

Written Testimony  
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The House Energy & Commerce Committee  
Subcommittee on Oversight and Investigations  
Friday April 28, 2023

***Summary***

- Bacterial and fungal infections are serious and growing health and fiscal threats.
- Unlike other drugs, antibiotics and antifungals lose their effectiveness when used, as microorganisms become resistant. Continuous innovation is needed, just to avoid falling behind.
- When new antibiotics receive FDA approval, they are mostly held in reserve, with low sales. As a result, \$150 billion in on-patent revenues have been lost from the market since 2001. Larger companies have mostly ceased their own R&D programs, leaving most of the innovation in the hands of very small companies. One hundred percent of the small companies with an approved antibiotic in the past decade have suffered economically, despite the success of FDA approval.
- Push incentives like CARB-X have successfully advanced new products but pull incentives like subscriptions are now needed. The combination will sustainably restore antibacterial innovation at an affordable price, based on the consensus from two decades of academic and policy work.

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<sup>1</sup> I testify today in my personal capacity as an academic. My testimony is not necessarily the opinion of Boston University, CARB-X, or any CARB-X funder.

***Written Testimony***

Superbugs have long been the enemies of civilization. From the Black Death in the Middle Ages (plague bacteria), to the recognition that cholera was caused by something in the water at the Broad Street pump, to modern bacterial and fungal infections – we have been locked in a ceaseless struggle with these microscopic foes.

For a brief period in the 20<sup>th</sup> Century, it looked like we had the upper hand. Antibiotics like penicillin were life savers – beginning with soldiers in World War 2. But even at the celebration for the Nobel Prize for penicillin in 1945, we knew that every time we use these drugs, we reduce their effectiveness for future patients. Unlike any other drug class, anti-infectives<sup>2</sup> decline in effectiveness through use. Genetic mutations and transfers amongst microbial life eventually result in superbugs immune to our best drugs.

For superbugs, today's drugs aren't enough. We must continually innovate to remain one step ahead.

The global death toll today is staggering: the world's most comprehensive study estimated 4.95 million people who died in 2019 suffered from drug-resistant bacterial infections, and at least 1.27 million of these deaths were directly caused by superbug bacteria.<sup>3</sup> The US and other countries mounted impressive efforts in past decades to reduce death and suffering from HIV,

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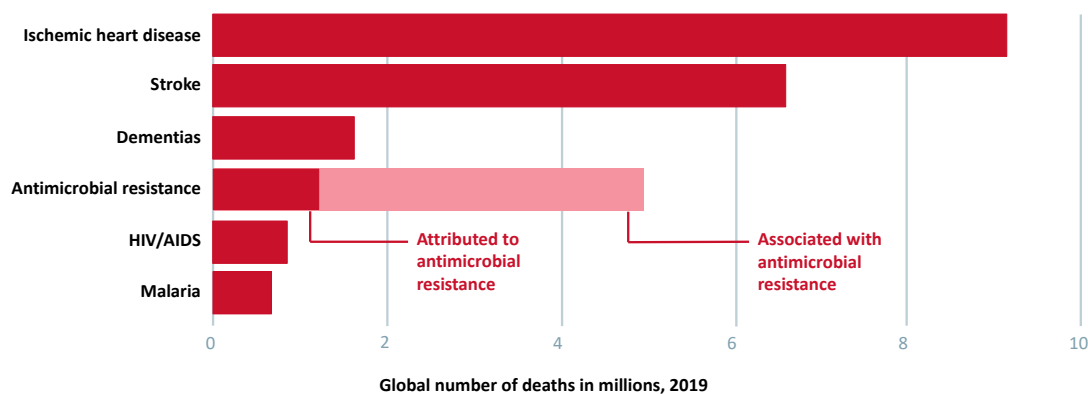
<sup>2</sup> Including antibacterials, antifungals, antiretrovirals, antivirals, and antiparasitics.

<sup>3</sup> IHME. The burden of antimicrobial resistance in G7 countries and globally.

<https://www.healthdata.org/infographic/burden-antimicrobial-resistance-g7-countries-and-globally>.

tuberculosis, and malaria. Through PEPFAR, The Global Fund, and other programs, death rates are declining for these diseases. Hard-fought progress saves lives (Fig. 1).

## How AMR compares to other causes of death



CARB-X

Feb 2023

Source: IHME's The burden of antimicrobial resistance in G7 countries and globally | <https://www.healthdata.org/infographic/burden-antimicrobial-resistance-g7-countries-and-globally>

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We have not made similar scale commitments against bacteria, and we are falling behind. As bad as the problem is today, a decade from now we could be unprepared against an even larger threat. These problems are exacerbated by conflict, displacement of people, and climate change.

