THE ANTIBIOTIC WEBINARS: 1

THE CRISIS IN ANTIBIOTIC RESEARCH AND DEVELOPMENT

At a time when existing antibiotics are becoming ineffective, pharma companies are not investing in R&D for new antibiotics. Is the world staring at a serious health emergency in the near future?

July 28, 2023

Presentation by: Rajeshwari Sinha, Sustainable Food Systems programme, CSE
Crisis 1: Antibiotics are becoming ineffective

- Burden of antibiotic resistance **huge and rising:**
  - ~ 5 million deaths worldwide associated with antibiotic resistance (2019)
  - ~1.3 million deaths directly attributed to it

- **Existing antibiotics** becoming ineffective as bacteria becoming resistant to them:
  - Critically important antibiotics losing power to kill bacteria (e.g., fluoroquinolones, aminoglycosides, carbapenems and cephalosporins)
  - Expensive antibiotics are now needed to be used (e.g., ceftazidime-avibactam); also impacting access

- Ultimately, treatment options are reducing
Crisis 2: Antibiotic development crisis

• The **Golden era** for antibiotic development was during 1950-1970.

• **No new class** of antibiotics developed since 1980s, especially against **Gram-negative bacteria**.

• Those developed over the last decade are considered inadequate to treat the **growing unmet need; growing resistance**
Crisis 3: Access

- There are access issues. As per a study, 11 out of 14 countries had access to less than half of 18 new antibiotics developed during 2010-19.

- Besides, these are variants of existing classes, and the targeted bacteria is likely to develop resistance against them earlier.

- Only few are exclusively designed to thwart the infectious Gram-negative bacteria.
Stagnant years! of antibiotic pipeline

The list of antibiotic candidates targeting world’s priority pathogens has remained stagnant, at least from 2017 onwards.

*As per World Health Organization’s priority pathogen list, 2017;
^Number of antibiotic candidates; Source: World Health Organization
Priority pathogens = unmet need = most are Gram-negatives

Prime threats
In 2017, World Health Organization listed 12 pathogens that are antibiotic resistant and need to be studied

WHO records antibacterial products in clinical and preclinical development for these priority pathogens, *M. tuberculosis* and *C. difficile*
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)

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

*Source: WHO database updated till late 2021; *WHO's Global Health Observatory on Health Research and Development*

**Agents that lack intrinsic antibacterial activity and work through other means:**

*Can't substitute traditional*

**Agents that act by directly targeting components necessary for bacterial growth or to kill the pathogen**
Small firms, big task

Clinical development pipeline

<table>
<thead>
<tr>
<th>Targeting</th>
<th>Phase 1: 22</th>
<th>Phase 2: 14</th>
<th>Phase 3: 9</th>
<th>Pre-registration: 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO priority pathogens</td>
<td>28</td>
<td>16</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

Developers in Phase 1: Bugworks Research, Juvabis, Entasis Therapeutics, Pfizer/Arix Pharmaceutical, KBP BioSciences Pharmaceutical Technical, MicuRX, Meiji Seika, Gpex Biopharma, Roche, Sero Therapeutics, TAXIS Pharmaceutical, Venatorx, Sinovent, Wockhardt

Developers in Phase 2: Debiopharm International, TenNor Therapeutics

Developers in Phase 3: Sichuan Pharmaceutical Holding Group, Glaxo SmithKline (GSK), Entasis Therapeutics, Alcera Therapeutics, Wockhardt, Iterum Therapeutics, Venatorx Pharmaceuticals/Global Antibiotic Research and Development Partnership (GARDP), Entasis Therapeutics/GARDP

Developers in Pre-registration: Fujifilm Toyama

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

<table>
<thead>
<tr>
<th>Targeting <em>Mycobacterium tuberculosis</em></th>
<th>Phase 1: 13</th>
<th>Phase 2: 6</th>
<th>Phase 3: 7</th>
<th>Pre-registration: -</th>
</tr>
</thead>
</table>

Developers in Phase 1: GSK, TB drug accelerator/Bill & Melinda Gates Foundation, Innovative Medicines for Tuberculosis Foundation, TB Alliance, Institute of Mediaira Medica, Institute of Mediaira Medica/TB Alliance

Developers in Phase 2: GSK, University of Munich, LegoChem Biosciences/Haithe Biopharm, Otsuka Pharmaceutical, TB Alliance/Sequella, TB Alliance/Bill and Melinda Gates Foundation, Qurient

