Antimicrobial Resistance: The Problem with Market Entry Rewards

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"[A prize system] would require more ingenuity in a legislator than the ingenuity of the whole body of Patentees united . . . for who are to be the proper judges of the merit of an invention; and who shall limit the sum at which it ought justly to be estimated?"

—Observations on the Utility of Patents (1791)[1]

ABSTRACT

To combat the growing threat of antimicrobial resistance, Congress has considered legislation such as the PASTEUR Act that would provide "market entry rewards" of up to $3 billion for each new FDA-approved drug. As policymakers consider such rewards, they should appreciate valuation challenges long known to the intellectual property community but under-acknowledged in health policy circles. For new drugs, these challenges include hidden government costs already expended, foregone opportunities to pursue alternate means of reducing patient morbidity and mortality, and the risk posed by creeping political influence to future value assessments. It will also be important for legislators to consider the disappointing outcomes of similar past laws, such as the GAIN Act.

I. INTRODUCTION

To combat the growing threat of treatment-resistant pathogens, several influential reports in the late 2010s proposed large "market entry rewards" to incentivize the development of new antibiotics.[2] Among them was one authored by the U.S.

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1 OBSERVATIONS ON THE UTILITY OF PATENTS AND ON THE SENTIMENTS OF LORD KENYON RESPECTING THAT SUBJECT 21 (London, Ridgway 3d ed. 1791).

2 NAT'L ACADS. OF SCIS., ENG'G, & MED., COMBATING ANTIMICROBIAL RESISTANCE AND PROTECTING THE MIRACLE OF MODERN MEDICINE 10 (2022) (stating that $500 million to $2 billion may be too high of an amount for market entry rewards); CHRISTINE ÅRDAL, DAVID FINDLAY, MILOJE SAVIC, YEHUDA CARMELI, INGE GYSSENS, RAMANAN LAXMINARAYAN, KEVIN OUTTERSON & JOHN H. REX, DRIVE AB, REVITALIZING THE ANTIBIOTIC PIPELINE: STIMULATING INNOVATION WHILE DRIVING SUSTAINABLE USE AND GLOBAL ACCESS (2018), https://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf; Gregory W. Daniel, Monika Schneider, Marianne Hamilton Lopez & Mark B. McClellan, *Implementation of a Market Entry Reward within the United States*, 46 J.L. MED. ETHICS 50 (2018); SELMA STERN, SIMON CHORZELSKI, LAURA FRANKEN, SIMON VÖLLER, HEINRICH RENTMEISTER & BENJAMIN GROSCH, BOS. CONSULTING GRP., BREAKING THROUGH THE WALL—A CALL FOR CONCERTED ACTION ON ANTIBIOTICS RESEARCH AND DEVELOPMENT (2017), https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Berichte/G

Presidential Advisory Council on Combating Antibiotic Resistant Bacteria, established by Executive Order,[3] which issued a report in 2017 suggesting a reward between $1 and $2 billion per drug[4] (independent of whether there was evidence that the new drugs improved patient outcomes). In 2020, 2021, and 2023, the Pioneering Antimicrobial Subscriptions To End Upsurging Resistance Act (PASTEUR Act) was repeatedly introduced in Congress, proposing to raise this amount to as much as $3 billion per drug payable over contract periods of not less than five years.[5] In the United Kingdom, a pilot program to pay developers of new priority antibiotics £10 million per year for ten years could yield $4 billion per new drug if other G20 nations contribute similarly, as some hope they will.[6]

The magnitude of the threat these proposals are designed to address is difficult to estimate directly and has largely been based on modeling. The U.S. Centers for Disease Control and Prevention (CDC) estimates that drug-resistant microbes are associated with 35,000 deaths in the United States each year,[7] and models predict global deaths from such infections will increase fourteen-fold by 2050 to 10 million.[8] However, a decade since those models were proposed,[9] the assumptions upon which they were based and their predictions have not come to pass. Evidence internationally and from the U.S. Department of Veterans Affairs show decreases in the prevalence

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UARD_Follow_Up_Report_Full_Report_final.pdf; JIM O'NEILL ET AL., TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS (2016), https://apo.org.au/sites/default/files/resource-files/2016-05/apo-nid63983.pdf; TOWARDS A NEW GLOBAL BUSINESS MODEL FOR ANTIBIOTICS: DELINKING REVENUES FROM SALES 1 (Charles Clift, Unni Gopinathan, Chantal Morel, Kevin Outterson, John-Arne Røttingen & Anthony So eds., 2015), https://www.chathamhouse.org/sites/files/chathamhouse/field/field_document/20151009NewBusinessModelAntibioticsCliftGopinathanMorelOutterson RottingenSo.pdf (proposing $3.5 billion per year in R&D incentives).

[3] *See* Exec. Order No. 13,676, 184 Fed. Reg. 56,931 (Sept. 23, 2014) (establishing the advisory committee under the Obama Administration); *see also* Exec. Order No. 13,708, 80 Fed. Reg. 60,271–72 (Oct. 5, 2015) (authorizing the continuation of the advisory committee).

[4] PRESIDENTIAL ADVISORY COUNCIL ON COMBATING ANTIBIOTIC RESISTANT BACTERIA, RECOMMENDATIONS FOR INCENTIVIZING THE DEVELOPMENT OF VACCINES, DIAGNOSTICS, AND THERAPEUTICS TO COMBAT ANTIBIOTIC-RESISTANCE 20 (2017).

[5] Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2023 (PASTEUR Act), S. 1355, 118th Cong., sec. 2, § 399OO-2(e) (2023); *see also* H.R. 3932, 117th Cong. (2021) (PASTEUR Act of 2021); H.R. 8920, 116th Cong. (2020) (PASTEUR Act of 2020).

[6] Asher Mullard, *UK Outlines Its Antibiotic Pull Incentive Plan*, 19 NATURE REVS. DRUG DISCOVERY 298, 298 (2020). Half this amount would come from the United States, according to a National Academy of Sciences Report. COMBATING ANTIMICROBIAL RESISTANCE AND PROTECTING THE MIRACLE OF MODERN MEDICINE, *supra* note 2, at 246.

[7] U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, *Executive Summary* of ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES, at vii (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/?CDC_AAref_Val=https://www.cdc.gov/DrugResistance/Biggest-Threats.html; *see also* INST. FOR HEALTH METRICS & EVALUATION, MEASURING INFECTIOUS CAUSES AND RESISTANCE OUTCOMES FOR BURDEN ESTIMATION (2024), https://vizhub.healthdata.org/microbe/ (estimating 38,831 U.S. deaths from antibacterial resistance in 2019).

[8] INTERAGENCY COORDINATION GRP. ON ANTIMICROBIAL RESISTANCE, NO TIME TO WAIT: SECURING THE FUTURE FROM DRUG-RESISTANT INFECTIONS: REPORT TO THE SECRETARY GENERAL OF THE UNITED NATIONS (2019), https://cdn.who.int/media/docs/default-source/documents/no-time-to-wait-securing-the-future-from-drug-resistant-infections-en.pdf?sfvrsn=5b424d7_6&download=true.

[9] *See* JIM O'NEILL ET AL., ANTIMICROBIAL RESISTANCE: TACKLING A CRISIS FOR THE HEALTH AND WEALTH OF NATIONS 5–6 (2014), https://wellcomecollection.org/works/rdpck35v.

of resistant bacteria.[10] On the other hand, seventeen of eighteen deaths associated with infection are of patients with susceptible bacteria, a group largely ignored in discussions of unmet medical needs.[11]

There are costs to the economy as well. A World Bank report, based on modeling assumptions that presume as yet unobserved increases in resistance, estimated that global economic losses from a failure to contain antimicrobial resistance would be at least $10 trillion from 2017 to 2050.[12] Figures such as these have been seized upon by intergovernmental collaborations,[13] public–private partnerships,[14] and others to raise the alarm on what has been termed a "global crisis" of antimicrobial resistance and to urge policies that promote the development of new drugs, including the use of market entry rewards. However, patients with resistant infections are older, sicker, and have more concomitant diseases; increased morbidity, mortality, and associated economic losses may be due to those factors independent of resistance. Indeed, attributable mortality (deaths due to infection rather than death from other diseases which occur

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[10] J. Xin Liao, Haley J. Appaneal, Anupama Menon, Vrishali Lopes, Kerry L. LaPlante & Aisling R. Caffrey, *Decreasing Antibiotic Resistance Trends Nationally in Gram-Negative Bacteria Across United States Veterans Affairs Medical Centers, 2011–2020*, 12 INFECTIOUS DISEASES & THERAPY 1835, 1839 (2023) ("From 2011 to 2020, resistance in all phenotypes decreased or remained stable, with no noted increases."); Ousmane Oumou Diallo, Sophie Alexandra Baron, Gregory Dubourg, Hervé Chaudet, Philippe Halfon, Sabine Camiade, Béatrice Comte, Stéphanie Joubert, Arnaud François, Philippe Seyral, François Parisot, Jean-Paul Casalta, Raymond Ruimy, Christophe Maruejouls, Jean-Christophe Achiardy, Sophie Burignat, Joseph Carvajal, Edouard Delaunay, Sandra Meyer, Pierre-Yves Levy, Patricia Roussellier, Patrick Brunet, Claude Bosi, Philippe Stolidi, Jean-Pierre Arzouni, Gisele Gay, Pierre Hance, Philippe Colson, Didier Raoult & Jean-Marc Rolain, *Major Discrepancy Between Factual Antibiotic Resistance and Consumption in South of France: Analysis of 539,037 Bacterial Strains*, 10 SCI. REPS. 18262, at *8 (2020) ("[O]ur study did not show a worrying increase in resistance to key antibiotics in our region over a 5-year period."); *see also* Fernando Baquero, *Threats of Antibiotic Resistance: An Obliged Reappraisal*, 24 INT'L MICROBIO. 499, 502 (2021) ("The key-difficulty is to discern between 'deaths in infected patients *with* antibiotic-resistant bacteria' and 'deaths in patients where the infection *is caused by* antibiotic-resistant bacteria . . . .'"); Cédric Abat, Pierre-Edouard Fournier, Marie-Thérèse Jimeno, Jean-Marc Rolain & Didier Raoult, *Extremely and Pandrug-Resistant Bacteria Extra-Deaths: Myth or Reality?*, 37 EUROPEAN J. CLINICAL MICROBIO. & INFECTIOUS DISEASES 1687, 1694 (2018) (noting "huge discrepancy between real deaths observed in our hospitals and the four previously mentioned alarmist reports"); Cédric Abat, Jean-Marc Rolain, Grégory Dubourg, Pierre-Edouard Fournier, Hervé Chaudet & Didier Raoult, *Evaluating the Clinical Burden and Mortality Attributable to Antibiotic Resistance: The Disparity of Empirical Data and Simple Model Estimations*, 65 CLINICAL INFECTIOUS DISEASES S58, S61 (2017) ("[T]he current fears and alarmist reports both in the scientific community and in the media might be far removed from reality.").

[11] Alexander Lawandi, Sameer S. Kadri & John H. Powers III, *Focusing on Antimicrobial Resistant Infections–Are We Missing the Forest for the Trees and the Patients for Pathogens?*, 2 FRONTIERS IN ANTIBIOTICS 1, at *2 (2023) (noting "a ratio [of] 17 deaths with susceptible pathogens for every 1 death with a DTR [difficult-to-treat, or resistant] pathogen").

[12] WORLD BANK GRP., DRUG-RESISTANT INFECTIONS: A THREAT TO OUR ECONOMIC FUTURE 29 (2017), http://documents1.worldbank.org/curated/en/323311493396993758/pdf/final-report.pdf.

[13] *See, e.g.*, INTERAGENCY COORDINATION GRP. ON ANTIMICROBIAL RESISTANCE, *supra* note 8, at 14 ("[A]dditional, sustained investments . . . are needed . . . to accelerate research and development [and] pull new products through to market."); *see also* U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, 2016–2020 TATFAR PROGRESS REPORT (2021), https://www.cdc.gov/drugresistance/pdf/2021-progress-report-508.pdf. TATFAR is a collaboration among Canada, European Union, Norway, United Kingdom, and the United States. *See Participants in TATFAR*, U.S. CTRS. FOR DISEASE CONTROL & PREVENTION (Apr. 19, 2024), https://www.cdc.gov/tatfar/php/members/?CDC_AAref_Val=https://www.cdc.gov/drugresistance/tatfar/members.html.

[14] *See, e.g.*, ÅRDAL ET AL., *supra* note 2; TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS, *supra* note 2.

with concomitant infection) is estimated at approximately 26%, meaning the greater part of the cost may be independent of infection.[15]

Proposals for antibiotic market entry rewards are only the most recent in a long history of proposals seeking to replace or supplement the patent system with prizes, the benefits of which have long been known.[16] Most notably, prizes allow inventions to be made available immediately to everyone at closer to the cost of production, without the temporarily high prices engendered under a patent system.[17] In the context of antibiotics, the benefits of a prize system are usually framed in terms of wider patient access,[18] an augmentation of current compensation mechanisms that systematically undervalue antibiotics,[19] and a reduction of the incentive to earn profits through overuse, thereby promoting the principle of antibiotic stewardship.

However, it is unclear why wider access is needed, as evidence shows that newer drugs are little-used in practice currently.[20] This is not due to lack of access but due to lack of evidence of their benefits for patients over available therapies and because of the rarity of patients with infections resistant to all available drugs. Furthermore, resistance is often defined as resistance to one or more drugs, without taking into account that one or more potentially effective older drugs may remain.[21] For example,

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[15] Antimicrobial Resistance Collaborators, *Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis*, 399 LANCET 629, 637 (2022) (noting 1.27 million deaths "attributable" to resistance and 4.95 million additional deaths "associated with" resistance); *see also id.* at 636 tbl.2 (providing regional and global mortality burdens associated with, and attributable to, bacterial resistance).

[16] *See, e.g.*, Michael Abramowicz, *Perfecting Patent Prizes*, 56 VAND. L. REV. 115, 128–70 (2003) (summarizing previous prize proposals); Steven Shavell & Tanguy van Ypersele, *Rewards Versus Intellectual Property Rights*, 44 J.L. & ECON. 525 (2001); Brian D. Wright, *The Economics of Invention Incentives: Patents, Prizes, and Research Contracts*, 73 AM. ECON. REV. 691 (1983); Michael Polanvyi, *Patent Reform*, 11 REV. ECON. STUDIES 61 (1944); 2 ROBERT A. MACFIE, COPYRIGHT AND PATENTS FOR INVENTIONS vi (Edinburgh: T. & T. Clark 1883); ROBERT A. MACFIE, RECENT DISCUSSION ON THE ABOLITION OF PATENTS FOR INVENTIONS IN THE UNITED KINGDOM, FRANCE, GERMANY, AND THE NETHERLANDS 84–86 (London: Longmans, Green, Reader & Dyer 1869).

[17] OBSERVATIONS ON THE UTILITY OF PATENTS, AND ON THE SENTIMENTS OF LORD KENYON RESPECTING THAT SUBJECT 20–21 (London 3d ed. 1791) ("[L]et the People instantly enjoy the benefit of his ingenuity."); *see also* Abramowicz, *supra* note 16, at 122 (explaining that prizes allow "the avoidance of deadweight loss that occurs when a person values a product at more than its marginal cost but less than its patent-protected price").

[18] *E.g.*, HELLE AAGAARD, ROHIT MALPANI & ANNA ZORZET, REACT EUR., ENSURING SUSTAINABLE ACCESS TO EFFECTIVE ANTIBIOTICS FOR EVERYONE—EVERYWHERE: HOW TO ADDRESS THE GLOBAL CRISIS IN ANTIBIOTIC RESEARCH AND DEVELOPMENT (2021), https://www.reactgroup.org/wp-content/uploads/2021/09/ReAct-Report-Ensuring-sustainable-access-to-effective-antibiotics-for-everyone-everywhere-How-to-address-the-global-crisis-in-antibiotic-Research-and-Development-March-2021.pdf.

[19] *E.g.*, Jonathan J. Darrow, Michael S. Sinha & Aaron S. Kesselheim, *When Markets Fail: Patents and Infectious Disease Products*, 73 FOOD & DRUG L.J. 361, 366 fig.4 (2018) (summarizing reasons why antibiotics are undervalued).

[20] *See, e.g.*, Asher Mullard, *Achaogen Bankruptcy Highlights Antibacterial Development Woes*, 18 NATURE REVIEWS DRUG DISCOVERY 411, 411 (2019) ("Since launching the drug for the treatment of cUTI [complicated urinary tract infection], it has earned less than US$1 million in sales.").

[21] Samir S. Kadri, Jennifer Adjemian, Yi Ling Lai, Alicen B. Spaulding, Emily Ricotta, D. Rebecca Prevots, Tara N. Palmore, Chanu Rhee, Michael Klompas, John P. Dekker, John H. Powers III, Anthony F. Suffredini, David C. Hooper, Scott Fridkin & Robert L. Danner, *Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents*, 67 CLINICAL INFECTIOUS DISEASES 1803, 1803 (2018) ("In 2008, the US Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control classified nonsusceptibility to ≥1 agent in ≥3 antimicrobial categories as multidrug resistant (MDR), and susceptibility limited to ≤2 categories as extensively drug-resistant (XDR)."); *see also*

there are over a dozen FDA-approved drugs for diseases due to methicillin-resistant *Staphylococcus aureus* (MRSA), yet mortality in these diseases has remained constant with a lack of evidence of improved outcomes from newer drugs.

The limitations of a prize system are also long-known, as this Article's 1791 epigraph reflects, and center on the difficulty of product valuation.[22] Despite this known challenge among scholars of innovation policy, the subject has received only light treatment in proposals for antimicrobial market entry rewards. The benefits of new antibiotics often are assumed based on their ability to inhibit growth of organisms in test tubes. Yet this biological activity does not automatically translate to improving the outcomes of patients with disease.[23] Several studies have been conducted estimating the amount of reward necessary to "pull" new antibiotics onto the market,[24] but most do not focus sufficiently (or at all) on the value of the products themselves, especially in relation to alternative means for reducing morbidity and mortality, or current evidence of the lack of additional benefit on improving patient outcomes with new antibiotics.

One partial exception is a 2014 analysis commissioned by the U.S. Department of Health and Human Services (HHS), which estimated quality-adjusted life year (QALY) benefits for future antibacterial drugs in order to calculate the present value of their "social returns."[25] However, valuing drugs that do not yet exist required assumptions that could prove substantially inaccurate, as the authors conceded, such as that individuals not responding to existing drugs would respond to future drugs, and that benefits of future drugs would be similar to those of existing drugs with respect

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Jeffrey R. Strich, Sarah Warner, Yi Ling Lai, Cumhur Y. Demirkale, John H. Powers III, Robert L. Danner & Sameer S. Kadri, *Needs Assessment for Novel Gram-negative Antibiotics in US Hospitals: A Retrospective Cohort Study*, 20 LANCET INFECTIOUS DISEASES 1172, 1173 (2020) ("Difficult-to-treat resistance (DTR), a recently introduced resistance metric, is defined as in-vitro non-susceptibility to all first-line, high-efficacy, low-toxicity drugs . . . .").

[22] *See, e.g.*, OBSERVATIONS ON THE UTILITY OF PATENTS, AND ON THE SENTIMENTS OF LORD KENYON RESPECTING THAT SUBJECT 21 (London 3d ed. 1791); *see also* Marlynn Wei, *Should Prizes Replace Patents? A Critique of the Medical Innovation Prize Act of 2005*, 13 B.U. J. SCI. & TECH. L. 25, 32 (2007) (referring to "the Scylla of undercompensation and Charybdis of overcompensation").

[23] John H. Powers, Scott R. Evans & Aaron S. Kesselheim, *Studying New Antibiotics for Multidrug Resistant Infections: Are Today's Patients Paying for Unproved Future Benefits?*, 360 BMJ 1, at *3 (2018) ("[D]rugs with promising preclinical and early clinical data can fail to show benefits for patients in later stage trials."); Dalia Deak, Kevin Outterson, John H. Powers & Aaron S. Kesselheim, *Progress in the Fight Against Multidrug-Resistant Bacteria? A Review of U.S. Food and Drug Administration–Approved Antibiotics, 2010–2015*, 165 ANNALS INTERNAL MED. 363, 370 (2016) ("None of the drugs demonstrated superior outcomes on patient survival or disability in their pivotal trials despite promising in vitro, animal, and pharmacokinetic data."); *see also* Mayookha Mitra-Majumdar, John H. Powers III, Beatrice L. Brown & Aaron S. Kesselheim, *Evidence at Time of Regulatory Approval and Cost of New Antibiotics in 2016-19: Cohort Study of FDA Approved Drugs*, 1 BMJ MED. e000227, at *6 (2022) ("The results of the three superiority trials were driven by surrogate outcomes of urine culture without superiority for patient outcomes.").

[24] *See* Kevin Outterson, *Estimating the Appropriate Size of Global Pull Incentives for Antibacterial Medicines*, 40 HEALTH AFFS. 1758, 1759 (2021) (summarizing five studies sponsored by governments and the World Health Organization); *see also id.* at 1761 ("This study had several limitations. First, the model did not estimate the value of antibacterial innovation to society but only the cost of bringing an innovative antibacterial to approval and sustaining it in the market thereafter.").

[25] AYLIN SERTKAYA, JOHN EYRAUD, ANNA BIRKENBACH, CALVIN FRANZ, NYSSA ACKERLEY, VALERIE OVERTON & KEVIN OUTTERSON, E. RSCH. GRP., ANALYTICAL FRAMEWORK FOR EXAMINING THE VALUE OF ANTIBACTERIAL PRODUCTS 3–24 (2024), https://aspe.hhs.gov/sites/default/files/migrated_legacy_files//44241/rpt_antibacterials.pdf.

to, for example, duration of illness avoided.[26] Current evidence does not validate these assumptions given the lack of demonstrated additional benefit of new drugs compared to older, less expensive therapies.[27] Few drugs have been studied in patients with resistant infections, and some appear to have worsened rather than improved patient outcomes.[28]

To appropriately prioritize and fund the development of new infectious disease treatments, a broader exploration of critical issues in valuation, beyond prize sufficiency and QALYs gained, is needed. This Article explores valuation issues that have not received sufficient attention in current debates of antibiotic market entry rewards. First, market entry rewards are likely to yield exceptionally high per-patient costs the rarer the disease, the less effective the new treatment, and the greater the subsidies already expended, even when taking into account beneficial externalities to third parties. Second, insufficient consideration has been given to alternate means of reducing morbidity and mortality, including from infectious diseases, despite the indispensable nature of such considerations to responsible resource allocation. Third, the need for any market entry reward at all is premised on the assumption that current incentives have led to few new antibiotics being approved, when in fact the pipeline of infectious disease therapies (which are not limited to antibiotics) is larger and healthier than is often framed. Fourth, experience with past incentive programs has shown that costs are often higher and benefits lower than expected, thanks in large part to difficulties in defining high-value products and limiting rewards accordingly. Fifth, additional considerations—often more subtle—create the risk that a prize system, even if initially successful in promoting antibiotic development, is likely to deteriorate in value over time due to a lack of cost transparency, conflicts of interest that divert attention from higher-value approaches, and attempts at political influence as the market redirects lobbying efforts toward a large new source of funds and hones those efforts over time.

