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Paradoxes of the antibiotic pipeline

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The escalating challenge of antimicrobial resistance (AMR) has led to a surge of global research and policy discourse on refilling an empty antibiotic pipeline. The empty pipeline metaphor is, however, wrought with paradoxes. Drawing on critical social sciences and humanities research on pharmaceutical innovation, this comment article presents five of the key paradoxes that structure contemporary innovation discourse: Was the so-called "Golden Age" of antibiotics really golden? Was rational drug design truly *rational* in terms of antibiotic development? Was the antibiotic pipeline really built on a foundation of scientific breakthroughs by an elite group of (male) inventors? How can antibiotics, powerful symbols of industrial power, be considered as market failures? How could the crisis of antibiotics become the golden hour of their policing? Rather than dissect each paradox, the article aims to complicate standard problem diagnoses and encourage creative new conceptualizations of inclusive antimicrobial innovation.

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Antimicrobials hold a seemingly paradoxical place in our present. Such medicines are tremendously useful, be it in healthcare settings with the treatment or control of infections (Podolsky, 2015) or in food production (Kirchhelle, 2020). However, since the 1930s, mass production and use of antimicrobials have both selected for and amplified antimicrobial resistance (AMR) (Landecker, 2015). The challenge lies in simultaneously regulating the use of antibiotics[1] and ensuring a continuous supply of new options to control resistance. In 2020, the Wellcome Trust asked a seemingly simple question: "Why is it so hard to develop new antibiotics?" (Wellcome, 2020). Like many organizations and researchers before, it categorized antibiotic development in the form of a pipeline, echoing linear narratives of innovation through production that have become staples in the late 20th and early 21st centuries. But this narrative is one that fractures under a more studied gaze, as its linearity is one filled with turns and offshoots. Rather than a cohesive and simple metaphor that easily yields itself to reality, the concept of an antibiotic pipeline is one filled with paradoxical assumptions and uncertainties requiring further research and discussion. As members of the DryAP project (Research Council of Norway, FRIPRO 314490) our work has been devoted to bringing historical explanations to the current policy debates on the empty pipeline, as well as analyzing the discussions of antimicrobials used to treat bacterial infections. This article seeks to address these other than linear materials and broaden the discussion on how these perspectives have been underutilized or unfulfilled within the concept of the empty pipeline narrative, often put forward within the field of antimicrobials. In one such vein, lies the deconstruction of the antibiotic pipeline as a narrative tool by pointing out the paradoxes that emerge from this narration. While the pipeline is a powerful metaphor, we argue that its underlying assumptions are often problematic as it suggests that a lack of new antibiotics is the main problem when it comes to imagining the future of antibiotics. Instead of staying within the semantic confines of the metaphor, the history behind it needs to be thoroughly unpacked within historical and policy-driven research.

In the following, we engage with five of the key paradoxes embedded within the antibiotic pipeline discourse. First: the notion of a golden age of antibiotic innovation that was far more fragmented than current narratives imply, second: the push for rational drug development or design that often underplayed the chance-based dimensions of antimicrobial innovation, third: the heroic narratives of (male) innovators driving development that stands in contrast to the highly diverse workforce driving both laboratory work and industrial production, fourth: the conceptualization of antimicrobials as 'market failures' even though the drugs themselves remained profitable as generics, and fifth: the incongruities behind funding for non-innovation related options within the AMR space. Rather than attempting to resolve these paradoxes, we intend this article to serve as a primer for further investigations, and as a call for readers to apply a similar methodological conception while reading the papers within this field.