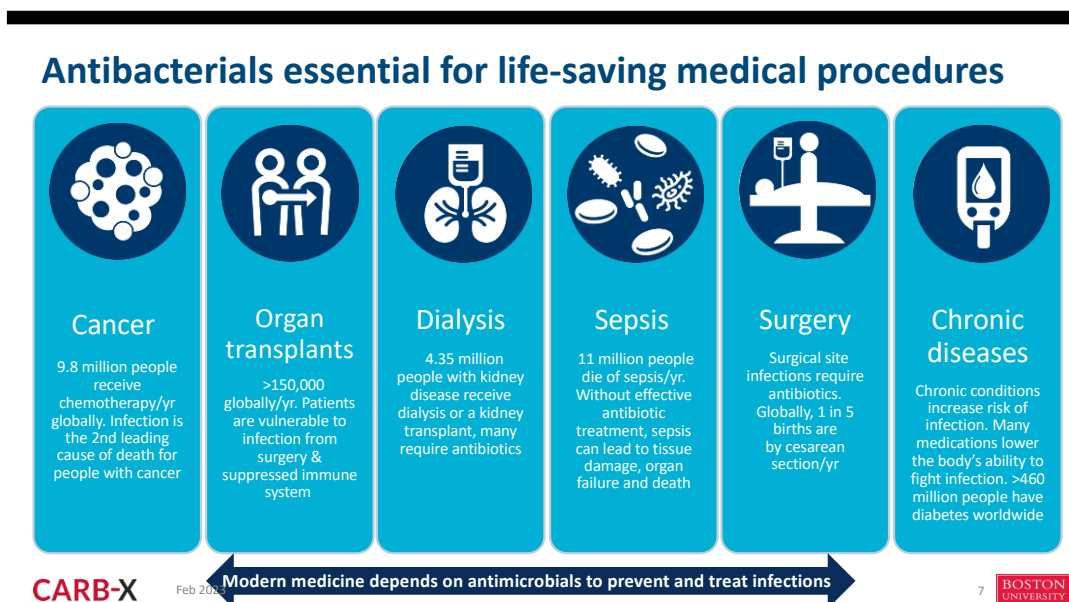
In the US, resistant bacteria kill 48,000 Americans per year, and sicken many more of our people who survive.<sup>4</sup> The trend is moving in the wrong direction for the last few years, with an increase of at least 15% during the first year of the pandemic.<sup>5</sup> The economic damage is also serious –

<sup>4</sup> <https://www.cdc.gov/drugresistance/national-estimates.html>

<sup>5</sup> <https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf>

more than \$4.6 billion each year in additional costs to our healthcare system, especially from longer hospital stays and more intensive services.<sup>6</sup> This economic estimate does not include productivity losses in economic activity and does not put any price on the human lives lost. These estimates are only from drug-resistant bacteria and don't yet include estimates from other superbugs like the fungi on the CDC threat list.

Americans rely on effective antibiotics and antifungals. Every hospital in your district, every cancer patient, every new mom with a C-section, any soldier with infections, or even folks my age thinking about knee or hip surgery – all of us depend on effective antibiotics and antifungals to enable modern medicine. But resistance eats away at the effectiveness of these wonderful drugs, like rust weakens a bridge. When antibiotics become less effective, everything in modern medicine becomes more difficult and less safe (Fig. 2).



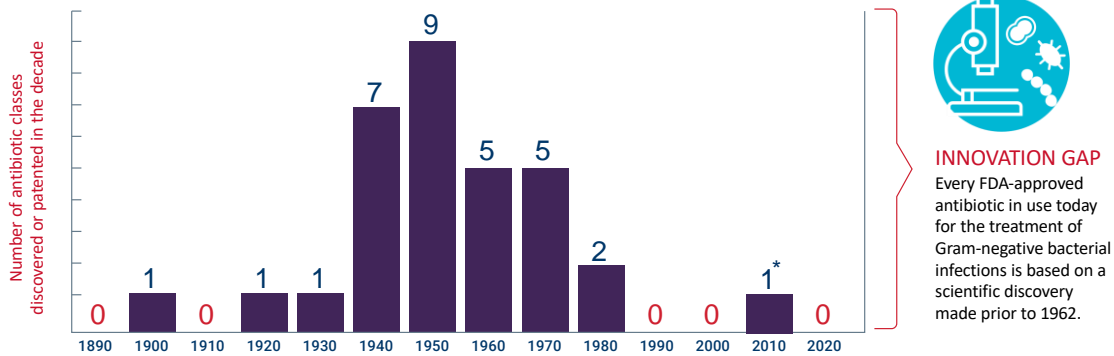
<sup>6</sup> <https://www.cdc.gov/drugresistance/solutions-initiative/stories/partnership-estimates-healthcare-cost.html>

This is a national security issue, threatening the readiness of the American workforce and health care system and imposing needless death, suffering, and expense on our people. But remember that antibiotic and antifungal drugs used today are gradually losing effectiveness. They must be continuously replaced to avoid falling behind.

