IFPMA

From resistance to resilience:
What could the future antibiotic pipeline look like?

Contents

The challenge of resistance

The World Health Organization (WHO) has identified antimicrobial resistance (AMR) as one of the biggest global health threats facing humanity.[1] Annually, AMR is directly responsible for approximately 1.2 million deaths around the world and is associated with approximately 5 million deaths.[2]

As bacteria evolve and become resistant to existing antibiotics, the challenge is growing. Some estimates suggest that without reversing this trend, AMR could lead to 10 million deaths a year by 2050, significant disruption to common surgical and medical interventions and a further 24 million people driven into extreme poverty.[3] It is estimated to lead to a global annual GDP loss of between 1.1% and 3.8% by 2050, with an annual shortfall of up to USD 3.4 trillion by 2030.[4]

To avoid this, we need to ensure that we have a continuous pipeline that delivers new, innovative antibiotics to treat patients with infections that have become resistant to existing antibiotics. These antibiotics should be used carefully and should be available to patients wherever in the world they live.

Annually, AMR is directly responsible for approximately

1.2m

deaths around the world and is associated with approximately 5 million deaths

AMR could lead to

10m

deaths globally a year by 2050

Left unchecked, AMR could lead to an annual global economic shortfall of up to USD

3.4tr

by 2030

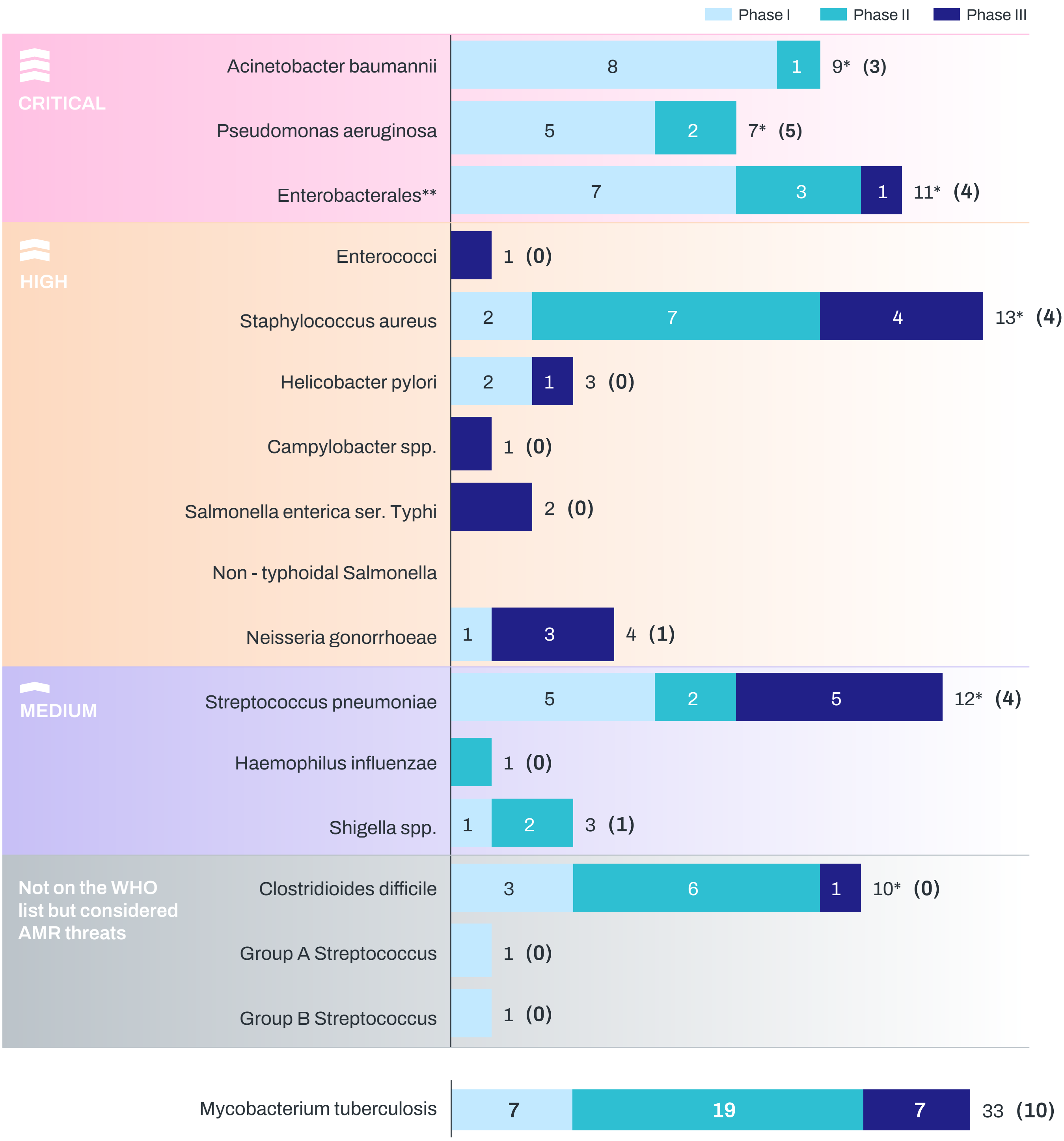
The current antibiotic pipeline is not sufficient to protect against increasing resistance

