

ANTIMICROBIAL RESISTANCE

Navigating obstacles in R&D and commercialization

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ANTIMICROBIAL RESISTANCE: NAVIGATING OBSTACLES IN R&D AND COMMERCIALIZATION

The lack of innovation surrounding the development of new antibiotics has resulted in an alarming situation, given the rising threat of antimicrobial resistance (AMR).

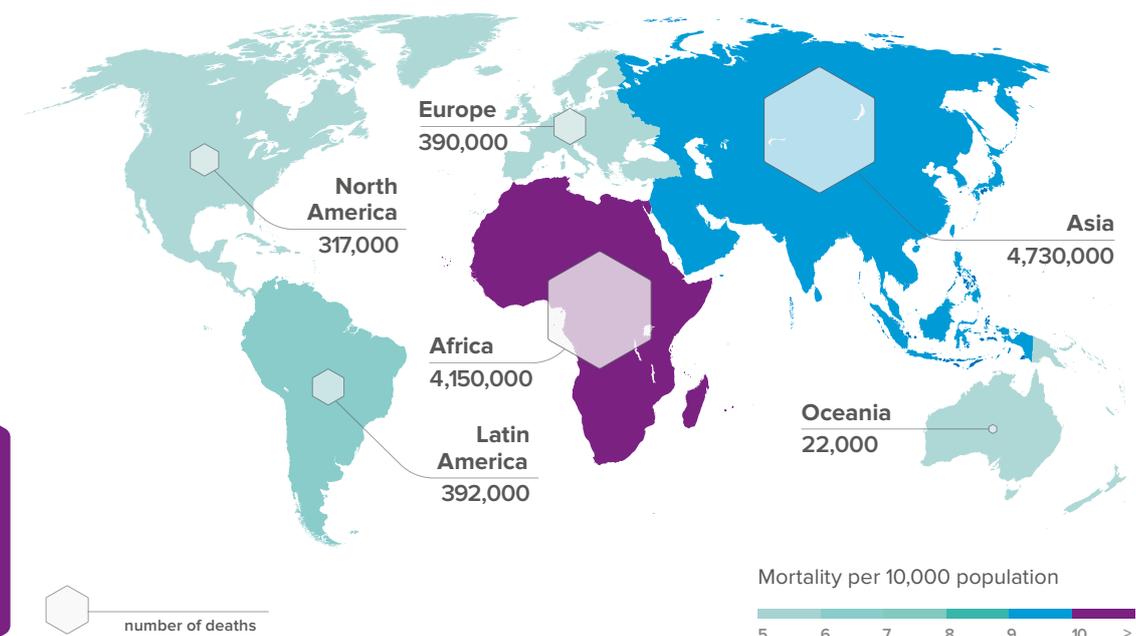
As a result, there is no single or straightforward way to combat AMR, nor to galvanize development of novel antibiotics. Although some positive measures have been introduced, further - and larger scale - action is needed.

Since the initial era of discovery in the mid-20th century, there has been a lackluster level of innovation in the antibiotics field, and today there are few novel antibiotic classes in development despite the urgency of medical need.

The lagging antimicrobial innovation has certainly made its impact felt. Estimates suggest that resistant infections underlie nearly 700,000 global deaths each year - a figure projected by some to rise to 10 million each year by 2050.¹