Paradox one: a golden age of antibiotics

Although the period between the 1930s and 1970s is often framed as a golden age of innovation, which needs to be revived, a closer look reveals significant tensions within mid-20th-century antibiotic innovation. The 1970s were fraught with three underlying problems that came to have effect when, later on, this pipeline was perceived as being empty: Firstly, despite being market successes, many early antibiotics were chance discoveries rather than the product of systematic screening (Leisner, 2020). In the 1970s, disenchantment with costly screening programs was growing in industries, which were also eyeing at faster returns (Daemmirch, 2004). Suggestions for how to economize this process (through automatization) or get rid of it (through Rational Drug Development) became a defining feature of the empty pipeline thereafter but failed to resolve problems (Bud, 2007; Santesmases, 2018). Secondly, the pharmaceutical industry has developed a tendency to market solutions to its self-created problems as new medicines. In the 1960s and 1970s, AMR and hospital infections, and increasing resistance to antimicrobials were considered attractive markets. Rather than focusing innovation on sustainable forms of microbial management, the industry went on a collision course with public health (Gradmann, 2013, 2016). Thirdly, in the pipeline itself, market research gained influence at the expense of innovation in molecular drug development. Growth based on generics, new indications for existing drugs, and repurposing rather than new molecules became a scenario for the future (Gaudillière, Ulrike, 2015).

Paradox two: rational drug development or design

The reduction of mass screening seen in the 1970s coincided with the rise of interest in Rational Drug Development (or Rational Drug Design), which was heralded as a way of ensuring that the sometimes prohibitively expensive research into creating a new drug was targeted at a compound that had the highest chances of success. By specifically targeting molecular structures already known to have antimicrobial effects, pharmaceutical companies hoped to minimize risks in developing new drugs and avoid wasting resources on ineffective compounds (Adam, 2005; Mahapatra and Karuppasamy, 2022). One successful case of this methodology includes linezolid, a novo synthetic drug that targets vancomycin-resistant bacteria (Monserrat-Martinez et al., 2019). However, it is one of the few accomplishments this system has seen when it comes to antimicrobials. Throughout the 1980s and 1990s, the high-throughput screening (HTS) method used to identify possible targets was incapable of breaching the cellular membrane(s) (especially in the cases of Gram-negative bacteria), leading to unclear results (Gajdács, 2019). By the early 2000s, a growing number of researchers began to express frustration about calls for rational drug design and argued that there remained insufficient knowledge about how bacterial structures worked in the first place (Lewis, 2013). While on the surface, the concept of direct targeting seemed logical, its lack of appropriate components to allow for appropriate screening methodology yielded few results, creating a paradox where the most logical step forward could be stymied by its own parameters (Silver, 2011).

Paradox three: the inhabitants and agents of the pipeline

This "rational approach" paradox is not the sole one that has dominated historical accounts of the experimental search for new antibiotics. Conventional narratives of antibiotics have usually been constructed around a small number of male participants who held leading positions. However, by following the trajectory of gender from the early identification of antibiotic activity and AMR to antimicrobial genetics of those resistances, it quickly becomes apparent that women played an essential role in driving innovation in the fields of culturing techniques, identifying active molecules, and optimizing the biochemical production processes (Santesmases, 2014; 2018). This recurring lack of historical recognition of women's contributions and the dismissal of the collective construction of knowledge is rooted in the same hierarchical system that structures the laboratory from within (Latour and Woolgar, 1979). In the different distribution of the daily laboratory work and the experimental practices, women were traditionally the ones observing, identifying, and isolating

microbes for drug manufacturing. Disregarding the social and intersectional dynamics inside the antibiotic pipeline—and its presence in the scientific knowledge produced and the regulations informed by it—is problematic as it leads to simplistic explanations of the innovation process that ends up reproducing them. A critical historical reconstruction that acknowledges the multiplicity and diversity of agents, and where they are hierarchically situated, is necessary to more accurately understand the complexity of the antibiotic pipeline: research priorities, innovation decision-making, and even how infections and microbes are approached in clinical practice and how antibiotic resistance is managed and regulated transnationally in the fear of an empty pipeline (Maccaro, 2021; Brives et al., 2021; Hinchliffe, 2022).