We reviewed the antibiotic pipeline data against bacterial pathogens identified by WHO as of the greatest concern,[5] and a further three pathogens identified by other public health agencies.[6] We recognize that tuberculosis (TB) – and resistant TB – remain a significant health challenge, but do not include it in this analysis. We find that:

- There have been only 10 new antibiotics or combinations approved by stringent regulatory authorities[7] between 2017 and 2023, only 2 of which are defined as innovative by the WHO.[8] None are considered to constitute a new class of antibiotics.
- There is currently just one antibiotic candidate in Phase III clinical trials across the four bacterial pathogens defined as a critical priority by WHO.
- Just two of the seven high-priority pathogens have innovative candidate antibiotics in development, with five having three or fewer candidates at any stage of clinical development.
- There is consensus from the WHO[9] and many other experts that the pipeline is not sufficient to meet the demands of increasing resistance in the priority pathogens.

In order to strengthen the pipeline of new antibiotics to keep ahead of the evolving bacteria, we need to ensure the right incentives are in place to support the investment needed to develop new products and bring them to patients. **New analysis[10] contained in this paper demonstrates the importance of such incentives in shoring up the future pipeline of antibiotics.**

Number of candidates in clinical development active against priority bacteria, by WHO priority category



* Pathogen has at least one asset in the pipeline supported by the AMR Action Fund

** Enterobacterales encompasses both carbapenem-resistant- and ESBL-producing Enterobacterales, which includes Escherichia coli and Klebsiella pneumoniae

(x) Numbers in parentheses represent number of WHO innovative candidates

NB: In this analysis, some candidates are counted more than once as they target multiple pathogens or are being trialled in multiple indications.

Data: Airfinity Visualization: Airfinity, simplified Refer to full slides in the footnotes section

Modelling the future antibiotic pipeline

We worked with predictive health intelligence and data analytics experts from Airfinity on new modelling that helps to build an understanding of how this pipeline might evolve over the next 10 years. The methodology and key assumptions used in the modelling can be found at the end of this paper. Based on those, two scenarios were developed:

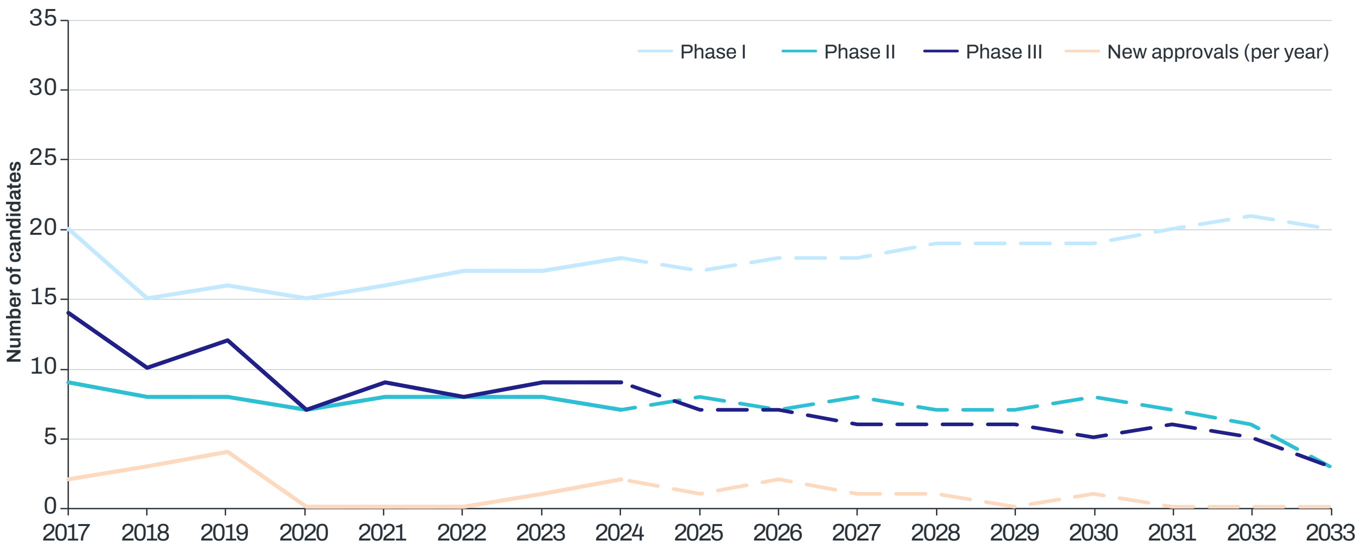
- **Scenario one** - No new incentives are introduced that could encourage investment into antibiotic R&D.
- **Scenario two** - Effective pull incentives are successfully introduced in 2025.