II. A $3 BILLION PRIZE PRESENTS AN EXCEPTIONALLY HIGH PER-PATIENT COST

Placing a value on the protection of human health or life is a challenging and controversial task. Nevertheless, academics and others have for decades observed the amount in dollars that governments have by their actions demonstrated a willingness to spend to achieve reductions in lost life.[29] For example, an analysis by a former

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[26] *Id.*

[27] Dafna Yahav, Noam Tau & Daniel Shepshelovich, *Assessment of Data Supporting the Efficacy of New Antibiotics for Treating Infections Caused by Multidrug-resistant Bacteria*, 72 CLINICAL INFECTIOUS DISEASES 1968, 1972 (2021) ("Promising preclinical data in terms of in vitro susceptibility, animal models, and pharmacokinetic/pharmacodynamic data, do not necessarily result in clinical superiority. This has been demonstrated for several new antibiotic drugs found to have reduced effectiveness or increased harm compared with older drugs, despite favorable preclinical data.").

[28] John H. Powers, *Scientific Evidence, Regulatory Decision Making, and Incentives for Therapeutics in Infectious Diseases: The Example of Cefiderocol*, 72 CLINICAL INFECTIOUS DISEASES e1112, e1112 (2021) ("The results show a numerical increase in deaths with cefiderocol compared to BAT [best available therapies] . . . .").

[29] W. Kip Viscusi, *The Value of Risks to Life and Health*, 31 J. ECON. LIT. 1912, 1942 (1993) ("The appropriate measure of the value of life from the standpoint of government policy is society's willingness to pay for [] risk reduction . . . ."); *see also* Nadia J. Sweis, *Revisiting the Value of a Statistical Life: An*

Branch Chief in the White House's Office of Management and Budget (OMB) calculated that enacted U.S. government regulations revealed a willingness to spend dramatically differing amounts, per life saved, on issues such as space heater safety ($100,000), airplane fire prevention ($200,000), seatbelt regulation ($300,000), children's sleepwear flammability ($1.3 million), and asbestos safety ($89 million).[30] Current OMB guidance observes that federal agencies "typically utilize central estimates of [the 'value of a statistical life' of] between $10 million to $12 million as of 2022."[31] If the $3 billion proposed market entry reward is applied to CDC's 2019 estimate of 35,000 deaths for drug-resistant pathogens,[32] the cost per life saved indefinitely into the future would appear to be well within the range of OMB's estimate, at just $8,571 per death avoided.[33]

However, the idealized assumptions implicit in this figure are unlikely to be true based on currently available evidence, beginning with the improbability of preventing 100% of deaths and uncertainty over the number of drugs needed to avoid even a substantial fraction of deaths due to drug-resistant pathogens. As noted above, these calculations also have little relevance to the far larger numbers of deaths due to organisms susceptible to currently available agents. Patients with susceptible organisms are unlikely to have improved outcomes based on novel interventions boasting mechanisms based on inhibiting bacterial growth, since they already have available effective options. Morbidity and mortality from infectious disease is a function not only of the genotype of the pathogen but also of the strength of the host's immune system.[34] Poor outcomes in patients with susceptible disease may be due to, for example, inaccurate diagnoses or disordered immune response to infection, which would likely benefit most from improved diagnostics, host-directed therapies, or prevention strategies, not new drugs targeted to resistant pathogens.

A. Drug-Resistant Pathogens Are Diverse but Often Rare

The figure of 35,000 annual U.S. deaths estimated to result from treatment-resistant pathogens is an aggregate of fifteen different diseases, both bacterial and fungal

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International Approach During COVID-19, 24 RISK MGMT. 259, 262 (2022) (The value of a statistical life is "definable as the tradeoff between wage and risk, while also accounting for the loss of leisure . . . [and] losses from foregone earnings.").

[30] John F. Morrall, *A Review of the Record*, 10 REGULATION 25, 30 tbl.4 (1986).

[31] OFF. OF MGMT. & BUDGET, CIRCULAR NO. A-4 50 (2023), https://www.whitehouse.gov/wp-content/uploads/2023/11/CircularA-4.pdf; *see also* U.S. DEP'T OF TRANSP., DEPARTMENTAL GUIDANCE ON VALUATION OF A STATISTICAL LIFE IN ECONOMIC ANALYSIS (2024), https://www.transportation.gov/office-policy/transportation-policy/revised-departmental-guidance-on-valuation-of-a-statistical-life-in-economic-analysis (utilizing a "value of a statistical life" in 2023 of $13.2 million).

[32] *See infra* note 35 and accompanying text.

[33] Morrall applied a 10% discount rate to both benefits (e.g., lives saved) and costs. *See* Morrall, *supra* note 30, at 25 ("Discounting costs but not benefits leads to absurd results, such as that . . . all rules yielding continuous benefits are worth any amount of immediate costs."). Following Morrall, a 10% discount rate was used to calculate the total number of lives saved indefinitely into the future and thereby calculate the range of $8,571 figure, a calculation that assumes 100% of deaths from all resistant pathogens would be avoided by a single drug, resistance would never develop, and the same number of people as described in the 2019 CDC report would die each year indefinitely into the future if the drug in question were not available.

[34] *See generally* William E. Paul, *Infectious Diseases and the Immune System*, 269 SCI. AM. 90, 95 (1993) (describing immune system responses to infection and explaining that differences in response "may partially explain why the outcomes of some infectious diseases differ from one person to the next").

(CDC's 2019 report did not include deaths from resistant viruses, protozoa, or helminths). Deaths attributable to individual pathogens necessarily constitute only a fraction of this total, including MRSA (the most deadly, at 10,600 deaths), carbapenem-resistant *Acinetobacter* (700), drug-resistant *Campylobacter* (70), drug-resistant tuberculosis (62), drug resistant *shigella* (<5), and drug-resistant *Neisseria gonorrhoeae* (no deaths reported).[35] These figures highlight the challenge of focusing on "pathogen-based" development[36] rather than patients and patient outcomes, as the numbers of patients with poor outcomes from an individual pathogen is small. In contrast, other types of non-antibiotic therapies, such as host-directed therapies, could potentially benefit those with disease from a variety of both susceptible and resistant pathogens. There is an economic case against pathogen-focused development as well. If a different drug is needed for each of these pathogens, a $3 billion market entry reward would present a cost-per-death-avoided that is five times higher than OMB's $12 million figure for two of the fifteen pathogens on CDC's list (**Table**), even before other idealized assumptions of these estimates are considered.

Table: Cost Per Death Avoided of a $3 Billion Market Entry Reward Under Idealized Assumptions

Cost/death avoided*	Deaths**	Resistant Pathogen***
n/a	-	Candida auris
n/a	-	Drug-resistant Neisseria gonorrhoeae
$ 60,000,000	5	Drug-resistant *Shigella*
$ 60,000,000	5	Drug-resistant *Salmonella* Serotype Typhi
$ 4,838,710	62	Drug-resistant tuberculosis
$ 4,285,714	70	Drug-resistant nontyphoidal *Salmonella*
$ 4,285,714	70	Drug-resistant *Campylobacter*
$ 666,667	450	Erythromycinresistant group A *Streptococcus*
$ 428,571	700	Carbapenem-resistant *Acinetobacter*
$ 416,667	720	Clindamycinresistant group B *Streptococcus*
$ 272,727	1,100	Carbapenem-resistant Enterobacteriaceae
$ 176,471	1,700	Drug-resistant *Candida*
$ 111,111	2,700	Multi-drug resistant *Pseudomonas aeruginosa*
$ 83,333	3,600	Drug-resistant *Streptococcus pneumoniae*
$ 55,556	5,400	Vancomycin-resistant *Enterococcus*
$ 32,967	9,100	ESBL-producing Enterobacteriaceae
$ 28,302	10,600	Methicillin-resistant *Staphylococcus aureus*
n/a	12,800	*Clostridioides difficile*

* Assumptions: 100% of deaths from each pathogen will be avoided with a single drug that received a $3 billion market entry reward; no other costs per drug; no change in annual deaths avoided; 10% discount rate

35 U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES 16–17 (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/?CDC_AAref_Val=https://www.cdc.gov/DrugResistance/Biggest-Threats.html.

36 Arturo Casadevall & Liise-anne Pirofski, *Microbiology: Ditch the Term Pathogen*, NATURE, Dec. 10, 2014, at 165 (2014) ("[T]he use of the term pathogen sustains an unhelpful focus among researchers and clinicians on microbes that could be hindering the discovery of treatments.").

for benefits (i.e., deaths avoided) indefinitely into the future, using the formula NPV = B/r, where NPV = net present value, B = benefits (deaths avoided) per year, and r = discount rate.

** *See* U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES 16–17 (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/?CDC_AAref_Val=https://www.cdc.gov/DrugResistance/Biggest-Threats.html.

*** *Clostridioides difficile* is not considered a resistant pathogen in the 2019 CDC report, and is included for burden of disease comparison only. CDC did not report any deaths for *Candida auris* or drug-resistant *Neisseria gonorrhoeae.*

Other factors would further raise the cost of deaths avoided. Total drug costs are not limited to the market entry reward alone,[37] most drugs fail during development,[38] and even successfully approved drugs are unlikely to prevent 100% of deaths.[39] It is also possible that non-drug interventions (e.g., hygiene) could lower the number of deaths per year in the absence of a new drug, increasing the cost per additional death avoided.[40] Competition for a $3 billion reward and the long development times required for new drugs could mean that multiple drug sponsors develop a drug for the same rare pathogen, perhaps gaining approval around the same time or within a few years of one another, necessitating the payment of multiple prizes.[41] Evolution of pathogens could lead to any number of phylogenetic branches, each potentially requiring its own new drug. Unlike seatbelts, children's sleepwear flammability standards, and other regulations considered by OMB, which can be expected to yield reductions in lost lives indefinitely into the future, any added health benefits of new antibiotics will wane from resistance, as has already occurred with existing antibiotics and is an inherent characteristic of antibiotics, highlighting why other approaches beyond antibiotics are needed. Once a new chemical entity is developed and rewarded, additional rewards may need to be paid for valuable follow-on inventions only indirectly related to resistance, such as better tasting pediatric formulations, smaller tablets for those with difficulty swallowing, injectable formulations that avoid use of a dextrose solution to meet the needs of diabetic patients, or heat-stable formulas for low-resource tropical settings.[42] Although a continuous stream of never-ending payments (such as proposed antibiotic subscription models[43]) is an unambiguous boon

37 *See infra* Part II.B.

38 *See* Neha K. Prasad, Ian B. Seiple, Ryan T. Cirz & Oren S. Rosenberg, *Leaks in the Pipeline: A Failure Analysis of Gram-Negative Antibiotic Development from 2010 to 2020*, 66 ANTIMICROBIAL AGENTS & CHEMOTHERAPY e0005422, at *1–2 (2022) (contrasting the 1980s, in which 40% of antibiotic candidates achieved approval within a median of six years, with the 2000s, in which just 17% received approval within twelve years).

39 *See infra* Part II.C.

40 *See infra* Part III.A.

41 *See* Steven Shavell & Tanguy van Ypersele, *Rewards Versus Intellectual Property Rights*, 44 J.L. & ECON. 525, 542 (2001) (The race to obtain a prize "leads to the possibility of overinvestment in research because the private return to being first may exceed its social value.").

42 *See* Jonathan J. Darrow, Victor Van de Wiele, Beatrice Brown & Aaron S. Kesselheim, *The Prevalence of Post-NDA Drug Patents and Their Relationship to the Timing of Generic Approval*, 42 NATURE BIOTECH. 1350, 1354 (2024) (providing examples of valuable follow-on inventions).

43 *See, e.g.*, MONIKA SCHNEIDER, GREGORY W. DANIEL, NICHOLAS R. HARRISON & MARK B. MCCLELLAN, DUKE MARGOLIS CTR. FOR HEALTH POL'Y, DELINKING US ANTIBIOTIC PAYMENTS THROUGH A SUBSCRIPTION MODEL IN MEDICARE (2020), https://healthpolicy.duke.edu/sites/default/files/2020-03/margolis_subscription_model.pdf.

to industry, it may not be the optimal approach to reducing the public's infectious disease burden.

On the other hand, a number of factors could lower estimates of cost per death avoided, helping to bring the two highest-cost pathogens below OMB's $12 million figure. For example, in the absence of a new drug that improves patient outcomes, the number of deaths per year from those pathogens could rise, perhaps dramatically, rather than remain constant, although current evidence suggests such increases have not occurred.[44] The CDC also did not include "non-hospitalized cases" or deaths outside the United States in its report (raising questions about international collaboration or, alternately, the extent to which U.S.-funded prizes should be justified based on benefits to those outside the United States). Drugs could also reduce morbidity for the 98.5% of patients (2,325,847 of 2,362,129 people) infected with treatment-resistant pathogens that, according to CDC's figures, did not die from them. If treatment with new antibiotics shortens hospital stays or reduces the need for organ transplants or other costly procedures, overall healthcare costs could be reduced. For example, one study found that MRSA was associated with attributable healthcare costs of $34,000 compared to $31,500 for methicillin-susceptible *Staphylococcus aureus*, permitting theoretical savings of $2,500 (~7%) per patient.[45] Yet other studies showed that, after adjusting for patient factors like severity of disease and co-morbid illness, there was no difference in outcomes between those with methicillin-resistant and susceptible disease.[46]

These factors and uncertainties make it difficult to estimate the true cost per death avoided—assuming evidence shows that a new intervention prevents death at all—except perhaps in hindsight after costs have already been expended and pharmaceutical companies have distributed profits to shareholders. Even then, it will be difficult to estimate the extent to which a drug successfully lowered morbidity and mortality in practice, especially to third parties who were never infected, in a way that could not have been accomplished through non-drug means. While discount rates for costs expended can be reasonably estimated based on market rates, the appropriate discount rate for future deaths avoided is more arbitrary, yet the rate chosen substantially affects estimated costs per life saved.[47]

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[44] *See supra* note 10.

[45] Robert J. Rubin, Catherine A. Harrington, Anna Poon, Kimberly Dietrich, Jeremy A. Greene & Adil Moiduddin, *The Economic Impact of* Staphylococcus aureus *Infection in New York City Hospitals*, 5 EMERGING INFECTIOUS DISEASES 9, 14 (1999).

[46] *See, e.g.*, Natasha E. Holmes, John D. Turnidge, Wendy J. Munckhof, J. Owen Robinson, Tony M. Korman, Matthew V.N. O'Sullivan, Tara L. Anderson, Sally A. Roberts, Sanchia J.C. Warren, Wei Gao, Benjamin P. Howden & Paul D.R. Johnson , *Vancomycin AUC/MIC Ratio and 30-Day Mortality in Patients with* Staphylococcus aureus *Bacteremia*, 57 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 1654, 1660 (2013) ("We found no association between achieving a vancomycin AUC/MIC of ≥400 (published target) . . . and reduction in . . . attributable mortality . . . ."); N.E. Holmes, J.D. Turnidge, W.J. Munckhof, J.O. Robinson, T.M. Korman, M.V.N. O'Sullivan, T.L. Anderson, S.A. Roberts, S.J.C. Warren, W. Gao, P.D.R. Johnson & B.P. Howden, *Vancomycin Minimum Inhibitory Concentration, Host Comorbidities and Mortality in* Staphylococcus aureus *Bacteraemia*, 19 CLINICAL MICROBIO. & INFECTION 1163, 1166 (2013) ("[V]ancomycin MIC is a marker of host or pathogen determinants rather than being causally associated with poor outcome.").

[47] *See supra* note 33.

B. There Are Costs Beyond the Market Entry Reward Itself

Following payment of a market entry reward, there will be ongoing costs to manufacture, distribute, administer, monitor, and evaluate the drug. Under the PASTEUR Act, these costs were to be borne in part by the drug sponsor as part of a subscription contract in return for the prize money, but after expiration of the contract, which was proposed to last as little as five years and in no event longer than associated patent terms or other exclusivity,[48] they would have had to be paid from other sources.

Transaction costs of a prize system itself must also be considered.[49] The PASTEUR Act bill provided that $6 billion would be allocated for 2024, some share of which would be used to administer the grant program, including establishing a payment office, a subscription contract office, and an advisory group, among other ongoing overhead costs.[50] Not more than 5% (i.e., $300 million) was to be used for a CDC-administered grant program to promote and measure judicious use of antimicrobial drugs as well as to measure and publicly report trends in antimicrobial use and pathogen resistance.[51]

Numerous other costs must be added to the market entry reward to understand the full costs of each new drug. These include existing programs or policies that provide both direct and indirect government funding before and after approval. Because of the uncertainty associated with the prize and its amount, investors will require a risk premium (i.e., a higher prize amount) to compensate for the added risk for any given level of investment.

1. Direct Government Funding of Research and Development

If enacted into law, market entry rewards would be only the latest addition to an accumulating array of taxpayer-funded programs that provide billions of dollars to subsidize the development and use of drugs from basic research to post-approval funding (**Figure 1**). The federal government has thus already taken steps to counterbalance undervaluation by the private market, providing billions of dollars in support of the development of antimicrobial treatments. The National Institute of Allergy and Infectious Diseases (NIAID, a part of the National Institutes of Health (NIH) founded in 1955) devotes about $1.8 billion annually to HIV/AIDS research and $2.6 billion to research in biodefense and emerging infectious diseases.[52] In 2010, the Biomedical Advanced Research Development Authority (BARDA), an agency of HHS, established the Broad Spectrum Antimicrobials program, which supports the

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[48] Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2023 (PASTEUR Act), S. 1355, 118th Cong., sec. 2, § 399OO-(f) (2023).

[49] *See* Steven Shavell & Tanguy van Ypersele, *Rewards Versus Intellectual Property Rights*, 44 J.L. & ECON. 525, 543 (2001).

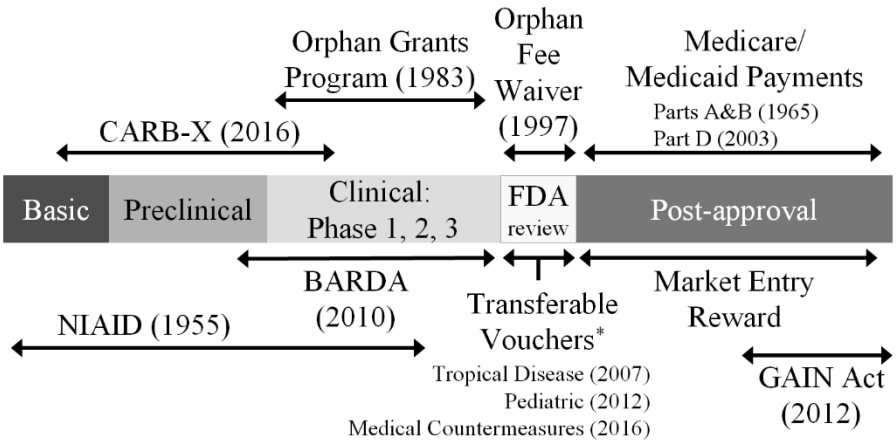
[50] *See* Ronald H. Coase, *The Problem of Social Costs*, 3 J. L. ECON. 1, 18 (1960) ("[T]he governmental administrative machine is not itself costless. It can, in fact, on occasion be extremely costly."); *see generally* Ronald H. Coase, *The Nature of the Firm*, 4 ECONOMICA 386 (1937) (explaining that firms can reduce the transaction costs otherwise borne by marketplace transactions).

[51] Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2023 (PASTEUR Act) § 399OO-3(d).

[52] U.S. DEP'T OF HEALTH & HUM. SERVS., NAT'L INSTS. OF HEALTH, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES: CONGRESSIONAL JUSTIFICATION FY 2024 13 (2024), https://www.niaid.nih.gov/sites/default/files/fy2024cj.pdf [hereinafter NIAID CONGRESSIONAL JUSTIFICATION FY 2024].

development of new products through mid- or late-stage clinical development.[53] The nonprofit Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), founded in 2016, has received at least $230 million from the U.S. government (including from NIH and BARDA) in funds and in-kind services along with substantial additional funding from other governments and foundations,[54] and has supported the early stage development of at least twenty-four therapeutics, sixteen vaccines or other preventatives, and eleven diagnostics.[55] These and other subsidies are illustrated in **Figure 1** and more fully explained, for pharmaceuticals generally, in previous writings.[56]

Figure 1: U.S. Government Subsidies of Research for New Antimicrobials



* Vouchers subsidize the approved product by being sold and used for the FDA review of an unrelated product.

Because early-stage government-funded investments are made years prior to a drug's availability, the government bears a cost of capital representing the foregone value of other investments that could have been made with the same money, such as investment in offshore wind energy generation or repair of bridges before fatal collapses occur. This cost of capital borne by the government has not always been appreciated in discussions of market entry rewards. For example, a 2022 report by the National Academy of Medicine supporting increased government funding of new antimicrobial products stated, without explanation or citation, that "[t]he cost of capital

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[53] John K. Billington, *The ABCs of the US Broad Spectrum Antimicrobials Program: Antibiotics, Biosecurity, and Congress*, 13 HEALTH SEC. 349, 349 (2015).

[54] CARB-X, ACCELERATING THE GLOBAL RESPONSE TO ANTIMICROBIAL RESISTANCE: ANNUAL REPORT 2020–2021 14 (2021), https://carb-x.org/wp-content/uploads/2021/10/CarbX_AR_20-21.pdf.

