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Viewpoint

The Antibacterial Research and Development Pipeline Needs Urgent Solutions

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ABSTRACT: Despite ongoing efforts to stimulate investment and research into the development of new antibiotics, the clinical pipeline remains insufficient, in particular to treat critical resistant Gram-negative bacterial infections. The two new reports released by the World Health Organization on the preclinical and clinical antibacterial pipeline show that the current clinical pipeline is very dry and dominated by derivatives of existing classes. There are only 32 antibacterials in the clinical pipeline that target the WHO priority pathogens, of which only 6 fulfill at least 1 of the innovation criteria as defined by the WHO. Further upstream, the preclinical pipeline review identified 252 antibacterial agents in preclinical development of which over one third are nontraditioanl products which highlights the degree of innovation in the preclinical pipeline. The pipeline is also heavily reliant on small- or medium-sized enterprises, which is unsustainable in the long run, and more investment, more players, and a rethinking of the market dynamics is needed. It is encouraging that the pharmaceutical industry, governments, and other concerned stakeholders are currently discussing new ideas.

Fighting antimicrobial resistance requires concerted action on many fronts.[1] The most cost-effective measures are without a doubt investments in better infection prevention and control in hospitals that will minimize hospital-acquired infections and, in parallel, improve the way existing antibiotics are used in hospitals and in the community to delay the inevitable rise of resistance levels. However, even if globally we were to achieve success on this front (and for the time being we are not), then we will also need new antibiotics in the long run to replace those that are becoming increasingly ineffective. The need for increased investment in research and development of new antibacterial treatments has been high on the agendas of the G7, the G20, and many other international fora.[2,3] This has translated into various new initiatives that are starting to show impact populating the clinical and preclinical antibacterial pipelines. The latter can be seen in the review of the preclinical antibacterial pipeline that was published by WHO in January 2020.[4] The report and the respective WHO online database capture 252 antibacterial agents being developed by 145 individual institutions against the 12 antibiotic-resistance bacteria on the WHO priority pathogens list, *Mycobacterium tuberculosis* and *Clostridioides difficile*. From the review, the preclinical antibacterial pipeline seems to be dynamic and scientifically diverse, including research projects from institutions with a wide geographical distribution. Over one-third of the projects are focused on nontraditional products, including many projects on phages and phage-derived products, antivirulence agents, immunomodulators, and microbiome-modifying therapies and potentiators, among others. This is in part due to new funding mechanisms, in particular, BARDA, CARB-X and NOVO REPAIR. However, let us not be overly enthusiastic. We estimate that the publicly available WHO database of the preclinical pipeline reflects more than 80% of the complete preclinical pipeline.[5] (The data at the product level is available and downloadable on the WHO Global Observatory on Health R&D: https://www.who.int/research-observatory/monitoring/processes/antibacterial_products_preclinical/en). Two hundred fifty-two projects may seem high, but the fact that the preclinical pipeline to a large extent consists of nontraditional products for which the regulatory pathway is not yet well established indicates that failure rates are likely to be even higher than average, meaning that at best only a handful of these projects will ever make it to market.

Looking at the clinical antibacterial pipeline is not very encouraging either: the third WHO annual pipeline analysis published in January 2020 contains 50 antibiotics and combinations (with a new therapeutic entity) and 10 biologicals in clinical phases 1 to 3 (Scheme 1).[6] Of these, 32 antibiotics are active against the WHO priority pathogens. The pipeline also includes 12 agents targeting tuberculosis and 6 targeting *C. difficile* infections. Of the 10 biological treatments in clinical development, 6 target *S. aureus*, 2 target *P. aeruginosa*, and 2 target *C. difficile*.

The 10 biological treatments (6 monoclonal antibodies, 2 polyclonal antibodies, and 2 phage-derived endolysins) are all developed as preemptive or adjunctive treatments, so while adding to the portfolio of options, they will be administered on

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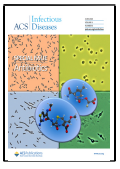

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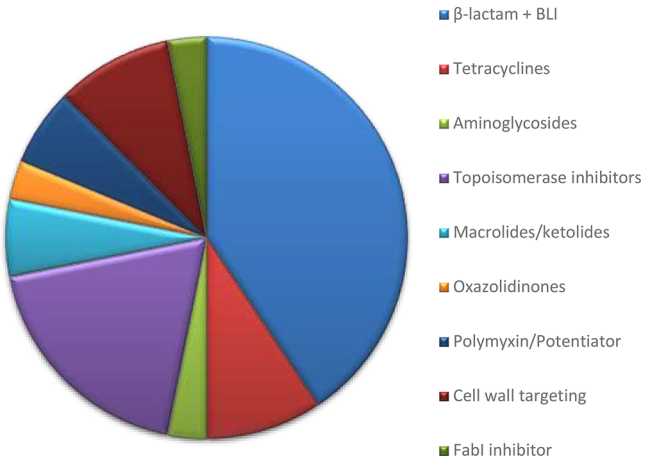
Scheme 1. Clinical Antibacterial Pipeline



top of traditional antibiotics or used to depopulate patients to prevent further dissemination and infections. They are thus unlikely to replace therapeutic antibiotics. It also remains to be seen what the clinical uptake of these agents will be.

The reality is that both the preclinical and the clinical antibacterial pipelines are driven by small- or medium-sized enterprises (SMEs). Major pharmaceutical companies are continuing to exit the field, and the AMR Industry Alliance reports that private investment is likely to continue to decline from an already very low level.[7] This is only partially compensated for by the funding provided by BARDA and GARDP, a foundation that was set up by WHO and the Drugs for Neglected Diseases initiative (DNDi) to develop new missing antibacterial treatments, the NOVO REPAIR Impact Fund, and other public funding initiatives.

