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GEORGETOWN LAW





# When Markets Fail: Patents and Infectious Disease Products

JONATHAN J. DARROW, MICHAEL S. SINHA, AND  
AARON S. KESSELHEIM\*

## ABSTRACT

New antibiotics and vaccines aimed at treating or preventing infectious diseases can be highly valuable public health innovations, particularly when these products address unmet medical needs. Although patents are considered the primary means of incentivizing new product development, reduced private investment in this area has led policymakers to create new and sometimes costly supplemental incentive schemes for antibiotics. But the legislative initiatives launched over the past 15 years to overcome the shortcomings of the patent system have had limited success, in part because they do not adequately address the reasons underlying the disconnect between patents and the antimicrobial market. We examine the market dynamics related to infectious disease products to describe why both patents and recent legislative interventions have underperformed in incentivizing the development of new infectious disease treatments and vaccines. We conclude by reviewing existing and proposed solutions with these dynamics in mind, to separate out the most from least promising interventions.

## I. INTRODUCTION

In the United States, patents are widely credited with providing important incentives for private investment in the discovery and development of new prescription drugs and vaccines. By allowing an innovator firm to temporarily exclude generic competitors, patents permit brand-name prescription drugs to be sold at high prices, which serve as a reward for the successful completion of the long and expensive process of new drug

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\* Program on Regulation, Therapeutics and Law (PORTAL), Harvard Medical School and Brigham & Women's Hospital. Dr. Darrow and Dr. Kesselheim are core members of CeBIL (Collaborative Research Program for Biomedical Innovation Law), a scientifically independent collaborative research program supported by a Novo Nordisk Foundation Grant (Grant number NNF17SA0027784). The work of Dr. Darrow, Dr. Sinha, and Dr. Kesselheim at PORTAL is funded by a grant from the Laura and John Arnold Foundation, with additional support from the Harvard Program in Therapeutic Science and the Engelberg Foundation. The authors thank Adam R. Houston and Ariel D. Stern for their helpful comments on earlier drafts, and Adrian J. Santiago Ortiz and Marie Zakarian for their assistance.

development.<sup>1</sup> Unfortunately, high prices also limit access to important new drugs, particularly among low-income patients.<sup>2</sup>

The infectious disease context presents an entirely different type of challenge to the patent system, one that derives not so much from pricing issues that prevent access once products are developed, but from a failure to sufficiently incentivize the development of new products in the first instance. This shortcoming arises because the incentive of high prices associated with patent exclusivity is inherently tied to market size and ability to pay,<sup>3</sup> and not to public health value or future costs avoided by the health care system as a whole. Many infectious disease markets are small and therefore do not offer sufficient profit potential even under monopoly conditions.

In part because the market-based patent system more generously incentivizes investment in products outside the infectious disease context, such products accounted for 85% of new drugs approved by the U.S. Food and Drug Administration (FDA) between 1987 and 2016, while the share of antibiotics and other antimicrobial products, already small, actually decreased over that time period (Figure 1).<sup>4</sup> Although antimicrobials have tremendous public health value and can in some cases be curative, sharp declines were seen in new antibiotic approvals, and vaccine approvals—perennially low—declined from a modest peak in 2006–2008 (Figures 2 and 3).<sup>5</sup> Although antiviral approvals increased, these increases were driven largely by drug discovery arising from public investment in HIV/AIDS research (30 drugs), which receives more than \$2 billion in annual federal research funding to supplement patent incentives.<sup>6</sup> Spillover effects from HIV research also contributed to advances in adjacent disease areas, such as Hepatitis B and C (3 and 9 drugs, respectively).<sup>7</sup> HIV and hepatitis products accounted for 42 (89%) of the 47 antiviral drugs approved since

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<sup>1</sup> *United States v. Univis Lens Co.*, 316 U.S. 241, 250 (1942); A. Samuel Oddi, *Un-Unified Economic Theories of Patents: The Not-Quite-Holy Grail*, 71 NOTRE DAME L. REV. 267, 305 (1996); Fritz Machlup, *An Economic Review of the Patent System*, Study No 15, Subcommittee on Patents, Trademarks, and Copyrights of the Senate Committee on the Judiciary, 85th Cong., 2d Sess., at 13 (1958).

<sup>2</sup> Ellen 't Hoen, *TRIPS, Pharmaceutical Patents, and Access to Essential Medicines: A Long Way from Seattle to Doha*, 3 CHI. J. INT'L L. 27 (2002); see also Jonathan J. Darrow, *Essential Medicines: Why International Price Discrimination May Increasingly Be the Wrong Solution to a Global Drug Problem*, 39 J. LAW MED. & ETHICS 291 (2011) (explaining why one proposed solution is problematic).

<sup>3</sup> Michael D. Bednarek, *Planning a Global Patent Strategy to Maximize Value: Where to Get the Most "Bang for Your Buck,"* 77 J. PAT. & TRADEMARK OFF. SOC'Y 381, 382 (1995) ("The value of the right to exclude . . . largely depends on the importance of the market covered by the patent. Market size is, of course, the principal determinant of market importance.").

<sup>4</sup> Jonathan J. Darrow & Aaron S. Kesselheim, *Drug Development and FDA Approval, 1938–2013*, 370(26) NEW ENG. J. MED. 2465 (2014), <http://www.nejm.org/doi/full/10.1056/NEJMp1402114> [<https://perma.cc/T9M6-T3XY>]; see generally Jonathan J. Darrow & Aaron S. Kesselheim, *Promoting Competition to Address Pharmaceutical Prices*, HEALTH AFF., Mar. 15, 2018, <https://www.healthaffairs.org/doi/10.1377/hpb20180116.967310/full/> (examining market factors that can lead to increased drug prices).