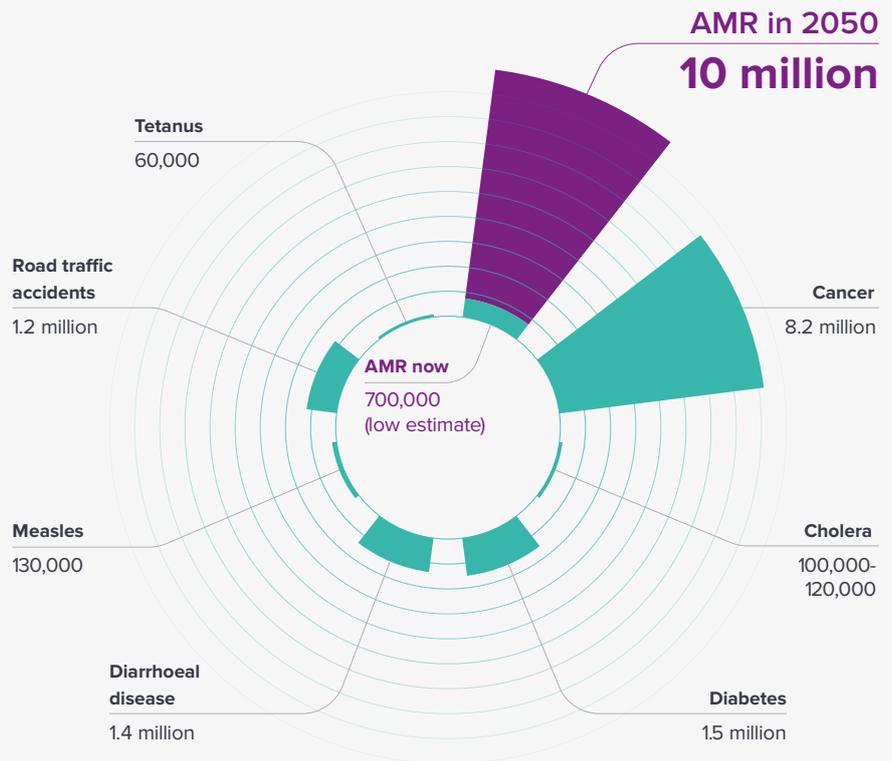
New resistance mechanisms are emerging and spreading globally, threatening our ability to treat common infectious diseases, resulting in prolonged illness, disability, and death. Each year in the US alone, the CDC reports that at least 2 million people contract an antibiotic-resistant infection, with an estimated annual attributable death toll of 23,000.²

Deaths attributable to AMR every year by 2050



Compounding the issue is the frequent and inappropriate use of antimicrobial therapy, causing even more rapid development of drug resistance. Combine this with the global market failure in antibiotic development and the result is a truly daunting public health challenge.

But under the current market model, antibiotic development is not a profitable undertaking, and only a handful of major drug manufacturers presently maintain R&D pipelines.¹ For complex financial, clinical, and regulatory reasons surrounding antimicrobial R&D, the pharmaceutical industry has lost the incentive to innovate.



Source: <https://amr-review.org>



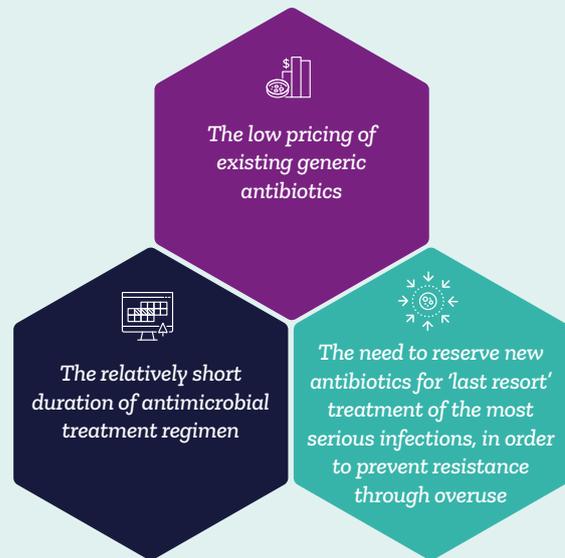
Why aren't drug companies stepping up?

The failure in the antimicrobial market is rooted in several causes.