[55] CARB-X, CARB-X COMPLETE PORTFOLIO, AS OF 5/13/24 (2024), https://carb-x.org/wp-content/uploads/2024/06/CARB-X-Pipeline-2024.5.13.pdf. An additional forty-four projects are listed as "formerly funded."

[56] *See generally* Jonathan J. Darrow & Donald W. Light, *Beyond the High Prices of Prescription Drugs: A Framework to Assess Costs, Resource Allocation, and Public Funding*, 40 HEALTH AFFS. 281, 282 exh.1 (2021) (summarizing government subsidies).

is not an expense that would apply to a government funder."[57] In fact, the cost of capital exists regardless of the source of funds or profit motive.[58] If governments did not experience costs related to the time value of money, they would find it prohibitively expensive to ever solicit bids from the private sector for long-term projects.

2. Direct Government Funding After Approval

The government also provides funding to purchase drugs after they are developed, such as through the Department of Veterans Affairs (1811), Medicare Parts A and B (1965), Medicaid (1965), the Children's Health Insurance Program (1997), and Medicare Part D (2003). Additional funds were made available via an administrative rule adopted in 2019 by the Centers for Medicare and Medicaid Services, which increased Medicare payments for certain antimicrobial treatments (independent of whether they improved patient outcomes compared to available drugs).[59] These post-approval funding mechanisms provide a reward for inventions in a similar manner to that of the patent system, namely by helping to ensure that inventors are compensated for their work through profits earned after approval. Although individual patients may not directly experience the cost of those profits, they experience them indirectly through higher premiums or taxes.

Proposals vary on whether drug sponsors receiving market entry rewards can also receive revenue from patients or insurers. The PASTEUR Act, for example, would apply a mixed system. Market entry rewards would be reduced by the revenue generated through Medicare Part A and Medicaid, but additional revenues could be generated through private sales, sales supported by local or state government funds,[60] or international sales.[61] ReAct Europe, one of the original participants in the European Union's and European Pharmaceutical Industry Association's DRIVE-AB initiative,[62] withdrew in 2017 in part due to objections to a similar type of "double dipping" that industry would be allowed under DRIVE-AB's proposal for how to best revitalize the antibiotic pipeline.[63]

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[57] COMBATING ANTIMICROBIAL RESISTANCE AND PROTECTING THE MIRACLE OF MODERN MEDICINE, *supra* note 2.

[58] *See generally* Eli Schwartz, *The Cost of Capital and Investment Criteria in the Public Sector*, 25 J. FIN. 135 (1970) (discussing considerations for a proper discount rate for government investments); *see also* LUCIANO GRECO & MARIANO MOSZORO, INT'L MONETARY FUND, PUBLIC VERSUS PRIVATE COST OF CAPITAL WITH STATE-CONTINGENT TERMINAL VALUE, WORKING PAPER WP/23/56, at 5 (2023), https://www.imf.org/en/Publications/WP/Issues/2023/03/10/Public-versus-Private-Cost-of-Capital-with-State-Contingent-Terminal-Value-530650 (noting longstanding disagreement on the appropriate rate of discount for public versus private investors).

[59] Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long- Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2020 Rates; Quality Reporting Requirements for Specific Providers; Medicare and Medicaid Promoting Interoperability Programs Requirements for Eligible Hospitals and Critical Access Hospital*s*, 84 Fed. Reg. 42,044 (Aug. 16, 2019) (final); *see also* 84 Fed. Reg. 19,158 (May 3, 2019) (proposed).

[60] Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2023 (PASTEUR Act), S. 1355, 118th Cong., sec. 2, § 399OO-2(j) (2023).

[61] Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2023 (PASTEUR Act) § 399OO-2(k)(2).

[62] ÅRDAL ET AL., *supra* note 2.

[63] *ReAct Responds to Final Report from DRIVE-AB*, REACT EUR. (Jan. 1, 2018), https://www.reactgroup.org/news-and-views/news-and-opinions/year-2018/reacts-response-to-drive-abs-final-report/.

3. Indirect Government Funding

Other indirect government funding in the form of tax or fee forbearance helps to subsidize drug development for rare infectious diseases, including tax credits for rare disease medicines (1983), waivers of FDA drug application fees for orphan drugs (1997), and tax exemptions for private philanthropy (e.g., Bill & Melinda Gates Foundation, 2000).[64] Direct post-approval government funding has been augmented indirectly by exclusivities and other creative means to increase private revenue. For example, in 2007 Congress enacted a "priority review voucher" program that developers of neglected tropical disease products can sell to third parties,[65] generating revenues that in the past have exceeded $90 million per product. Similar programs for rare pediatric disease vouchers and medical countermeasures were added in 2012 and 2016, respectively. In the 2012 Generating Antibiotic Incentives Now Act (GAIN Act), Congress authorized five-year extensions of exclusivity for "qualified infectious disease products,"[66] with qualification possible based on surrogate endpoints rather than improved patient outcomes, helping to ensure that both government and private payers continue to pay high prices for an extended period of time. A number of drug approvals have benefited from GAIN Act designation, but none has been demonstrated to improve patient outcomes.[67]

4. Businesses Will Require a Higher Prize to Compensate for Prize Uncertainty

Businesses make investment decisions based on the expected net present value of the various investment options, which for each potential project is a function of both the certainty and amount of expected future profits. All else equal, greater uncertainty reduces expected net present value. A fixed prize amount provides certainty, but risks over- or under-compensating a new drug if the value it delivers is lower or higher than expected. To help ensure prize money corresponds to drug value, the PASTEUR Act provided for prize amounts to be determined at the time of approval. Tentative prize amounts were to be provided upon submission of a request for designation, which could be submitted after an investigational new drug application is granted by FDA, marking the beginning of permissible human trials.[68]

Despite these efforts, the PASTEUR Act would have introduced new elements of uncertainty into the investment process. Almost by definition, robust clinical evidence typically will not be available at the time an investigational new drug application is granted. Such evidence may be limited even when a product becomes FDA-approved, a problem that critics have highlighted as particularly acute for drugs addressing urgent needs in smaller patient populations.[69] Many of the criteria for qualification listed in

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[64] *See* Darrow & Light, *supra* note 56, at 1, 282 exh.1.

[65] FDA Amendments Act, Pub. L. No. 110-85, § 1102, 121 Stat. 823, 972 (2007).

[66] FDA Safety and Innovation Act, Pub. L. No. 112-144, § 801, 126 Stat. 993, 1077 (2012).

[67] *See, e.g.*, Mitra-Majumdar et al., *supra* note 23, at *6 ("The results of the three superiority trials were driven by surrogate outcomes of urine culture without superiority for patient outcomes.").

[68] Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2023 (PASTEUR Act), S. 1355, 118th Cong., sec. 2, § 399OO-1 (2023).

[69] *See, e.g.*, Beatrice L. Brown, Mayookha Mitra-Majumdar, Krysten Joyce, Murray Ross, Catherine Pham, Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *Trends in the Quality of Evidence Supporting FDA Drug Approvals: Results from a Systematic Literature Review*, 47 J. HEALTH POLITICS

the PASTEUR Act, such as new mechanisms of action or characterization as part of a new drug "class" (which is not clearly defined), do not necessarily translate into improved patient outcomes.

Recognizing that new evidence is likely to emerge after designation and even after drug approval, the proposed PASTEUR Act allowed for reevaluation of the tentative contract price at least two years after designation, as well as of the "final" contract price at least one year after the contract period begins.[70] How such evaluations would be performed and evaluated, especially in critically ill patients, remains unclear.[71] The tradeoff between certainty and appropriate valuation is to some extent inherent in any prize system, and it would be difficult or impossible to remove all uncertainty without sacrificing appropriate valuation, and vice versa. Nevertheless, the result is that higher prize amounts will be required to compensate for this uncertainty, raising the cost per death avoided.

C. New Drugs Will Not Prevent All Morbidity or Mortality

If a drug is less than 100% effective in eliminating mortality, the cost per death avoided would rise. Even when "effective" antibiotics are available and used, deaths can still occur in large numbers, including within the United States. For example, a study of New York City hospitals reported that methicillin-resistant *Staphylococcus aureus* was associated with an attributable mortality rate of 21% (590/2780), but 8% (810/10,770) died from methicillin-susceptible *Staphylococcus aureus*, meaning that more people died from susceptible strains than from resistant strains (810 vs. 590).[72] Another study showed that seventeen of eighteen (94%) deaths associated with infection occur in patients with organisms susceptible to currently available drugs.[73] A new antibiotic with in vitro activity against resistant organisms would be unlikely to benefit these patients.

Notwithstanding the rise in treatment-resistant tuberculosis and a growing human population, the number of yearly U.S. deaths from tuberculosis fell by nearly two-

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POL'Y & L. 649, 657 (2022) ("Compared to drugs approved between 1995 and 1997, drugs approved between 2015 and 2017 were less frequently randomized (94% vs. 82%), double-blinded (80% vs. 68%), or controlled with an active comparator (44% vs. 29%), and they more frequently relied on single-arm trials (9% vs. 18%)."); Sanket S. Dhruva, Jonathan J. Darrow, Aaron S. Kesselheim & Rita F. Redberg, *Strategies to Manage Drugs and Devices Approved Based on Limited Evidence: Results of a Modified Delphi Panel*, 111 CLINICAL PHARMACOLOGY & THERAPEUTICS 1307, 1308 (2022) ("The tradeoff of quicker market availability is that there is often less certainty about safety and effectiveness at the time of FDA approval."); Chul Kim & Vinay Prasad, *Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent Overall Survival: An Analysis of 5 Years of US Food and Drug Administration Approvals*, 175 JAMA INTERNAL MED. 1992, 1993 (2015) ("Our results suggest that the FDA may be approving many costly, toxic drugs that do not improve overall survival.").

[70] Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2023 (PASTEUR Act) § 399OO-2(f)(4).

[71] *See, e.g.*, Brian P. Epling & John H. Powers, *Cefiderocol and the Need for Higher-Quality Evidence: Methods Matter for Patients*, 66 ANTIMICROBIAL AGENTS & CHEMOTHERAPY e0076622, at *1 (2022) (highlighting the limitations of propensity score matching in observational studies).

[72] Rubin et al., *supra* note 45, at 14; *see also* U.S. GOV'T ACCOUNTABILITY OFF., GAO/HEHS/NSIAD/RCED-99-132, ANTIMICROBIAL RESISTANCE: DATA TO ASSESS PUBLIC HEALTH THREAT FROM RESISTANT BACTERIA ARE LIMITED 9 (1999) (discussing the Rubin et al. data).

[73] *See* Lawandi et al., *supra* note 11, at *2.

thirds in the three decades leading up to 2021, from 1,713 to 602.[74] Of the 602, only 78 were multi-drug resistant (defined by CDC as resistant to at least isoniazid and rifampin), indicating that the large majority of deaths were associated with strains of tuberculosis that were not resistant to available treatments.[75] Globally, about 90% of annual deaths estimated to occur from treatable infectious disease are not caused by resistant bacteria,[76] suggesting the limited extent to which a new antibacterial would be likely to reduce infectious disease mortality and the importance of considering the cost-effectiveness of alternate existing measures that could reduce such deaths. Too great a focus on "innovation," in other words, may come at the expense of adequate investment in the maintenance and use of existing proven technologies,[77] as can be seen in the persistent shortages in the United States of low-cost and effective antibiotics.[78] Historically, deaths from infectious diseases decreased before the development of the first antibiotic thanks to improved sanitation and public health measures.[79] More recently, deaths from Ebola virus disease decreased markedly with better supportive care before development of specific therapy.[80] The focus on drugs

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[74] *Reported Tuberculosis in the United States, 2022*, U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.cdc.gov/tb/statistics/reports/2022/default.htm (Nov. 15, 2023).

[75] *Id.* at tbl.11.

[76] Stig Wall, *Prevention of Antibiotic Resistance – An Epidemiological Scoping Review to Identify Research Categories and Knowledge Gaps*, 12 GLOB. HEALTH ACTION, June 1, 2020, at 2 (700,000 deaths due to antibiotic resistance versus 5.7 million deaths due to treatable infections); *see also* Powers et al., *supra* note 23, at 2 ("[M]ost patients do not have unmet medical needs since at least one effective therapy remains for them."); INTERAGENCY COORDINATION GRP. ON ANTIMICROBIAL RESISTANCE, *supra* note 8, at 4 ("[I]nadequate access to antibiotics alone kills nearly 6 million people annually . . . ."); ÅRDAL ET AL., *supra* note 2, at 4 ("[I]t is estimated that ten times as many people die from a lack of access to antibiotics as from resistance.").

[77] *See* LEE VINSEL & ANDREW L. RUSSELL, THE INNOVATION DELUSION: HOW OUR OBSESSION WITH THE NEW HAS DISRUPTED THE WORK THAT MATTERS MOST 10 (Penguin Random House 2020) ("[W]e have researched how the gospel of innovation has affected transportation, computing, and other technological systems, while reflecting on the overlooked fields of infrastructure and maintenance.").

[78] *See, e.g.*, Jonathan J. Darrow, Erin R. Fox & Timo Minssen, *Statutory Thickets and Drug Shortages: Accumulating Legislation as an Underlying Cause*, 51 AM. J. L. & MED. (forthcoming Summer 2025) (on file with author); DIERDRE COGAN, KARRAR KARRAR & JAYASREE K. IYER, ACCESS TO MED. FOUND., SHORTAGES, STOCKOUTS AND SCARCITY: THE ISSUES FACING THE SECURITY OF ANTIBIOTIC SUPPLY AND THE ROLE FOR PHARMACEUTICAL COMPANIES (2018), https://accesstomedicinefoundation.org/medialibrary/resources/5d848ddd0b2ac_Antibiotic-Shortages-Stockouts-and-Scarcity_Access-to-Medicine-Foundation_31-May-2018.pdf; Bander Balkhi, Lita Araujo-Lama, Enrique Seoane-Vazquez, Rosa Rodriguez-Monguio, Sheryl L. Szeinbach & Erin R. Fox, *Shortages of Systemic Antibiotics in the USA: How Long Can We Wait?*, 4 J. PHARM. HEALTH SERVS. RESEARCH 13 (2012).

[79] Elina Hemminki & Anneli Paakkulainen, *The Effect of Antibiotics on Mortality from Infectious Diseases in Sweden and Finland*, 66 AM. J. PUB. HEALTH 1180, 1182 (1976) ("None of these showed an additional decline in death rates after the introduction of antibiotic drugs.").

[80] Francois Lamontagne, Robert A. Fowler, Neill K. Adhikari, Srinivas Murthy, David M. Brett-Major, Michael Jacobs, Timothy M. Uyeki, Constanza Vallenas, Susan L. Norris, William A. Fischer II, Thomas E. Fletcher, Adam C. Levine, Paul Reed, Daniel G. Bausch, Sandy Gove, Andrew Hall, Susan Shepherd, Reed A. Siemieniuk, Marie-Claude Lamah, Rashida Kamara, Phiona Nakyeyune, Moses J. Soka, Ama Edwin, Afeez A. Hazzan, Shevin T. Jacob, Mubarak Mustafa Elkarsany, Takuya Adachi, Lynda Benhadj, Christophe Clément, Ian Crozier, Armando Garciaai, Steven J. Hoffman & Gordon H. Guyatt, *Evidence-based Guidelines for Supportive Care of Patients with Ebola Virus Disease*, 391 LANCET 700, 700 (2018) (noting a decrease in the Ebola case fatality rate from 70% to 40% following implementation of better supportive care). *See generally* William A. Fischer & David A. Wohl, *Combining Vaccines, Optimised Supportive Care, and Therapeutics for Ebola Virus Disease Increases Survival*, 24 LANCET INFECTIOUS DISEASES 560 (2024) (arguing for a multi-pronged approach to improve Ebola outcomes).

may take away from non-pharmacological interventions that could improve patient outcomes more effectively, with fewer side effects, or at decreased cost.

It can also be difficult to know the true number of deaths attributable to a pathogen, since many people with infections, drug-resistant or not, will die while hospitalized or soon thereafter. One study of MRSA bacteremia, for example, found an attributable mortality rate of 1.3% for susceptible strains versus 23.4% for resistant strains through the use of a matched cohort design, but thirty-day all-cause mortality was fourteen times higher for those with susceptible strains (18% vs. 1.3%) and more than twice as high (53% vs. 23.4%) for those with resistant strains.[81] The authors also conceded that most previous studies "could not find a higher mortality rate among patients with bacteremia involving MRSA" than with bacteremia involving susceptible strains, and that "patients infected with MRSA tend to be older, sicker, and more debilitated," making the cohort matching process imperfect and outcome comparisons difficult.[82] Another study, of patients infected with pandrug-resistant *Acinetobacter baumannii*, noted that such patients "are typically severely ill with chronic underlying comorbidities" and found all-cause thirty-day mortality of 24% versus 58% for those colonized versus infected.[83] The concept of "colonization" itself highlights the imperfect correlation between drug resistance and morbidity, since healthy people are often colonized with resistant pathogens without experiencing any of the adverse physical characteristics associated with infection.[84] A global study in 2019 evaluating the impact of antimicrobial resistance found attributable mortality of 26%.[85]

D. "Superbugs" Often Have Been Less Deadly Than Assumed

Bacterial resistance was described even before Robert Koch's 1890 lecture[86] setting forth his four famous criteria ("Koch's postulates") for establishing that a particular microorganism caused a particular disease. In 1887, a microbiologist working at the Pasteur Institute observed that different organisms developed resistance to antiseptics to different extents, and that, if given the right conditions, they could likely become even more resistant.[87] The implications of resistance were realized just as quickly after

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[81] Stijn I. Blot, Koenraad H. Vandewoude, Eric A. Hoste & Francis A. Colardyn, *Outcome and Attributable Mortality in Critically Ill Patients with Bacteremia Involving Methicillin-Susceptible and Methicillin-Resistant* Staphylococcus aureus, 162 ARCHIVES INTERNAL MED. 2229, 2231 tbl.1, 2232 (2002).

[82] *Id.*

[83] S. Karakonstantis, A. Gikas, E. Astrinaki & E.I. Kritsotakis, *Excess Mortality Due to Pandrug-Resistant Acinetobacter baumannii Infections in Hospitalized Patients*, 106 J. HOSP. INFECTION 447, 448, 449 tbl.1 (2020); *see also* Powers et al., *supra* note 23, at 2 ("Those infected with resistant organisms are generally older, more critically ill, and have a greater incidence of renal insufficiency than patients with susceptible infections.").

[84] *See, e.g.*, Philip L. Graham, Susan X. Lin & Elaine L. Larson, *A U.S. Population-Based Survey of* Staphylococcus aureus *Colonization*, 144 ANNALS INTERNAL MED. 318, 322 (2006) ("Jernigan and colleagues . . . found that among healthy adults presenting to a primary care clinic for routine care, 24.7% were colonized with *S. aureus* and 3% were colonized with MRSA.").

[85] Antimicrobial Resistance Collaborators, *supra* note 15, at 637.

[86] Robert Koch, *Ueber Bakteriologische Forschung*, VORTRAG IN DER 1. ALLGEMEINEN SITZUNG DES X. INTERNATIONALEN MEDICINISCHEN CONGRESSES (1890) (Ger.), *available at* https://wellcomecollection.org/works/cqdyvnpb.

[87] M.G. Kossiakoff, *De la Propriété que Possèdent les Microbes de s'Accommoder aux Milieux Antiseptiques*, 10 ANNALS INST. PASTEUR: J. MICROBIOLOGIE 465, 476 (1887) (Fr.) ("[M]ais ils ne prouvent

the development of antibiotics as they were after the development of antiseptics.[88] Concerns over the lethal consequences of antibacterial resistance were famously expressed by Alexander Fleming in his 1945 Nobel lecture,[89] when the discoverer of penicillin warned that a person could "easily underdose himself, and by exposing his microbes to non-lethal quantities of the drug make them resistant," and thereby cause the death of the next person infected.[90] In 1957, Robert Schnitzer, who helped develop the tuberculosis treatment isoniazid, could already write that "[d]rug resistance is as old as chemotherapy"—the term "chemotherapy" in the 1950s still referring to the use of synthetic chemicals to treat infectious disease,[91] rather than to the term's current principal meaning within the field of oncology.[92]

Following the market entry of penicillin, a flurry of development during the "golden era" of antibiotics took place, with dozens of antibiotics entering the market from the late 1940s to the early 1970s.[93] But the halcyon days in which physicians anticipated the end of infectious disease were short-lived. Even before the burst of innovation had ended, fears of a post-antibiotic era emerged. In 1980, the National Academy of Sciences issued a report addressing concerns that subtherapeutic doses of antibiotics in animal feed might be harmful to human health,[94] and in 1984 Congress held a two-day hearing on antibiotic resistance at which a CDC official recounted "instances when resistance has compromised therapy and resulted in the death of infected patients."[95]

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pas que, dans d'autres conditions plus favorables à l'acclimatation, les micro-organismes ne pourraient pas devenir plus capables de résister à l'action des antiseptiques.").

[88] *See* Spyros N. Michalaes, Konstantinos Laios, Alexandros Charalabopoulos, George Samonis & Marianna Karamanou, *Joseph Lister (1827-1912): A Pioneer of Antiseptic Surgery*, 14 CUREUS e32777, at *4 (2022) (describing Lister's work on carbolic acid antiseptics).

[89] Alexander Fleming, Nobel Lecture on Penicillin (Dec. 11, 1945), https://www.nobelprize.org/uploads/2018/06/fleming-lecture.pdf; *see also* SCOTT PODOLSKY, THE ANTIBIOTIC ERA 216 n.160 (2015); Stuart B. Levy, *Antibiotic Resistance*, 4 INFECTION CONTROL 195 (1983); M.M. SWANN, K.L. BLAXTER, HI. FIELD, J.W. HOWIE, I.A.M. LUCAS, E.L.M. MILLAR, J.C. MURDOCH J.H. PARSONS & E.G. WHITE, JOINT COMMITTEE ON THE USE OF ANTIBIOTICS IN ANIMAL HUSBANDRY AND VETERINARY MEDICINE, REPORT PRESENTED TO PARLIAMENT (UK), at 60 (1969), https://downloads.regulations.gov/FDA-2010-D-0094-0003/attachment_1.pdf ("[T]here has been a dramatic increase over the years in the numbers of strains of enteric bacteria of animal origin which show resistance to one or more antibiotics."); John Lear, *Taking the Miracle Out of Miracle Drugs*, 42 SATURDAY REV. 35 (1959); ROBERT J. SCHNITZER & E. GRUNBERG, DRUG RESISTANCE OF MICROORGANISMS (N.Y. Acad. Press 1957).