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<thead>
<tr>
<th>Targeting <em>Clostridium difficile</em></th>
<th>Phase 1: 5</th>
<th>Phase 2: -</th>
<th>Phase 3: 4</th>
<th>Pre-registration: 1</th>
</tr>
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Developers in Phase 2: Crestone, Deinove, Acrux Pharmaceutical, MGB Biopharma; Developers in Phase 3: Summit Therapeutics
Small firms, big task

Clinical development pipeline

<table>
<thead>
<tr>
<th>NON-TRADITIONAL ANTIBIOTIC CANDIDATES*: 34</th>
<th>Phase 1: 12</th>
<th>Phase 2: 15</th>
<th>Phase 3: 5</th>
<th>Pre-registration: 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeting WHO priority pathogens</td>
<td>21</td>
<td>7</td>
<td>10</td>
<td>3</td>
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<tr>
<td>Developers in Phase 1: Multwell Biosciences, Aptorum Group, Eagle Pharmaceuticals, GSK, Locus Biosciences, Servatus, Trelis Bioscience;</td>
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<td>Developers in Phase 2: Aridis Pharmaceuticals, Aridis Astra Zeneca/MedImmune, BiomX, Gamaleya Research Institute of Epidemiology and</td>
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<td>Microbiology, Lumen Bioscience, Riovant Sciences/Inuron BioTechnology, AlpiPharma AS, Adaptive Phage Therapeutics, BioAegis Therapeutics,</td>
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<td>Felix Biotechnology/Yale University</td>
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<tr>
<td>Developers in Phase 3: Tashkent Pediatric Medical Institute, Aridis Pharmaceutical, Contratec</td>
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<td>Developers in Pre-registration: Atox Bio</td>
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<tr>
<td>Targeting Mycobacterium tuberculosis</td>
<td>1</td>
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<tr>
<td>Developer in Phase 1: Bioversys/GSK</td>
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<td>Targeting Clostridiodes difficile</td>
<td>12</td>
<td>4</td>
<td>5</td>
<td>2</td>
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<tr>
<td>Developers in Phase 1: Artugen Therapeutics, Lumen Bioscience, Nubiyota/Takeda, Ferring (Ribiolyts)</td>
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<tr>
<td>Developers in Phase 2: Finch Therapeutics, Da Volterra, ImmunMed, Synthetic Biologics, Vedanta Biosciences</td>
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<td>Developers in Phase 3: Ferring Pharmaceuticals, Seres Therapeutics</td>
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<td>Developers in Pre-registration: Biome Bank</td>
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Near-future scenario bleak

- **Only five** in phase 3
- **Only two** in pre-registration stage
- **None for M. tuberculosis** (only one in phase 1)
Long-term scenario also **not promising**!

- **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.
Most big pharmaceutical companies have all but quit research and development of new antibiotics

High-risk, low-return is the excuse for major pharma companies quitting antibiotic research, an argument that flies in the face of the humongous profits it makes through other drugs
Abandoned cause!

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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*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 III 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.
Departure Trail
Exit timeline of major pharma companies; key mergers and acquisitions

**Early 2000s**
- Eli Lilly of the US, a pioneer in antibiotic development, stops developing the drugs; Bristol Meyers Squibb, a global bio-pharma giant based in the US, too stops developing antibiotics.

**2014**
- US’ Merck & Co, known for funding discovery of streptomycin, used to treat TB, acquires Cubist Pharmaceuticals for $9.5 billion, a global leader in antibiotics.

**2015**
- US’s AbbVie, which is working on an antibiotic candidate, acquires Pharmacia for $21 billion to strengthen commercial presence in oncology, Swiss multinational Roche ends its 2-year old collaborations with Polyphor for an experimental antibiotic.

**2016**
- AstraZeneca, UK-based multinational, sells development rights of its late-stage small molecule antibiotics business to Pfizer.

**2018**
- Novartis, which had 32 antimicrobial projects in its pipeline till 2016, shuts down its antibacterial research.
- France’s Sanofi outsources its anti-infective R&D to Germany’s biotech firm Evotec.
- Johnson & Johnson scraps development of cadazoloid, an antibiotic for treating C difficile.

**2019**
- Bristol Meyers Squibb in a $74 billion deal acquires Celgene, a company that focuses on oncology, immunology, inflammation and cardiovascular disease.
- Small antibiotic developers, Melinta Therapeutics, Achaogen and Aradigm file for bankruptcy.
- Eli Lilly acquires Loxo Oncology for $8 billion.

**2020**
- Tetraphase Pharma, which in 2015 had an evaluation of $1.8 billion following development of antibiotic Xerava used for stomach infection, was acquired for $43 million by US’ Ta Jolla Pharma.

**2021**
- Novartis acquires GSK’s cephalosporin antibiotics business of three established brands (Zinnek, Zinacef and Fortum) for $500 million.