### ***Superbugs need new drugs***

For the past two decades, I have studied the pipeline for new drugs. I have some good news and bad news. First, the bad news. For drugs already in human testing, there is an embarrassing shortfall: about four dozen antibiotics compared to more than a thousand cancer drugs. Cancer drugs make money, so future cures are always moving towards patients. Antibiotics lose money in our current reimbursement system, with predictable results on innovation (Fig. 3).

## **AMR innovation is lagging**

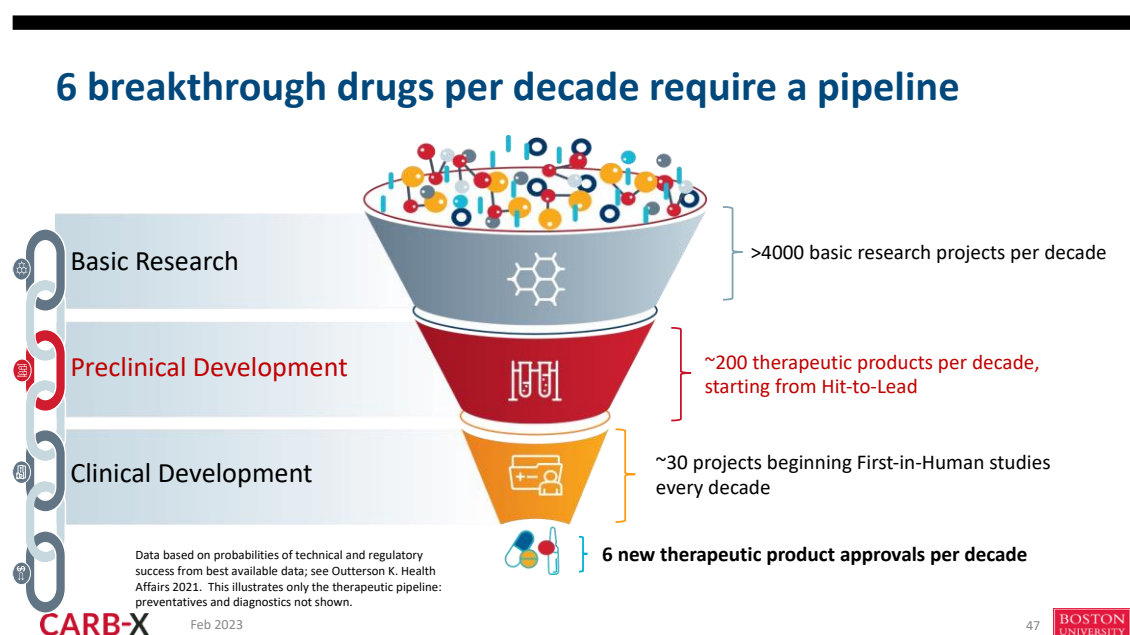


\* Cefiderocol was approved by FDA in 2019 and EMA in 2020. The FDA-approved label for cefiderocol classifies the drug as a cephalosporin, and therefore not a new class but certainly a new mechanism of action. Some experts consider cefiderocol to be a first-in-class sideromycin. The predecessors to cefiderocol were discovered at Shionogi in the early 1990s. CID 2019;69(7):S538-S543

\* This chart excludes bedaquiline, which is the first drug in a new class to treat tuberculosis.

Source: Pew Charitable Trusts; Deak D, Powers JH, Outterson K, Kesselheim AS. Progress in the Fight Against Multidrug Resistant Bacteria?: A Review of FDA Approved Antibiotics 2010-2015. ANNALS OF INTERNAL MED. 2016 MAY 31. DOI: 10.7326/M16-0291.

But there is also good news. The preclinical pipeline is filled with outstanding products, the fruit of investments by the organization I lead, CARB-X, which has invested over \$400 million dollars since 2017. CARB-X is supported by BARDA/ASPR, Wellcome, the United Kingdom, Germany, and the Gates Foundation. We have been successful these first 6 years in our primary mission, by delivering 18 therapeutic, diagnostic, and prevention products into first-in-human clinical testing. This preclinical pipeline is amazingly innovative, but fragile from the need for additional public push incentives and private investment. Data from the Global AMR R&D Hub suggests that push incentives are underfunded by several hundred million dollars per year globally if the goal is to bring 6 highly impactful new antibiotics to FDA approval in the next decade (Fig. 4).<sup>7</sup>