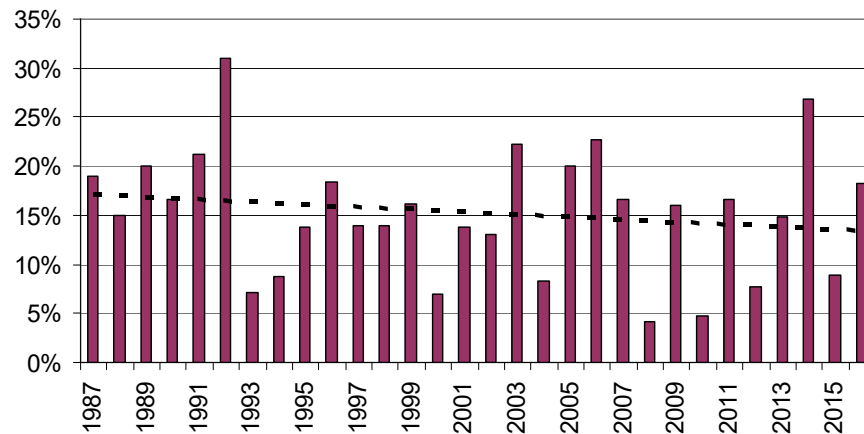
<sup>5</sup> *10x'20 Progress: Development of New Drugs Active Against Gram-Negative Bacilli: An Update from the Infectious Diseases Society of America*, 56(12) CLIN. INFECTIOUS DISEASES 1685, 1687 (2013).

<sup>6</sup> *U.S. Federal Funding for HIV/AIDS: Trends Over Time*, KAISER FAMILY FOUND., Nov. 9, 2017, <https://www.kff.org/global-health-policy/fact-sheet/u-s-federal-funding-for-hiv-aids-trends-over-time/> [<https://perma.cc/L49V-MZLS>].

<sup>7</sup> *Targeted Drug Development: Why Are Many Diseases Lagging Behind?*, FOOD & DRUG ADMIN., July 2015, at 11, <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM454996.pdf>; Erik De Clercq, *The Design of Drugs for HIV and HCV*, 6 NATURE REV. DRUG DISCOVERY 1001, 1010 (2007).

1987. Similar levels of public investment have not been directed to antibiotic development.

*Figure 1: Yearly Approvals of Antimicrobial\* Drugs as a Percentage of All New Drug Approvals by the U.S. FDA, 1987–2016*



Vaccine data not included. The dotted trendline shows a gradual decline in approvals.

\* Antimicrobials were defined as those falling within one of the following World Health Organization Anatomical Therapeutic Classification Codes: J Anti-infectives for systemic use; P Antiparasitic products, insecticides and repellents; D01 Antifungals for dermatological use; G01 Gynecological anti-infectives and antiseptics; S03 Eye and ear preparations with anti-infectives; A07A Intestinal anti-infectives; D07C Corticosteroids, combinations with antibiotics; R05X Other cold preparations; S01A Anti-infectives; S01C Anti-inflammatory agents and anti-infectives in combination; S02A Anti-infectives; S02C Corticosteroids and anti-infectives in combination; A01AB Anti-infectives and antiseptics for local oral treatment; A02BD Combinations for eradication of *Helicobacter pylori*; D09AA Ointment dressings with anti-infectives; D10AF Anti-infectives for treatment of acne; R02AB Antibiotics.

Figure 2: Approvals in Four Antimicrobial Categories, by Five-Year Periods, as a Percentage of All New Drug Approvals by the U.S. FDA, 1987–2016

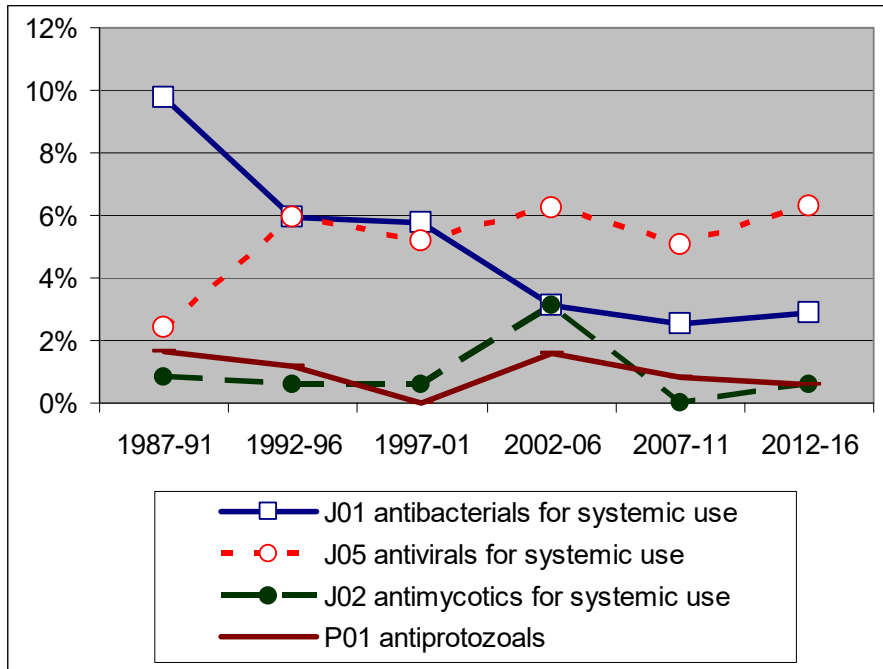
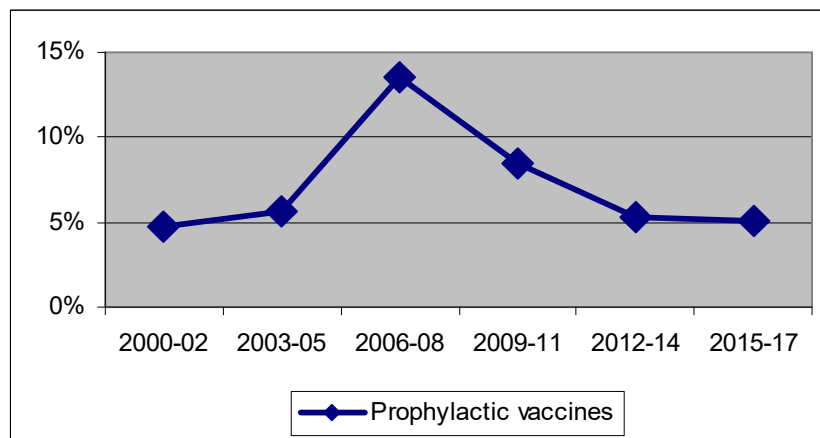


Figure 3: Vaccine Approvals, by Three-Year Periods, as a Percentage of All New Drug and Vaccine Approvals by the U.S. FDA, 2000–2017



In light of increasing recognition of the inadequacy of patents in the infectious disease context, numerous proposals have been disseminated—and some enacted—to



provide additional incentives. However, these controversial proposals have been labeled by some as useless and by others as excessive.<sup>8</sup> This article explores several key reasons why the patent system is often insufficient in the unusual market for infectious disease products, and reviews the alternative approaches to innovation that have been implemented or proposed.