[90] Fleming, *supra* note 89.

[91] *See* Avram Goldstein, *Antibacterial Chemotherapy*, 240 NEW ENG. J. MED. 98, 98 (1949) ("[T]he word 'chemotherapy' means the treatment of parasitic disease by direct chemical attack upon invading organisms—viruses, fungi, bacteria, spirochetes, protozoa, or helminths.").

[92] *See* John Matthias, *The Chemotherapy of Malignant Disease: Practical and Experimental Considerations*, 41 POSTGRAD. MED. J. 268, 268 (1965) ("The term chemotherapy was introduced by Ehrlich to describe the specific and effective treatment of infectious disease by chemical substances. It is currently also applied to the treatment of malignant disease.").

[93] MATT MCCARTHY, SUPERBUGS: THE RACE TO STOP AN EPIDEMIC 18 (Penguin Random House 2019) (describing the 1950s as a "golden era" of antibiotic development); Henry E. Simmons & Paul D. Stolley, *This Is Medical Progress? Trends and Consequences of Antibiotic Use in the United States*, 227 JAMA 1023, 1025 tbl.1 (1974) (illustrating rapid antibiotic innovation).

[94] NAT'L RSCH. COUNCIL, The EFFECTS ON HUMAN HEALTH OF SUBTHERAPEUTIC USE OF ANTIMICROBIALS IN ANIMAL FEEDS (Nat'l Acads. Press 1980), https://nap.nationalacademies.org/cart/download.cgi?record_id=21.

[95] *See Antibiotic Resistance: Hearings Before the Subcomm. on Investigations and Oversight of the H. Comm. on Sci. and Tech.*, 98th Cong., 2d Sess. 10 (1984).

By the early 1990s, commentators already began to warn of a looming "crisis" in antimicrobial resistance[96] and contemplated the "end of antibiotics."[97]

Despite the rise of antimicrobial resistance and especially of antibacterial resistance, the extent to which death rates from resistant bacteria or other pathogens have changed over time is unclear. CDC's 2019 report noted an overall trend toward decreasing deaths due to antibiotic resistance since its 2013 report (44,000 vs. 35,000),[98] but for many individual pathogens, CDC reported a death count of "N/A" or indicated that its 2013 and 2019 data cannot be compared.[99] Other sources are similarly ambiguous. An influential 2004 white paper from the Infectious Disease Society of America estimated that 90,000 annual U.S. deaths were caused by bacterial infections, 70% of which were resistant to at least one drug,[100] producing a figure (63,000) that exceeds the 44,000 and 35,000 CDC estimates from 2013 and 2019, but the figures do not reflect the same methodology or definitions (for example, the latter two figures including not only bacteria but also fungi).[101] In the 2019 report itself, CDC noted an increase in some measure of resistant pathogens (such as cases over time, or percent resistance over time, etc.) for five pathogens, a decrease for six pathogens, and no change or not enough information for seven pathogens.[102] It is important to appreciate that CDC's estimates were based on complex methodology using matched cohorts, extrapolation, and statistical inference, and were not actual counts.[103]

Studies internationally and in the United States have noted decreases in the incidence and prevalence of resistant bacteria that do not match the predictions produced by modeling assumptions,[104] and overall mortality rates from resistant pathogens did not clearly increase between 1980 and 2014.[105] Instead, mortality rates

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[96] *See* PODOLSKY, *supra* note 89, at 1 ("IN MARCH 1994 . . . both experts and the media increasingly turned their attention to the 'crisis' of antibiotic resistance . . . ."); *see also* David B. Jack, *Drug-Resistant Bacteria: Responding to the Infectious Disease Crisis*, 2 MOLECULAR MED. TODAY 499 (1996); Arturo Casadevall, *Crisis in Infectious Diseases: Time for a New Paradigm?*, 23 CLINICAL INFECTIOUS DISEASES 790 (1996); Harold C. Neu, *The Crisis in Antibiotic Resistance*, SCIENCE, Aug. 21, 1992, at 1064.

[97] Sharon Begley & Martha Brant, *The End of Antibiotics?*, NEWSWEEK, Mar. 27, 1994, at 47.

[98] U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, *Executive Summary* of ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES, at vii (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/?CDC_AAref_Val=https://www.cdc.gov/DrugResistance/Biggest-Threats.html; U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES 3 (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/?CDC_AAref_Val=https://www.cdc.gov/DrugResistance/Biggest-Threats.html.

[99] U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES 16–17 (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/?CDC_AAref_Val=https://www.cdc.gov/DrugResistance/Biggest-Threats.html.

[100] *Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates . . . A Public Health Crisis Brews*, INFECTIOUS DISEASE SOC'Y OF AM., July 2004, https://www.idsociety.org/globalassets/idsa/policy--advocacy/current_topics_and_issues/antimicrobial_resistance/10x20/statements/070104-as-antibiotic-discovery-stagnates-a-public-health-crisis-brews.pdf.

[101] U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES 3 (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/?CDC_AAref_Val=https://www.cdc.gov/DrugResistance/Biggest-Threats.html.

[102] *Id.* at 3, 16–17.

[103] *Id.*

[104] *See supra* note 10.

[105] Victoria Hansen, Eyal Oren, Leslie K. Dennis & Heidi E. Brown, *Infectious Disease Mortality Rates in the United States, 1980–2014*, 316 JAMA 2149, 2150 fig.E (2016).

varied like a sine wave between three and five deaths per 100,000 people,[106] representing about 10% of overall infectious disease mortality.[107] What clearly increased during that thirty-four-year period was mortality from antibiotic-induced *Clostridioides difficile* ("*C. diff*") infections, which rose from near zero prior to 1990 to more than two per 100,000 in 2014.[108] *C. diff* is not considered an antibiotic-resistant pathogen by CDC,[109] but is caused by both appropriate and inappropriate antibiotic use, pointing to the need for non-antibiotic approaches to reducing the infectious disease burden.

The cases and deaths reported in CDC's 2019 report are not the equivalent of clinical trials, but nevertheless provide one measure of mortality rates. If the reported deaths are divided by reported cases, estimated mortality rates ranged from 0.01% for drug-resistant *Shigella* (77,000 infections and <5 deaths) to 9% for vancomycin-resistant *Enterococcus* (54,500 cases and 5,400 deaths). The rate for carbapenem-resistant Enterobacteriaceae, which CDC referred to as "nightmare bacteria," was 7.7% (13,100 cases and 1,100 deaths).[110] Rates reported in the literature can sometimes be much higher, possibly due to infection type (e.g., sepsis vs. infection at other sites), underlying reason for hospitalization (e.g., hypertensive crisis vs. immune-compromising condition), treatment regimens (e.g., monotherapy vs. combination therapy), follow-up period (e.g., thirty days vs. ninety days), definitions of "resistance" (e.g., resistance to one drug vs. multiple drugs), or other factors.[111] Non-fatal infections can result in severe morbidity or contribute to early death beyond the end of study periods. Studies rarely adjust for patient factors such as underlying co-morbidities and severity of illness.

The distinction between resistant versus susceptible microorganisms is also not as binary as the terms might imply, and FDA maintains a website advising drug sponsors

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[106] Hansen et al., *supra* note 105, at 2149, 2150 fig.E. An assessment of the global burden of treatment-resistant bacteria (excluding resistant fungi or other pathogen types) estimated the death rate at thirteen per 100,000 in 2019 for high income countries, but differing methodologies make figures from different studies difficult to compare. *See* Antimicrobial Resistance Collaborators, *supra* note 15, at 629, 636 tbl.2; *see also id.* at 637 fig.2 (showing estimates of death rates for "High-income North America").

[107] Hansen et al., *supra* note 105, at 2149, 2149 tbl.

[108] *Id.* at 2149, fig.E.

[109] U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES 17 (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/?CDC_AAref_Val=https://www.cdc.gov/DrugResistance/Biggest-Threats.html ("*C. difficile* is not a resistant infection but is related to antibiotic use and antibiotic resistance.").

[110] *Id.* at 16–17.

[111] *See, e.g.*, Enrico Maria Trecarichi & Mario Tumbarello, *Therapeutic Options for Carbapenem-Resistant Enterobacteriaceae Infections*, 8 VIRULENCE 470, 471–76 tbl.1 (2017) (reporting mortality rates ranging from 25.2% to 49.1% across eleven studies); Hsiu-Yin Chiang, Eli N. Perencevich, Rajeshwari Nair, Richard E. Nelson, Matthew Samore, Karim Khader, Margaret L. Chorazy, Loreen A. Herwaldt, Amy Blevins, Melissa A. Ward & Marin L. Schweizer, *Incidence and Outcomes Associated With Infections Caused by Vancomycin-Resistant Enterococci in the United States: Systematic Literature Review and Meta-Analysis*, 38 INFECTION CONTROL & HOSP. EPIDEMIOLOGY 203, 209–11 tbl.3 (2017) (reporting mortality rates ranging from 9.1% to 50.2% across six studies); Xingran Du, Xinfeng Xu, Jing Yao, Kaili Deng, Sixia Chen, Ziyan Shen, Lihua Yang & Ganzhu Feng, *Predictors of Mortality in Patients Infected with Carbapenem-Resistant Acinetobacter baumannii: A Systematic Review and Meta-Analysis*, 47 AM. J. INFECTION CONTROL 1140, 1143 (2019) (reporting a mortality rate of 33.7% vs. 86.1% in patients treated with "appropriate" vs. "inappropriate" empiric therapy).

of the standards for antimicrobial susceptibility testing (AST).[112] Infectious disease specialists use AST to measure the minimum inhibitory concentration (MIC) of a given drug, which in turn defines the "breakpoint," or the concentration of an antimicrobial drug above which a pathogen is categorized as resistant.[113] In reality, susceptibility lies along a spectrum and breakpoints are not static but can be updated as new information becomes available about evolving pathogens and patient outcomes.[114] Although clinicians may assume breakpoints are always defined based on patient outcomes, this is not necessarily the case. Instead, when insufficient clinical data exist to define a breakpoint, epidemiological cut-off values based on in vitro laboratory data are often defined to "capture" more resistant organisms in surveillance—circular reasoning since resistance should reflect worse patient outcomes. Recent suggested changes in breakpoints may cause more harm than good since the evidence does not demonstrate these changes would improve patient outcomes.[115] More generally, resistance is often defined differently based on which drugs are of greatest interest and not based on clinically relevant definitions of how many effective drugs potentially remain for patient care.[116]

III. ALTERNATIVES MAY REDUCE MORBIDITY AND MORTALITY AT LOWER COST

There is little question that the prospect of a $3 billion reward would lead to more investment in antibiotic research, and likely to a greater quantity of new antibiotics. However, a more important question is whether those funds could reduce morbidity and mortality to a greater extent if spent in other ways. Proposals for market entry rewards have generally assumed that such rewards would be made available in addition to other strategies to reduce antimicrobial resistance, such as stewardship,

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[112] U.S. FOOD & DRUG ADMIN., FDA-RECOGNIZED ANTIMICROBIAL SUSCEPTIBILITY TEST INTERPRETIVE CRITERIA (2024), https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria. The maintenance of this website was mandated by the 21st Century Cures Act. *See* Pub. L. No. 114–255, § 3044, 130 Stat. 1033, 1114–21 (2016).

[113] Lucien Barnes, Douglas M. Heithoff, Scott P. Mahan, John K. House & Michael J. Mahan, *Antimicrobial Susceptibility Testing to Evaluate Minimum Inhibitory Concentration Values of Clinically Relevant Antibiotics*, 4 STAR PROTOCOLS 102512, at *1–2 (2023).

[114] Jean B. Patel, Kevin Alby, Romney Humphries, Melvin Weinstein, Joseph D. Lutgring, Samia N. Naccache & Patricia J. Simner, *Updating Breakpoints in the United States: A Summary from the ASM Clinical Microbiology Open 2022*, 61 J. CLINICAL MICROBIO. e01154-22, at *2 (2023); *id.* at 4 ("Reasons for considering a breakpoint revision . . . include the emergence of new types of antimicrobial resistance . . . .").

[115] Pranita D. Tamma & John H. Powers, *Do Patient Data Really Support the Clinical and Laboratory Standards Institute Recommendation for Lowering Third-generation Cephalosporin Interpretive Breakpoints?*, 57 CLINICAL INFECTIOUS DISEASES 624, 624 (2013) ("A 3-fold lowering of breakpoints of third-generation cephalosporins against Enterobacteriaceae means that clinicians would increasingly prescribe broad spectrum antibiotics to treat common gram-negative infections, in direct conflict with the need to conserve the effectiveness of existing agents."); Pranita D. Tamma, Harold Wu, Jeffrey S. Gerber, Alice J. Hsu, Tsigereda Tekle, Karen C. Carroll & Sara E. Cosgrove, *Outcomes of Children with Enterobacteriaceae Bacteremia with Reduced Susceptibility to Ceftriaxone: Do the Revised Breakpoints Translate to Improved Patient Outcomes?*, 32 PEDIATRIC INFECTIOUS DISEASE J. 965, 965 (2013) ("[B]y lowering the MIC breakpoints and forgoing ESBL testing, laboratories may report ESBL-producing organisms as 'susceptible' to piperacillin-tazobactam or cefepime based on in vitro testing, which might not be representative of in vivo susceptibilities . . . .").

[116] Kadri et al., *supra* note 23, at 1803 (2018).

surveillance, and better diagnostics, but this assumption should not be read to imply that there are no tradeoffs in the relative amounts of funds allocated to these different tools or to other equally worthy goals. In any system that employs budgeting, such as that of a government or legislature, the use of funds to achieve one goal necessarily means that those same funds cannot be spent to achieve the same goal in a different way. It is possible that alternative uses of market entry reward funds could be more effective if spent on alternative means of reducing morbidity and mortality from antimicrobial resistance, or from other causes. Any proposal for a market entry reward should consider such tradeoffs and opportunity costs.

A. Alternative Means Can Reduce Infectious Disease Mortality

Past experience has demonstrated that non-drug interventions can effectively reduce or eliminate diseases from large geographic regions, or even eradicate them entirely.[117] From the late nineteenth century through 1940, mortality in the United States fell more than during any other documented period in American history, nearly all of which was due to declines in infectious disease.[118] From 1900 to 1937 alone, overall infectious disease mortality declined by 64%, from 797 deaths per 100,000 to 283 per 100,000.[119] These reductions occurred with limited, if any, effective antibiotics.[120] The production of penicillin, generally considered to be the first antibiotic, did not achieve commercial scale until 1944.[121]

Meaningfully effective viral treatments, to the extent they exist even today, came later as well. Nevertheless, burdens of viral disease dramatically decreased. Yellow fever, for example, the cause of major viral epidemics throughout the United States in the late 1800s,[122] was under control by around 1905 despite the absence of effective treatments.[123] More recently, viral outbreaks of Severe Acute Respiratory Syndrome

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[117] *See generally* Ian T.T. Liu & Jonathan J. Darrow, *Reconsidering Eradication to Address the Global Infectious Disease Burden*, 24 QUINNIPIAC HEALTH L.J. 279 (2021) (arguing for a revival of global eradication efforts).

[118] David Cutler & Grant Miller, *The Role of Public Health Improvements in Health Advances: The Twentieth-Century United States*, 42 DEMOGRAPHY 1, 1 (2005); *see also* David S. Jones, Scott H. Podolsky & Jeremy A. Greene, *The Burden of Disease and the Changing Task of Medicine*, 366 NEW ENG. J. MED. 2333, 2336 (2012) (referring to an online graphic, *Top 10 Cases of Death in the United States, 1900–2010*, MASS. MED. SOC'Y (2012), https://www.nejm.org/doi/full/10.1056/NEJMp1113569, that illustrates the top ten causes of disease from 1900 to 2010, including the dramatic decline in infectious disease in the early twentieth century).

[119] Gregory L. Armstrong, Laura A. Conn & Robert W. Pinner, *Trends in Infectious Disease Mortality in the United States During the 20th Century*, 281 JAMA 61, 63 (1999).

[120] *See* ANTIBIOTICS IN HISTORICAL PERSPECTIVE 3–7 (David L. Cowen & Alvin B. Segelman eds. 1981) (describing evidence of antimicrobial medicines dating to 50,000 BC).

[121] William Kingston, *Antibiotics, Invention and Innovation*, 29 RSCH. POL'Y 679, 684 (2000).

[122] Margaret Humphreys, *How Four Once Common Diseases Were Eliminated from the American South*, 28 HEALTH AFFS. 1734 (2009); *see generally* KHALED J. BLOOM, THE MISSISSIPPI VALLEY'S GREAT YELLOW FEVER EPIDEMIC OF 1878 (La. State Univ. Press 1993) (describing epidemics in New Orleans and Memphis).

[123] J.H. Bauer, *Yellow Fever*, 55 PUB. HEALTH REPS. 362, 362 (1940); *see also* U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, CDC YELLOW BOOK 2024, https://wwwnc.cdc.gov/travel/yellowbook/2020/travel-related-infectious-diseases/yellow-fever (last visited May 13, 2024) ("No specific medications are available to treat YF [yellow fever] virus infections.").

(SARS, 2003), Ebola (2014), and Zika (2015) each abated despite the absence of effective drug treatments.[124]

Instead, the factors thought to have most contributed to the declines in mortality in the early twentieth century were not drugs but improved nutrition, hand and food washing, milk pasteurization, meat inspection, clean water, and improved sanitation.[125] Additional means for reducing the infectious disease burden include surveillance,[126] quarantine, vector control, and supportive care. In many populations and clinical contexts, effective vaccination (which has been described as "the most beautiful discovery that was ever made in medicine"[127]) is another important means for reducing the infectious disease burden. The influenza vaccine, first developed in 1936,[128] helped reduce death rates from influenza and pneumonia by 81% between 1950 (76.7 per 100,000) and 2010 (14.9 per 100,000).[129] The COVID-19 pandemic was addressed almost entirely with vaccines and non-pharmacologic interventions, with available drug treatments offering limited benefit and high cost.[130] With Ebola and Smallpox, identifying cases and vaccinating both contacts and contacts-of-contacts ("ring vaccination") was found to be an effective strategy.[131]

When deciding whether $3 billion per drug is an appropriate amount to devote to market entry rewards, legislators should ask whether more lives could be saved by directing some or all of that $3 billion to alternate interventions. For example, spending on awareness campaigns or other incentives could help increase influenza

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[124] *Frequently Asked Questions About SARS*, U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, https://archive.cdc.gov/#/details?url=https://www.cdc.gov/sars/about/faq.html (May 3, 2005) ("SARS-CoV is being tested against various antiviral drugs to see if an effective treatment can be found."); *see also Zika Virus*, WORLD HEALTH ORG. (Dec. 8, 2022), https://www.who.int/news-room/fact-sheets/detail/zika-virus ("There is no specific treatment available for Zika virus infection."); Press Release, U.S. Food & Drug Admin., FDA Approves First Treatment for Ebola Virus (Oct. 14, 2020), https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-ebola-virus ("Today, the U.S. Food and Drug Administration approved Inmazeb (atoltivimab, maftivimab, and odesivimab-ebgn), a mixture of three monoclonal antibodies, as the first FDA-approved treatment for *Zaire ebolavirus* (Ebola virus).").

[125] Cutler & Miller, *supra* note 118, at 2.

[126] *See generally Global Antimicrobial Resistance and Use Surveillance System (GLASS) Report 2022*, WORLD HEALTH ORG. (2022), https://iris.who.int/bitstream/handle/10665/364996/9789240062702-eng.pdf?sequence=1 (describing a global coordination system established in 2015 by the World Health Organization to monitor pathogen resistance).

[127] *See* Eugenia W. Herbert, *Smallpox Inoculation in Africa*, 16(4) J. AFRICAN HIST. 539, 539 (1975).

[128] Stanley Plotkin, *History of Vaccination*, 111 PROC. NAT'L ACAD. SCI. 12283, 12284 tbl.1 (2014).

[129] Jones et al., *supra* note 118, at 2336 (see the accompanying interactive graphic, *Top 10 Cases of Death in the United States, 1900–2010*, MASS. MED. SOC'Y (2012), https://www.nejm.org/doi/full/10.1056/NEJMp1113569, which provides the number of influenza/pneumonia deaths by year).

[130] *See, e.g.*, ChangWon C. Lee, Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *Origins and Ownership of Remdesivir: Implications for Pricing*, 40 J.L. MED. & ETHICS 613, 615 (2020) ("[A]pproximately 4.8% lower mortality was observed among patients who received remdesivir (7.1%) compared to those receiving placebo (11.9%), but the difference was not . . . statistically significant.").

[131] Stefano Merler, Marco Ajelli, Laura Fumanelli, Stefano Parlamento, Ana Pastore y Piontti, Natalie E. Dean, Giovanni Putoto, Dante Carraro, Ira M. Longini Jr., M. Elizabeth Halloran & Alessandro Vespignani, *Containing Ebola at the Source with Ring Vaccination*, 10 PLOS NEGLECTED TROPICAL DISEASES e0005093, at *6 (2016) ("[R]ing vaccination of contacts and contacts of contacts using the highly efficacious rVSV-ZEBOV vaccine can effectively contain an [Ebola] outbreak when $R_e \leq 1.6$."); Frank Fenner, *Global Eradication of Smallpox*, 4 REVIEWS OF INFECTIOUS DISEASES 916, 918 (1982) (explaining that "vaccination of persons surrounding a suspect case" was more effective than mass vaccination).

vaccination rates, which range from just 30% to 60% across different states,[132] helping to reduce the approximately 37,000 deaths in the United States that occur each year from influenza[133]—more than die from all resistant pathogens combined. Alternately, $3 billion could perhaps help the NIAID more quickly achieve its goal of creating a universal influenza vaccine that can be effective if administered once, rather than every year,[134] a project currently funded at $270 million annually.[135] Another potential use of funds would be to facilitate the development of alternative interventions such as phage, host-directed therapies, and microbiome therapies, since part of the issue with antibiotic resistance is the harm caused by antibiotics themselves.