Scenario one: The antibiotic pipeline without new incentives

We applied known progression rates for clinical development in infectious disease to the current antibiotic pipeline and modelled it forwards 10 years. The picture is clear: without additional investment, the pipeline is expected to continue to gradually decline. This is particularly apparent from 2026 onwards when existing funding for late-stage (Phase II and III) studies is expected to decline.

This scenario assumes some continued funding is available annually for early-stage research (up to Phase I). Whilst we expect eight approvals over the next decade, we expect the late-stage pipeline to decline significantly meaning that there are just three candidate antibiotics in Phase III in 2033. The number of antibiotic candidates entering clinical trials has stagnated in recent years, with few continuing to late-phase clinical research. When looking at the fate of all antibiotic candidates in clinical development reported by the WHO between 2017 and 2022, just 10 were eventually approved by 2023 by at least one stringent regulatory authority, and about five times as many terminated along the way. Just 2 of those 10 approved were classed as "innovative" by the WHO.[11]

When we project forward, in 10 years' time, the pipeline is expected to contain 26 treatments, of which only 6 are in the late stages (Phase II and III) of development.



Data: Airfinity   Visualization: Airfinity, simplified

Scenario two: The impact of introducing effective pull incentives on the antibiotic pipeline

We expect that the introduction of effective incentives in 2025 will attract significant additional investment, primarily from private investors, leading to a substantial impact on the future antibiotic pipeline. We assume that the incentives are big enough to attract the investment needed to avoid delays in progress for all antibiotics that succeed in the previous phase of development. The total amount needed to provide a sufficient return on successful development and thereby incentivize private investment has been well-studied and quantified.[12]

By unlocking additional investment from private investors, supported by continued public/private push funding, we expect to see 19 new approvals by 2033, compared to 8 without the introduction of effective incentives.

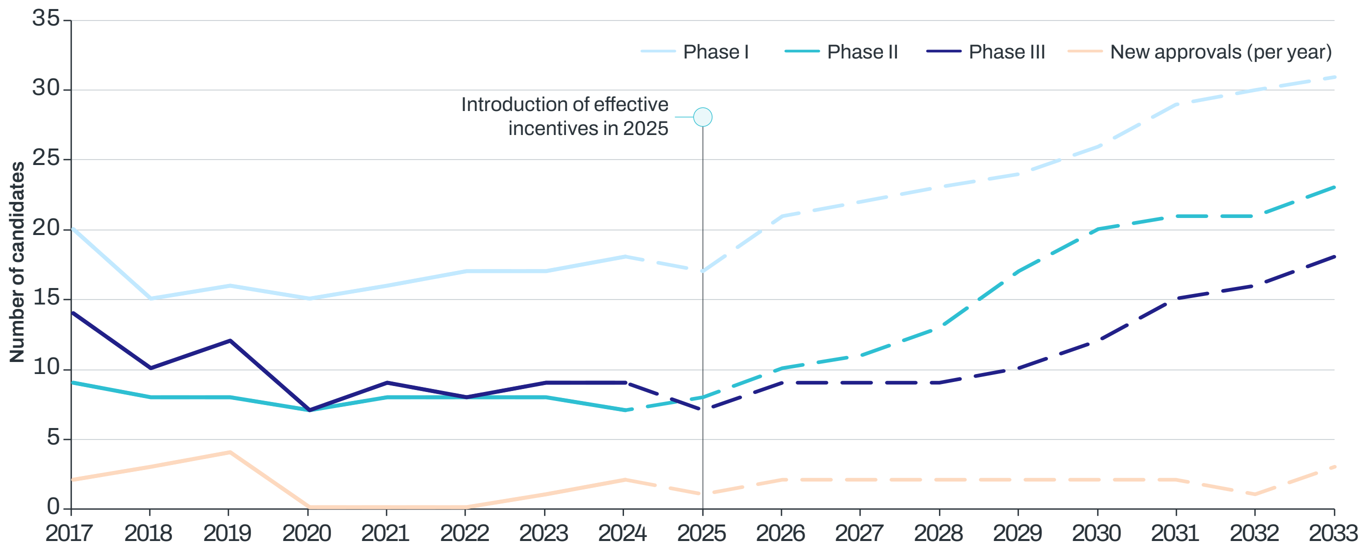
Beyond approved treatments, introducing effective incentives would have a significant impact on the number of candidates in clinical trials. In 2033, the pipeline would consist of 72 treatments, of which 41 are in the late stages.

