ophthalmology [11], others [1]</td>
</tr>
<tr>
<td>Bristol-Myers Squibb $46.1 billion</td>
<td>$9.5 billion (20.6%)</td>
<td>91</td>
<td>Solid tumors [47], hematology [22], immunology [10], Fibrotic disease [2], cardiovascular [6], neuroscience [4]</td>
</tr>
<tr>
<td>Pfizer $100.3 billion</td>
<td>$11.4 billion (11.4%)</td>
<td>89</td>
<td>Anti infectives [7: bacterial 2], rare diseases [12], immunology and immunology [14], Internal medicine [10], oncology [32], vaccines [14: bacterial 6]</td>
</tr>
<tr>
<td>Novartis $50.9 billion</td>
<td>$9.9 billion (19.6%)</td>
<td>81</td>
<td>Biosimilars [2], cardiovascular [8], global health [9], hematology [14], immunology [15], neuroscience [9], ophthalmology [4], respiratory and allergy [2], solid tumors [18]</td>
</tr>
<tr>
<td>GlaxoSmithKline $29.3 billion</td>
<td>$5.4 billion (18.3%)</td>
<td>75</td>
<td>Infectious diseases [41], bacterial 8, bacterial vaccine 10, HIV [5], oncology [16], Immunology: respiratory [8], opportunity driven [4]</td>
</tr>
<tr>
<td>Johnson &amp; Johnson $94.9 billion</td>
<td>$14.6 billion (15.4%)</td>
<td>74</td>
<td>Cardiovascular and metabolism [7], immunology [12], Infectious Diseases and Vaccines, Global Public Health [14], bacterial vaccine 1, oncology [28], neuroscience [8], Pulmonary hypertension [5]</td>
</tr>
<tr>
<td>AbbVie $58 billion</td>
<td>$7.1 billion (12.2%)</td>
<td>63</td>
<td>Immunology [7], neuroscience [10], ophthalmology [26], eye care [3], aesthetics [10], other specialties [7: bacterial 1]</td>
</tr>
<tr>
<td>Gilead Sciences $27.3 billion</td>
<td>$5 billion (18.3%)</td>
<td>60</td>
<td>Viral diseases [17], inflammatory disease [4], oncology [38], fibrotic diseases [1]</td>
</tr>
<tr>
<td>Sanofi $42.9 billion</td>
<td>€6.7 billion (15.7%)</td>
<td>53</td>
<td>Oncology [15], immunology and inflammation [14], neurology [5], rare blood disorder [4], rare disease [5], vaccines [10: bacterial 3]</td>
</tr>
<tr>
<td>Eli Lilly and Company $28.5 billion</td>
<td>$7.2 billion (25.3%)</td>
<td>50</td>
<td>Cancer [9], diabetes and obesity [20], immunology [10], neurodegeneration [7], pain [4]</td>
</tr>
<tr>
<td>Merck &amp; Co $59.2 billion</td>
<td>$13.5 billion (22.8%)</td>
<td>39</td>
<td>Antiviral [5], cardiovascular [4], endocrinology [1], neuroscience [2], oncology [22], respiratory [2], vaccines [3: bacterial 2]</td>
</tr>
<tr>
<td>Amgen $26.3 billion</td>
<td>$4.4 billion (16.7%)</td>
<td>36</td>
<td>Bone [2], cardiometabolic [4], hematology/ oncology [18], inflammation [9], metabolic disorders [1], nephrology [1], Neuroscience [11]</td>
</tr>
<tr>
<td>Biogen $10.1 billion</td>
<td>$2.2 billion (21.8%)</td>
<td>22</td>
<td>Alzheimer’s disease and dementia [5], genetic neurodevelopmental disorders [1], multiple sclerosis [2], neuromuscular disorders [3], neuropsychiatry [2], neurovascular [1], Parkinson’s disease and movement disorders [5], specialized immunology [3]</td>
</tr>
<tr>
<td>Viatris $16.2 billion</td>
<td>$0.65 billion (4.1%)</td>
<td>NA*</td>
<td>Cardiovascular, neurology, pain/osteoarthritis, urology, psychiatry</td>
</tr>
</tbody>
</table>

*Selected by Down To Earth to represent a cross-section of high-earning, global pharmaceutical firms; *Includes infectious disease; Information could not be accessed; Note: Data updated till June 2, 2023; Source: Compiled by CSE- DTE Data Centre
Hollow pipeline
Industry attributes to antibiotic market failure; venture capitalists also moved away to more profitable areas

- Out of **1007 molecules** in clinical pipeline of 15 global pharmaceuticals, **only 13 are antibacterial candidates**, being developed by **four companies**. 8 out 13 are by one company (GSK).
  - **411** candidates were found to be developed for cancer;
  - **150** for immunology, allergy, inflammation or respiratory diseases;
  - **84** for cardiology, metabolism or renal disease areas.

The BIG EXODUS is not only because of high risk low return (due to often cited market failure) but also because of profits in other areas. As reflected through blockbuster drugs in profitable areas like cancer, autoimmune disorders, metabolic diseases.
What can be done to aid small and medium companies that have entered antibiotic research.
Support research and market
Growing consensus on the need to support antibiotic R&D through investments via, broadly, two types of approaches—push and pull

**Push incentives**
- Involve funding the *early stage* of antibiotic development, from discovery to clinical trials
- Provide *direct support* through grants, loans and tax incentives
- Involves *non-profits, industry, government*
- *Funder shares risk of failure*, can help bring down development costs
- E.g., CARB-X, GARDP, AMR Action Fund

**Pull incentives**
- Provide a *known return on investment* to those who have developed a novel antibiotic, and *help bring it into the market*
- E.g. market entry rewards, tradeable exclusivity vouchers, accelerated approvals
- *Largely driven by governments*. Do not address the risk of failure in the early-stage development
- US, UK, Japan, Sweden, France and Germany are considering
- In 2020, the UK implemented a pilot of a *subscription model* (delinked monetary reward from sales); Sweden also piloted a *partially-delinked reimbursement* model.

After about a decade of push incentives, it is clear their success has been less than required; they are not enough and need to be supplemented. On the other hand, the impact of pull incentives initiated in recent years remains to be seen.
Critical reforms needed
To stimulate the antibiotic R&D ecosystem for a sustainable and equitable antibiotic access worldwide

• Greater public financing and reforms are needed such as related to market, reimbursements, regulatory approvals, cost of new antibiotics and clinical trials. Governments will have to play a greater role. Policymakers need to be aware about the financing rationale and needs.

• Governments need to come together for a coordinated response in terms of prioritising antibiotics and developers, testing and piloting incentives and removing access barriers. Action needed by G20 countries. Unless major economies come together, individual country efforts will have limited long-term gains.

• Need to strike the right balance in public-private partnership for antibiotic development. Notion that governments should take up the entire antibiotic development is not backed by many. On the other hand, public financing should not just be about bring back the big pharma companies.

• Role of countries like India with a big antibiotic generics industry that provides access to cheap antibiotics across borders to be reflected upon.
Time to consider antibiotics as a ‘global public good’

- **Public goods** are non-excludable (meaning they are made available to all) and non-rivalrous (meaning they can be enjoyed over and over again by anyone without diminishing the benefits they deliver to others). They can be local, national or global.

- **Markets** often cannot optimally supply public goods. Incentives for private players are lacking.

- **Governments have to intervene** due to the scale of coordination required, lack of power to enforce regulations and challenges of distribution.

- **Antibiotics** have attributes of ‘global public good’. They may not fit the strictest definition but their benefit to society makes them as close to a ‘global public good’ as one can be.
Thank you!
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