It is important to investigate how the cost-effectiveness of alternate interventions compares to that of drug treatment, but such analyses are rarely part of market entry reward proposals. A report by the Organization for Economic Cooperation and Development (OECD) assessed the cost-effectiveness of interventions such as hand-hygiene, disinfection, and delayed prescriptions, concluding that more prudent use of antibiotics (i.e., hospital-based stewardship) would avert the largest numbers of annual deaths related to drug-resistant pathogens (10,000 across thirty-four countries under an optimistic scenario).[136] Unfortunately, the OECD did not report the cost-effectiveness of incentives for new drug development.[137]

A World Bank report estimated $9 billion in worldwide spending was needed to help contain antimicrobial resistance, but proposed allocating less than $0.7 billion (8%) to the support of research leading to new drugs[138] and cautioned against high expectations for "new miracle cures."[139] Instead, the World Bank suggested the bulk of the expenditures should be devoted to interventions such as sanitation and clean

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[132] Alice P.Y. Chiu, Jonathan Dushoff, Duo Yu & Daihai He, *Patterns of Influenza Vaccination Coverage in the United States from 2009 to 2015*, 65 INT'L J. INFECTIOUS DISEASES 122, 123 (2017).

[133] *Past Seasons Estimated Influenza Disease Burden*, U.S. CTRS. FOR DISEASE CONTROL & PREVENTION (2024), https://www.cdc.gov/flu-burden/php/data-vis/past-seasons.html; *see also Age-Adjusted Death Rates for Selected Causes of Death, by Sex, Race, and Hispanic Origin: United States, Selected Years 1950–2018*, U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, https://www.ncbi.nlm.nih.gov/books/NBK569311/table/ch3.tab5/; Jones et al., *supra* note 118, at 2333; Barbara J. Jester, Timothy M. Uyeki, Anita Patel, Lisa Koonin & Daniel B. Jernigan, *100 Years of Medical Countermeasures and Pandemic Influenza Preparedness*, 108 AM. J. PUB. HEALTH 1469, 1470 (2018) (amantadine was approved in 1966 but lost effectiveness to resistance by 2005, while newer drugs merely "lessen the duration" of influenza).

[134] *See* Michelle C. Crank, John R. Mascola & Barney S. Graham, *Preparing for the Next Influenza Pandemic: The Development of a Universal Influenza Vaccine*, 219 J. INFECTIOUS DISEASES S107, S107 (2019) ("In this collection of articles [2–15], we review the scientific opportunities for developing influenza vaccines with broad coverage, commonly referred to as 'universal' influenza vaccines . . . ."); *see generally* Emily J. Erbelding, Diane J. Post, Erik J. Stemmy, Paul C. Roberts, Alison Deckhut Augustine, Stacy Ferguson, Catharine I. Paules, Barney S. Graham & Anthony S. Fauci, *A Universal Influenza Vaccine: The Strategic Plan for the National Institute of Allergy and Infectious Diseases*, 218 J. INFECTIOUS DISEASES 347 (2018) (setting forth the NIAID's strategic plan).

[135] NIAID CONGRESSIONAL JUSTIFICATION FY 2024, *supra* note 52, at 21.

[136] ORG. FOR ECON. COOPERATION & DEVELOPMENT, EMBRACING A ONE HEALTH FRAMEWORK TO FIGHT ANTIMICROBIAL RESISTANCE 252 (2023), https://www.oecd.org/content/dam/oecd/en/publications/reports/2023/09/embracing-a-one-health-framework-to-fight-antimicrobial-resistance_39e8cd70/ce44c755-en.pdf; *see also id.* at 105–06 (describing "elimination" versus "replacement" scenarios).

[137] *Id.* at 251–324.

[138] WORLD BANK GRP., *supra* note 12, at 28 tbl.1.

[139] *Id.* at 9.

water, human and animal vaccinations, reduced use of antibiotics in agriculture, universal healthcare, expansion of prescription-only status, stewardship programs, infection prevention and control measures, and public awareness campaigns.[140] Similarly, the global nonprofit *Médecins Sans Frontièrs* (Doctors Without Borders) has opposed the PASTEUR Act on the basis that other approaches, such as funding diagnostic tests or stewardship, would "cost dramatically less."[141]

Congress should also consider that the costs of drug treatment extend beyond financial costs in a way that the costs of alternate interventions generally do not. Vaccines, for example, were specifically excluded from the PASTEUR Act's proposed incentives[142] even though they are known to have extremely low compensable adverse event rates of less than about one in a million doses (<0.0001%) and might benefit patients with both susceptible and resistant disease.[143] By contrast, about 20% of patients receiving antibiotics experience adverse drug events,[144] which can range from hearing loss and seizures to liver toxicity and acute kidney injury requiring life-long dialysis and potentially leading to early death.[145]

Perhaps the most famous of these adverse events is superinfection with *C. diff*, which causes a disease once known as "antibiotic-associated colitis,"[146] reflecting its primary cause: the use of antibiotics.[147] More people in the United States die from *C. diff* each year (12,800) than from any single drug-resistant pathogen (MRSA is second, with 10,600 deaths), and the antibiotic-induced condition is responsible for a third as many deaths as all drug-resistant pathogens combined (35,000).[148] Antibiotic use has also been associated with longer-term adverse health conditions, such as weight gain

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[140] *Id.* at 27–28.

[141] MÉDECINS SANS FRONTIÈRES [DOCTORS WITHOUT BORDERS], THE PASTEUR ACT IS NOT THE WAY FOR THE US GOVERNMENT TO ADDRESS ANTIMICROBIAL RESISTANCE 2 (2023), https://www.msfaccess.org/pasteur-act-not-way-us-government-address-antimicrobial-resistance.

[142] Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2023 (PASTEUR Act), S. 1355, 118th Cong., sec. 2, § 399OO-6(1)(B)(ii) (2023).

[143] *See* HEALTH RES. & SERVS. ADMIN., NATIONAL VACCINE INJURY COMPENSATION PROGRAM DATA REPORT 1 (2024), https://www.hrsa.gov/sites/default/files/hrsa/vicp/vicp-stats-05-01-24.pdf ("Approximately 60 percent of all compensation awarded . . . comes as [a] result of a negotiated settlement between the parties in which HHS has not concluded, based upon review of the evidence, that the alleged vaccine(s) caused the alleged injury.").

[144] Jennifer Curran, Jennifer Lo, Valerie Leung, Kevin Brown, Kevin L. Schwartz, Nick Daneman, Gary Garber, Julie H.C. Wu & Bradley J. Langford, *Estimating Daily Antibiotic Harms: An Umbrella Review with Individual Study Meta-Analysis*, 28 CLINICAL MICROBIO. & INFECTION 479, 485, 487 tbl.2 (2022).

[145] *See* Pranita D. Tamma, Edina Avdic, David X. Li, Kathryn Dzintars & Sara E. Cosgrove, *Association of Adverse Events With Antibiotic Use in Hospitalized Patients*, 177 JAMA INTERNAL MED. 1308, 1310 tbl.1 (2017) (e.g., renal toxicity); *see also* Kevin J. Downs & Jennifer L. Goldman, *Too Much of a Good Thing: Defining Antimicrobial Therapeutic Targets to Minimize Toxicity*, 109 CLINICAL PHARMACOLOGY & THERAPEUTICS 905, 908 (2021) (e.g., hepatotoxicity); C. Lanvers-Kaminsky et al., *Drug-induced Ototoxicity: Mechanisms, Pharmacogenetics, and Protective Strategies*, 101 CLINICAL PHARMACOLOGY & THERAPEUTICS 491, 492 tbl.1 (2017) (ototoxicity).

[146] Scott R. Curry, *Clostridium Difficile*, 37 CLINICS IN LAB. MED. 341, 341 (2017).

[147] U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES 71 (2019), https://www.cdc.gov/antimicrobial-resistance/data-research/threats/?CDC_AAref_Val=https://www.cdc.gov/DrugResistance/Biggest-Threats.html.

[148] *Id.* at 6.

(which also explains why antibiotics are used in livestock production[149]), diabetes, asthma, multiple sclerosis, inflammatory bowel disease,[150] and susceptibility to future infections more generally.[151] While it is often stated that antibiotics allow treatment for other diseases like cancer, antibiotics themselves may impair the efficacy of cancer therapies.[152] Research in these areas is ongoing, and the full extent of antimicrobial-associated harms is likely not yet appreciated.

B. Antimicrobial Development May Become More Difficult and Expensive Over Time

Reports of the dwindling antibiotic pipeline have observed that fewer large pharmaceutical companies are seeking to develop new antibiotics. However, this trend may be due not only to market conditions but also to increasing difficulty in creating new antibiotics.[153] Between 1995 and 2001, GlaxoSmithKline invested $100 million to screen half a million potential new antibiotics using newly acquired genetic sequence information, but the effort turned out to be "a big waste of time," and its failure "prompted a radical shift in corporate strategy."[154] According to a twenty-one year veteran of Merck's antibacterial discovery program writing in 2011, few new antibiotic classes had been developed over the past twenty-five years "even though discovery programs have been in place at large and small pharmaceutical companies as well as academic laboratories over this period."[155] Supporting these sentiments, a workshop on "Technological Challenges in Antibiotic Discovery and Development" sponsored by the National Academy of Sciences described failed efforts, including those based on genomics, crystallography, and bioinformatics that were "not . . .

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[149] Jay P. Graham, John J. Boland & Ellen Silbergeld, *Growth Promoting Antibiotics in Food Animal Production: An Economic Analysis*, 122 PUB. HEALTH REPS. 79, 81 (2007) ("Early studies, conducted from 1950 to 1960, showed mean increases in body weight of 8.5%–8.8% using penicillin and 10.2%–12.3% using tetracyclines.").

[150] Anjelique Schulfer & Martin J. Blaser, *Risks of Antibiotic Exposures Early in Life on the Developing Microbiome*, 11 PLOS PATHOGENS e1004903, at *4 (2015).

[151] Claire Roubaud-Baudron, Victoria E. Ruiz, Alexander M. Swan Jr., Bruce A. Vallance, Ceren Ozkul, Zhiheng Pei, Jackie Li, Thomas W. Battaglia, Guillermo I. Perez-Perez & Martin J. Blaser, *Long-Term Effects of Early-Life Antibiotic Exposure on Resistance to Subsequent Bacterial Infection*, 10 MBIO e02820-19, at *9 (2019).

[152] Mitchell S. von Itzstein. Amrit S. Gonugunta, Thomas Sheffield, Jade Homsi, Jonathan E. Dowell, Andrew Y. Koh, Prithvi Raj, Farjana Fattah, Yiqing Wang, Vijay S. Basava, Shaheen Khan, Jason Y. Park, Vinita Popat, Jessica M. Saltarski, Yvonne Gloria-McCutchen, David Hsiehchen, Jared Ostmeyer, Yang Xie, Quan-Zhen Li, Edward K. Wakeland & David E. Gerber, *Association Between Antibiotic Exposure and Systemic Immune Parameters in Cancer Patients Receiving Checkpoint Inhibitor Therapy*, 14 CANCERS 1327, at *13 (2022) ("[P]atients receiving antibiotics have consistently been found to have inferior disease control and survival, an effect attributed to changes in the gut microbiome.").

[153] *See* David M. Livermore, *Discovery Research: The Scientific Challenge of Finding New Antibiotics*, 66 J. ANTIMICROBIAL CHEMOTHERAPY 1941, 1942 (2011) (discussing failed approaches).

[154] MATT MCCARTHY, SUPERBUGS: THE RACE TO STOP AN EPIDEMIC 20–21 (Penguin Random House 2019).

[155] Lynn L. Silver, *Challenges of Antibacterial Discovery*, 24 CLINICAL MICROBIO. REVS. 71, 72 (2011).

particularly successful,"[156] and the challenges of synthesizing complex molecular structures that otherwise looked promising.[157]

There are many promising approaches to address evolving infectious diseases, including bacteriophage therapy, CRISPR,[158] probiotics and microbiome therapies, lysins, and antibodies,[159] and it is unlikely that scientists are nearing the end of the antimicrobial pipeline just yet. Nevertheless, two critical uncertainties remain. First, the length of the pipeline is not known. Prudent antimicrobial policy should not proceed under the assumption that the pipeline is indefinitely long any more than prudent water or climate policies should proceed under the assumptions that underground aquifers can never be exhausted[160] or that the atmosphere can absorb unlimited amounts of greenhouse gases—as was once widely believed.[161] Second, even if human ingenuity could allow the pipeline to have no end, it is possible that as low-hanging fruit are harvested, it will become increasingly difficult and costly to identify, develop, produce, and administer drugs the further along the pipeline development efforts proceed.

The ability to create successful antibiotics also requires toxic specificity toward the pathogen and avoidance of toxicity to the human host. Existing antibiotics already do not perfectly thread this needle, referred to as the therapeutic index or therapeutic window, as can be seen in the renal and other toxicities of colistin, vancomycin, and many other antibiotics.[162] Microorganisms have evolved strategies to survive in anaerobic environments, near volcanic vents at the bottom of the ocean, and even in proximity to radioactive waste.[163] Humans, with their far longer generation spans,

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[156] DOUGLAS FRIEDMAN & JOE ALPER, NAT'L RSCH. COUNCIL, TECHNOLOGICAL CHALLENGES IN ANTIBIOTIC DISCOVERY AND DEVELOPMENT: A WORKSHOP SUMMARY 7 (2014), https://www.ncbi.nlm.nih.gov/books/NBK190333/.

[157] *Id.* at 13.

[158] *See generally* Danielle M. Pacia, Beatrice L. Brown, Timo Minssen & Jonathan J. Darrow, *CRISPR-Phage Antibacterials to Address the Antibiotic Resistance Crisis: Scientific, Economic, and Regulatory Considerations*, 11 J. L. BIOSCIS. lsad030 (2024) (describing the potential of CRISPR and bacteriophage technologies in treating infection).

[159] *See* John Rex, Holly Fernandez Lynch, I. Glenn Cohen, Jonathan J. Darrow & Kevin Outterson, *Designing Development Programs for Non-traditional Antibacterial Agents*, NATURE COMMC'NS, July 31, 2019, at 3417 tbl.1 (listing categories of non-traditional antibiotics).

[160] *See, e.g.*, *Water Resources: Hearing Before the S. Select Comm. on National Water Resources*, 86th Cong., 1st Sess. 563 (1960) (statement of Fred Cooper, Idaho State Reclamation Ass'n) ("Ground water resources appear almost limitless.").

[161] Walter Monk, Namoi, Oreskes & Richard Muller, *Gordon James Fraser MacDonald*, *in* 84 BIOGRAPHICAL MEMOIRS 236 (Nat'l Acads. Press 2004), https://nap.nationalacademies.org/cart/download.cgi?record_id=10992 ("[T]he long-held assumption that the land, water, and air can absorb waste products in unlimited quantities was wrong.").

[162] Kalin M. Clifford, Ashley R. Selby, Kelly R. Reveles, Chengwen Teng, Ronald G. Hall II, Jamie McCarrell & Carlos A. Alvarez, *The Risk and Clinical Implications of Antibiotic-Associated Acute Kidney Injury: A Review of the Clinical Data for Agents with Signals from the Food and Drug Administration's Adverse Event Reporting System (FAERS) Database*, 11 ANTIBIOTICS 1367, 1367 (2022) ("The majority of antibiotics commonly used in clinical practice can contribute to [acute kidney injury]."); *see generally* Kevin J. Downs & Jennifer L. Goldman, *Too Much of a Good Thing: Defining Antimicrobial Therapeutic Targets to Minimize Toxicity*, 109 CLINICAL PHARMACOLOGY & THERAPEUTICS 905 (2021) (cataloging particular drugs and associated toxicities).

[163] *See* Sarah Jane Butterworth, Franky Barton & Jonathan Richard Lloyd, *Extremophilic Microbial Metabolism and Radioactive Waste Disposal*, 27 EXTREMOPHILES 1, 5 (2023) (radioactive environments);

evolve more slowly and are unlikely to ever thrive naturally in such environments. If microbial resistance is a war between humans and pathogens, the economics heavily favor the pathogens. Pathogen adaptation occurs continuously and without monetary investment or conscious effort in contrast to the substantial expenditures and efforts required of humans to develop, administer, monitor, and conserve new drug products. It is not known whether, as researchers proceed further along the antimicrobial pipeline, toxicity to humans will become increasingly difficult and costly to avoid.

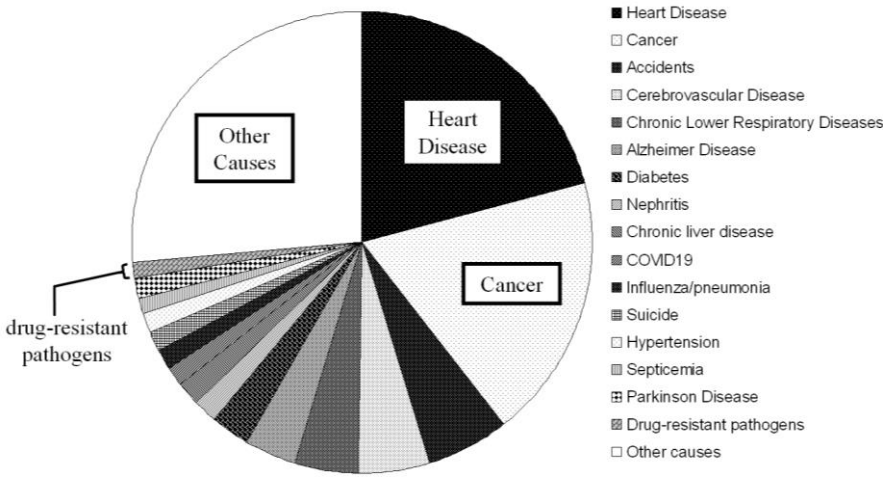
C. Other Approaches to Reducing Morbidity and Mortality

Congress should also consider whether the funds allocated to market entry rewards could save more lives in other ways that may or may not be related to infectious disease. Deaths due to drug-resistant pathogens are not a discrete category considered by CDC when determining the leading causes of death, but if they were, CDC's estimate of 35,000 annual deaths (dwarfed by the number of deaths associated with susceptible pathogens) would not be listed among the top fifteen leading causes. In the United States in 2023, more people were provisionally estimated to have died from suicide (43,854), chronic liver disease (52,179), diabetes mellitus (95,113), Alzheimer disease (114,036), chronic lower respiratory diseases (145,277), automobile and other accidents (195,888), cancer (613,260), and heart disease (680,221) (**Figure 2**).[164] Congress could hold hearings or direct the Secretary of HHS to determine the cost-effectiveness of efforts directed to saving lives through, for example, responsible gun ownership (suicide and accidents), reduced tobacco consumption (chronic lower respiratory disease, cancer, and heart disease), more responsible use of alcohol and acetaminophen (liver disease), expanded hepatitis B virus vaccination and development of a vaccine against hepatitis C virus (liver disease), dietary education (diabetes, cancer, and heart disease), revised automobile or workplace standards (accidents), and so on.

id. at 6 (hypersaline environments); *id.* at 7 (extremes of alkalinity); *id.* at 8 (deep-sea hydrothermal vents, hot springs); *id.* at 9 tbl.3 (combinations of extreme conditions).

[164] *Provisional Mortality Statistics*, U.S. CTRS. FOR DISEASE CONTROL & PREVENTION (2024), https://wonder.cdc.gov/controller/datarequest/D176;jsessionid=E33D732545FFBB4ACC2D24C7E614 ("Data in this table is from time period:Year/Month: 2023 (provisional)"); *see also* Sally C. Curtin, Betzaida Tejada-Vera & Brigham A. Bastian, *Deaths: Leading Causes for 2021*, 73 NAT'L VITAL STATS. REPS. 1, 9 tbl.C (2024) (listing the top ten causes for 2021); Kenneth D. Kochanek, Sherry L. Murphy, Jiaquan Xu & Elizabeth Arias, U.S. CTRS. FOR DISEASE CONTROL & PREVENTION, MORTALITY IN THE UNITED STATES, 2022, NCHS DATA BRIEF NO. 492, at *5 (2024), https://www.cdc.gov/nchs/data/databriefs/db492.pdf (indicating a total U.S. mortality of 3.28 million in 2022).

Figure 2: Annual Deaths in the United States: Drug Resistant Pathogens vs. All Other Causes*



*Sources: CDC 2019 (drug-resistant pathogens); CDC 2023 provisional data (all other causes)

Deliberate efforts to consider the cost-effectiveness of alternate resource allocation options would help Congress save the most lives. Even without such a systematic evaluation, however, anecdotal comparisons can be helpful in understanding how the benefits of large market entry rewards compare to other expenditures of funds. As the National Academy of Sciences has explained, an antimicrobial market entry reward of "$1 billion is comparable to FDA's entire [annual] budget for food safety," while "the CDC's total [annual] budget request . . . was $6.6 billion."[165] Another point of comparison is the annual amount spent globally to purchase all antibiotics other than generics, which totaled just $8 billion in 2021 (down from a high of $21 billion in 2001).[166]

D. The Fire Extinguisher Metaphor

Proponents of market entry rewards have described new antibiotics as fire extinguishers, implying that outbreaks of drug-resistant pathogens are like fires.[167] In

[165] COMBATING ANTIMICROBIAL RESISTANCE AND PROTECTING THE MIRACLE OF MODERN MEDICINE, *supra* note 2.

[166] Jacob Madden & Kevin Outterson, *Trends in the Global Antibiotics Market*, NATURE REVS. DRUG DISCOVERY, Feb. 15, 2023, at 174; *see also* TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS, *supra* note 2, at 6 ($4.7 billion).

[167] *See, e.g.*, Helen W. Boucher, Thomas M. File, Vance G. Fowler, Amanda Jezek, John H. Rex & Kevin Outterson, *Antibiotic Development Incentives that Reflect Societal Value of Antibiotics*, 72 CLINICAL INFECTIOUS DISEASES e420, e420 (2021) ("Antibiotics are the fire extinguishers of medicine: like an actual fire extinguisher, the existence of effective antibiotics ensures day-to-day safety even if it is not used to put out an infection."); PRESIDENTIAL ADVISORY COUNCIL ON COMBATING ANTIBIOTIC RESISTANT BACTERIA,

some ways, the metaphor is apt: Outbreaks of drug-resistant pathogens can strike unpredictably, require a rapid response, can be deadly, and spread harm to others if not quickly contained. If fire extinguishers are available and an effective surveillance system is in place, harm can be avoided. Payment for both fire extinguishers and antibiotics must be made in advance of when they are needed. Until then, both can be held in reserve, creating a type of insurance value even when they are not used.