When we compare the projected number of candidates in clinical trials in 2033 without the introduction of new incentives with the projection in the same year should effective incentives be introduced, we see:

Number of candidates in:	S1	S2
Phase III clinical trials	**3**	**18**
Phase II clinical trials	**3**	**23**
Phase I clinical trials	**20**	**31**
Number of new approvals	8	19

* S1: Scenario one (without new incentives)

* S2: Scenario two (with effective incentives)



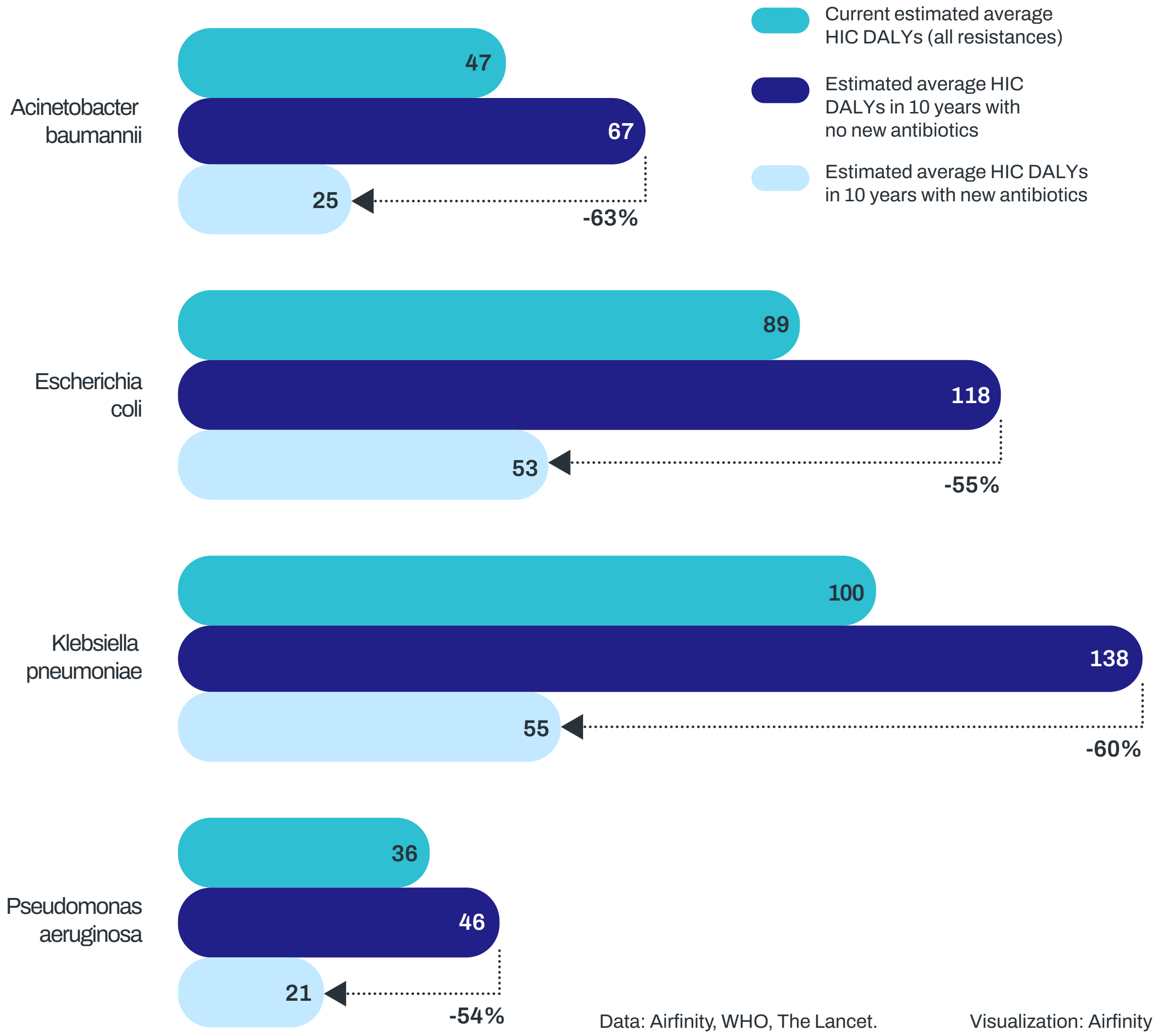
Data: Airfinity Visualization: Airfinity, simplified

The impact of a stronger antibiotic pipeline

To estimate the potential population health benefits from a more robust pipeline of antibiotics, we separately modelled the expected disability-adjusted life years (DALY) burden from four WHO critical priority pathogens under two different assumptions.