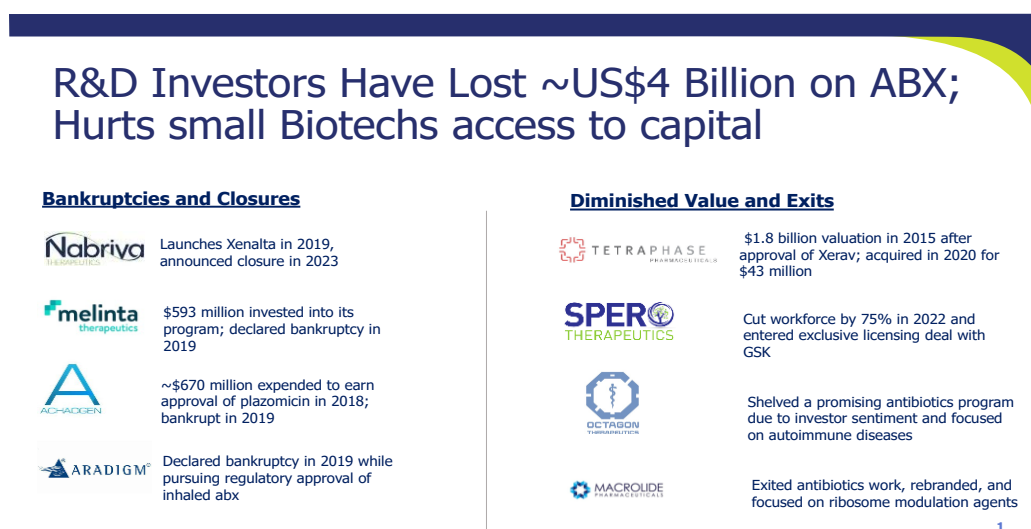


<sup>7</sup> Kevin Outterson, Presentation at the Meeting of the Global Leaders Group on Antimicrobial Resistance, Feb. 8, 2023.

## ***Holding antibiotics in reserve drives companies into bankruptcy***

Antibiotics are valuable, but the market is broken: scientists work on new antibiotics for decades. Most fail because science is hard. FDA approval is a time for celebration in all other therapeutic areas – but for new antibiotics, the payday never comes. Because of resistance, doctors rightly want to reserve the newest antibiotic for the future, putting them on the shelf, behind glass like a fire extinguisher. The fire extinguisher company gets paid when preparedness starts, not when the fire starts. We are paying for new antibiotics only after the fire. A new drug that isn't used much in the early years can't make money.<sup>8</sup>

In the last decade, seven antibiotics have been approved by the FDA from small companies.<sup>9</sup> Every one of them has either gone bankrupt or their R&D investors lost their shirts, as non-generic sales of antibiotics are in free fall over the past two decades (Fig. 5).<sup>10</sup>



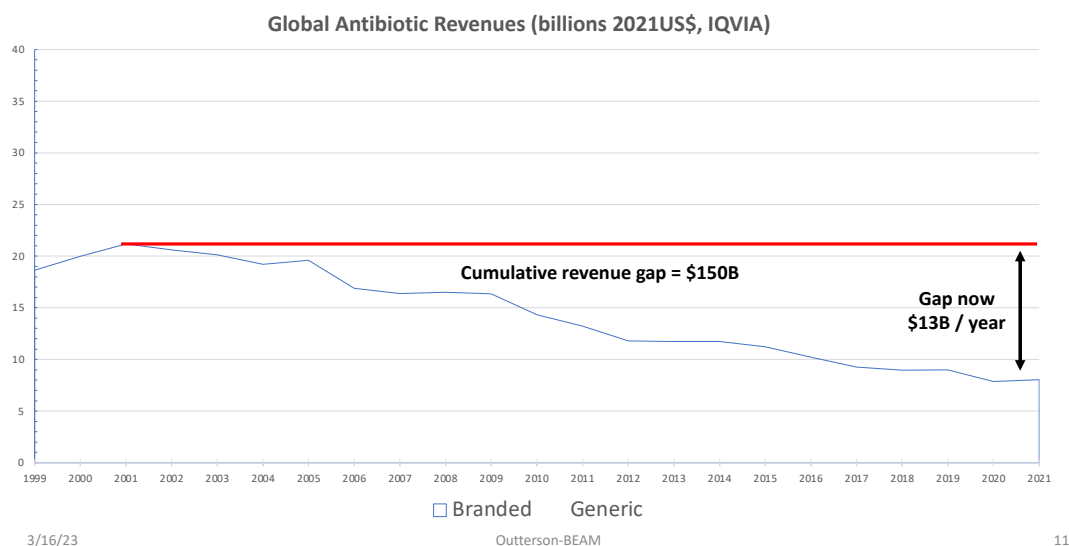
<sup>8</sup> <https://amr.solutions/fire-extinguishers-of-medicine/> (John Rex).

<sup>9</sup> Lefamulin (2019, Nabriva), omadacycline (2019, Paratek), eravacycline (2018, Tetrachase), plazomycin (2018, Achaogen), meropenem/ vaborbactam (2017, Melinta), delafloxacin (2017, Melinta), oritavancin (2014, Melinta).

<sup>10</sup> Madden J, Outterson K. Trends in the global antibiotics market. Nat Rev Drug Disc. 2023 Mar; 22(3):174.