## II. THE UNUSUAL INFECTIOUS DISEASE MARKET: SMALL VOLUME, LOW PRICES

The patent system increases profit potential by allowing firms to exclude competitors and thereby capture a larger share of the relevant market. But markets that are too small to generate adequate profits are less likely to attract business interest. For certain infectious disease medicines, such as treatments for multidrug-resistant organisms, the market may be so small that even the ability to capture most or all of the market may be insufficient.

The causes for small market size in the infectious disease context are complex, influenced by biological, social, and political factors, and incompletely characterized in the literature. Because market size is a function of volume and price, we organize causative factors of small market size into those primarily related to product volume, those primarily related to price, and those related to both volume and price (Figure 4). To further aid analysis, we consider both prophylactic vaccines and treatments, including antibiotics, anti-virals, anti-fungals, and anti-parasitics.

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<sup>8</sup> Kevin Outterson & Anthony McDonnell, *Funding Antibiotic Innovation with Vouchers: Recommendations on How to Strengthen a Flawed Incentive Policy*, 35(5) HEALTH AFFAIRS 784, 784 (2016); Adrian Towse & Priya Sharma, *Incentives for R&D for New Antimicrobial Drugs*, 18 INT'L J. ECON. BUS. 331, 336 (2011); Aaron S. Kesselheim & Kevin Outterson, *Fighting Antibiotic Resistance: Marrying New Financial Incentives to Meeting Public Health Goals*, 29(9) HEALTH AFF. 1689, 1691 (2010).

Figure 4: Factors that Limit Expected Market Size for Antimicrobial Products

Factors	Treatments	Vaccines	High efficacy is contributing cause	Social factor	Political factor	Biological factor
<i>Factors primarily affecting volume</i>						
Cures and preventions require fewer doses	●	●	✓			■
Positive externalities	●	●	✓			■
Effective products destroy their own markets	●	●	✓			■
Stewardship	●					■
Uncertainty over future prevalence	●					■
Few patients (because strain is emerging)	●					■
<i>Factors primarily affecting price</i>						
Ability to pay / poor patient groups	●			■		
Ethical considerations	●		✓		■	
Concentrated buyer groups (e.g., government)		●	✓		■	
<i>Factors affecting price and volume</i>						
Patient and product characteristics		●		■		
Underestimation of risk		●		■		

#### A. Factors Primarily Affecting Expected Product Volume

The expected volume of a given market may be small either because there are few potential buyers or because each buyer is expected to demand only a small quantity of product. Uncertainty over market volume can also affect expected profits, such as where there is uncertainty as to when or to what extent disease outbreaks will occur.

##### *Few buyers for emerging infectious disease medicines*

Small markets have long been known to lead to challenges in incentivizing private investment in drug development. In 1983, Congress recognized that small market size was delaying the development of drugs for certain rare (orphan), primarily non-infectious diseases such as Huntington's disease, amyotrophic lateral sclerosis,

muscular dystrophy, and Tourette's syndrome.<sup>9</sup> In response, it passed the Orphan Drug Act to provide tax incentives, research grants, and seven-year statutory exclusivity to stimulate research and development for drugs that treat any disease "occur[ing] so infrequently in the United States that there is no reasonable expectation that the cost of developing" a treatment will be recovered.<sup>10</sup> The following year, the definition was expanded to also include diseases annually affecting fewer than 200,000 people in the United States, regardless of expected return on investment.<sup>11</sup>

The market for emerging infectious diseases is small because, by definition, emerging diseases initially affect few people. In 2013, the most recent year for which data are available, the Centers for Disease Control and Prevention (CDC) estimated that drug-resistant tuberculosis, *Pseudomonas aeruginosa*, and *Salmonella typhi* affected about 1042, 6700, and 3800 people, respectively, in the United States each year, while vancomycin-resistant *Staphylococcus aureus* affected approximately 2 people each year.<sup>12</sup> These diseases therefore are only about 3% or less as prevalent as diseases defined as rare under the Orphan Drug Act.

Although drug-resistant pathogens may affect small numbers of people at first, treatments are needed well in advance of contagion. The urgency derives not only from the unmet needs of current patients, but from the inability of the patent-based market to respond quickly enough to prevent substantial suffering or loss of life once prevalence increases. Product development can take too long to help those affected during the first waves of epidemics or pandemics,<sup>13</sup> even after taking into account the various FDA expedited pathways that can be used in cases of urgent need.<sup>14</sup>

Even where experimental vaccines are already in development at the time of an outbreak, a lack of patient-ready prophylactics or treatments can be deadly. After an Ebola outbreak began in West Africa in 2014, 5837 people received an experimental

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<sup>9</sup> Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049, 2049 (1983).

<sup>10</sup> *Id.* § 526(a)(2), 96 Stat. at 2050 (codified as amended at 21 U.S.C. § 360bb(a)(1)).

<sup>11</sup> Health Promotion and Disease Prevention Amendments of 1984, Pub. L. No. 98-551, 98 Stat. 2815, 2817 (1984). The legislative history suggests the change was made out of concern that the need to file detailed financial reports justifying the orphan designation could discourage manufacturers from utilizing the program, which in Congress's view outweighed concerns expressed by the Office of Management and Budget that the amended provision might be over-inclusive, conferring the act's incentives on high priced drugs that could later turn out to recover all of their costs and become profitable. *See* 130 Cong. Rec. S14253-54, S14255 (Oct. 11, 1984) (statement of Sen. Hatch); *id.* at S14255 (statement of Sen. Kassebaum).

<sup>12</sup> *Antibiotic Resistance Threats in the United States*, CENTERS FOR DISEASE CONTROL & PREVENTION (2013), <https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf> [<https://perma.cc/P3QA-HFC4>].

<sup>13</sup> *See* Thomas J. Hwang, Jonathan J. Darrow & Aaron S. Kesselheim, *The FDA's Expedited Programs and Clinical Development Times for Novel Therapeutics, 2012-2016*, 318(21) J. AM. MED. ASS'N 2137, 2138 (2017); *see also* Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *Speed, Safety, and Industry Funding: From PDUFA 1 to PDUFA 6*, 377(23) NEW ENG. J. MED. 2278, 2280 fig.1 (2017) (illustrating that FDA review times alone can exceed 10 months).