Without new incentives and with no new antibiotics to treat these resistant infections, the burden in high-income countries (HICs) would be expected to increase by about 35% on average in 10 years compared to today. However, if effective incentives are introduced, and new antibiotics against these pathogens approved as a result, these are expected to help deliver a reduction in the DALY burden of more than 50% compared to no new antibiotics. While this impact was only modelled for HICs due to data and model limitations, a similar benefit would be expected globally.

Potential average burden (estimated average DALYs per 100,000) of critical priority bacteria in high-income countries in 10 years with and without new antibiotics



Data: Airfinity, WHO, The Lancet. Visualization: Airfinity

Discussion

There is broad consensus that we must strengthen the pipeline of new antibiotics, so that the world is prepared to manage resistance as it continues to worsen. But despite repeated warnings, bankruptcies of specialized antibiotic biotech companies, the exodus of expert antibiotic researchers to other areas[13] and the recognition that the pipeline is insufficient, government action remains limited.

The urgency of combating the threat of antimicrobial resistance is rightly being prioritized at major international fora, including the UN General Assembly in 2024, the G7, G20, and key meetings hosted by Saudi Arabia, the UK and Sweden. An additional suite of policy and practical actions are needed to drive forward the pipeline of antibiotics and ensure these are available.

The fundamental challenge facing investors in antibiotic R&D is the lack of an economic return for most products, because they should be used in limited volumes, often as reserve products. This has resulted in a recognition of the need for novel mechanisms to encourage greater investment and rebuild the pipeline. Current efforts from a wide range of initiatives provide important "push funding" that supports much of the early pipeline development. However, while it's crucial to ensure this funding continues, there's a pressing need to establish a long-term economic model that offers end-to-end sustainability on a global basis for antibiotic R&D. This demands robust and effective pull incentives.

While we are seeing promising action with the novel subscription model being rolled out in the UK, we need other major economies to act. Critical for success will be advancing a similar proposal now existing in Canada, up-scaling the antibiotic revenue guarantee pilot in Japan, as well as advancing legislative proposals in the United States and the EU. These are tentative signs of progress, but not yet sufficient to unlock the additional R&D investment to bring to market a diverse arsenal of new treatments. Not all new antibiotics will be equally valuable, and several value frameworks are under discussion to inform incentive value for individual antibiotics. The UK developed and tested a practical approach for its subscription model, which expands on the WHO innovative criteria by considering aspects such as relative effectiveness and addressing unmet clinical need, and the pharmacological and health system benefit afforded by a new antibiotic.