Data from my 2023 publication in *Nature Reviews Drug Discovery* demonstrates the \$150 billion cumulative revenue gap in on-patent antibiotic sales since 2001, which has driven so many companies from the field (Fig. 6).

## Global antibiotic markets: decades of generic growth, but \$150B decline in the engine behind R&D



### ***Subscription programs + push incentives will restore innovation at an affordable price***

Now is the time to respond to this national security crisis. Push incentives alone will not be enough. We must also change the way we pay for antibiotics. After nearly two decades studying this problem,<sup>11</sup> G7 governments are creating antibiotic subscriptions to reward innovation while

<sup>11</sup> Major reports include [Bad Bugs, No Drugs](#) (IDSA, 2004), [ASPE/HHS](#) (2014), [President's Council of Advisors on Science & Technology](#) (2014), [Chatham House](#) (UK, 2015), [AMR Review](#) (UK, 2016), [GUARD/BCG](#) (German Federal Ministry of Health, 2017), [PACCARB](#) (2017), [DRIVE-AB](#) (EU, 2018), [GAO](#) (2020), [Duke-Margolis](#) (2020), [BCG](#) (2022), [PwC for HERA](#) (EU, 2022), London School of Economics for the Swedish Presidency of the Council of the European Union (2023, not yet released). I was a co-author of three of these reports (and a fourth underway for a G7 government but not yet public) and was interviewed or testified as an expert for eight others. Believe me when I say this problem has been adequately studied by governments and think tanks.



allowing the new antibiotic to be used sparingly at first.<sup>12</sup> If Congress creates a subscription program, Americans will get the new antibiotics we need – sitting on the shelf ready to go, like that fire extinguisher – and the companies will also get what they need to incentivize their R&D activities: reasonable profits instead of bankruptcy. Action by the US would also galvanize other G7 countries to contribute their fair share as well.

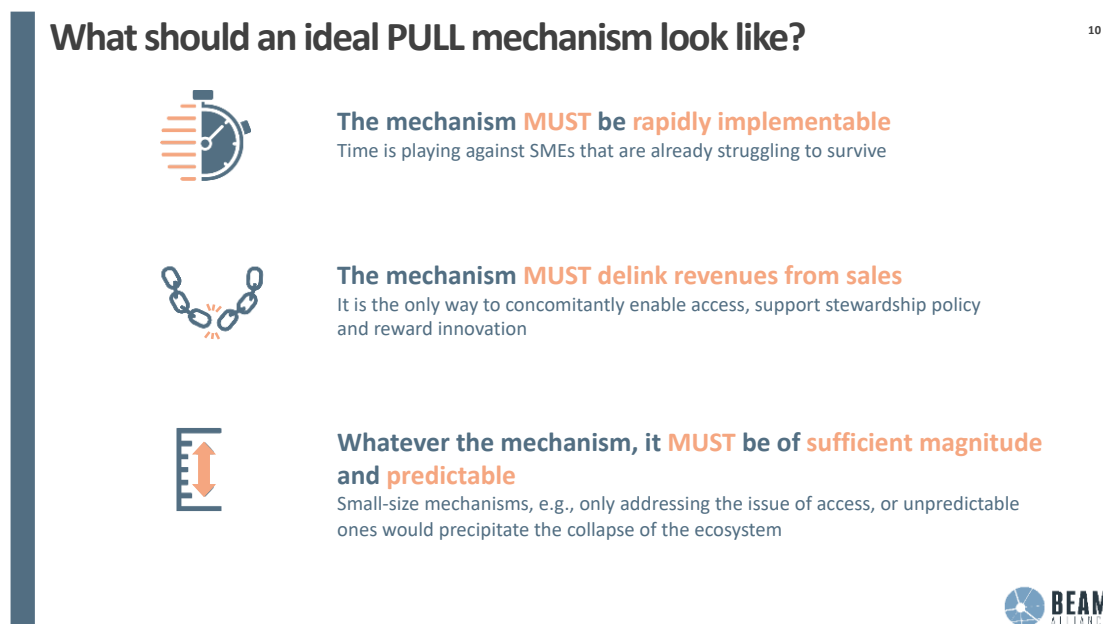
Antibiotic subscriptions should be crafted carefully to ensure that U.S. taxpayers get what they need without overpaying. For example, they must focus only on the most promising new drugs, which has been the consensus position since the Chatham House report in 2015. Creating a subscription asks drug developers to aim for a target; let's make sure we create high but attainable targets so that subscriptions result in *better* antibiotics and antifungals.

While earlier proposals suggested paying pull incentives in a lump sum (often called a market entry reward), the DRIVE-AB Report for the European Commission also recommended it could be paid over longer periods of time to reduce the risk of lemons or non-compliance. The UK subscription is moving to a 10-year payment period. The proposed PASTEUR Act in the previous 117<sup>th</sup> Congress spread the pull incentive over the longer of 10 years or the remaining patent and exclusivity period, which will incentivize the sponsor to minimize patent extensions and facilitate generic entry after the subscription contract is concluded.