A comparison of the antibacterial pipeline to the more than 5700 clinical development projects targeting different forms of cancer[8] shows clearly that the 60 products constitute a very limited pipeline, particularly considering the average success rate of about 14%. However, it is even more worrying that of the 32 antibacterials that target the WHO priority pathogens, only 6 of these agents fulfill at least 1 of the innovation criteria as defined by the WHO expert group (absence of known cross resistance, new class, new target; new mode of action). Only two of these are active against the critical MDR Gram-negative bacteria: two boronate β-lactamase inhibitors (taniborbactam + cefepime and VNRX-7145 + ceftibuten) in phases 3 and 1, respectively, targeting CRE. The additional four innovative treatments constitute two new topoisomerase inhibitors (zoliflodacin and gepotidacin) in phase 3, a new FabI inhibitor (afabicin) in phase 2, and a novel FtsZ inhibitor (TXA709) in phase 1.

Most of the agents in development are in fact derivatives of existing classes. Forty percent of the pipeline targeting WHO priority pathogens consists of additional β-lactam and β-lactamase inhibitor combinations, with a major gap in activity against metallo-β-lactamase (MBL) producers. From the perspective of a drug developer, the advantage of following this strategy is that they can rely on a well-characterized, validated clinical pathway to market. Very often first in class also does not equal best in class, meaning that optimized derivatives can have better safety or efficacy profiles. On the downside, some level of cross-resistance and fast adaptation of bacterial populations can be expected. The state of the pipeline reflects the fact that finding novel compounds with new binding sites and new modes of action is very difficult and risky. Finding compounds with more than one binding site to avoid single-step resistance, which are able to penetrate the outer layer of Gram-negative cell walls and avoid being pumped out immediately by efflux pumps, is scientifically very challenging on top of the fact that these agents need to kill bacteria without being (too) toxic at the required concentration.

In light of the average development time from phase 1 until approval of approximately 7 years and the average progression rates, the current clinical pipeline could lead to approximately 11 new antibiotic approvals in the next 5 years, but the majority of those would be agents of existing classes. However, the current economic environment for antibacterial research and development unfortunately makes it likely that fewer agents than that will make it to market approval. Overall, the clinical pipeline remains insufficient to tackle the challenge of increasing emergence and spread of antibiotic resistance. It fails to address the problem of extensively or pan-drug-resistant Gram-negative bacteria, in particular, carbapenem-resistant *A. baumannii* and *P. aeruginosa*.

Since July 1, 2017, eight new antibiotics that have been approved by the FDA and EMA (delafloxacin, vaborbactam + meropenem, eravacycline, omadacycline, relebactam + imipenem/cilastatin, lefamulin, plazomicin, and pretomanid). Of these, only two, vaborbactam + Meropenem and lefamulin, represent a new chemical class. All the others are derivatives of known classes such as the two tetracyclines eravacycline and omadacycline.

The common challenge is that their clinical advantages over existing treatment regimens are not clearly established and not underpinned by clinical trial outcomes when noninferiority trials show only that new treatments equal the standard of care. How can you convince clinicians of the potential value of these drugs in this situation if, in addition, the new products are more expensive than existing (generic) antibiotics? It is evident that in the current market environment most of them will struggle to find a place in the treatment landscape and in treatment guidelines and formularies. Consequently, small companies will find it difficult to survive economically. The bankruptcy of Achaogen, the company that marketed plazomicin, and the recent Chapter 11 bankruptcy filing of Melinta, which had four antibiotics on the market including delafloxacin and meropenem-vaborbactam, are telling examples.

It is clear that more public engagement is needed and that it cannot be sustainable if reimbursement schemes and payers do not remunerate new, more effective, and innovative treatments that can overcome existing resistance mechanisms. It is, however, too easy to just ask for more money and higher prices; resources also have to be used more efficiently. Existing resources flowing into research and development and any new pull mechanism should focus only on those agents in the pipeline that are innovative and/or add significant clinical value and consequently have a chance to survive on the market. The major pharmaceutical companies also need to reengage and stop freeriding on public investment. It is encouraging that the industry, governments, and other concerned stakeholders are currently discussing new ideas, and it is hoped that we will see major new contributions over the coming years that allow new antibacterial treatments that have significant added clinical value to survive on the market.

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In order to support these efforts, the AMR division of the WHO will continue to provide guidance and endeavor to coordinate efforts that tackle the current R&D gap.[9] WHO will maintain the global priority pathogen list of antibiotic-resistant bacteria to guide research and development investments and will continue to track the antibacterial preclinical and clinical development pipeline against priority pathogens and work closely with the Global Antimicrobial Resistance Research and Development Hub. WHO will also publish target product profiles that can assist companies and foundations in developing treatments that are adding significant public health value. WHO will continue to support GARDP as an independent global research and development entity as well as other existing and future research and development initiatives to ensure that these efforts focus on public health needs.

In addition, the AMR division works closely with governments to support the implementation of national action plans on antimicrobial resistance. This includes strengthening multisectoral governance, advocacy and awareness initiatives, and strengthening national surveillance systems. WHO also supports national and hospital efforts to monitor the consumption and use of existing antibiotics and provide guidance on the implementation of antimicrobial stewardship programs linked to infection prevention and control measures. Only through a holistic One Health approach can antimicrobial resistance be contained.

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Notes

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