<sup>14</sup> Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *New FDA Breakthrough-Drug Category: Implications for Patients*, 370 NEW ENG. J. MED. 1252, 1253 (2014); *see also* Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *The FDA Breakthrough Drug Designation: Four Years of Experience*, 378(15) NEW ENG. J. MED. 1444, 1451 (2018) (noting increasing use of the breakthrough pathway).

vaccine that proved to be highly effective,<sup>15</sup> but the intervention came too late for the 28,646 people who contracted the disease during the outbreak and the 11,323 people who died.<sup>16</sup> Prior to 2014, the average annual number of cases of Ebola was 62 (deaths: 41), and the largest ever Ebola outbreak, in 2000, infected 425 people, of whom 224 died.<sup>17</sup>

*Producer uncertainty over volume*

Although some infectious disease products are sufficiently rare to fall within the provisions of the Orphan Drug Act, rarity operates differently in the infectious disease context. Many of the non-infectious diseases that motivated the Orphan Drug Act are rare because the genetic defects that are believed to contribute to those diseases occur infrequently. Because genetic disorders generally persist throughout a person's life and human genes are transmitted only through inheritance, the prevalence of these disorders is unlikely to change rapidly. By contrast, adaptive microbial mutations, horizontal transmissibility, and the ability of medicines or the immune system to rid the body of microorganisms can sometimes lead to sudden and dramatic changes in infectious disease prevalence.

Recent outbreaks of influenza,<sup>18</sup> Zika,<sup>19</sup> cholera,<sup>20</sup> and Ebola demonstrate the unusual volatility of many infectious diseases, including their potential to rapidly create large markets or shrink down into small ones. In extreme cases, global contagion can occur in a matter of months, as happened during the 1917 influenza pandemic,<sup>21</sup> which infected an estimated 500 million people of whom 50 to 100 million died.<sup>22</sup> On the other hand, development efforts may halt when outbreaks unexpectedly diminish or resolve. Less than two years after the World Health Organization declared Zika an international public health emergency, Sanofi announced it was discontinuing development of two Zika virus vaccines due to a

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<sup>15</sup> *Final Trial Results Confirm Ebola Vaccine Provides High Protection Against Disease*, WHO NEWS RELEASE, Dec. 23, 2016, <http://www.who.int/mediacentre/news/releases/2016/ebola-vaccine-results/en/> [<https://perma.cc/J2XD-62HE>].

<sup>16</sup> Stefano Merler et al., *Containing Ebola at the Source with Ring Vaccination*, 10 PLOS NEGLECTED TROP. DIS. e0005093, at 2 (2016).

<sup>17</sup> *Ebola Virus Disease Distribution Map: Cases of Ebola Virus Disease in Africa Since 1976*, CENTERS FOR DISEASE CONTROL & PREVENTION, May 15, 2018, <https://www.cdc.gov/vhf/ebola/history/distribution-map.html> [<https://perma.cc/AL89-VGZ3>].

<sup>18</sup> Associated Press, *Obama Declares Swine Flu National Emergency*, NBC NEWS, Oct. 25, 2009, [http://www.nbcnews.com/id/33459423/ns/health-cold\\_and\\_flu/t/obama-declares-swine-flu-national-emergency/#.WfJRwI9Swuo](http://www.nbcnews.com/id/33459423/ns/health-cold_and_flu/t/obama-declares-swine-flu-national-emergency/#.WfJRwI9Swuo) [<https://perma.cc/BQA2-ALTR>].

<sup>19</sup> Sabrina Tavernise & Donald G. McNeil, *Zika Virus a Global Health Emergency*, W.H.O. SAYS, N.Y. TIMES, Feb. 1, 2016, <https://www.nytimes.com/2016/02/02/health/zika-virus-world-health-organization.html> [<https://perma.cc/67J9-TXWA>].

<sup>20</sup> Camila Domonoske, *U.N. Admits Role in Haiti Cholera Outbreak that Has Killed Thousands*, NAT'L PUB. RADIO, Aug. 18, 2016, <http://www.npr.org/sections/thetwo-way/2016/08/18/490468640/u-n-admits-role-in-haiti-cholera-outbreak-that-has-killed-thousands> [<https://perma.cc/7NR8-7AG4>].

<sup>21</sup> JOHN M. BARRY, *THE GREAT INFLUENZA: THE STORY OF THE DEADLIEST PLAGUE IN HISTORY* (2004).

<sup>22</sup> Jeffrey K. Taubenberger & David M. Morens, *1918 Influenza: The Mother of All Pandemics*, 12 EMERGING INFECTIOUS DISEASES 15, 15 (2006).

decline of new infections and new limits on U.S. government funding.<sup>23</sup> Businesses therefore face great uncertainty when estimating market size for certain infectious disease treatments. This uncertainty is compounded by the limited patent term, since producers must not only correctly predict that contagion will occur, but that it will occur within twenty years of patent filing.<sup>24</sup>

*Cures and preventions require fewer doses than treatments*

The completeness with which modern-day antibiotics and other antimicrobials can eradicate the underlying cause of once-deadly infectious diseases is one of the great success stories of modern medicine, and contrasts with the chronic or incomplete treatments often available in other disease categories (antiviral medications taken chronically, such as HIV treatments, represent an exception). Yet from a business perspective, rapid therapeutic success limits sales potential, since fully recovered patients no longer need medicine.

Drugs in other therapeutic categories that must be taken on an ongoing basis—such as statins for lowering cholesterol or insulin for managing blood sugar in diabetes—provide a much more favorable business model. Similarly, treatments that offer only partial or symptomatic relief, such as many cancer or psychiatric medications, mean that companies have greater opportunities to make small, serial improvements in efficacy and generate revenue from second-, third-, and later-generation products.