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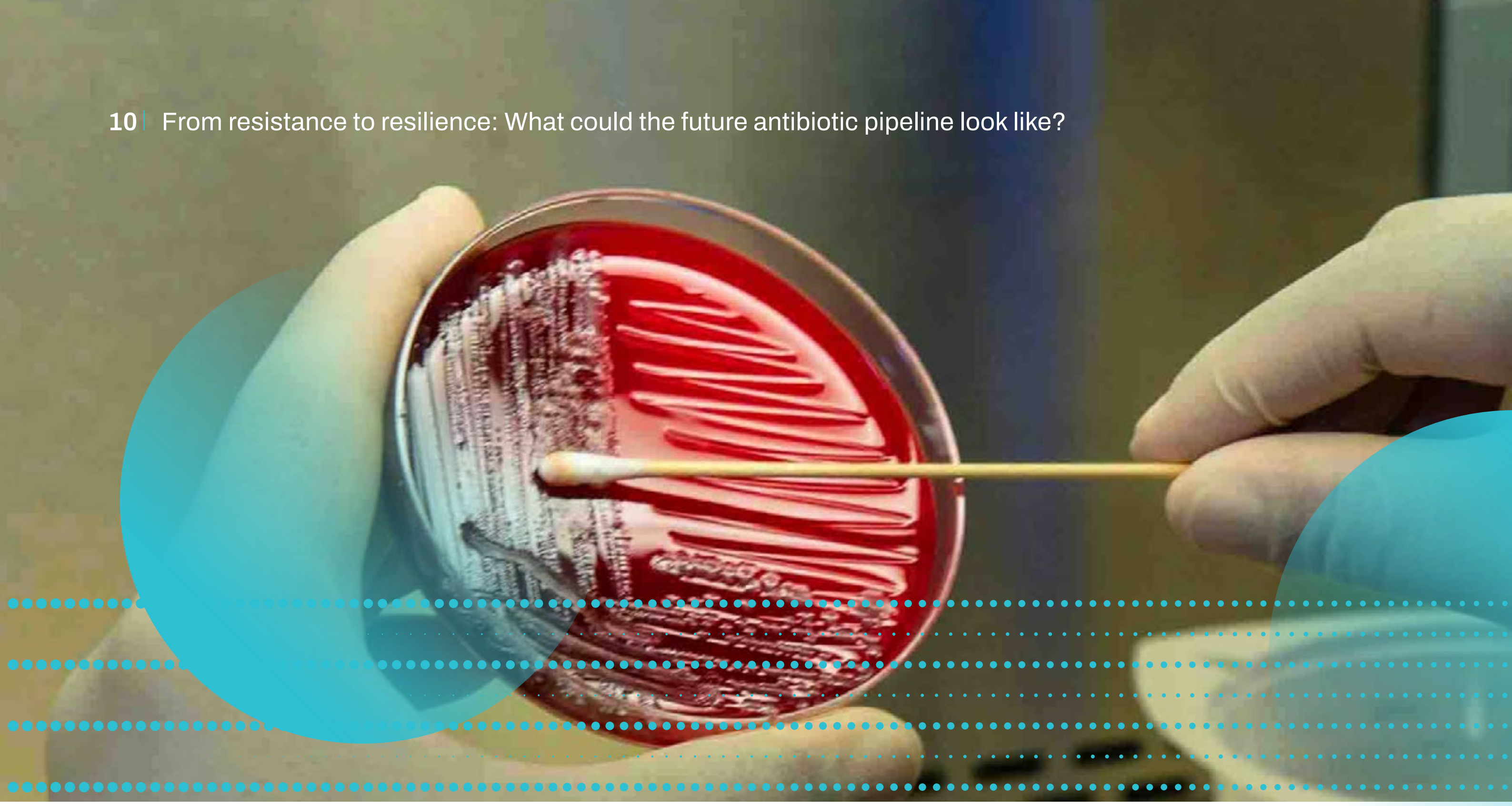
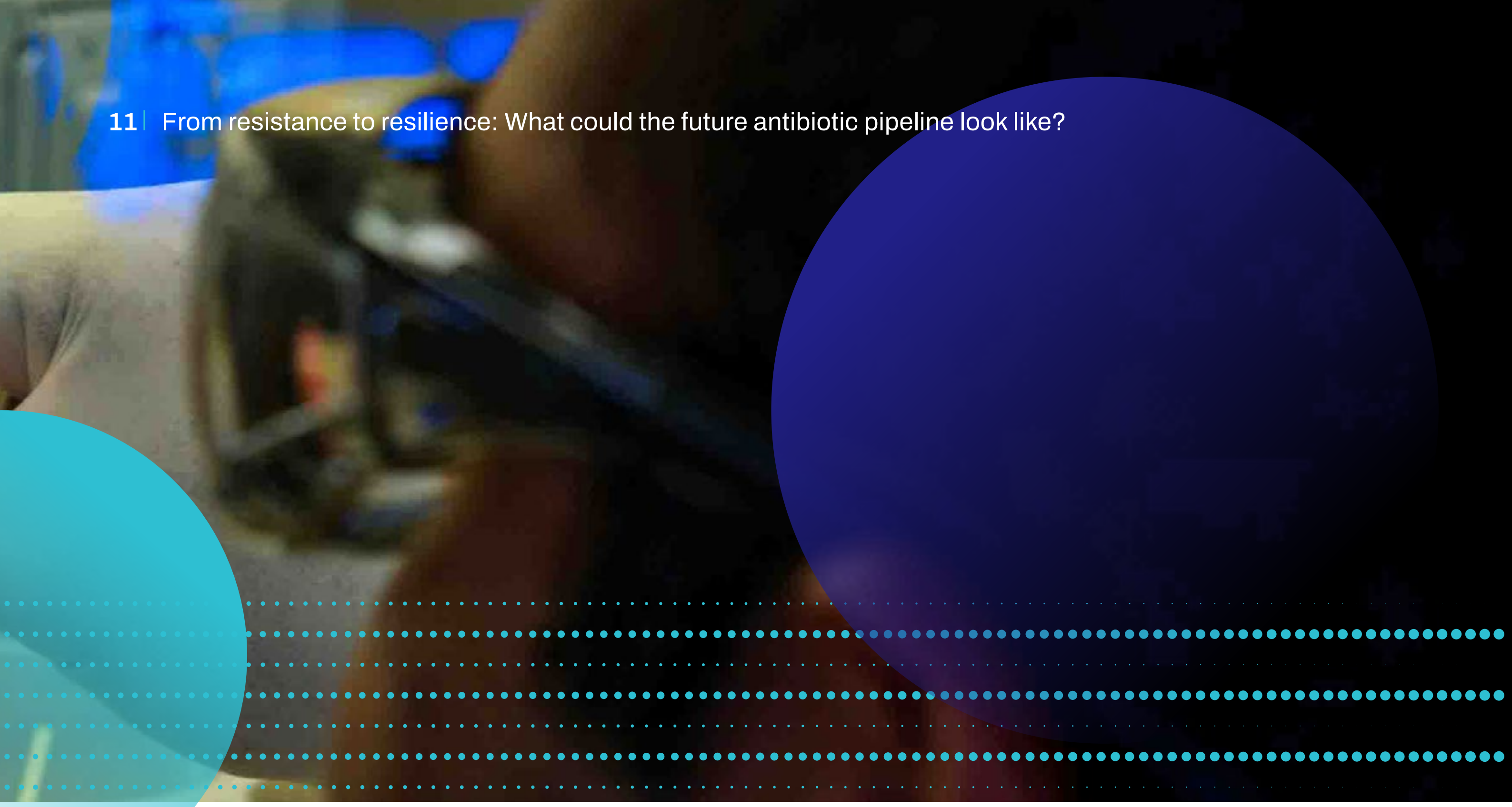


