Low interest in antibiotic research & development (R&D) on the part of the pharmaceutical industry over the last two decades has left us with insufficient antibiotic R&D pipelines to meet future demand. Extensively drug-resistant (XDR) and pan drug-resistant (PDR) bacteria are increasing and new antibiotics against such pathogens are urgently needed.

**Reasons for current insufficient pipelines**

- **Expertise:** Many years of neglecting antibiotic discovery diminished the pool of experience as experts were forced to move to other areas.
- **Basic research:** The field was not attractive to funders and academic institutions, which resulted in basic research not getting enough attention.
- **Science:** The scientific challenges are huge. Some of these include penetration through the bacterial cell wall and efflux in Gram-negative bacteria, high protein binding, poor solubility, compounds not amendable to medicinal chemistry, toxicity, high mutation frequency. Toxicity is the most important reason for high early attrition.
- **Clinical development:** Enrolling patients with infections caused by XDR or PDR in randomized controlled trials is challenging, time-consuming and expensive.
- **Economics:** Low return on investment compared with highly profitable medical fields caused pharmaceutical and venture capital companies to abandon the field.

**What can we expect for the next 2-7 years?**

Very few drugs have reached the clinical development stage. Most of those that have reached clinical trials target Gram-positive pathogens – a field with available therapeutic options. The few antibiotics against Gram-negative pathogens in clinical development are improved compounds of known antibiotic classes and are addressing specific resistance mechanisms of this class. They are reducing the rate of resistance in specific species but are usually not solving the problem of XDR or PDR Gram-negative bacteria.

**Current players in antibacterial drug discovery**

- **Universities:** Many academic groups depend on grants. Funding requirements push them into drug discovery and "translational studies". Due to short-term grants, lack of required diverse expertise and most drug discovery activities being incompatible with academic career paths, academic groups would be better equipped to support drug discovery with vital basic research.
- **Publicly funded research institutions:** They may conduct independent research but often have Contract Research Organisation-like functions or are organized as public-private partnerships to support regional economy.
- **Small and medium sized enterprises (SMEs):** Start-ups are often spin-off companies from universities or are acquiring technologies from universities. Antibacterial drug discovery has shifted to small companies that usually have an academic background.
- **Global pharmaceutical companies:** Most of the pharmaceutical companies have abandoned the field, although there is still some interest in antibiotic discovery at Genterch, GSK, Merck, Novartis, Roche and Sanofi-Aventis.

**What can we expect beyond 2020s?**

A few novel antibacterial drugs that would introduce a new class of antibiotics or a new mode of action are in early phases of R&D. As a high attrition rate is inherent in drug discovery, it would require many more drug candidates than that to increase the chance of enough reaching the clinical development stage. Innovation requires reinvigorating basic research on the biology of bacterial targets, as well as research on penetrating the Gram-negative bacterial cell wall and avoiding efflux. Little success in antibacterial drug discovery and innovation has driven many research groups to pursue non-traditional approaches.

These include:

- **Targeted therapies** (traditional antibiotics, antibodies): Active against a single pathogen, especially *Staphylococcus aureus* or *Pseudomonas aeruginosa*
- **Adjunctive therapies:** Examples include drugs targeting virulence factors, biofilm formation, immune system stimulation, modifying the microbiome, and phages. All these approaches still require an active antibiotic for the therapy.
- **Potentiators:** A second drug improves the activity of an antibiotic by inhibiting resistance determinants (e.g. beta-lactamase-inhibitors, efflux pump inhibitors), facilitating the penetration, or changing the sensitivity of the bacterial cell.

Most of these future approaches require a strong tie to diagnostics. Currently, there is no realistic regulatory pathway for adjunctive therapies.

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**Drive-AB** (Driving reinvestment in R&D and responsible antibiotic use) is a collaborative project supported by the European Innovative Medicines Initiative (IMI). DRIVE-AB has been launched to find ways policymakers can stimulate innovation, sustainable use and equitable access to antibiotics to meet public health needs. DRIVE-AB engages with all interested stakeholders during the three-year project to develop, test and implement new economic models for antibiotic research & development and use. DRIVE-AB will present its preliminary findings on June 2, 2016 in Amsterdam, and the final report will be delivered in September 2017.