Unlike the antimicrobial market, the number of people in need of vaccines can be much larger than the prevalence of the corresponding disease, since vaccines may be sold to all those potentially at risk. Vaccines for rare diseases may therefore not qualify under the Orphan Drug Act, which excludes vaccines that would be given to more than 200,000 persons per year, regardless of disease prevalence.<sup>25</sup>

Despite relatively high patient volume, however, the per-person unit demand for vaccines can be even more limited than it is for cures. Although repeated vaccinations are possible, the CDC adult immunization schedule does not include recommendations for boosters for most vaccines,<sup>26</sup> and a patient may receive a given vaccine sequence only once in his or her lifetime. Most vaccine sequences do not exceed three doses,<sup>27</sup> and some immunizations consist of a single injection per vaccine or even less: The three-vaccine combination of measles, mumps, and rubella, for example, is recommended as a two-dose sequence,<sup>28</sup> or only 2/3 of an injection per vaccine.

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<sup>23</sup> Peter Loftus, *Sanofi Stops Work on Two Zika Vaccines*, WALL ST. J., Sept. 6, 2017, <https://www.wsj.com/articles/sanofi-stops-work-on-two-zika-vaccines-1504734084> [<https://perma.cc/2HHD-C389>].

<sup>24</sup> See generally Reed F. Beall, Jonathan J. Darrow & Aaron S. Kesselheim, *A Method for Approximating Future Entry of Generic Drugs*, \_\_ VALUE IN HEALTH \_\_ (2018) (in press) (explaining that even the date on which exclusivity will end can only be estimated).

<sup>25</sup> 21 C.F.R. § 316.21(b)(8)(i) (2016).

<sup>26</sup> See *Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States, 2017*, CENTERS FOR DISEASE CONTROL & PREVENTION, at 2–3, <https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf> [<https://perma.cc/V8WJ-4Y6V>].

<sup>27</sup> *Id.*

<sup>28</sup> *MMR Vaccine: What You Need to Know*, VACCINE INFORMATION STATEMENT, CENTERS FOR DISEASE CONTROL & PREVENTION, Apr. 20, 2012, at 1, <https://www.cdc.gov/vaccines/hcp/vis/vis-statements/mmr.pdf> [<https://perma.cc/J3DE-H58M>].

*Positive externalities mean lower volume*

Products that prevent or resolve infection benefit not only the patients who are vaccinated or treated, but also those who are not consumers of these medical products but whose risk of acquiring the disease is nevertheless mitigated. These positive externalities, which are not present for non-infectious disease products, contribute to high public health value but also mean that some people may free-ride, knowingly or unknowingly, by relying on or benefiting from others who obtain treatment while declining or not needing to pay for the treatment themselves.<sup>29</sup>

*Effective products undermine their own markets*

To the extent a medicine is effective in preventing further transmission—one of the key benefits that produces high public health value—it prevents growth in market demand. At the extreme, eradication of an infectious disease (as with smallpox in the 1970s) could cause a market for an antibiotic or other antimicrobial product to collapse, creating tremendous public health value but entirely eliminating sales potential. By contrast, if a cure were developed for a non-infectious disease, the potential market for that medicine would never fall below the incidence rate, that is, the number of people who are newly diagnosed with a disease during a give time period.

In exceptional cases, a collapsed market might be buoyed if fear of terrorism or other disease resurgence prompts governments to hedge against unlikely risks. In 2011, for example, the U.S. government committed \$433 million to obtain 1.7 million doses of a smallpox antiviral medication, which supplements its existing \$1 billion stockpile of smallpox vaccine.<sup>30</sup> Few diseases, however, are likely to prompt similar funding.<sup>31</sup>

*Stewardship limits sales volume*

The emergence of antibiotic resistance necessitates the sparing and appropriate use of antibiotics to preserve effectiveness, a concept known as “stewardship,”<sup>32</sup> and advocacy for this practice has intensified in recent years.<sup>33</sup> However, the need for stewardship is in tension with limited patent and other statutory exclusivity terms, which motivate brand-name drug manufacturers to generate as much revenue as possible before exclusivity expires and generic firms enter the market. Because preclinical development and clinical trials needed for regulatory approval take up

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<sup>29</sup> Paul Fine, Ken Eames & David L. Heymann, “Herd Immunity”: *A Rough Guide*, 52 *VACCINES* 911, 914 (2011); Jason B. Harris et al., *Cholera*, 379 *LANCET* 2466, 2472 (2012).

<sup>30</sup> David Willman, *Cost, Need Questioned in \$433-Million Smallpox Drug Deal*, L.A. TIMES, Nov. 13, 2011, <http://articles.latimes.com/print/2011/nov/13/nation/la-na-smallpox-20111113> [<https://perma.cc/68GR-UN3S>]; Donald G. McNeil, *Wary of Attack with Smallpox, U.S. Buys Up a Costly Drug*, N.Y. TIMES, Mar. 12, 2013, <http://www.nytimes.com/2013/03/13/health/us-stockpiles-smallpox-drug-in-case-of-bioterror-attack.html> [<https://perma.cc/74LD-GPEE>].

<sup>31</sup> See 2016 *Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Strategy and Implementation Plan*, U.S. DEP’T OF HEALTH & HUMAN SERVS., at 20, [https://www.medicalcountermeasures.gov/media/36937/2016\\_phemce\\_sip.pdf](https://www.medicalcountermeasures.gov/media/36937/2016_phemce_sip.pdf) [<https://perma.cc/UAD8-DKPV>].

<sup>32</sup> See Kevin Outterson et al., *Repairing the Broken Market for Antibiotic Innovation*, 34 *HEALTH AFF.* 277, 278 (2015).

<sup>33</sup> See, e.g., Aaron S. Kesselheim & Kevin Outterson, *Improving Antibiotic Markets for Long Term Sustainability*, 11 *YALE J. HEALTH L. POL’Y & ETHICS* 101, 122 (2011).

some of the twenty-year patent period, infectious disease products experience a median of 14.4 years of market exclusivity.<sup>34</sup> This tension between the patent term and stewardship is not present for most non-infectious disease treatments, which, unlike antimicrobials, do not face diminished effectiveness over time as microorganisms develop resistance.

### *B. Factors Primarily Affecting Expected Price*

Even when expected product volumes are adequate, disadvantaged patient populations and the negotiating power of governments or other purchasers can limit prices, and therefore profit potentials, of antimicrobial products.