Our modelling reinforces the economic and health imperative to act boldly. Maintaining the current unsustainable economics of antibiotic R&D will lead to a continued decline in the pipeline. However, with the right incentives in place, we can expect to see the pipeline strengthened – not just in terms of approved products and better access and availability supported by a sustainable market, but also in terms of number of candidates in clinical research. An important question we do not attempt to answer is how many and how diverse a pipeline of antibiotics do we need, which needs to be addressed for the design of incentives.

However, we are deeply concerned by the continued gradual decline in the antibiotic pipeline and seek to stimulate further discussion to reverse this trend. We believe that our data presents an additional, compelling case for governments to act now to bring forward the incentives needed to move from resistance to resilience. We hope it crystalizes policy makers attention, advances the discussion and helps focus on shaping the future pipeline through the introduction of appropriate incentives.

Key methodological approaches and assumptions used in this analysis

- The pipeline includes small molecule, direct-acting antibiotic WHO clinical pipeline data up to 2021, augmented with other antibiotics and progress as identified from public data by Airfinity. Only first approvals are considered, and fixed-dose combinations are only included if at least one entity is new.
- We assumed three new Phase I assets per year without new incentives up until 2030, based on continuation of current push funding, and 2 new Phase I assets per year after that under scenario one; and an increase to six new Phase I assets per year with effective incentives under scenario two, reflecting additional investments and adequate funding support.
- The rates of progression from Phase I to II, Phase II to III and Phase III to approval for scenario one are based on the continued decline in progression rates seen between two BIO Infectious Disease data series, 2006 to 2015[14] and 2011 to 2020.[15] For scenario two, we maintained the 2011-2020 rates of progression to reflect the additional investments that we assume would halt the decline, i.e. avoid the delays and challenges in progression, which we attributed to a lack of funding. The report rates we draw from are those for new molecular entities targeting infectious disease, excluding vaccines and biologics.
- The scientific failure rates are assumed to remain constant in both scenarios.
- The modelling of DALY growth up until 2033 under the "no new antibiotics" assumption is based on the continuation of current trends in resistant cases and mortality increase. Under the "new antibiotics" assumption, we apply a consistent reduction to the current burden of resistance based on reported effectiveness from available clinical trial data, and/or real-world data from recently approved antibiotics. The model does not consider differences between different syndromic infections and assumes new antibiotics remain fully effective throughout the period studied.



Footnotes

1 WHO, 2019. "Ten threats to global health in 2019". https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019

2 The Lancet, Antimicrobial Resistance Collaborators, 2022. "Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis." https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext

3 UN Environment Programme (UNEP), 2023. "Bracing for Superbugs: Strengthening environmental action in the One Health response to antimicrobial resistance." https://www.unep.org/resources/superbugs/environmental-action

4 World Bank, working paper, 2017. "Drug-Resistant Infections: A Threat to Our Economic Future". https://www.worldbank.org/en/topic/health/publication/drug-resistant-infections-a-threat-to-our-economic-future

5 WHO, 2017. "Priority pathogens list for R&D of new antibiotics." https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed

6 While we recognize there are additional treatment modalities available, we have limited the analysis to direct-acting small molecule antibiotics or combinations targeting WHO priority pathogens, C. difficile, Group A Streptococcus, and Group B Streptococcus.

7 Only first approvals are considered, and fixed-dose combinations are only included if at least one entity is new.

8 According to the WHO, an innovative antibiotic needs to meet least one of four criteria: i) new chemical class, ii) new target, iii) new mode of action, and/or no cross-resistance to other antibiotic classes.