There are critical differences, however, that limit the usefulness of the metaphor for policymakers. First, there is often limited evidence that the antibiotic "extinguisher" will actually work when needed. Current studies often enroll patients without resistance who are, on average, younger and healthier. Whether these drugs would be effective in older and sicker patients with resistance remains unstudied, and theorized benefits are based on assumptions from animal models and in vitro testing. Second, fires do not evolve resistance to fire extinguishers. While improvements in fire extinguisher technology are always possible, once an investment is made in a fire extinguisher design, products using that design can be manufactured and distributed in perpetuity. Third, while investment in any new technology can be costly, policymakers should consider whether a new fire extinguisher could be designed for less than $3 billion. There are several different types of fires—Class A (solid), B (liquid), C (electrical), D (metallic), and K (cooking grease/oil)[168]—but this number is far fewer than the number of distinct pathogens that exist, even before considering the dexterity with which microorganisms can mutate and evolve resistance. Fourth, infectious "fires" sometimes can be due to the host's disordered immune response and may not be addressed by new antibiotics that address pathogens without considering human immune dysfunction. A recent study, for example, showed improved survival in patients with severe pneumonia through the use of steroids as host immune modifiers in addition to antibiotics.[169]

For any particular goal, the optimal mix of tools to achieve that goal will depend in part on the cost and benefit of each tool. Describing an antibiotic as a fire extinguisher makes it easy to understand why it is desirable to have new antibiotics, which may help promote political acceptability, but it elides the real-world analysis with which

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RECOMMENDATIONS FOR INCENTIVIZING THE DEVELOPMENT OF VACCINES, DIAGNOSTICS, AND THERAPEUTICS TO COMBAT ANTIBIOTIC-RESISTANCE 18 (2017) ("Much as the residents of an apartment building benefit when a fire extinguisher prevents a kitchen fire from becoming a building fire, promptly treating an infection with an effective antibiotic benefits both the treated patient and all the individuals who now will never need to take the antibiotic because the infection was halted at the source."); Kevin Outterson, John H. Rex, Tim Jinks, Peter Jackson, John Hallinan, Steve Karp, Deborah T. Hung, Francois Franceschi, Tyler Merkeley, Christopher Houchens, Dennis M. Dixon, Michael G. Kurilla, Rosemarie Aurigemma & Joseph Larsen, *Accelerating Global Innovation to Address Antibacterial Resistance: Introducing CARB-X*, 15 NATURE REVS. DRUG DISCOVERY 589, 589 (2016).

[168] *Choosing and Using Fire Extinguishers*, FED. EMERGENCY MGMT. AGENCY, https://www.usfa.fema.gov/prevention/home-fires/prepare-for-fire/fire-extinguishers/ (Apr. 1, 2023).

[169] Pierre F. Dequin, Ferhat Meziani, Jean-Pierre Quenot, Toufik Kamel, Jean-Damien Ricard, Julio Badie, Jean Reignier, Nicholas Heming, Gaëtan Plantefève, Bertrand Souweine, Guillaume Voiriot, Gwenhaël Colin, Jean-Pierre Frat, Jean-Paul Mira, Nicolas Barbarot, Bruno François, Guillaume Louis, Sébastien Gibot, Christophe Guitton, Christophe Giacardi, Sami Hraiech, Sylvie Vimeux, Erwan L'Her, Henri Faure, Jean-Etienne Herbrecht, Camille Bouisse, Aurélie Joret, Nicolas Terzi, Arnaud Gacouin, Charlotte Quentin, Mercé Jourdain, Marie Leclerc, Carine Coffre, Hélène Bourgoin, Céline Lengellé, Caroline Caille-Fénérol, Bruno Giraudeau & Amélie Le Gouge, *Hydrocortisone in Severe Community-Acquired Pneumonia*, 388 NEW ENG. J. MED. 1931, 1938 (2023) ("[E]arly hydrocortisone therapy reduced the rate of death by day 28 among patients who had been admitted to the ICU for severe community-acquired pneumonia.").

legislators must grapple if they wish to make responsible decisions about how to reduce morbidity and mortality to the greatest extent and at the lowest cost. If the metaphor of a fire extinguisher is to help legislators appropriately allocate funds, it must be presented alongside the metaphors of smoke detectors (surveillance), fire doors (quarantine), fire towers (central coordination), fire hydrants (drug distribution), flame-retardant fabric (vaccines), propane heater clearance rules (human-wildlife separation), and other technology or rules used to effectively prevent or mitigate losses from fires.

IV. ANTIMICROBIAL APPROVALS ARE MORE ROBUST THAN DESCRIBED

In 1994, an article in *Science* magazine described a worrisome "dearth of new antibiotics in the pipeline,"[170] a concern that has been repeated and amplified in the thirty years since.[171] In 2003, the Institute of Medicine observed that "not one new class of antibiotics is in advanced development,"[172] and the following year the Infectious Disease Society of America (IDSA) warned that the antibiotic pipeline was "drying up."[173] In 2010, IDSA reiterated its concerns over the "antibacterial drug pipeline problem" and urged the creation of a sustainable global antibacterial drug R&D enterprise that would produce ten new systemic antibacterial drugs by 2020 as part of its 10x'20 Initiative.[174]

A. The Number of Anti-infective Drug Approvals Has Not Decreased

Despite such skeptical characterizations of the antibiotic pipeline, the private market has produced a steady stream of new antimicrobial products (not limited to antibiotics). Between 1982 and 2023, FDA's Center for Drug Evaluation and Research (CDER) approved an impressive 208 new anti-infectives (excluding vaccines and other products approved by FDA's Center for Biologics Evaluation and Research (CBER)), or an average of 9.9 new molecular entities or novel biologics per two-year period (**Figure 3**). As indicated by the nearly horizontal trendline in Figure 3, approvals have not diminished, although there has been variation among categories of

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[170] John Travis, *Reviving the Antibiotic Miracle?*, SCIENCE, Apr. 15, 1994, at 361.

[171] *See, e.g.*, Scott C. Blanchard, *A Much-Needed Boost for the Dwindling Antibiotic Pipeline*, 70 MOLECULAR CELL 3 (2018); *The World Is Running Out of Antibiotics, WHO Report Confirms*, WORLD HEALTH ORG. (Sept. 20, 2017), https://www.who.int/news/item/20-09-2017-the-world-is-running-out-of-antibiotics-who-report-confirms; J.M. Conly & B.L. Johnston, *Where Are All the New Antibiotics? The New Antibiotic Paradox*, 16 CAN. J. INFECTIOUS DISEASE MED. MICROBIO. 159 (2005).

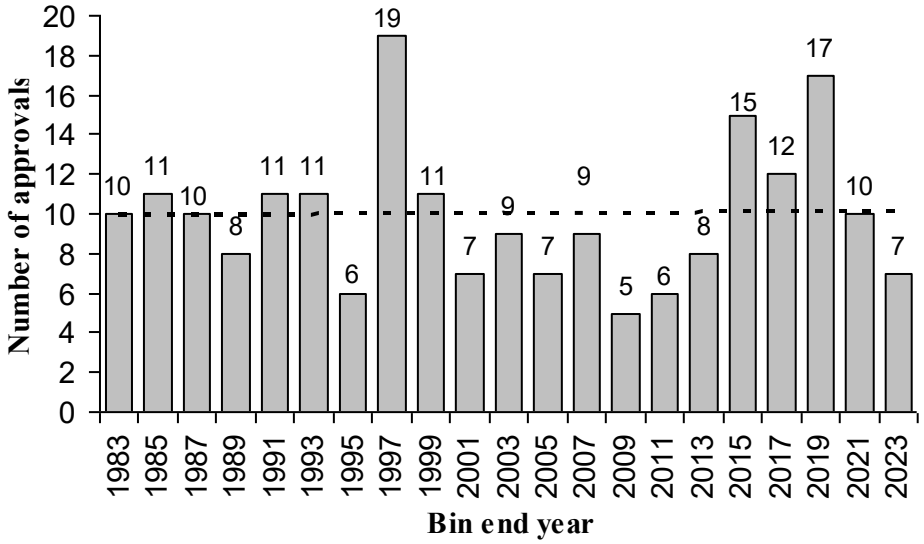
[172] MICROBIAL THREATS TO HEALTH: EMERGENCE, DETECTION, AND RESPONSE 14 (Inst. of Med., Mark S. Smolinski et al. eds. 2003).

[173] INFECTIOUS DISEASE SOC'Y OF AM., BAD BUGS, NO DRUGS: AS ANTIBIOTIC DISCOVERY STAGNATES . . . A PUBLIC HEALTH CRISIS BREWS 14 (2004), https://www.idsociety.org/globalassets/idsa/policy--advocacy/current_topics_and_issues/antimicrobial_resistance/10x20/statements/070104-as-antibiotic-discovery-stagnates-a-public-health-crisis-brews.pdf ("The Pipeline of New Antibiotics Is Drying Up").

[174] David N. Gilbert, Robert J. Guidos, Helen W. Boucher, George H. Talbot, Brad Spellberg, John E. Edwards Jr, W. Michael Scheld, John S. Bradley & John G. Bartlett, The Infectious Disease Soc'y of Am., *The 10 x '20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020*, 50 CLINICAL INFECTIOUS DISEASES 1081, 1082 (2010).

antimicrobials, such as a decrease in antibacterials and an increase in antivirals.[175] Morbidity and mortality for viral infection is high, and very few antiviral drugs were approved until the 1990s.[176] By contrast, by the 1990s the antibacterial field was already crowded with half a century of accumulated approvals.[177] Given this commercial and public health context, it is unsurprising and not necessarily undesirable that the focus should shift to the development of anti-infectives other than antibacterials.

Figure 3: Number of Antimicrobial Products Approved by FDA, Binned by Two-Year Period



Drug development times for antimicrobial products excluding pre-clinical development average 5.9 years,[178] suggesting that any effect of IDSA's 10x'20 initiative would not have been seen until at least 2016.[179] Whether due to IDSA's urging, products already in the pipeline, or other factors such as decreasing evidence

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[175] Darrow et al., *supra* note 19, at 364 fig.3 (2018).

[176] *See, e.g.*, Erik de Clercq & Guangdi Li, *Approved Antiviral Drugs over the Past 50 Years*, 29 CLINICAL MICROBIO. REVIEWS 695, 697 fig.1 (2016) (illustrating approvals from 1959 to 2016).

[177] *See, e.g.*, Henry E. Simmons & Paul D. Stolley, *This Is Medical Progress? Trends and Consequences of Antibiotic Use in the United States*, 227 JAMA 1023, 1025 tbl.1 (1974) (listing twenty-five "major" antibiotics first marketed from 1948 to 1972); Brad Spellberg, John H. Powers, Eric P. Brass, Loren G. Miller & John E. Edwards Jr, *Trends in Antimicrobial Drug Development*, 31 CLINICAL INFECTIOUS DISEASES 1279, 1280 fig.1 (2004) (illustrating sixteen new antibacterial approvals from 1983–87, and fewer after that).

[178] Jonathan J. Darrow, Mehdi Najafzadeh, Kristina Stefanini & Aaron S. Kesselheim, *Regulatory Approval Characteristics of Antimicrobial vs. Non-antimicrobial Products, 1984–2018: An Evaluation of FDA Flexibilities*, 20 LANCET INFECTIOUS DISEASES e159, at *4 (2020).

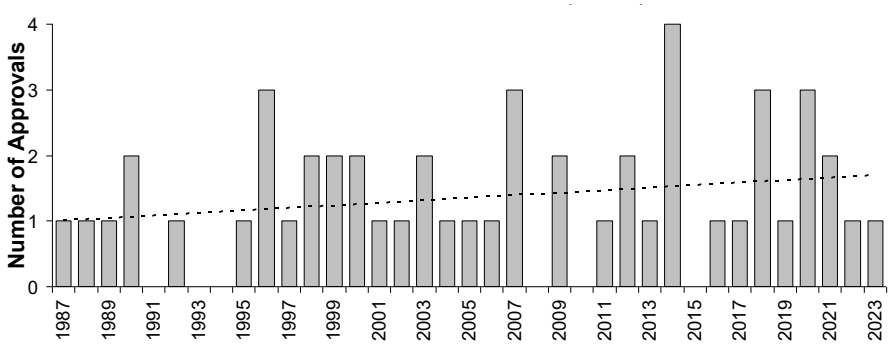
[179] In any event, the IDSA's initiative was not specifically funded and indicated support from eight societies of health professionals but without mention of any particular drug company or industry commitment. *See* Gilbert et al., *supra* note 174, at 1082.

required prior to marketing,[180] the goal of ten new systemic antibiotics by 2020 was exceeded, with manufacturers obtaining approval of fourteen such products by 2019.[181]

B. The Number of First-In-Class Anti-infective Drug Approvals Has Not Decreased

Although no first-in-class small-molecule anti-bacterials were approved from 2010 to 2023, twenty-one first-in-class anti-infective drugs were approved during this period along with an additional twenty-nine such drugs from 1987 to 2009 (**Figure 4**), suggesting continued innovation in the infectious disease space.[182] These drugs spanned a wide range of disease types, including viral (HIV, Hepatitis C, influenza, COVID-19, human papillomavirus, and smallpox), fungal, protozoal, mycobacterial (tuberculosis), helminthic (roundworm), and ectoparasitic (head lice). Seven first-in-class small-molecule antibacterial products were approved from 1996 to 2007, with two additional biologic antibacterials approved in 2012 (raxibacumab; anthrax) and 2016 (bezlotoxumab; *C. diff*).

Figure 4: First-in-Class Anti-infectives Approved 1987–2023*



*Drugs represented**:** **HIV**: zidovudine (1987); saquinavir (1995); nevirapine (1996); enfuvirtide (2003); raltegravir (2007); maraviroc (2007); ibalizumab (2018); fostemsavir (2020); lenacapavir (2022). **Cytomegalovirus**: ganciclovir (1989); fomivirsen (1998); letermovir (2017); maribavir (2021). **Hepatitis C virus**: boceprevir (2011); sofosbuvir (2013); ledipasvir/ sofosbuvir (2014); ombitasvir/paritaprevir/ ritonavir/dasabuvir (2014). **COVID-19**: remdesivir (2020); nirmatrelvir/ritonavir (2023). **Influenza**: zanamivir (1999); baloxavir (2018). **Other Viral**: imiquimod (human papilloma virus (HPV), 1997);

[180] Enrique Seoane-Vazquez, Rosa Rodriguez-Monguio & John H. Powers III, *Analysis of US Food and Drug Administration New Drug and Biologic Approvals, Regulatory Pathways, and Review Times*, *1980–2022*, SCI. REPS., Feb. 9, 2024, at *7 (2024) ("Previous studies found a decrease in the quality of the evidence derived from clinical trials . . . .").

[181] Helen Boucher, *Have We Made Progress in the 10 X' 20 Initative?*, CONTAGION LIVE (Apr. 9, 2020), https://www.contagionlive.com/publications/contagion/2020/april/have-we-made-progress-in-the-10-20-initiative.

[182] *See* Michael Lanthier, Kathleen L. Miller, Clark Nardinelli & Janet Woodcock, *An Improved Approach to Measuring Drug Innovation Finds Steady Rates of First-in-class Pharmaceuticals, 1987-2011*, 32 HEALTH AFFS. 1433, app. exh.A (2013) (1987 to 2011 data). For 2012 to 2023, first-in-class drugs were identified using the FDA's annual novel new drug reports. *See, e.g.*, U.S. FOOD & DRUG ADMIN., ADVANCING HEALTH THROUGH INNOVATION: NEW DRUG THERAPY APPROVALS 2023 (2024), https://www.fda.gov/media/175253/download?attachment.

docosanol (herpes simplex virus, 2000); palivizumab (respiratory syncytial virus, 1998); sinecatechins (HPV, 2006); tecovirimat (smallpox, 2018). **Fungal**: naftifine (tinea, 1988); fluconazole (*Candida*, 1990); atovaquone (AIDS-associated *Pneumocystis jirovecii* pneumonia, 1992); caspofungin (aspergillosis, 2001); tavaborole (*Trichophyton rubrum and mentagrophytes*, 2014); ibrexafungerp (*Candida*, 2021). **Protozoal**: eflornithine (African trypanosomiasis, 1990); nitazoxanide (*Cryptosporidium parvum*, 2002); artemether/lumafantrine (*Plasmodium falciparum* (malaria), 2009); miltefosine (leishmaniasis, 2014). **Mycobacterial**: bedaquiline (multi-drug resistant tuberculosis, 2012); pretomanid (extensively drug resistant tuberculosis, 2019). **Bacterial**: fosfomycin (urinary tract infection, 1996); quinupristin/dalfopristin (vancomycin-resistant *Enterococcus faecium* 1999); linezolid (MRSA, vancomycin-resistant *Enterococcus faecium*, 2000); daptomycin (MRSA, *Streptococcus*, others, 2003); telithromycin (*Streptococcus pneumoniae* (including multi-drug resistant isolates), *Haemophilus influenzae*, others, 2004); tigecycline (MRSA, others, 2005); retapamulin (*Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus pyogenes*, 2007); raxibacumab (*Bacillus anthracis* (anthrax), 2012); bezlotoxumab (*C. diff*, 2016). **Other**: ivermectin (*Strongyloides stercoralis* (roundworm), 1996); benzyl alcohol (head lice, 2009); abametapir (head lice, 2020).

C. Many Additional Anti-infective Products Have Been Approved by FDA's Center for Biologics Evaluation and Research

Most analyses of new drugs focus on the novel pharmaceutical approvals that are highlighted each year in FDA's annual new drug approval publication,[183] but this publication summarizes only those products approved by CDER.[184] Although it includes both small-molecule drugs and biologics approved by CDER, it does not include products approved by CBER, such as gene therapies, vaccines, probiotics, and blood products, many of which can be relevant to addressing the infectious disease burden. In 2023 alone, CBER approved: an immune globulin for the treatment of primary humoral immunodeficiency (Alyglo);[185] vaccines for Chikungunya (Ixchiq), meningococcal groups A/B/C/W/Y (Penbraya), respiratory syncytial virus (Abrysvo and Arexvy), and anthrax (Cyfendus); and a fecal microbiota transplant (Vowst) for the prevention of *C. diff* recurrence.[186]

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[183] The title of this publication has changed over time. *See, e.g.*, U.S. FOOD & DRUG ADMIN., ADVANCING HEALTH THROUGH INNOVATION: NEW DRUG THERAPY APPROVALS 2023 (2024), https://www.fda.gov/media/175253/download?attachment; U.S. FOOD & DRUG ADMIN., NOVEL DRUGS 2015 (2016), https://public4.pagefreezer.com/browse/FDA/10-06-2024T13:24/https:/www.fda.gov/drugs/development-approval-process-drugs/novel-drug-approvals-fda; U.S. FOOD & DRUG ADMIN., NOVEL NEW DRUGS 2014 SUMMARY (2015) (on file with author).

[184] *See* U.S. FOOD & DRUG ADMIN., ADVANCING HEALTH THROUGH INNOVATION: NEW DRUG THERAPY APPROVALS 2023 1 (2024), https://www.fda.gov/media/175253/download?attachment ("This report captures CDER's 2023 approvals. FDA's Center for Biologics Evaluation and Research (CBER) also approves important biologics . . . .").

[185] *See* U.S. FOOD & DRUG ADMIN., SUMMARY BASIS FOR REGULATORY ACTION, ALYGLO (IMMUNE GLOBULIN INTRAVENOUS, HUMAN-STWK) (BLA 125743) 4 (Jan. 13, 2024), https://www.fda.gov/media/175227/download (primary humoral deficiency includes, e.g., Common Variable Immunodeficiency, Wiskott-Aldrich Syndrome, Severe Combined Immunodeficiency, and congenital agammaglobulinemia, and patients suffering from primary humoral deficiency "experience recurrent and severe bacterial infections").

[186] *See 2023 Biological License Application Approvals*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/2023-biological-license-application-approvals (Jan. 24, 2024).

V. MARKET ENTRY REWARDS WILL YIELD MORE TREATMENTS THAN CURES

The history of pharmaceutical regulation reveals a consistent pattern: Congress enacts laws designed to achieve a particular goal, and businesses respond by technical compliance but in a way that differs from what Congress envisioned. For example, the 1983 Orphan Drug Act, as amended, defined a rare disease as one that affects fewer than 200,000 people per year.[187] In response, businesses "salami-sliced" indications,[188] such as by testing their drugs in narrow populations, knowing that physicians can prescribe off-label and that additional indications can be approved later. In the text of the Orphan Drug Act itself, Congress enumerated five exemplary diseases the legislation was intended to address: Huntington's disease, myoclonus, ALS, Tourette Syndrome, and muscular dystrophy.[189] But of the 420 orphan-designated drugs approved from 1983 to 2023, few have targeted any of these conditions, while many have addressed "slices" of larger disease categories such as cancer. Forty years after the enactment of the Orphan Drug Act, none of the five exemplary diseases has a cure, and available medications are primarily symptomatic and low-value.[190] A similar pattern has already emerged with more recent efforts to encourage the development of new antibiotics, including the GAIN Act and voucher programs, and similar problems are likely to emerge with proposals for prizes, such as the PASTEUR Act. For example, the PASTEUR Act would delegate to a committee the determination of qualifying criteria and how those criteria affect payment, which could lead to changing definitions over time in a way that would, in turn, allow more and more drugs to qualify even absent evidence of improved patient outcomes.

A. The GAIN Act Demonstrates Challenges in Defining Both Product Value and Prize Amounts

After receiving testimony from a broad range of groups, including IDSA,[191] legislators enacted the 2012 GAIN Act for the ostensible purpose of incentivizing critical antibiotics. However, despite broad input and deliberation, the Act contained at least two serious flaws. First, it provided five years of additional exclusivity to be

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[187] Health Promotion and Disease Prevention Amendments of 1984, Pub. L. No. 98-551, sec. 2, § 1706, 98 Stat. 2815, 2817 (1984) (amending the Orphan Drug Act).

[188] *See* Patricia J. Kenney, *The Orphan Drug Act: Is It a Barrier to Innovation? Does It Create Unintended Windfalls?*, 43 FOOD DRUG COSMETIC L.J. 667, 678 (1988).

[189] Orphan Drug Act, Pub. L. No. 97-414, § 1, 96 Stat. 2049, 2049 (1983).