#### *Poor patients cannot pay high prices*

If a disease is prevalent, but mainly affects those who are poor—as is the case for many diseases that are prevalent in developing countries—drug manufacturers may find more attractive opportunities elsewhere. The World Health Organization (WHO) recognizes 20 “neglected” tropical diseases, 19 of which are infectious, that affect more than 1 billion people in 149 countries,<sup>35</sup> but which are generally ignored by for-profit drug manufacturers because revenue potential is limited. Despite public and private efforts to develop treatments for neglected diseases, the number of drugs approved to treat these conditions has remained low.<sup>36</sup>

Immigration from developing countries can increase prevalence rates of neglected tropical diseases within the United States. For example, Chagas disease, a parasitic infection that thrives in underprivileged housing conditions and rural areas throughout much of Central and South America, is estimated to affect 300,000 people—primarily immigrants—within the United States.<sup>37</sup> Even if domestic prevalence rates rise as a result of immigration, however, the U.S. market is likely to remain both relatively small and under-resourced.

#### *Governments and foundations exert downward price pressure*

Governments are major buyers of vaccines and can help buoy and stabilize volume. But this role may also limit the average price achievable by sellers. In the United States, government purchases account for over half of the vaccine market,<sup>38</sup> but unlike Medicare, which is governed by a statute that bars the government from negotiating pharmaceutical prices, the Secretary of Health and Human Services can negotiate

<sup>34</sup> Bo Wang, Jun Liu & Aaron S. Kesselheim, *Variations in Time of Market Exclusivity Among Top-Selling Prescription Drugs in the United States*, 175 J. AM. MED. ASS'N INTERNAL MED. 635, 636 (2015).

<sup>35</sup> *Neglected Tropical Diseases*, WORLD HEALTH ORG., [http://www.who.int/neglected\\_diseases/diseases/en/](http://www.who.int/neglected_diseases/diseases/en/) [<https://perma.cc/W2Z4-9HE3>].

<sup>36</sup> Celine Aerts et al., *Are Public-Private Partnerships the Solution to Tackle Neglected Tropical Diseases? A Systematic Review of the Literature*, 121 HEALTH POL'Y 745, 748 (2017); Belen Pedrique et al., *The Drug and Vaccine Landscape for Neglected Diseases (2000–11): A Systematic Assessment*, 1 LANCET GLOBAL HEALTH 371, 371 (2013); Joshua Cohen et al., *Development of and Access to Products for Neglected Diseases*, 5 PLOS ONE e10610, at 2 (2010).

<sup>37</sup> *Parasites—American Trypanosomiasis (also known as Chagas Disease): Epidemiology and Risk Factors*, CENTERS FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/parasites/chagas/epi.html>.

<sup>38</sup> Frank A. Sloan et al., *Financing Vaccines in the 21st Century: Assuring Access and Availability*, INST. OF MED., 1, 4, 138 (2003), <https://www.nap.edu/catalog/10782/financing-vaccines-in-the-21st-century-assuring-access-and-availability> [<https://perma.cc/A86H-SXC6>].

vaccine prices.<sup>39</sup> The CDC pays less than \$20 per dose of hepatitis A virus and hepatitis B virus vaccines, and does not pay more than \$155 per dose for any vaccine,<sup>40</sup> suggesting the cost of a hepatitis C virus vaccine, if one were developed, would be only a small fraction of the cost of hepatitis C virus treatment, which can approach \$100,000.<sup>41</sup>

Other government efforts to promote access to these high-value products, such as by minimizing out-of-pocket costs to patients, can also limit revenue potential. Under the 2010 Patient Protection and Affordable Care Act, it is difficult for health insurers to pass along the costs of vaccines to patients.<sup>42</sup> Co-payments or other forms of patient cost-sharing for immunizations recommended by the CDC are specifically disallowed.<sup>43</sup> In turn, insurers offer minimal vaccine reimbursement to providers, meaning there are limited financial incentives for providers to administer vaccines.<sup>44</sup> One survey showed that about one-third of family practice physicians were considering giving up immunizations because of the unaddressed costs to their practices.<sup>45</sup>

Globally, governments or charitable organizations such as the Clinton Foundation<sup>46</sup> or the Gates Foundation<sup>47</sup> may secure funding to purchase large quantities of infectious disease products, but these organizations naturally use their buying power and public purpose to negotiate lower prices, sensibly preferring less expensive generics when available. When no generics are available due to patent protection, governments can issue compulsory licenses or threaten to do so, exerting downward price pressure. One study found that 21 (88%) of 24 global compulsory licensing episodes involved infectious disease products.<sup>48</sup> Of those 21, compulsory licenses were most often associated with HIV/AIDS medicines (17 episodes), with the remainder addressing pandemic influenza and anthrax (2 episodes each). Compulsory licensing is not limited

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<sup>39</sup> 42 U.S.C. § 1396s(d) (2017).

<sup>40</sup> *Vaccines for Children Program: CDC Vaccine Price List*, CENTERS FOR DISEASE CONTROL & PREVENTION, July 3, 2017, <https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/> [ <https://perma.cc/BCS7-F97K>].

<sup>41</sup> Susan York Morris, *Hepatitis C Treatment Costs: What You Should Know*, HEALTHLINE.COM, Feb. 22, 2016, <https://www.healthline.com/health/hepatitis-c-treatment-cost#1> [ <https://perma.cc/3JP9-2WCU>].

<sup>42</sup> See Patient Protection and Affordable Care Act, Pub. L. No. 111-148, Sec. 1001, § 2713, 124 Stat. 119, 131 (2010).

<sup>43</sup> 42 U.S.C. § 300gg-13(a) (2017).

<sup>44</sup> Sloan et al., *supra* note 34, at 98–101.

<sup>45</sup> See Elisabeth Rosenthal, *The Price of Prevention: Vaccine Costs Are Soaring*, N.Y. TIMES, July 2, 2014, at A1.

<sup>46</sup> Press Release, *Clinton Foundation and UNITAID Announce Price Reductions on 16 AIDS Medicines for 66 Developing Countries*, CLINTON FOUND., May 8, 2007, <https://www.clintonfoundation.org/main/news-and-media/press-releases-and-statements/press-release-clinton-foundation-and-unitaid-announce-price-reductions-on-16-aid.html> [ <https://perma.cc/GU6X-KYKV>].

<sup>47</sup> Kate Kelland, *Africa to Get State-of-Art HIV Drugs for \$75 a Year*, REUTERS, Sept. 21, 2017, <https://www.reuters.com/article/us-health-aids-medicines-exclusive/exclusive-africa-to-get-state-of-art-hiv-drugs-for-75-a-year-idUSKCN1BW169> [ <https://perma.cc/68YA-9PW9>].