9 WHO, 2022. "Antibacterial products in clinical development for priority pathogens". https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/antibacterial-products-in-clinical-development-for-priority-pathogens

10 Airfinity data, 2024. Accessible at https://www.ifpma.org/publications/from-resistance-to-resilience-what-could-the-future-antibiotic-pipeline-look-like/

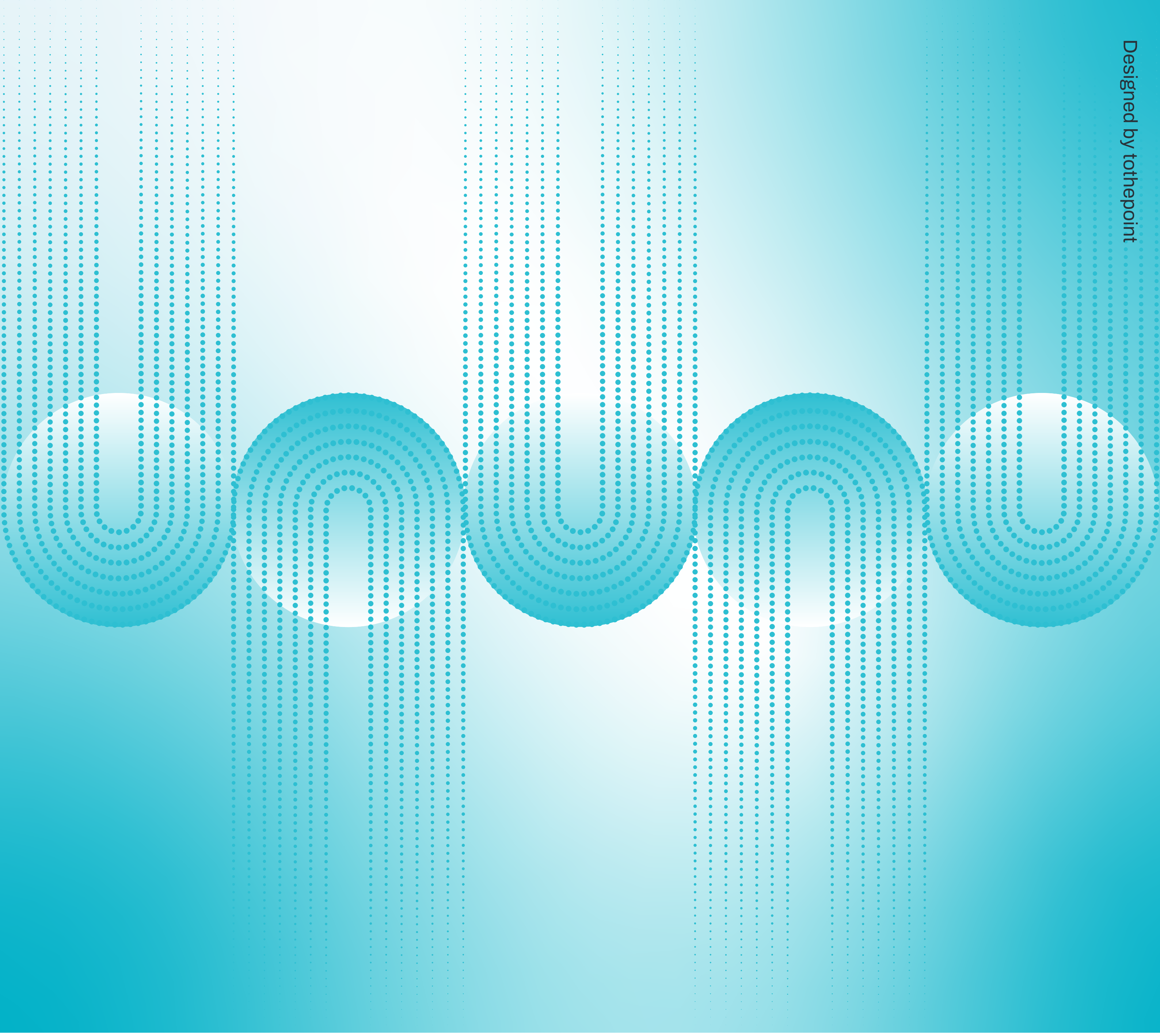
11 WHO, 2022, Analysis of the antibacterial pipeline. https://www.who.int/observatories/global-observatory-on-health-research-and-development/analyses-and-syntheses/antimicrobial-resistance/analysis-of-the-antibacterial-pipeline

12 Health Affairs, Kevin Outterson, 2021. "Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines". https://www.healthaffairs.org/doi/abs/10.1377/hlthaff.2021.00688

13 AMR Industry Alliance, 2024. "Leaving the lab: tracking the decline in AMR R&D professionals". https://www.amrindustryalliance.org/wp-content/uploads/2023/02/Leaving-the-Lab_final-1.pdf

14 Biotechnology Innovation Organization (BIO), Clinical Development Success Rates 2006-2015. https://www.bio.org/sites/default/files/legacy/bioorg/docs/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf

15 Biotechnology Innovation Organization (BIO), Clinical Development Success Rates and Contributing Factors 2011–2020. https://www.bio.org/clinical-development-success-rates-and-contributing-factors-2011-2020



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