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Review

Antibiotic innovation for future public health needs

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ABSTRACT

Background: The public health threat of antibiotic resistance has gained attention at the highest political levels globally, and recommendations on how to respond are being considered for implementation. Among the recommended responses being explored for their feasibility is the introduction of economic incentives to promote research and development of new antibiotics. There is broad agreement that public investment should stimulate innovation and be linked to policies promoting sustainable and equitable access to antibiotics. Though commonly used, the term 'innovation' is not based on a common understanding.

Aims: This article aims to initiate discussion on the meaning of 'innovation' in this context.

Sources: Literature and expert opinion.

Content: As the definition of a novel class (novel scaffold, novel pharmacophore), a novel target (novel binding site) and a novel mode of action—the three traditional criteria for 'innovation' in this context—may be confounded by the complexities of antibacterial drug discovery, a biological and outcome-oriented definition of innovation is presented to initiate discussion. Such an expanded definition of innovation in this specific context is based on the overarching requirement that a drug not be affected by cross-resistance to existing drugs in the organisms and indications for which it is intended to be used, and that it have low potential for high-frequency, high-level single-step resistance if intended as a single drug therapy.

Implications: Policy makers, public health authorities and funders could use such a comprehensive definition of innovation to prioritize where publicly funded incentives should be applied.

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Introduction

Recent national and international high-level policy initiatives highlight the growing awareness of the increasing bacterial resistance to current antibiotics. This public health threat is receiving significant political attention. Multiple concerted actions concerning human and animal health, as well as pharmaceutical production and environmental sector policies, are recommended and need to be implemented. Considered urgent are: robust surveillance globally, responsible and optimized use of existing antibiotics, better infection control, increased research activities in the antibacterial field, restricting antibiotic use in animals, limiting antibiotic pollution of the environment, and economic incentives to stimulate and incentivize research, discovery and development of new antibacterial drugs to fill the neglected pipelines [1]. Such incentives will require substantial public investment.

There is broad agreement that public investment should stimulate innovation and be linked to policies that promote sustainable and equitable access to antibiotics. The critically needed innovation in antibacterial drug discovery is expected to counteract the increasing trend of multidrug-resistant (MDR), extensively drug-resistant (XDR) and even pan-drug-resistant (PDR) pathogens, especially Gram-negative bacteria, as outlined in the recently published WHO priority pathogen list for research and development [2]. The often-used term 'innovation' has been used in a broad and indiscriminate way and has lost its specific meaning. If policy initiatives are implemented, the requirement for innovativeness as a prioritization tool needs to be discussed and defined. Europe's Innovative Medicines Initiative has financed a project, DRIVE-AB (i.e. Driving reinvestment in research and development for antibiotics and advocating their responsible use, www.drive-ab.eu), to

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provide scientific evidence for new reward models and to test the feasibility of their implementation [3]. If stimulating innovation in antibacterial drug discovery and development is to be a major factor of economic incentives, there is a need to reach a workable definition of 'innovation' and this is vital for matching public investment with future public health needs. As priority-setting requires a broad discussion and consensus considering the complexities of discovery, this article aims to initiate discussion on the meaning of 'innovation' in this context. The discussion is focused on conventional, directly acting, antibacterial drugs that have not previously been used in human or veterinary medicine worldwide. Other approaches, such as preventive strategies, immunomodulatory, adjunctive therapies that target virulence or resistance gene regulators, monoclonal antibodies, topical drugs and antibiotics against *Mycobacterium tuberculosis*, are not covered in this article.

Current clinical antibiotic pipelines and short-term perspective

Nearly all antibiotic classes being used today were discovered during the Golden Age of antibiotic innovation, which extended from the 1940s to the 1960s [4]. Numerous modifications of the initial discoveries improved their utility and extended the life of these antibiotic classes. Efforts to modify the chemical structures were focused on circumventing emerging class-specific target-based or drug-modifying resistance mechanisms or on lower affinity for efflux pumps, as well as improving pharmacokinetics and extending the activity spectrum. The β-lactam class exemplifies best the success of this strategy. Methicillin and the isoxazolylpenicillins (staphylococcal penicillins) were introduced following the rising frequency of resistance to penicillin due to the production of penicillinases. Third-generation cephalosporins were introduced to solve the problem of β-lactamases like TEM, ceftriaxone enabled a once-a-day dosing due to its extended half-life, and ceftazidime and ceftolozane included *Pseudomonas aeruginosa* in their Gram-negative spectrum. Despite these successes, the ever-increasing range of β-lactamases required an alternative approach. The concept of a protector drug was born—the combination of vulnerable β-lactams with a β-lactamase inhibitor. After the great success of the combinations amoxicillin/clavulanic acid and piperacillin/tazobactam this concept has been revived and is still one direction of research and development efforts (Fig. 1).