Among the causes are those outlined in figure 1. To put it simply - not only is the antimicrobial market challenging and expensive, but the financial rewards for AMR innovation can be low and unpredictable. Many are divesting or selling anti-infective assets and portfolios or filing for bankruptcy altogether.¹

Pharmaceutical stewardship frameworks in clinical practice have sought to counter the growing problem of antibiotic resistance and drug misuse. By optimizing treatment and restricting the inappropriate use of antimicrobials, they seek to preserve the life of any given anti-infective molecule. With these new stewardship initiatives, the use of novel and new antibiotics have been reserved for later lines of therapy in order to preserve the efficacy and slow the rate of resistance to these agents. As a result, manufacturers are seeing a low return on investment for their novel agents.³

Figure 1 - failures in the antimicrobial market



Antibiotic reimbursement - an unsuccessful stimulus

Currently, Medicare and private buyers reimburse antibiotics as part of a bundled payment for in-patient treatments under Diagnosis Related Groups (DRG) payments.⁴

Under a DRG, a hospital receives a fixed amount (around \$15-20k per patient), which covers all ancillary costs including drugs (excluding physician costs). But the higher the cost of those drugs, the less financially viable it is for the hospital to prescribe them.

For instance, this flawed reimbursement model means that few hospitals are stocking AVYCAZ. A novel antibiotic manufactured by Allergan, it has been proven to be a superior antibiotic with lower mortality compared to generics. AVYCAZ costs approximately \$8,000 for a 10-day course, with no generic currently on the market. The drug was approved in 2015, with analyst projections estimating a yield of \$360m in 2024. Today, GlobalData places that figure at \$140m in 2024, with actual 2018 global sales only reaching \$94.6m, according to Allergan's fourth quarter report for 2018.⁵



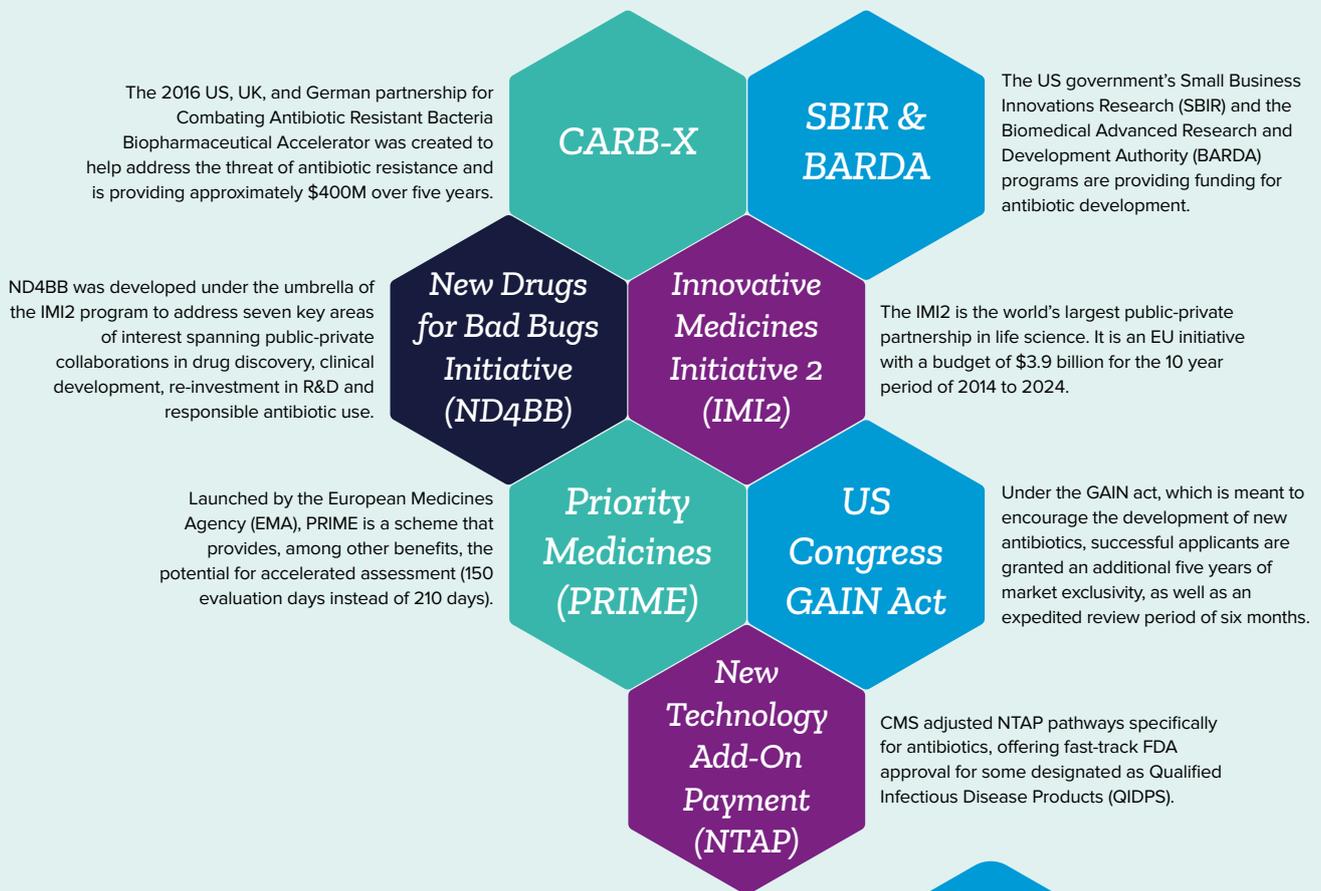
A turning tide?