<sup>48</sup> Reed Beall & Randall Kuhn, *Trends in Compulsory Licensing of Pharmaceuticals Since the Doha Declaration: A Database Analysis*, 9 PLOS MED. e1001154 (2012); see also Kyung-Bok Son & Tae-Jin Lee, *Compulsory Licensing of Pharmaceuticals Reconsidered: Current Situation and Implications for Access to Medicine*, GLOBAL PUB. HEALTH 1, 4 (2017) (finding that approximately 73% of compulsory licensing attempts addressed infectious disease products).



to developing countries. In 2016, Germany issued a compulsory license for raltegravir (Isentress), an HIV medicine, determining the patent holder was entitled to only a 4% license fee.<sup>49</sup>

### *Ethical considerations and public pressure*

Public pressure to lower drug prices will naturally be greatest for the most highly effective drugs, based on the ethical principle that patients should not be denied access to life-saving or life-sustaining therapy regardless of ability to pay.<sup>50</sup> For example, when Gilead decided to price sofosbuvir (Sovaldi), a direct-acting hepatitis C virus treatment, at \$84,000 for a 12-week course,<sup>51</sup> articles in the popular press and academic literature roundly condemned the announcement.<sup>52</sup> Responding to the market environment, Gilead offered steep discounts that depressed the average price at which the drug was sold.<sup>53</sup> Revenues for sofosbuvir/ledipasvir (Harvoni), a subsequent hepatitis C product sold by Gilead initially for as much as \$95,000 for a course of treatment, fell precipitously just two years after the drug was approved in 2014.<sup>54</sup>

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<sup>49</sup> Ulrich Worm, *German Federal Patent Court Determines License Fee for a Compulsory License Under HIV Drug Patent*, MAYER BROWN, Dec. 19, 2017, [https://www.allaboutipblog.com/2017/12/german-federal-patent-court-determines-license-fee-for-a-compulsory-license-under-hiv-drug-patent/?utm\\_source=Mondaq&utm\\_medium=syndication&utm\\_campaign=View-Original](https://www.allaboutipblog.com/2017/12/german-federal-patent-court-determines-license-fee-for-a-compulsory-license-under-hiv-drug-patent/?utm_source=Mondaq&utm_medium=syndication&utm_campaign=View-Original) [<https://perma.cc/X3U3-PLA6>].

<sup>50</sup> Richard A. Spinello, *Ethics, Pricing and the Pharmaceutical Industry*, 11 J. BUS. ETHICS 617, 618 (1992).

<sup>51</sup> Carolyn Y. Johnson & Brady Dennis, *How an \$84,000 Drug Got Its Price: 'Let's Hold Our Position . . . Whatever the Headlines,'* WASH. POST, Dec. 1, 2015; see generally Nathalie Vernaz et al., *Drug Pricing Evolution in Hepatitis C*, 11 PLOS ONE e0157098, at 2 (2016) (summarizing the evolution in cure rates, as well as prices, of Hepatitis C medicines).

<sup>52</sup> *Dare to Refuse the Exorbitant Price of Sovaldi!*, 23 PRESCRIBING INT'L 278 (2014); Robert Steinbrook & Rita F. Redberg, *The High Price of the New Hepatitis C Virus Drugs*, 174 JAMA INTERNAL MED. 1172, 1172 (2014); Michael McCarthy, *Hepatitis C Drug Maker Puts Profit Ahead of Patients, US Senate Report Charges*, 351 BRITISH MED. J. h6573, at 1 (2015); Margot Sanger-Katz, *Why the Price of Sovaldi is a Shock to the System*, N.Y. TIMES, Aug. 6, 2014, <https://www.nytimes.com/2014/08/07/upshot/why-the-price-of-sovaldi-is-a-shock-to-the-system.html> [<https://perma.cc/Z6NA-EGGM>]; Andrew Pollack, *High Cost of Sovaldi Hepatitis C Drug Prompts a Call to Void Its Patents*, N.Y. TIMES, May 19, 2015, <https://www.nytimes.com/2015/05/20/business/high-cost-of-hepatitis-c-drug-prompts-a-call-to-void-its-patents.html> [<https://perma.cc/ZPM3-GXCG>]; Olga Khazan, *The True Cost of an Expensive Medication*, ATLANTIC, Sept. 25, 2015, <https://www.theatlantic.com/health/archive/2015/09/an-expensive-medications-human-cost/407299/> [<https://perma.cc/7UB2-HWNP>].

<sup>53</sup> Rebecca Robbins, *Forced to Discount Pricey Hepatitis C Drugs, Gilead Misses Sales Target*, STAT NEWS, Apr. 28, 2016, <https://www.statnews.com/2016/04/28/gilead-hepatitis-c-revenue-down/> [<https://perma.cc/FFG2-645A>]; Ed Silverman, *Ooh la la: France Negotiates a Steep Discount for Sovaldi from Gilead*, WALL ST. J., Nov. 20, 2014, <https://blogs.wsj.com/pharmalot/2014/11/20/ooh-la-la-france-negotiates-a-steep-discount-for-sovaldi/> [<https://perma.cc/7TW5-QJNT>].

<sup>54</sup> Anne Steele, *Gilead Revenue Falls as Hepatitis Drug Sales Drop*, MARKETWATCH, Feb. 7, 2017, [https://secure.marketwatch.com/story/gilead-revenue-falls-as-hepatitis-drug-sales-drop-2017-02-07?link=MW\\_home\\_latest\\_news](https://secure.marketwatch.com/story/gilead-revenue-falls-as-hepatitis-drug-sales-drop-2017-02-07?link=MW_home_latest_news) [<https://perma.cc/VD8U-2RVA>]; Tess Stynes, *Gilead Sales of Hepatitis C Drugs fall 19%; Harvoni Misses Expectations as Competition from Rival Drugs, Pricing Pressures Intensify*, WALL ST. J., July 25, 2016; Arlene Weintraub, *Merck Swallows \$2.9B Write-Down of Experimental Hep C Drug as Market Plummet*, FIERCE PHARMA, Feb. 24, 2017, <https://www.fiercepharma.com/pharma/merck-swallows-1-9b-writedown-experimental-hep-c-drug-as-market-plummet> [<https://perma.cc/XSFW-LMF5>].

