CONTINUING EDUCATION

NOW IS THE TIME FOR NEW ANTIBIOTICS RESEARCH

Antimicrobial resistance is a serious threat to global health. Prateek Jain, a biopharma insights analyst who co-chaired a session entitled "Superdrugs for superbugs" at the 2019 FIP Congress, gives a preview of the current situation and of new strategies to target the threat that will be discussed.

In the past three decades, the increasing number of bacteria that are acquiring immunity to currently available antibiotics has become a serious threat to global public health. With the rise of resistance to the most widely used treatments and few new antibiotics in development, experts foresee a return to a pre-antibiotics era, with people dying routinely from seemingly minor infections. The number of deaths that will be attributable globally to antimicrobial resistance by 2050 is estimated to be around 10 million per year. Because of pathogens acquiring resistance to almost all available antibiotic classes, even "last-resort" antibiotics have become ineffective in certain reported cases. If we do not act now, the situation will get much worse.

Currently, there is a lack of treatment options for multidrug resistant and extensively drug resistant gram-negative pathogens, which can cause severe or deadly infections that pose a particular threat in nursing homes and hospitals. Moreover, most molecules in the clinical pipeline are modifications of existing classes of antibiotics, thereby offering only short-term solutions. The paradox is that on one hand we want pharmaceutical companies to research and

develop new antibiotics and on the other we do not want to use these new antibiotics; in other words, these products should sit on the shelf until they are really needed by patients.

Challenges

With advances in our understanding of human disease and the discovery of new treatments, it might seem implausible that finding new antibiotics is proving arduous. In reality, the complex set of challenges with this class of medicines has led to there being only a handful of companies active in this area. Barriers include the complexity of the science and clinical trials process, but also the challenging commercial environment.

The science is complex and the clinical trials are lengthy Since the antibiotics development process is complicated and the clinical trials lengthy, the process poses a huge challenge for research, and bringing new antibiotics to market entails substantial investment. Clinical trials for antibiotics require a large sample size and years are needed to establish a new molecule's non-inferiority over the current standard of care. Yet despite the billion-dollar research and years of discovery, these medicines do not — and should not — get used very often.

Antibiotics are not lucrative for investors Developing antibiotics is not as profitable as developing treatments for other therapeutic areas, such as oncology, rare diseases or chronic illnesses. Antibiotics research lost its traction owing to the heavily genericised market, shorter treatment courses, a lower tolerance for high prices, and the best drugs being left on the shelf, reserved for use as a last resort in order to minimise the emergence of drug resistance. This means that pharmaceutical companies do not tend to recover their costs. Consequently, the development of novel therapies has not been a priority for most pharmaceutical companies; major companies have spun off their early/mid stage assets or have a limited presence.

Physicians prefer generics over new brands According to Zeeshan Khan, specialist in internal medicine at Kings College Hospital Dubai, UAE, in a market where a notable percentage of physicians indicate that their prescribing of incrementally better branded

antibiotics is frequently limited by the cost of the agents, investors' return on investment takes a hit, and they are pushed further away from this area of research. Therefore, the burden of demonstrating the value for money of a new antibiotic often falls on its developer. Dr Khan was a speaker at the "Superdrugs for superbugs" session.

Strategies

In order to address the challenges, a number of strategies are now being applied.

Funding and incentives are supporting research projects With new incentives such as the Generating Antibiotic Incentives Now (GAIN) Act in the USA, funding from CARB-X (Combating Antibiotic Resistant Bacteria), and private funds from the Bill & Melinda Gates Foundation, among others, companies that had lost interest in antibiotics research are now pursuing the discovery of new molecular entities. There are other programmes, such as the new technology add-on payment (NTAP) as a mechanism to facilitate market access for eligible antibiotics, which is being granted by the US Centers for Medicare & Medicaid Services. But the industry would like to seek further incentives, such as tax credits.

Regulatory bodies are helping In recent years, the US Food and Drug Administration, in order to incentivise the development of new molecules (particularly for the treatment of antibiotic resistant pathogens), has implemented several measures. One of the measures employed is the LPAD (limited population antibacterial drug) pathway, an approach allowing approval of antibiotics based on smaller, faster clinical trials. Developers can evaluate antibiotics that target serious or life-threatening infections with high unmet need in well-defined populations (e.g., in patients with infections due to carbapenem-resistant Enterobacteriaceae or multidrug-resistant Pseudomonas).

Antimicrobial resistance surveillance The World Health Organization's plan for action on antimicrobial resistance (AMR) includes public-private R&D partnerships and international collaborations to expedite research and innovation. The US Centers for Disease Control has

invested in combating AMR by means of education and improvement of antimicrobial stewardship (AMS) in several countries. Their goal is to cut down inappropriate prescription of antibiotics at doctors' offices by 50% and at hospitals by 20%. An AMS programme is employed to enable the judicial use of antibiotics by improvement and measurement of the four Rs: the Right antibiotic, at the Right dose, at the Right time, for the Right duration. An effective AMS programme can promote positive patient outcomes, contain the development of resistance and reduce health care costs. AMS, by practising the use of correct antibiotics, is an ally to novel drug development. The programme can support the need for more efficacious and pathogen-specific therapies over empirical or trial-and-error practice.

During the 2019 FIP world congress participants learnt much from the session on "Superdrugs for superbugs: Antibiotics of the future". The session comprised presentations on (i) the unmet need attained by recently launched antibiotics in practice, (ii) the strategies being pursued to innovate and collaborate in AMS to use antibiotics effectively, and (iii) new antibiotics under research. A presentation on emerging and non-traditional approaches to antimicrobial drug development briefly reviewed the clinical stage molecules, especially those targeting the gram-negative ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and Enterobacter species), and CDC urgent or WHO critical threat pathogens

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