However, a shift in thinking is underway as the public health implications of a drying pipeline of new antibiotics have sunk in.

Bodies including the WHO, the FDA and the European Medicines Agency all acknowledge that novel clinical and regulatory approaches are now needed to incentivize innovation, with each taking steps to open such development pathways.

The US, EU and UK are all exploring meaningful ways to intervene,⁶ with increased funding and innovative regulatory pathway incentives, including those outlined in Figure 2 below.

Figure 2. Incentivizing antibiotic R&D



"Not only is the antimicrobial market challenging and expensive, but the financial rewards for AMR innovation can be low and unpredictable."

Regulators, policy-makers, and manufacturers have all recognized what is at stake with the growing threat of AMR and have begun working together to fashion these approaches to remove regulatory barriers and re-energize research.

Outside of the aforementioned partnerships and regulatory pathways, perhaps the most intriguing new incentivization technique exists outside the U.S. The UK is leading the way by piloting a 'Delinked' Payment Model. The government announced in 2019 that the National Health Service would test a 'subscription-style model' that pays pharma companies upfront for access to antibiotics, based on their usefulness to the NHS.⁷ That would guarantee an income from a successfully developed drug even if it were held in reserve.

A payment model that delinks profits from the volume of antibiotics sold and pays companies for the public health value of a new antibiotic is the type of 'pull' incentive that antibiotic development advocates believe is necessary to get more new antibiotics into R&D.⁷

The NHS will experiment with buying an antibiotic 'service' from drug companies, paying them up-front for access to effective antibiotics.⁸ In this way, payment for newly developed antibiotics will not be based on the volume of drugs sold, but will focus instead on the tenets of stewardship to re-emphasize their public health value while still promoting innovation.

While the outcomes of the delinked model are yet to be seen, it is clear that addressing the market failure requires wide-reaching global action that so far is lacking. No path yet exists for implementation of a delinkage model in the US, where market structures more attuned to the American healthcare system have been viewed more favorably.



References

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To be determined

In light of the underwhelming pipeline for new antibiotics and the growing threat that antimicrobial resistance places on public health, it is clear that a new global business model for antibiotic R&D is an impending necessity.

The current and unsustainable status quo pits conflicting forces against one another - between the upfront basic research challenges, the growing calls for stewardship, the availability of low cost and effective generics, and the inappropriate use of antibiotics, the proliferation of drug resistance is directly at odds with the commercialization potential of novel therapies.

Small and large drug manufacturers as well as public and private payers, public health officials, economists, and regulatory agents must come together to evaluate major proposed incentive models and assess their effectiveness in encouraging antibiotic R&D activities.



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