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<sup>12</sup> Subscription programs or revenue guarantees are officially launched or announced in England and Japan. The EC is expected to release a proposal for a pull incentive within weeks. Canada has announced a Council of Canadian Academies Panel to report back to the government on a pull incentive for Canada.

The [BEAM Alliance](#), representing small antimicrobial companies in Europe, has proposed ideal features of pull incentives (Fig. 7).



- The call for **rapid implementation** reflects the urgency of the medical situation, as well as the business urgency for small companies with less than a year of cash on hand with which to fund R&D operations.
- **Delinking** revenues from sales solves the key R&D problem with antibiotics and antifungals by rewarding the sponsor for bringing a high-quality new drug to the market, even if it will be used only in modest volumes in the early years. Delinking also supports proper stewardship since incentives to oversell are no longer present.

- On the issue of “**sufficient magnitude**”, *Health Affairs* published my comprehensive estimate of the appropriate size of antibacterial subscriptions in 2021, using only publicly available data in a fully transparent expected net present value model (Fig. 8).<sup>13</sup>

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 The People-to-People Health  
 Foundation, Inc.

By Kevin Outterson

## Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines

- Best estimate for a global antibacterial subscription = **\$3.1B (range: \$2.2B-\$4.8B)** per drug over 10 years, fully delinked
  - The PASTEUR Act is within this range, as is the global pull incentive implied by the UK pilot
- Best estimate for a global partially delinked program (MERs / TEEs) = **\$1.6B (range: \$900M-\$2.6B)**
- **Both push and pull incentives are necessary** for sustainable and robust antibacterial drug development

Outterson

Outterson K. Estimating the appropriate size for global antibacterial pull incentives. *Health Affairs* 2021 <https://pubmed.ncbi.nlm.nih.gov/34724432/>

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- The “fair share” of these costs that should be borne by each G7 government + the European Union has been presented in several conferences<sup>14</sup> and was adopted in a November 2019 analysis by the Center for Global Development.<sup>15</sup> As a result of this

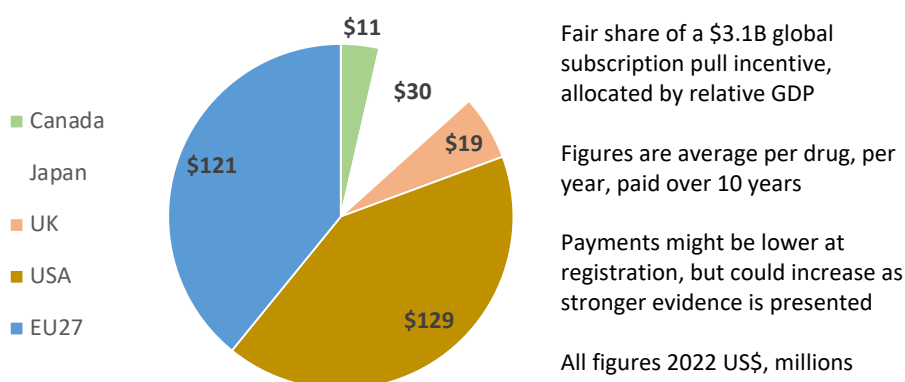
<sup>13</sup> Outterson K. Estimating the appropriate size of a global antibacterial pull incentive. *Health Affairs*. 2021; 40(11):1758-1765.

<sup>14</sup> E.g., Outterson, K. [ISPOR](https://open.bu.edu/handle/2144/42568) (Vienna, Austria, Nov. 8, 2022); HGPI (Tokyo, Japan, Sept. 22, 2022). Open access data: <https://open.bu.edu/handle/2144/42568> (Fair Share).

<sup>15</sup> <https://www.cgdev.org/blog/world-needs-new-antibiotics-proposed-us-program-develop-them-would-pay-281>.

work, we now know the required size of an antibiotic subscription in the US, as well as the fair share for other wealthy countries (Fig. 9).