[190] *See, e.g.*, Paolo Tornese, Stefania Lalli, Antoniangela Cocco & Alberto Albanese, *Review of Disease-Modifying Drug Trials in Amyotrophic Lateral Sclerosis*, 93 J. NEUROLOGY, NEUROSURGERY & PSYCHIATRY 521, 521 (2022) ("Amyotrophic lateral sclerosis (ALS) is a fast-progressing deadly neurodegenerative disease for which there is no effective symptomatic treatment."); Aaron S. Kesselheim & Jerry Avorn, *Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy*, 316 JAMA 2357, 2357 (2016) ("The main FDA scientific reviewers all opposed approval, but Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research, overruled them, suggesting that the extremely small increase in dystrophin might conceivably translate to clinical benefit.").

[191] *See, e.g.*, *Antibiotic Resistance and the Threat to Public Health, Hearing Before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 111th Cong., 2d Sess. v (2010) (noting testimony from CDC and NIAID); *Promoting the Development of Antibiotics and Ensuring Judicious Use in Humans: Hearing before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 111th Cong., 2d Sess. v (2012) (noting testimony from FDA, BARDA, IDSA, the American Medical Association, and others).

added to the end of existing exclusivity periods, thus failing to adequately appreciate that augmented cash flows far in the future will have a small net present value when discounted to the time that investment decisions are made, which generally occurs years before FDA approval.[192] By contrast, the six-month pediatric exclusivity period that Congress authorized[193] in 1997 to be added to the end of existing patent or regulatory exclusivity periods is intended to incentivize not the initial investment decision, but the decision to invest in additional clinical trials in pediatric populations, which often happens long after the initial drug approval and shortly before other exclusivity is set to expire.[194] This means each dollar of pediatric exclusivity incentive has greater value because expected cash flows are discounted over a much smaller number of years. The five-year GAIN Act period was also appended equally to the end of existing five- and seven-year exclusivities already available to new drugs, and to the end of three-year exclusivity sometimes available for modifications of existing drugs,[195] tending to create a larger net present value for modifications, for which the five-year exclusivity extensions would be discounted a smaller number of years.

Second, and more importantly, qualifying products were broadly defined to include drugs addressing serious infections caused by "resistant pathogen[s]," without defining "resistant" or requiring that the new drug provide any advantage over existing alternatives with respect to patient outcomes.[196] Given the loose criteria, it is unsurprising that 87% (thirteen of fifteen) of new antibiotics approved from 2015 to 2019 received Qualified Infectious Disease Products (QIDP) designation, even though most were likely in the preclinical or clinical pipeline prior to the GAIN Act.[197] The GAIN Act also excluded vaccines, biologics such as phage or fecal microbiota products, anti-parasitics, antivirals, and anthelmintic products from eligibility, and did not address poor outcomes from susceptible disease at all. The GAIN Act thus focused on particular pathogens and types of products instead of patient outcomes, a flaw similar to that seen with the PASTEUR Act.

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[192] Jonathan J. Darrow & Aaron S. Kesselheim, *Incentivizing Antibiotic Development: Why Isn't the Generating Antibiotic Incentives Now (GAIN) Act Working?*, 7 OPEN F. INFECTIOUS DISEASES 1, 2 fig.1 (2020).

[193] Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105–115, § 111, 111 Stat. 2296, 2305–09 (1997).

[194] *See* Michael S. Sinha, Mehdi Najafzadeh, Elizabeth K. Rajasingh, James Love & Aaron S. Kesselheim, *Labeling Changes and Costs for Clinical Trials Performed Under the US Food and Drug Administration Pediatric Exclusivity Extension, 2007 to 2012*, 178 JAMA INTERNAL MED. 1458, 1461–62 tbl.1 (2018) (illustrating, for many drugs, the short period of time between grant of pediatric exclusivity and expiration of existing exclusivity).

[195] For insight into how frequently modifications of drugs are eligible for three-, five-, or seven-year exclusivity, see Jonathan J. Darrow, Mengdong He & Kristina Stefanini, *The 505(b)(2) Drug Approval Pathway*, 74 FOOD & DRUG L.J. 403, 410 fig.5 (2019).

[196] FDA Safety and Innovation Act, Pub. L. No. 112-144, § 801, 126 Stat. 993, 1078–79 (2012).

[197] Mitra-Majumdar et al., *supra* note 23, at 3, 6.

B. Transferable Vouchers Face Similar Valuation Challenges as the GAIN Act

Another attempt by Congress to incentivize greater innovation was the creation of "priority review vouchers,"[198] which either can be used by the applicant or sold to a third party to speed the FDA review of an unrelated new drug product, thus allowing the drug sponsor of that unrelated drug product to begin earning revenues sooner. Three such programs have been authorized, including vouchers for neglected tropical diseases (2007),[199] rare pediatric diseases (2012),[200] and medical countermeasures (2016),[201] each of which could potentially apply to infectious disease treatments. The statutory list of eligible neglected tropical diseases, for example, includes tuberculosis, malaria, cholera, Ebola, Zika, and more than a dozen other named infectious diseases, as well as "any other infectious disease for which there is no significant market in developed nations," as designated by the Secretary of HHS.[202]

In 2018, legislators introduced a bill called the REVAMP Act that would have provided transferable exclusivity vouchers worth an estimated $1 billion or more to manufacturers of products targeting "critical need" pathogens, but the bill did not impose any particular effectiveness threshold, requiring only that the product be "intended to treat" one of the identified pathogens.[203] Industry has supported the creation of similar voucher programs specifically for antibiotics that would either allow priority FDA review (thereby accelerating the beginning of revenue streams) or the extension of the end of exclusivity periods (thereby extending the end of revenue streams) on unrelated products.[204]

Transferable exclusivity extensions as incentives for new antimicrobial products have been criticized as "extraordinarily inefficient," with estimates of their costs ranging from $187 million[205] (if transferability is restricted to certain drugs) to $4.8 billion per drug.[206] Earlier voucher programs helped incentivize companies to obtain FDA approval of at least three drugs for rare diseases primarily affecting populations outside the United States, but the drugs had already long been available outside the

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198 *See generally* David B. Ridley, Henry G. Grabowski & Jeffrey L. Moe, *Developing Drugs for Developing Countries*, 25 HEALTH AFFS. 313 (2006) (proposing priority review vouchers).

199 FDA Amendments Act, Pub. L. No. 110-85, § 1102, 121 Stat. 823, 972 (2007).

200 FDA Safety and Innovation Act, Pub. L. No. 112-144, § 908, 126 Stat. 993, 1094 (2012) (codified at 21 U.S.C. § 360ff).

201 21st Century Cures Act, Pub. L. No. 114–255, § 3086, 130 Stat. 1033, 1144 (2016).

202 FDA Amendments Act, Pub. L. No. 110-85, sec. 1102, 121 Stat. 823, 972–73 (2007). Ebola (a filovirus) and Zika were added later. *See* 21 U.S.C. § 360n (2024).

203 H.R. 6294, Re-Valuing Anti-Microbial Products Act of 2018 (REVAMP Act), 115th Cong.; *see also* H.R. 3231, REVAMP Act of 2019, 116th Cong.; Lisa Schnirring, *Bipartisan Bill Proposes New 'Pull' Incentives for Priority Antibiotics*, UNIV. MINN.: CTR. FOR INFECTIOUS DISEASE RSCH. & POL'Y (June 29, 2018), http://www.cidrap.umn.edu/news-perspective/2018/06/bipartisan-bill-proposes-new-pull-incentives-priority-antibiotics.

204 *See, e.g.*, JOHNSON & JOHNSON, POSITION ON ANTIMICROBIAL RESISTANCE 8–9 (June 2023), https://www.jnj.com/about-jnj/policies-and-positions/our-position-on-antimicrobial-resistance.

205 Benjamin N. Rome & Aaron S. Kesselheim, *Transferrable Market Exclusivity Extensions to Promote Antibiotic Development: An Economic Analysis*, 71 CLINICAL INFECTIOUS DISEASES 1671, 1674 (2020).

206 Kevin Outterson & Anthony McDonnell, *Funding Antibiotic Innovation with Vouchers: Recommendations on How to Strengthen a Flawed Incentive Policy*, 35 HEALTH AFFS. 784 (2016).

United States and thus were not likely the types of new treatments Congress envisioned.[207] A similar exclusivity extension proposal in Europe has been criticized for, along with its high cost, failing to ensure that any resulting drugs provide real value.[208]

C. The PASTEUR Act Would Face Similar Valuation Challenges

The proposed PASTEUR Act incorporated features that attempted to address some of the shortcomings of previous legislation. Although technically structured as a subscription contract to be paid over time rather than as a lump sum prize, the PASTEUR Act provided that the payout would begin within 180 days of the contract grant, and that 50% of the final contract year's payment amount could be paid during the first year of the contract.[209] These provisions would accelerate payments and thereby help minimize the time value of money problem associated with delayed compensation schemes, such as those under the GAIN Act. The PASTEUR Act provided for a minimum payout of $750 million, adjusted for inflation,[210] helping to reduce the uncertainty of the prize amount faced by drug sponsors. The Act also helped to minimize the problem of multiple parties producing similar drugs by use of a designation process,[211] which could occur early in the clinical development cycle, but past experience has shown that FDA is willing to work with industry to ensure that similar products can be approved with distinctive indications, even if clinically meaningful distinctions have not been established.[212]

The PASTEUR Act sought to address the challenge of product valuation by requiring the Secretary of HHS, in consultation with a committee and an advisory group, to develop a list of eligible infections as well as regulations that set forth "favored characteristics" of drugs that would address those infections.[213] The favored characteristics that were required, however, did not ensure that the drugs that resulted would reduce morbidity and mortality by any particular amount (or at all) compared to existing treatments. For example, the enumerated characteristics of treating a listed

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[207] Darrow et al., *supra* note 19, at 376 (the drugs were benznidazole, miltefosine, and artemether-lumafantrine, for Chagas disease, leishmaniasis, and malaria, respectively).

[208] Astrid Berner-Rodoreda, Frank Cobelens, Anne-Mieke Vandamme, Günter Froeschl, Jolene Skordis, Elil Renganathan, Ellen t'Hoen, Mario Raviglione, Albrecht Jahn & Till Bärnighausen, *Transferable Data Exclusivity Vouchers Are Not the Solution to the Antimicrobial Drug Development Crisis: A Commentary on the Proposed EU Pharma Regulation*, 9 BMJ GLOB. HEALTH e014605, at *2 (2024) ("It may also not produce much benefit in terms of generating truly novel antimicrobials.").

[209] Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2023 (PASTEUR Act), S. 1355, 118th Cong., sec. 2, § 399OO-2(g)(3) (2023).

[210] *Id.* § 399OO-2(e)(2).

[211] *Id.* § 399OO-1.

[212] *See, e.g.*, Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *The FDA Breakthrough Drug Designation: Four Years of Experience*, 378 NEW ENG. J. MED. 1444, 1449 (2018) ("[B]reakthrough status was rescinded for the hepatitis C treatments elbasvir–grazoprevir . . . and sofosbuvir–velpatasvir . . . after the approval of sofosbuvir–ledipasvir . . . and dasabuvir–ombitasvir–paritaprevir–ritonavir . . . , which were highly active against hepatitis C virus infection, curing 94% or more of patients. But in both cases, new breakthrough designations were then granted for these drugs on the basis of their benefits in particular subgroups of patients.").

[213] Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2023 (PASTEUR Act) § 399OO(c).

infection, containing a novel active moiety, being a member of a new antibiotic class, or having a novel mechanism of action or novel chemical scaffold,[214] do not necessarily imply a safer or more effective drug. Just as "surrogate endpoints" have been criticized for not necessarily predicting clinical outcomes,[215] the PASTEUR Act's surrogate criteria for drug value would not ensure that new antibiotics have improved therapeutic properties. One potential interpretation of the PASTEUR Act is that it would ensure compensation for manufacturers of drugs that qualified for the GAIN Act but did not sell well because of a of lack evidence of improved outcomes combined with increased cost. The PASTEUR Act did include "improve[ed] clinical outcomes"[216] among its valuation criteria, but did not exclude drugs without such improved outcomes from its scope or require any particular amount of improvement if improvement was demonstrated. The absence of any defined benefit threshold has previously plagued FDA's breakthrough therapy program,[217] its other expedited development programs,[218] and drug approval in general.[219] A similar pattern is likely to occur if the PASTEUR Act were to be enacted.

The PASTEUR Act also faces additional challenges. Although the Act directed the Secretary of HHS to "make efforts to increase the participation of domestic private payors and international payors in subscription contracts,"[220] these other payers would likely face higher prices because the sponsor's control over prices would effectively be limited to those non-federal payers.[221] The proposed Act thus would become part

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[214] *Id.* § 399OO(c)(2).

[215] Anushka Walia, Alyson Haslam & Vinay Prasad, *FDA Validation of Surrogate Endpoints in Oncology: 2005–2022*, 34 J. CANCER POL'Y 100364, at *4 (2022) (noting that studies "often fail to find strong correlations between surrogates and survival"); William S. Weintraub, Thomas F. Lüscher & Stuart Pocock, *The Perils of Surrogate Endpoints*, 36 EUR. HEART J. 2212, 2217 (2015) ("[T]he uncertainty of surrogates must limit their use in phase III trials . . . to avoid potential risk to public health.").

[216] Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2023 (PASTEUR Act) § 399OO(c)(2)(B).

[217] *See* Darrow et al., *supra* note 212, at 1450 ("[N]ew drugs can meet technical requirements for the [breakthrough] designation . . . despite having only modest efficacy."); Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *New FDA Breakthrough-Drug Category: Implications for Patients*, 370 NEW ENG. J. MED. 1252, 1255 (2014) ("The 27 breakthrough-therapy designations granted by the FDA in the first 9 months of 2013 is unlikely to represent a sudden and dramatic increase in the pace of pharmaceutical innovation . . . .").

[218] *See, e.g.*, Jonathan J. Darrow, *Few New Drugs Deserve Expedited Regulatory Treatment*, 27 J. MANAGED CARE & SPECIALTY PHARMACY 685, 687 (2021) ("Of 135 drug-indication pairs approved from 1999 to 2012 for which quality adjusted life-year (QALY) data were available, 46 (34%) provided a median incremental benefit of about 0.1 QALY, and another 59 (44%) offered a median gain of just 0.003 QALY."); Jonathan J. Darrow & Reed F. Beall, *Expedited Regulatory Review of Low Value Drugs*, 15 HEALTHCARE POL'Y 35 (2020).

[219] Jonathan J. Darrow, *Pharmaceutical Efficacy: The Illusory Legal Standard*, 70 WASH. & LEE L. REV. 2073, 2133 (2013) ("[W]hile the *evidence* standard may be substantial, the efficacy standard itself is almost entirely illusory.").

[220] Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2023 (PASTEUR Act) § 399OO-2(k).

[221] MÉDECINS SANS FRONTIÈRES [DOCTORS WITHOUT BORDERS], THE PASTEUR ACT IS NOT THE WAY FOR THE US GOVERNMENT TO ADDRESS ANTIMICROBIAL RESISTANCE 2 (2023), https://www.msfaccess.org/pasteur-act-not-way-us-government-address-antimicrobial-resistance ("MSF USA is concerned that the Act would . . . drive up prices of PASTEUR-supported novel antimicrobials in all markets besides federal procurement . . . ."); *see also* Jonathan J. Darrow, *The Perils of Increasing Medicaid*

of a decades-long history of "parry and reposte" in which government-defined prices in one segment of the pharmaceutical marketplace are followed by rising prices in the remainder of the market, creating an upward price spiral in that part of the market in which prices are not regulated.[222] The PASTEUR Act also contained provisions to promote antibiotic stewardship, including required public disclosure of resistance data and triennial updating of clinical guidelines,[223] but the sponsor's ability to earn additional revenues from sales to private and international buyers would create an incentive to increase sales volume.

VI. ADDITIONAL CONSIDERATIONS

Rationales offered in favor of large market entry rewards have focused on the need to produce new antimicrobials and especially antibacterials, but in so doing have not always considered the more subtle challenges or competing interests that could undermine the long-term efficient functioning of the proposed system. These include challenges in cost transparency that will undermine long-term accountability, financial incentives that exist alongside health benefits and could divert attention from higher value (but perhaps lower profit) alternatives, and the potential for private influence over government decision-making.

A. Lack of Cost Transparency Undermines Appropriate Valuation

In a market system, prices are kept in check by demand: If a business raises prices too much, volume declines, causing the business to earn less than it would have if prices had been lower.[224] This dynamic helps to ensure that prices never rise beyond the value of the products with which they are associated. In the field of healthcare, however, there is significant discomfort in placing a dollar value on the health benefits that a drug or any other intervention confers,[225] even when benefits are exceedingly small or unproven. Reflecting this dominant social ethic, governments have sought to ensure that healthcare is available regardless of a patient's ability to pay[226] or of the cost of a particular pharmaceutical,[227] and scholars have estimated potential savings

Rebates for Drugs with Accelerated Approval, 2 JAMA HEALTH F. e213184 *1 (2021) (explaining that limiting payments under federal programs "shift[s] the financial burden from Medicaid to other payers").

[222] Darrow et al., *Statutory Thickets*, *supra* note 78.

[223] *E.g.*, Pioneering Antimicrobial Subscriptions to End Upsurging Resistance Act of 2023 (PASTEUR Act) §§ 399OO-2(c)(3)–(4), 399OO-3.

[224] *See* MICHAEL E. CAFFERKY, BREAKEVEN ANALYSIS: THE DEFINITIVE GUIDE TO COST-VOLUME-PROFIT ANALYSIS 75 (New York: 2d ed. 2014) (providing a formula that allows a businessperson to calculate "the minimum percent change in sales volume at the *new* price needed to generate the same level of profit").

[225] *See, e.g.*, Peter J. Neumann & Joshua T. Cohen, *QALYs in 2018—Advantages and Concerns*, 319 JAMA 2473, 2473 (2018) ("Concerns include that QALYs are not patient focused, may be used as rationing tools by health insurers, and may be perceived as dehumanizing.").

[226] *See, e.g.*, Consolidated Omnibus Budget Reconciliation Act of 1985 (Emergency Medical Treatment and Active Labor Act), Pub. L. No. 99-272, sec. 9121, § 1867, 100 Stat. 82, 164 (1986) (codified as amended at 42 U.S.C. § 1395dd).

[227] *See* 42 U.S.C. § 1395w-104(b)(3)(G)(iv) (2024) ("Required inclusion of drugs in certain categories and classes").

from generic drug usage without adjusting for the increase in volume that economic theory typically predicts will occur when prices fall.[228]

Even if the PASTEUR Act's prize amounts were easily calculable in advance, which they are not, the prize system itself would be part of an increasingly complicated funding environment in which it is difficult to know the total cost of the drugs that result. The accumulation of subsidies described above (Figure 1)—research funding, exclusivity extensions, tax benefits, fee waivers, subscription contract payments, and so on[229]—mean that, from a societal perspective, it is difficult to determine how much one treatment costs versus another, even if the nominal end-user price is clear, which it often is not.[230] For example, when new hepatitis C virus treatments were approved, commentators evaluated the cost effectiveness of those drugs on the basis of the retail or wholesale price of the drug compared to alternative interventions, such as liver transplants.[231] But when new drug development is subsidized in myriad ways, both direct and indirect, a straightforward comparison of the price of the "final step" does not reflect economic reality. The cost-effectiveness considerations that physicians and insurers face when making individual treatment or coverage decisions, in other words, are not the same as the cost-effectiveness decisions that legislators face when designing market entry rewards or other tools to achieve social policy goals.

Even the prize value itself is not as transparent as it first seems. In the case of the PASTEUR Act, payout of the prize would occur over a contract period, the length of which would be initially uncertain and could be extended, and the dollar value of which could be adjusted years after the initial drug approval occurred. Even if total non-prize subsidies of a drug could be calculated, the total subsidies provided by government for a given drug can be known only in hindsight, when it is too late to make a decision to decline investing in a particular drug. This approach mirrors the U.S. healthcare system in general, where patients often cannot know the price of the healthcare products or services they receive until a "surprise bill" is received in the mail weeks or months after the fact, when it is too late to decline treatment or consider

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[228] *See, e.g.*, Jennifer S. Haas, Kathryn A. Phillips, Eric P. Gerstenberger & Andrew C. Seger, *Potential Savings from Substituting Generic Drugs for Brand-Name Drugs: Medical Expenditure Panel Survey, 1997–2000*, 142 ANNALS INTERNAL MED. 891, 892 (2005) ("We then estimated the annual savings that would result if each person in the sample switched from a brand-name drug to a corresponding generic formulation . . . ."); Michael A. Fischer & Jerry Avorn, *Potential Savings from Increased Use of Generic Drugs in the Elderly: What the Experience of Medicaid and Other Insurance Programs Means for a Medicare Drug Benefit*, 13 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 207, 209 (2004) ("We applied the [generic] price per unit . . . to the number of pills, tablets or capsules dispensed in the brand-name prescriptions.").

[229] *See supra* Part II.B.

[230] *See* Sharona Hoffman & Isaac Buck, *Specialty Drugs and the Health Care Cost Crisis*, 55 WAKE FOREST L. REV. 55, 66 (2020) (explaining that pharmacy benefit managers negotiate discounts such that insurers pay "far less" than the list price of the drug); *see generally* ROBIN FELDMAN, DRUGS, MONEY AND SECRET HANDSHAKES: THE UNSTOPPABLE GROWTH OF PRESCRIPTION DRUG PRICES (Cambridge Univ. Press 2019) (exploring issues surrounding pharmacy benefit managers).

[231] *See, e.g.*, Margot Sanger-Katz, *$1,000 Hepatitis Pill Shows Why Fixing Health Costs Is So Hard*, N.Y. TIMES (Aug. 2, 2014), https://www.nytimes.com/2014/08/03/upshot/is-a-1000-pill-really-too-much.html ("[U]se of the drug [sofosbuvir] has the potential to actually save money over the long run" because it can help avoid costs associated with chronic liver disease, including liver transplants costing "nearly $600,000" each.); Mehdi Najafzadeh, Karin Andersson, William H. Shrank, Alexis A. Krumme, Olga S. Matlin, Troyen Brennan, Jerry Avorn, Niteesh K. Choudhry, *Cost-Effectiveness of Novel Regimens for the Treatment of Hepatitis C Virus*, 162 ANNALS INTERNAL MED. 407, 409 (2015) ("[C]osts of sofosbuvir . . . are based on the wholesale acquisition costs.").

other options.[232] A lack of price transparency makes it difficult to assess the most cost-effective approach to reducing morbidity and mortality from resistant pathogens.