The last years have seen a resurgence of discovery and development activities, mostly in small companies, often with the concept of modifying compounds in existing classes using cutting-edge methods to fix specific class-related resistance problems [5]. Basing a drug discovery project on a well-validated lead carries less risk than starting from scratch. Most antibiotics in clinical development are modifications of classes that have been extensively used in human or animal health (Fig. 1). The downside of modifying known chemical structures is that, usually, multiple mechanisms of resistance exist for every class of antibiotics and not all relevant resistance mechanisms can be addressed by chemical modification. Some cross-resistance to existing antibiotics usually remains. Hence, due to the selection of less common resistance mechanisms or the appearance of previously unknown ones [6,7] modifications within existing antibiotic classes may only buy some time [8]. In the long run, innovation is needed to find novel drugs without pre-existing cross-resistance that can be further improved in future efforts.

How to define innovation?

Although there is general agreement that we need 'innovation' in antibiotic research and development to respond now to anticipated future medical needs, the lack of clarity around 'innovation' itself presents a challenge. The word innovation is one of the most commonly used terms in national and international initiatives that address the antibiotic resistance problem, but what is meant by 'innovation' or how different stakeholders interpret the term is

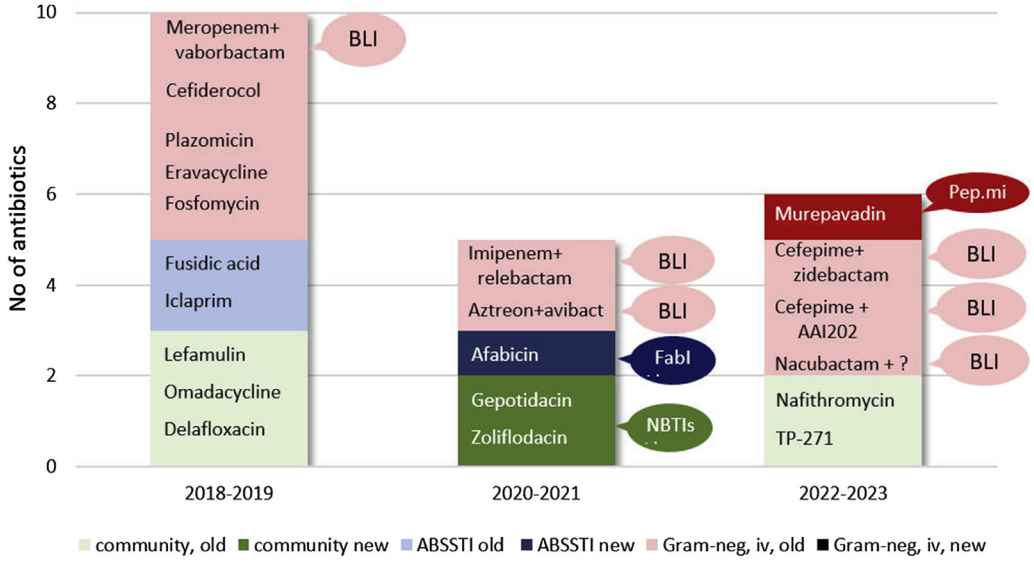

Fig. 1. Potential US Food and Drug Administration approval of selected new antibiotics (systemic small molecules) according to their perceived innovation potential; attrition rates apply. Definitions: old: modifications of currently used chemical scaffolds (human or animal health); new: new chemical scaffolds; community: antibiotics targeted at community-acquired infections, usually focused on Gram-positive bacteria but also include respiratory pathogens and *Neisseria gonorrhoeae*, oral formulations available; NBTIs: Novel Bacterial type II Topoisomerase Inhibitors; ABSSTI: acute bacterial skin and soft tissue infections, usually focused on Gram-positive bacteria; BLI: β-lactamase inhibitor (vaborbactam, relebactam, avibactam, zidebactam, nacubactam, AAI202); aztreon + avibact: aztreonam + avibactam; Pep.mi: Peptidomimetic, murepavadin for *Pseudomonas aeruginosa*; FabI: FabI inhibitor specific for staphylococci; cephalosporins (cefiderocol, novel transport mechanism into the bacterial cell, potential for cross-resistance not fully elucidated); aminoglycoside (plazomicin); fluoroquinolone (delafloxacin (Approved by FDA in June 2017); tetracycline (eravacycline, omadacycline, TP-271); pleuromutilin (lefamulin); macrolide/ketolide (nafithromycin); registered in Europe: fosfomycin, fusidic acid.