## “Fair share” pull incentive targets within G7+EU27



Source: Outterson 2023, <https://open.bu.edu/handle/2144/42568>

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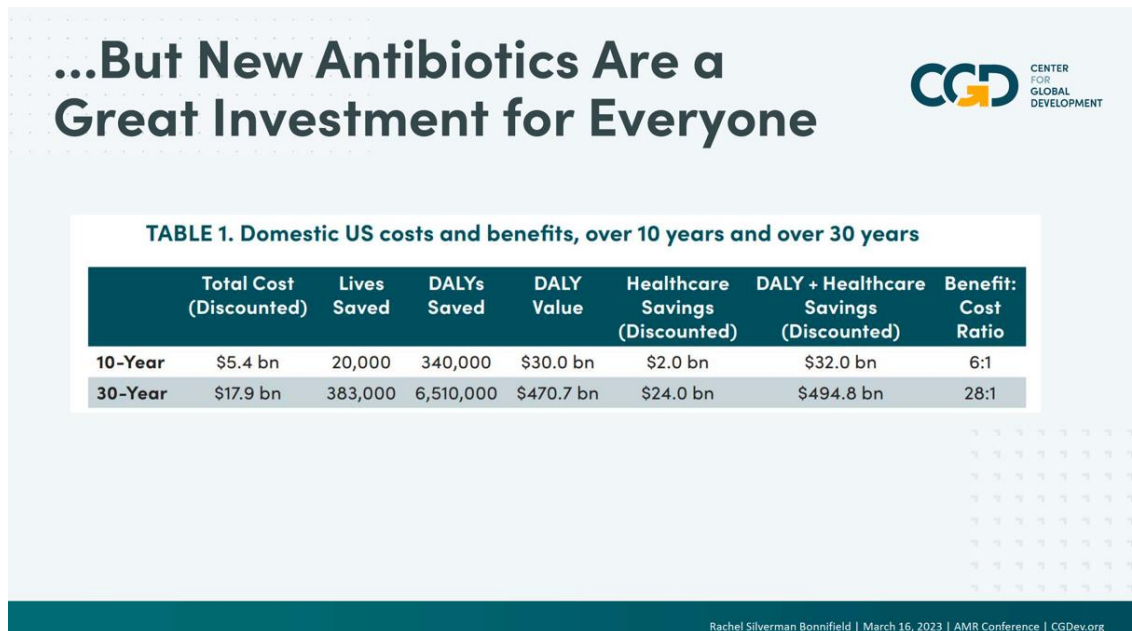
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While the figure above are average amounts, ranges are appropriate for subscription payments, with higher payments going to drugs meeting higher standards. With the evidence available at FDA approval, qualifying drugs can start at an appropriate point and increase over time if stronger evidence is presented of the importance of the new drug.<sup>16</sup>

Subscriptions will be remarkably good value for the US taxpayer. The Center for Global Development forecasts a financial return on investment for Americans of 6:1 over a decade (Fig. 10).<sup>17</sup>

<sup>16</sup> Rex JH, & Outterson K (2016). Antibiotic reimbursement in a model delinked from sales: a benchmark-based worldwide approach. *LANCET INFECTIOUS DISEASES*, 16(4), 500-505. doi:[10.1016/S1473-3099\(15\)00500-9](https://doi.org/10.1016/S1473-3099(15)00500-9).

<sup>17</sup> <https://www.cgdev.org/blog/world-needs-new-antibiotics-proposed-us-program-develop-them-would-pay-281>.



From recent data I published in *Nature Reviews Drug Discovery*, we know that a US subscription would cost less than what we spent on on-patent antibiotics less than ten years ago.<sup>18</sup> This is affordable because we did it ourselves, very recently. It is time to invest in the future of antibiotics and antifungals once again.

By restoring some common sense to the market for antibiotics, subscriptions will bend the curve towards innovation. Globally, the health impact is striking: subscriptions will save 9.9 million lives over the next 3 decades, according to the Center for Global Development.<sup>19</sup>

<sup>18</sup> Madden J, Outterson K. Trends in the global antibiotics market. *Nat Rev Drug Disc.* 2023 Mar; 22(3):174.

<sup>19</sup> <https://www.cgdev.org/blog/world-needs-new-antibiotics-proposed-us-program-develop-them-would-pay-281>.

I know this not just based on the work of many experts, but because I have seen the future. At CARB-X, we see the most promising new antibiotic candidates 10 – 15 years before their potential FDA approval. That future is bright so long as you continue to support push incentives from CARB-X and BARDA and complement them with a new pull incentive like the antibiotic subscription in the PASTEUR Act. At CARB-X, we mainly work with very small start-up companies with highly innovative new products, including phages, diagnostics, vaccines, and many first-in-class products. Eighteen of these companies have initiated first-in-human testing. The future can be filled with a sustainable supply of new antibiotics. I am confident because at CARB-X we know this pre-clinical pipeline intimately. The key barriers today are economic, which is why we need both push and pull incentives.

Threats from bacteria and fungi are significant today and will be worse tomorrow. If you want a steady stream of life-saving innovation in a decade, you must act today. We need the fire extinguisher before the fire starts. Let's be well prepared, so bacteria and fungi don't steal a march on the health of Americans.

Thank you for your attention today. Additional information on CARB-X is found in the Appendix.