**2022**
- Spero Therapeutics, an antibiotic developer, halts its commercialisation activities, lays off 75 per cent of its staff.

**2023**
- Sanofi acquires Prevencion Bio for $2.9 bn to bolster its immune-mediated disease pipeline.
- Novartis acquires Chinook Therapeutics for $3.2 billion to bolster innovative drugs, renal pipeline. Nebiva Therapeutics, a firm that launched Xenleta to treat bacterial pneumonia, announces closure.

Source: Media reports, company websites, annual reports of firms
Antibiotic market failure?

- **High cost** of antibiotic development with new molecules getting harder to find
- Antibiotics are usually **inexpensive** to keep them affordable; sell in a **lower volume** than chronic conditions, like diabetes, hypertension and cancer
- To delay resistance, developers **cannot push to sell them** at least in the first few years, which could be the best time to recover huge cost of development
- By the time a new antibiotic becomes the first or second line of treatment, there is the **risk of losing revenues** to the low-cost generic options
- **Unpredictability** due to sporadic nature of infections and outbreaks
- **In the US, the total annual sales of 17 of the 18 new antibiotics launched between 2010 and 2019 was about $715 million; similar to the sale of one new oncology product during the period**
But **BIG EXODUS** - is also because of profits in other areas
Blockbuster drugs indicates profitable areas – cancer, autoimmune...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Companies</th>
<th>Sales in 2021 (in $ billion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comirnaty (a vaccine against COVID-19)</td>
<td>Pfizer, BioNTech</td>
<td>36.8</td>
</tr>
<tr>
<td>Humira (monoclonal antibody used to treat diseases like rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease and plaque psoriasis)</td>
<td>AbbVie</td>
<td>20.7</td>
</tr>
<tr>
<td>Spikevax (vaccine against COVID-19)</td>
<td>Moderna</td>
<td>17.7</td>
</tr>
<tr>
<td>Keytruda (humanised antibody used to treat melanoma, non-small cell lung cancer, head and neck cancer, Hodgkin lymphoma, uraethelial carcinoma, gastric cancer)</td>
<td>Merck &amp; Co.</td>
<td>17.2</td>
</tr>
<tr>
<td>Eliquis (anti-coagulant used to treat nonvalvular atrial fibrillation, deep vein thrombosis and pulmonary embolism)</td>
<td>Bristol Myers Squibb, Pfizer</td>
<td>16.73</td>
</tr>
<tr>
<td>Revlimid (small molecule drug used to treat myelodysplastic syndrome, multiple myeloma, lymphoma, follicular lymphoma)</td>
<td>Bristol Myers Squibb</td>
<td>12.8</td>
</tr>
</tbody>
</table>

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<th>Drug</th>
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<th>Sales in 2021 (in $ billion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imbruvica (small molecule drug used to treat mantle cell lymphoma, chronic lymphocytic leukemia, Waldenstrom’s macroglobulinemia, marginal zone lymphoma, chronic graft-versus-host disease)</td>
<td>AbbVie, Johnson &amp; Johnson</td>
<td>9.8</td>
</tr>
<tr>
<td>Stelara (monoclonal antibody used to treat plaque psoriasis, psoriatic arthritis, Crohn’s disease, ulcerative colitis)</td>
<td>Johnson &amp; Johnson</td>
<td>9.1</td>
</tr>
<tr>
<td>Eylea (glycoprotein used to treat wet age-related macular degeneration, diabetic macular edema, diabetic retinopathy, macular edema)</td>
<td>Regeneron, Bayer</td>
<td>8.9</td>
</tr>
<tr>
<td>Biktarvy (small molecule drug used for HIV)</td>
<td>Gilead Sciences</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Source: www.fiercepharma.com

As part of AMR action fund, some big companies have committed few hundred million dollars collectively spread over the next several years.

The question remains if major pharma can be absolved of the responsibility of developing antibiotics, especially when it is earning handsomely through a few drugs.
Teething troubles
Small-medium developers which are trying to pick up the slack

- Small companies account for **80 per cent** of new antibiotic discoveries, large companies **12 per cent**, and non-profit institutes and universities **8 per cent**
- But they 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 in 2019: e.g. Melinta Therapeutics (recovered later), Achaogen (after USFDA approved use of its antibiotic in one condition and not in other)
  - Faced diminished values: e.g. Tetraphase Pharmaceuticals (from $1.8 billion to $43 million)
- 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
- Some small companies are also **diversifying**. Bugworks Research India Pvt, is now also developing drugs for oncology

*A 2022 report by biotechnology innovation organisation; **2020 article of Nature
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 nonrivalarous (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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