B. Conflicts of Interest in Surgeries and Chemotherapy Regimens

Proponents of market entry rewards have sometimes explained that a failure to develop new antibiotics would mean a return to the "dark age" of medicine,[233] in which surgeries, organ transplants, and chemotherapy all come with a higher risk of resistant infection.[234] It is difficult to assess the extent to which a new antibacterial could reduce morbidity and mortality from these three categories of procedures or treatments in comparison to alternative approaches. For example, traditional chemotherapy is cytotoxic and is often compared to "carpet bombing,"[235] hinting at its destructive effects on patient bodies as well as on their cancers. By contrast, some newer cancer immunotherapies are more targeted and are associated with better outcomes when antibiotics are not used.[236] Ironically, antibiotics themselves may impair the efficacy of targeted cancer immune therapies.[237] Whether a $3 billion market entry reward would be better spent on ensuring traditional chemotherapy can occur with a lower risk of infection (i.e., the approach favored by proponents of market entry rewards), or should instead be devoted to developing more targeted cancer treatments that do not inadvertently destroy healthy tissue, is a question that has received little treatment in the discussion over market entry rewards. Concerns of a return to the medical dark ages also do not take into account advances in medical care since the pre-antibiotic era of the 1930's, such as mechanical ventilation, fluid resuscitation, and vasopressors.

Organ recipients must take immunosuppressive drugs for the rest of their lives to prevent the body from rejecting the donor organ, but these treatments also suppress

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[232] *See generally No More Surprises: Protecting Patients from Surprise Medical Bills: Hearing Before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 116th Cong., 1st Sess. 163 (2019) (statement of Peter Welch, Representative from Vermont) ("[C]onsumers . . . are totally powerless . . . .").

[233] *See, e.g.*, O'NEILL ET AL., *supra* note 9, at 11.

[234] Kim Lewis, *The Science of Antibiotic Discovery*, 181 CELL 29, 30 (2020); *see also Superbugs: The Impact of Antimicrobial Resistance on Modern Medicine: Hearing Before the Subcomm. on Primary Health and Retirement Security of the S. Comm. on Health, Education, Labor, and Pensions*, 118th Cong., 1st Sess. 13–14 (2023) (statement of Helen Boucher, Dean, Tufts School of Medicine) (listing the ways in which antibiotic resistance impacts medicine); ÅRDAL ET AL., *supra* note 2, at 4.

[235] *See, e.g.*, Kamran Shahid, Mustafa Khalife, Raetasha Dabney & Alexandria T. Phan, *Immunotherapy and Targeted Therapy—The New Roadmap in Cancer Treatment*, 7 ANNALS TRANSLATIONAL MED. 595, 595 (2019); David G. Nathan, *The Cancer Treatment Revolution*, 188 TRANS. AM. CLINICAL & CLIMATOLOGICAL ASS'N 317, 317 (2007).

[236] *See, e.g.*, von Itzstein et al., *supra* note 152 ("Numerous cohort studies have demonstrated that patients receiving antibiotics around the time of [immune checkpoint inhibitor] initiation experience inferior . . . overall survival.").

[237] Stephen J. Blake, Yochai Wolf, Ben Boursi & David J. Lynn, *Role of the Microbiota in Response to and Recovery from Cancer Therapy*, NATURE IMMUNOLOGY, Nov. 6, 2023, at 309 ("[E]vidence from the past decade indicates that variation in the . . . microbiota . . . makes an important contribution to the patient-to-patient variation observed in the efficacy of ICB and CAR T cell therapy, as well as conventional treatments such as chemotherapy."); *see also* Yuan Gao, Qingyao Shang, Wenyu Li, Wenxuan Guo, Alexander Stojadinovic, Ciaran Mannion, Yan-gao Man & Tingtao Chen, *Antibiotics for Cancer Treatment: A Double-edged Sword*, 11 J. CANCER 5135, 5142 (2020) ("Under normal physiological conditions, the balanced state of the microbiome has an immune protective effect, as the cell wall of the dominant bacterial community is the stimulator of certain immune cells.").

the body's ability to fight infection and cancer.[238] While investing in a new antibiotic to facilitate the continued use of transplant rejection drugs is one option, it might also be asked whether prize funds, or some share of them, should instead be used to develop technologies that would free transplant recipients from the burden of taking immunosuppressive drugs for the rest of their lives.[239]

While it is unlikely that any single technology could avoid the need for all surgeries, it might be asked whether other non-drug interventions—better operating room air filtration systems, patient skin disinfection, donor organ screening, etc.[240]—could reduce the risk of peri-operative infection more effectively or at lower cost than could the development of new antibiotics. Non-pharmacologic interventions may also be less likely to be undermined by antibiotic resistance, such that any advances could contribute to a more durable improvement and would benefit patients with both susceptible and resistant infections.

The effectiveness of antibiotics in surgical site infections also has been questioned. Even before prophylactic antibiotic use was standard surgical practice, antibiotics were neither a necessary nor sufficient condition for avoiding surgical site infections. According to one source, site infection rates ranged from 1% to 40% without prophylaxis, depending in part on the extent of contamination of the original wound.[241] With prophylaxis, a Cochrane systematic review concluded that "it is uncertain whether antibiotics reduce the incidence of surgical site infections."[242] In addition, the use of more robotic and laparoscopic surgeries requiring smaller incisions and resulting in faster healing times makes prior evidence on surgical prophylaxis questionable in current practice environments. Despite the appealing logic that effective antibiotics will reduce morbidity and mortality associated with surgical site infections, definitive evidence of the magnitude of the benefit is less clear than proponents of market entry rewards have sometimes assumed or implied.

Greater clarity is available, however, for the financial earnings associated with surgeries, chemotherapy, and organ transplants. Surgical interventions are among the highest revenue-earning activities of hospitals, with orthopedic surgery (hip

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[238] Cher Enderby & Cesar A. Keller, *An Overview of Immunosuppression in Solid Organ Transplantation*, 21 AM. J. MANAGED CARE S12, S16 (2015) ("Transplant recipients are maintained on one or a combination of [immunosuppressive] agents for the remainder of their life."); *id.* at S20 ("The current approach to transplantation has been the use of combined immunosuppressive regimens to avoid rejection, with the consequent adverse effects from this therapy, such as opportunistic infections, cancer, and many others.").

[239] *See, e.g.*, Amanda B. Keener, *Saving Face: The Search for Alternative to Life-Long Immunosuppression for Face Transplants*, NATURE, May 5, 2016, at 449 ("Sachs has been working toward the goal of tolerance since the 1980s, when he showed that transplanting donor bone marrow into recipient mice, and thereby inducing mixed chimerism, prevented the rejection of skin grafts in the absence of drugs.").

[240] A.M. Spagnolo, G. Ottria, D. Amicizia, F. Perdelli & M.L. Cristina, *Operating Theatre Quality and Prevention of Surgical Site Infections*, 54 J. PREVENTIVE MED. HYGIENE 131, 134 (2013) ("[T]he specific features of the airflow system which enable SSIs [surgical site infections] to be contained are ventilation (dilution), air distribution, room pressurization (infiltration barrier) and filtration (contaminant removal)."); *see id.* at 133 (skin preparation).

[241] *Id.* at 131, 132.

[242] Samuel Chan, Samantha Ng, Hooi P. Chan, Elaine M. Pascoe, Elliott Geoffrey Playford, Germaine Wong, Jeremy R. Chapman, Wai H. Lim, Ross S. Francis, Nicole M. Isbel, Scott B. Campbell, Carmel M. Hawley & David W. Johnson, *Perioperative Antibiotics for Preventing Post-Surgical Site Infections in Solid Organ Transplant Recipients (Review)*, COCHRANE DATABASE SYSTEMATIC REVS., 2020, at *13.

replacements, for example), estimated to yield hospital revenues of more than $3.2 million per surgeon per year.[243] The global market for organ transplants has been estimated at $7.1 billion,[244] while annual spending on oncology drugs in the United States alone is expected to reach $125 billion by 2027.[245] These industries are associated with powerful lobbying groups, including the Pharmaceutical Research and Manufacturers of America (PhRMA, branded drugs), Advanced Medical Technology Association (AdvaMed, medical devices), the American Hospital Association (hospitals), and the American Medical Association (physicians), among others. While these groups advocate on behalf of the patients that benefit from their products and services, they also advocate for the financial interests of their members. New antivirals, antiparasitics, and vaccines are generally considered less important within the peri-operative environment,[246] or as part of chemotherapy[247] or organ transplantation regimens.[248] Despite their importance to public health, new antivirals, antiparasitics, and vaccines also did not receive sufficient support to be included in the PASTEUR Act, suggesting a connection between the healthcare sector's financial interests and resulting legislation.

C. Political Influence

The smaller the number of decision-makers and the larger the sum of money that those decision-makers control, the easier and more tempting it is for market participants to try and influence the associated decisions. This pressure is likely to be exerted increasingly over time as parties that stand to benefit learn to influence the proposed PASTEUR Act's advisory group members, committee members, or others involved in creating the prize rules or administering the program once those rules are established. Influence can be exerted through the hope or promise of future

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[243] MERRITT HAWKINS, 2019 PHYSICIAN INPATIENT/OUTPATIENT REVENUE SURVEY 15 (2019), https://www.amnhealthcare.com/siteassets/candidate-blog/physician/merritthawkins_revenuesurvey_2019.pdf.

[244] Custom Market Insights, *Global Organ Transplantation Market Size/Share Worth USD 21.5 Billion by 2032 at a 9.5% CAGR*, YAHOO FINANCE (Nov. 29, 2023), https://finance.yahoo.com/news/latest-global-organ-transplantation-market-200000025.html; *see also* MARK A. SCHNITZLER, M. VALAPOUR, M.A. SKEANS, D.A. AXELROD, K.L. LENTINE, H.B. RANDALL, J.J. SNYDER, A.K. ISRANI & B.L. KASISKE, ORGAN PROCUREMENT AND TRANSPLANTATION NETWORK (OPTN) AND SCIENTIFIC REGISTRY OF TRANSPLANT RECIPIENTS (SRTR), OPTN/SRTR 2014 ANNUAL DATA REPORT 169 (2014), https://www.amjtransplant.org/action/showPdf?pii=S1600-6135%2822%2900621-9 (noting Medicare spending of $4.2 billion for solid organ transplant recipients in 2013).

[245] IQVIA INST., THE USE OF MEDICINES IN THE U.S. 2023: USAGE AND SPENDING TRENDS AND OUTLOOK TO 2027 50 (May 2, 2023), https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-use-of-medicines-in-the-us-2023. Not all of this is spending is devoted to traditional chemotherapy drugs.

[246] *See* Dale W. Bratzler, E. Patchen Dellinger, Keith M. Olsen, Trish M. Perl, Paul G. Auwaerter, Maureen K. Bolon, Douglas N. Fish, Lena M. Napolitano, Robert G. Sawyer, Douglas Slain, James P. Steinberg & Robert A. Weinstein, *Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery*, 70 AM. J. HEALTH-SYSTEMS PHARMACY 195, 197–98 tbl.1 (2013).

[247] Randy A. Taplitz, Erin B. Kennedy & Christopher R. Flowers, *Antimicrobial Prophylaxis for Adult Patients with Cancer-Related Immunosuppression: ASCO and IDSA Clinical Practice Guideline Update Summary*, 14 J. ONCOLOGY PRAC. 692, 693–94 (2018) (discussing antivirals that guard against reactivation for those already seropositive as well as vaccines as "other" recommended prophylactic measures).

[248] *See* Judith A. Anesi, Emily A. Blumberg & Lilian M. Abbo, *Perioperative Antibiotic Prophylaxis to Prevent Surgical Site Infections in Solid Organ Transplantation*, 102 TRANSPLANTATION 21, 22 tbl.1 (2018).

employment ("revolving door"),[249] donations to political campaigns, or any other device that can be imagined or has been used throughout history.[250] It might be questioned, for example, whether political influence has already affected proposals for market entry rewards, which are proposed to apply to antibacterial treatments but not vaccines, the latter providing an even larger public health benefit and suffering from underinvestment for an even longer period of time.[251] The proposed PASTEUR Act directed the Secretary of HHS to develop regulations defining the favored characteristics of eligible treatments and how those characteristics affect the prize amount, and these regulations could be updated over time. With no similar prize as a motivation, efforts directed to influencing government support of non-pharmacological strategies such as clean water, stewardship, better nutrition, and revised quarantine policies tend to receive more limited lobbying funds.[252]

Large government contracts can create political pressures to continue funding projects even when objective need or merit wanes, as has occurred with military and construction projects.[253] If market entry rewards are to efficiently serve their purpose, the government would need the political will to deny or reduce rewards for initially promising products that are effective but that turn out to provide more limited therapeutic value than expected. At the same time, the evidence-based lowering of rewards is also potentially problematic, since adjusting rewards downward could result in negative publicity, exacerbate uncertainty, and send a chilling message to future drug developers.

VII. CONCLUSION

Winston Churchill once quipped that "democracy is the worst form of government—except for all those other forms that have been tried from time to

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[249] *See generally* Laura Karas, *FDA's Revolving Door: Reckoning and Reform*, 34 STANFORD L. & POL'Y REV. 1 (2023) (discussing the potential influence of the revolving door on FDA decisions).

[250] *See* Elizabeth R. Glode, *Advising Under the Influence?: Conflicts of Interest Among FDA Advisory Committee Members*, 57 FOOD & DRUG L.J. 293 (2002); *see also* Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *Speed, Safety, and Industry Funding: From PDUFA 1 to PDUFA 6*, 377 NEW ENG. J. MED. 2278 (2017) (discussing the growth of industry funding of the FDA).

[251] *See, e.g.*, INST. OF MED., VACCINE SUPPLY AND INNOVATION 61 (Nat'l Acads. Press 1985), https://www.ncbi.nlm.nih.gov/books/n/nap599/pdf/ ("[D]uring the 1970s and early 1980s, commercial biologics R&D became a less attractive investment than R&D involving other pharmaceuticals."); *see also* Marjorie Sun, *The Vexing Problem of Vaccine Compensation*, SCIENCE, Mar. 1, 1985, at 1012 (expressing concern that vaccine liability was "dampening incentives to improve old vaccines or develop new ones").

[252] *See, e.g.*, MICHAEL GREGER, HOW NOT TO DIE x–xi (Flatiron Books 2015) ("During my medical training, I was offered countless steak dinners and fancy perks by Big Pharma representatives, but not once did I get a call from Big Broccoli.").

[253] *See, e.g.*, LNP Editorial Board, *Bridge to Nowhere Will Stand as a Symbol of Failure*, LANCASTER ONLINE (June 29, 2016), https://lancasteronline.com/opinion/bridge-to-nowhere-will-stand-as-a-symbol-of-failure/article_f1d421b2-3d5e-11e6-a21d-df86409301a7.html; *A $3 Billion Government Boondoggle: Congress Pushes a Fighter Jet Engine the Military Says It Doesn't Want or Need*, ABC NEWS (May 19, 2010), https://abcnews.go.com/Blotter/joint-strike-fighter-billion-boondoggle/story?id=10692337; Leslie Wayne, *A Final Push for the Bedeviled, Beloved Osprey*, N.Y. TIMES (July 6, 2003), https://www.heraldtribune.com/story/news/2003/07/06/a-final-push-for-bedeviled/28755696007/; *see also* Jonathan J. Darrow, *Government Pharmaceutical Development to Address High Prices: Challenges Ahead*, 55 THERAPEUTIC INNOVATION & REG. SCI. 1103, 1104 (2021) (discussing lobbying and other problems of government decision-making).

time."[254] As legislators and commentators explore the options for incentivizing antimicrobial development, a similar picture emerges: The patent system may be the worst means to incentivize innovation—except for all the others that have been tried or proposed. While the need for stewardship and positive third party externalities may make the antimicrobial environment somewhat atypical[255] and deserving of creative alternative incentive mechanisms, the problem of market entry rewards—now as when the opening article quote from 1791 was penned—remains related to the challenge of product valuation. Experience with the Orphan Drug Act, GAIN Act, and voucher programs has revealed how difficult it can be to specify workable criteria that will reliably bring forth high value products and that are resistant to political influence. While the therapeutic value of the products that result is uncertain and no particular minimum threshold value (other than zero) has been required or proposed,[256] the cost of a $3 billion market entry reward is comparatively easy to measure. Because of a growing array of government subsidies both before and after drug approval, however, the full measure of a drug's cost is greater than the market entry reward and increasingly nontransparent. Little consideration has been given to the number of lives that could be saved with alternate uses of the same funds, including alternate means of reducing morbidity and mortality from resistant infections.

Another signpost to help orient the discussion over market entry rewards is found in Rachel Carson's 1962 book *Silent Spring*, which more than sixty years ago critiqued attempts to control disease-carrying insects with pesticides. "No responsible person contends that vector-borne disease should be ignored,"[257] she concluded, after describing the damage resulting from campaigns to carpet-bomb the environment with pesticides and the microbial resistance that ensued. Similarly, no responsible person contends that resistance to antibiotics should be ignored or that better solutions are not needed. The question is to what extent the centerpiece of efforts to control disease should consist of the Sisyphean task of creating new antibiotics, knowing that each costly "solution" is, at best, a temporary reprieve from the inevitable march of nature. And while the harm from pesticides may be easier to detect as deceased fauna give rise to a "silent spring," the known and potential harms from carpet-bombing the body with antibiotics and resultant deleterious effects on the host microbiome, vital organs, and immune system may have likely been underestimated.

If the fire extinguisher metaphor risks disproportionately emphasizing novel antimicrobials to the detriment of alternative mitigation strategies, another ubiquitous metaphor conceals a more fundamental vulnerability in any long-term strategy premised on antimicrobial products. Market entry rewards and the products they seek to incentivize have become conceptually annealed to the metaphor of an inexhaustible "pipeline" of new antimicrobials, as if new raw materials necessarily lie just beyond reach if only we devote enough resources to drilling deeper. In fact, it is not known

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[254] HC Deb (11 Nov. 1947) (444), cols. 206–07, https://api.parliament.uk/historic-hansard/commons/1947/nov/11/parliament-bill#:~:text=Many%20forms%20of,time%20to%20time (Statement of Winston Churchill).

[255] *See generally* Darrow et al., *supra* note 19, at 366 fig.4 (summarizing reasons why antibiotics are atypical and undervalued).

[256] *See generally* Jonathan J. Darrow, *Pharmaceutical Efficacy: The Illusory Legal Standard*, 70 WASH & LEE L. REV. 2073 (2013) (explaining that, in general, no particular efficacy threshold other than zero is required for FDA approval).

[257] RACHEL CARSON, SILENT SPRING 266 (Boston: Mariner Books Classics 1962) (2002 ed.).

how deep the antibiotic well runs or how costly or feasible it will be to extract new treatments.

Optimistic portrayals of market entry rewards also have been paired with pessimistic framing of recent patterns of investment and productivity. Many first-in-class antimicrobials have been approved over the past three decades to address a broad range of pathogen types, including more than a half-dozen first-in-class anti-bacterials, even before considering vaccines and other CBER approvals. Promising microbiome therapeutics have reduced recurrence of *C. diff*,[258] and the use of steroids has been shown to reduce the need for mechanical ventilation in patients suffering from bacterial pneumonia.[259] Substantial government resources have already been allocated to advancing basic research and clinical development, and additional sums have more recently been allocated to post-approval funding through an accumulating array of direct and indirect government subsidies and incentives. While these public funds help to advance antimicrobial development, they are also part of an increasingly labyrinthine funding system that lacks transparency, frustrating rational allocation decisions and reducing the likelihood of public accountability.

There remains an undeniable and substantial threat to human life caused by drug-resistant pathogens, and one that sources generally agree is likely to get worse over time. While market entry rewards may be neither necessary nor sufficient for safeguarding health or life, they are one of several tools for the government to consider as part of a larger strategy and should receive a fair, evidence-based evaluation alongside other options.[260] As policymakers debate the merits of the various options, it will be important to appreciate the costs of drug development already borne by the government, the long-known challenges of prize valuation, past disappointments in defining high-value drug products, the temporary nature of pharmaceutical solutions to infectious disease threats, the possibility of alternate means to achieve reductions in morbidity and mortality, and the risk posed by creeping political influence to the long-term integrity of any market entry reward system.

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[258] Paul Feuerstadt, Thomas J. Louie, Bret Lashner, Elaine E.L. Wang, Liyang Diao, Jessica A. Bryant, Matthew Sims, Colleen S. Kraft, Stuart H. Cohen, Charles S. Berenson, Louis Y. Korman, Christopher B. Ford, Kevin D. Litcofsky, Mary-Jane Lombardo, Jennifer R. Wortman, Henry Wu, John G. Auniņš, Christopher W.J. McChalicher, Jonathan A. Winkler, Barbara H. McGovern, Michele Trucksis, Matthew R. Henn & Lisa von Moltke, *SER-109, an Oral Microbiome Therapy for Recurrent* Clostridioides difficile *Infection*, 386 NEW ENG. J. MED. 220, 224 (2022) ("The percentage of patients with recurrence [of *C. diff*] was significantly lower in the SER-109 [treatment] group than in the placebo group (12% and 40%, respectively . . .).").

[259] Naveed Saleem, Adarsh Kulkarni, Timothy Arthur Chandos Snow, Gareth Ambler, Mervyn Singer & Nishkantha Arulkumaran, *Effect of Corticosteroids on Mortality and Clinical Cure in Community-Acquired Pneumonia*, 163 CHEST 484, 490 (2023) ("Patients receiving adjunctive corticosteroids showed a lower risk of requiring ventilation compared with those receiving standard care alone (4.2% vs 7.1% . . .)."). Mortality, however, was not significantly different. *Id.*

[260] *See* ORG. FOR ECON. COOP. & DEVELOPMENT, EMBRACING A ONE HEALTH FRAMEWORK TO FIGHT ANTIMICROBIAL RESISTANCE 169 (2023), https://www.oecd.org/els/embracing-a-one-health-framework-to-fight-antimicrobial-resistance-ce44c755-en.htm (summarizing more than twenty push and pull incentives for promoting new drug development).