Professor Kevin Outtersen

Boston, Massachusetts  
April 28, 2023

## Appendix A: CARB-X background

- The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) is a global non-profit partnership based at Boston University that accelerates antibacterial research and development.<sup>20</sup> CARB-X awards non-dilutive funding and provides scientific, regulatory and business expertise to support early-stage development of innovative products that aim to prevent, diagnose and treat the drug-resistant infections caused by the most dangerous bacteria identified by the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) priority lists.<sup>21</sup>
- The 2015 U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) called for a CARB product accelerator to bring “inventors and researchers together with start-up companies to explore creative ideas that could lead to the development of new antibiotics or non-traditional therapies.”<sup>22</sup> The U.S. Department of Health and Human Services Biomedical Advanced Research and Development Authority (BARDA), part of the Administration for Strategic Preparedness and Response (ASPR), co-founded CARB-X with the Wellcome Trust and the U.S. National Institutes of Health (NIH) in 2016. Since then, Germany’s Federal Ministry of Education and Research (BMBF), the United Kingdom Government's Global Antimicrobial Resistance Innovation Fund (UK GAMRIF), and the Bill & Melinda Gates Foundation have joined and supported the initiative. CARB-

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<sup>20</sup> <https://carb-x.org/>.

<sup>21</sup> <https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed>; <https://www.cdc.gov/drugresistance/biggest-threats.html>;

<sup>22</sup> [https://www.cdc.gov/drugresistance/pdf/national\\_action\\_plan\\_for\\_combating\\_antibiotic-resistant\\_bacteria.pdf](https://www.cdc.gov/drugresistance/pdf/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf).

X is hosted at Boston University. CARB-X has also been endorsed and mentioned in declarations from G7 and G20 governments alike.<sup>23</sup>



A **global** non-profit partnership developing antibiotics, vaccines and diagnostics to fight drug-resistant bacteria



BILL & MELINDA  
GATES foundation



13 Apr 2023



- CARB-X is the most successful global public-private partnership acting as a push incentive and pipeline coordinator in the early stages of antibacterial product development. CARB-X runs competitive funding calls to select the best science from around the world (more than 1,200 applications were submitted from 39 different countries), employing rigorous application standards (with a < 8% acceptance rate). The selected projects receive scientific, regulatory, and business support in addition to non-dilutive grants via a lean and efficient organization (95% of funding goes to product developers via direct awards or technical and in-kind support). In only six years CARB-X has already accelerated 92 R&D candidates (including new classes of antibiotics and

<sup>23</sup> <https://carb-x.org/carb-x-news/gardp-and-carb-x-welcome-renewed-commitment-by-g7-leaders-to-address-antimicrobial-resistance/>; <https://carb-x.org/carb-x-news/carb-x-welcomes-g20-call-to-action-on-amr/>.



non-traditional agents, vaccines and other preventatives such as CRISPR-phage, microbiome-modifying agents and antibodies, and rapid diagnostics), 18 of which entered or completed first-in-human clinical trials. Among these 18 R&D candidates, 2 have already reached the market, 7 have advanced development partnerships and 12 remain in active clinical development.<sup>24</sup>

## Product developers supported by CARB-X since 2017



CARB-X

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- While CARB-X's primary focus is accelerating antibacterial innovation, its funders and staff also actively supports stewardship and access to ensure that products funded and supported by CARB-X are used responsibly and are made accessible to patients who need them. CARB-X-funded product developers are contractually obligated to develop a Stewardship and Access Plan for their funded product, outlining what strategies they will deploy to ensure responsible stewardship and appropriate access in low- and middle-

<sup>24</sup> [https://carb-x.org/wp-content/uploads/2021/06/Carb-X\\_FactSheet\\_7-31-21.pdf](https://carb-x.org/wp-content/uploads/2021/06/Carb-X_FactSheet_7-31-21.pdf).

income countries (LMICs). Many of the R&D projects accelerated by CARB-X target pathogens that cause the greatest health challenges in low- and middle-income countries.

## CARB-X funding comes with a contractual obligation for Stewardship & Access Plans (SAPs)

- Product developers prepare a nonconfidential SAP when product enters pivotal clinical trials
  - Every CARB-X PD has agreed to the same terms
- SAP updated and published on CARB-X website when product is first approved by any of the FDA, EMA (or national authorities), MHRA, or PMDA
  - Updated following any significant market or product changes
- Obligations survive termination/expiration of CARB-X funding; follows the product to the expiration of Project IP Rights
- Wellcome Trust succeeds to CARB-X's rights, if need be



### CARB-X

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- In addition to funding product development worldwide, CARB-X has been a driving force in preserving, solidifying and empowering the global antibacterial R&D community, creating and maintaining a network of expertise and support to help product developers and their projects succeed. This comprehensive support is a distinct strength of the CARB-X accelerator model. CARB-X's Research & Development Team works closely with more than 120 subject matter experts from around the world, and the CARB-X Global Accelerator Network consisting of several accelerator organizations, to provide scientific, technical and business support tailored to the needs of each project and product developer.<sup>25</sup>

<sup>25</sup> <https://carb-x.org/partners/global-accelerator-network/>.