Paradox four: antibiotics as market failures

A similar paradox involves the often uncritically accepted narrative that antibiotics have become unprofitable 'market failures' requiring increased public intervention due to their inability to compete with more profitable other products. This narrative ignores the fundamental structural shifts within the pharmaceutical industry and university sector that have taken place since the 1980s, as well as the fact that most antimicrobials remained profitable—making market expectations rather than the products themselves the problem. The pharmaceutical industrial system that grew through the expansion and integration of research and development (R&D) efforts for the successful marketing of antibiotics in the 1950s started disintegrating in the 1980s. Pharmaceutical companies shifted to new managerial doctrines that focused on maximizing shareholder value, and the prioritization of investment in a more limited number of highly profitable drugs and trimmed in-house development costs via a program of mergers and acquisitions and increasingly outsourced high-risk early-stage innovation to biotech start-ups (Sunder Rajan, 2017; Timmermann et al., 2019; Dutfield, 2020; Roy, 2023). The financialized managerial focus on short-cycle value generation was mirrored in academia, where a new echelon of administrators used changing intellectual property laws to implement rigorous patenting regimes and encourage "spinning out" technologies via start-up companies. While the 1990s saw significant breakthroughs in the development of recombinant DNA of new antiviral drugs and cancer treatments, relatively lower profit margins for antimicrobials and misplaced hopes in targeted drug innovation led to underinvestment. Rather than being market failures, one could also say that antimicrobials were failed by the markets and an increasingly financialized conceptualization of private and public innovation (Roy, 2023; Åkerfeldt and Svensson, 2023).

Paradox five: rise of non-innovation related policy, lack of funding

The final paradox in this paper looks at how the emphasis on drug development often drowns out additional recommendations on managing AMR globally. While there is a clear need for new drugs, recommendations within reports, such as the 2015 WHO's Global Action Plan on Antimicrobial Resistance, include infection prevention and control (IPC) and access programs that are continually underfunded. The need for both has long been discussed, as has the inclination for governments and industry to search for drugs as a solution to disease over IPC methods (Packard, 2016). In this sense, the AMR field imitates many of the global health concerns that came before it. However, the empty pipeline phenomenon presents the possibility of a reinvigoration of IPC efforts as the notion of no new drugs circulates attention back onto calls for improved water, sanitation, hygiene, and living conditions, as well as improved access to current drugs that may still be efficacious in communities where they were not previously available (Aagaard et al., 2021). The improvement of infection prevention and control methods could offer a far larger health benefit to nations worldwide (Ackers et al., 2020), and highlight access inequities and inequalities that persist as a global challenge. In this case, the empty pipeline narrative and its implications for AMR may lead to improved health outcomes globally as these policies continue to take shape.

Conclusion

While the gloomy image of a future without antibiotics first sparked the notion of an empty drug pipeline in the 1990s (Overton et al., 2021), the persistent presence of the metaphor is contributing to an oversimplification of the factors facing the antibiotic development space. It perpetuates a fixation with technological solutions, replacing an older antibiotic utopia with a dystopian vision of their absence as the main problem of antibiotic policies. It creates a picture of a dichotomy in which the problem could be summarized in an anachronistic fashion by stating that "we are in an arms race against microbes" (Else, 2019)—and calling for drug development as the answer. The assembled paradoxes discussed briefly in this article are markers of how this pipeline cannot be condensed to a linear path of innovation to production but must be considered in how it has been constructed and used historically and in historicizing its impact. These paradoxes draw attention to the need for more questions to be asked, and more alternative perspectives to be applied to the pipeline narrative as a whole. Now, and in the future, more work is needed to fully examine the paradoxes surrounding this framework and to further emphasize the understanding that the antimicrobial pipeline is more complex than the metaphor suggests.

Data availability

Data sharing is not applicable to this research as no data were generated or analyzed.

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Note

1 Antibiotics are substances that specifically target bacteria. They are a type of antimicrobials, which refer to any substance that targets any type of microbe, including viruses. However, the terms antibiotics and antimicrobials are often used interchangeably, and this article will use the terms in this way throughout.

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Competing interests

Mirza Alas Portillo, Isabel M. Gómez Rodríguez, Christoph Gradmann, and Erin L. Paterson were collection guest editors for this journal at the time of acceptance for publication. The manuscript was assessed in line with the journal's standard editorial processes, including its policy on competing interests. The other authors declare no other conflicts or competing interests. All authors received funding from the Norwegian Research Council (FRIPRO 314490).

Ethical approval

Ethical approval was not required as the study did not involve human participants.

Informed consent

Informed consent was not required as the study did not involve human participants.

Additional information

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