### C. Factors Affecting Both Expected Volume and Price

Patient and product characteristics in the infectious disease market differ from those in the non-infectious disease market in important ways that tend to minimize both the prices companies can charge and the willingness of patients to accept even free or low-cost products.

#### *Patient and product characteristics reduce demand*

Unlike most medicines, vaccines must be sold to those who are still healthy. Individuals not suffering from illness who underestimate potential disease risks may have a very low willingness to accept product risks (both real and perceived), costs, or even the inconvenience of a visit to a doctor's office,<sup>55</sup> thereby reducing demand. In addition, many vaccines are administered by injection, which is disfavored by many patients,<sup>56</sup> particularly children,<sup>57</sup> and requires provider involvement with administration.

#### *Underestimation of risk reduces demand*

In general, antimicrobial treatments and vaccines have high rates of efficacy.<sup>58</sup> When sufficiently high treatment efficacy and vaccine utilization combine to dramatically reduce disease prevalence, some may no longer perceive a positive benefit-risk ratio from immunization, in part because of fading memories of suffering and mortality.<sup>59</sup> Contributing to cost-benefit miscalculations is the natural tendency of patients to believe they are less likely than average to experience negative health events, a phenomenon known as optimistic bias.<sup>60</sup> This can cause demand to fall, resulting in vulnerable populations with increased susceptibility to disease outbreaks.<sup>61</sup>

<sup>55</sup> Phaedra S. Corso et al., *Assessing Preferences for Prevention Versus Treatment Using Willingness to Pay*, 22 MED. DECISION MAKING S92, S97 (2002).

<sup>56</sup> Simone Wright et al., *Fear of Needles: Nature and Prevalence in General Practice*, 38 AUSTRALIAN FAM. PHYSICIAN 172, 173 (2009); Yael Nir et al., *Fear of Injections in Young Adults: Prevalence and Associations*, 68 AM. J. TROP. MED. & HYGIENE 341, 342 (2003).

<sup>57</sup> Emuella M. Flood et al., *A Survey of Children's Preferences for Influenza Vaccine Attributes*, 29 VACCINE 4334, 4337 (2011); Emuella M. Flood et al., *Parent Preferences for Pediatric Influenza Vaccine Attributes*, 50 CLINICAL PEDIATRICS 338, 343 (2011); Anna Taddio et al., *Reducing the Pain of Childhood Vaccination: An Evidence-Based Clinical Practice Guideline (Summary)*, 182 CANADIAN MED. J. 1989, 1999 (2010); David Fassler, *The Fear of Needles in Children*, 55 AM. J. ORTHOPSYCHIATRY 371, 375 (1985).

<sup>58</sup> Jonathan J. Darrow & Aaron S. Kesselheim, *A New Wave of Vaccines for Non-Communicable Diseases: What Are the Regulatory Challenges?*, 70 FOOD & DRUG L. J. 243, 246 (2015).

<sup>59</sup> Martin Kaufman, *The American Anti-Vaccinationists and their Arguments*, 41 BULL. HIST. MED. 463, 464 (1967).

<sup>60</sup> Neil D. Weinstein, *Unrealistic Optimism About Future Life Events*, 39 J. PERSONALITY & SOC. PSYCH. 806, 808 (1980); Neil D. Weinstein, *Unrealistic Optimism About Susceptibility to Health Problems*, 5 J. BEHAV. MED. 441, 450 (1982).

<sup>61</sup> Robert M. Wolfe & Lisa K. Sharp, *Anti-Vaccinationists Past and Present*, 325 BRIT. MED. J. 430, 431 (2002); see also Kaufman, *supra* note 59, at 464 (“[A]s the memory of the disease slowly receded into the past, vaccination fell into disuse.”); Emily Oster & Geoffrey Kocks, *After a Debacle, How California Became a Role Model on Measles*, N.Y. TIMES, Jan. 16, 2018, <https://www.nytimes.com/2018/01/16/upshot/measles-vaccination-california-students.html> [<https://perma.cc/C3RK-62ZV>] (noting that a 2014 measles outbreak in California that sickened at least 159 people was “the result of an inability to persuade a significant share of Californians that vaccines were important” but that “earlier generations knew [that] people die of measles, and of whooping cough, and of other diseases that vaccines can prevent”).

Even with the aid of government programs that provide vaccines at no cost, such as the federal Vaccines for Children Program,<sup>62</sup> some still decline to vaccinate their children or be vaccinated themselves.

### III. RECENT LEGISLATIVE EFFORTS

For these reasons, the patent system has proven inadequate in stimulating private investment in certain infectious disease markets, inspiring legislators to explore several creative options.

#### *Priority review vouchers*

2007, Congress created a priority review voucher program<sup>63</sup> that seeks to overcome weak market incentives by linking the development of new infectious disease products to the profitability of entirely unrelated products. The link is created by the use of special vouchers, which FDA confers to sponsors that obtain approval of drugs for certain tropical diseases, such as malaria, Zika, yaws, and schistosomiasis. The sponsor can use the vouchers to obtain priority review of an unrelated new drug application, or sell the voucher to another manufacturer to do so. Because FDA aims to review applications given a priority designation within six months rather than the standard 10 months, revenue generation of the unrelated product can potentially occur four months earlier, while the patent expiration date of that product remains unchanged.

This general model of extending the exclusivity period of an unrelated product has been broadly proposed to incentivize the development of all new and important antibiotics,<sup>64</sup> and can be accomplished either by extending the end of the patent period for the unrelated product or advancing its approval date. So far, Congress has authorized the priority review voucher program to apply only to neglected tropical disease products, not all antibiotics (although other statutes have extended the incentive to rare pediatric diseases and medical countermeasures for chemical or other types of warfare), and has provided for expedited approval but not patent extension. (Limited patent extensions have been available since the 1980s to compensate for time lost to regulatory or patent office review,<sup>65</sup> but these provisions are not targeted to infectious disease products.) Because priority review vouchers can be used as soon as ninety days after they are received<sup>66</sup> to speed the entry of non-infectious disease products, they are less reliant on distant revenue streams, and not at all reliant on the size of the targeted infectious disease market.

Ten years after their creation, however, vouchers have been awarded for only five tropical disease drugs—none of which was a therapeutic breakthrough—and have not

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<sup>62</sup> 42 U.S.C. § 1396s (2017).

<sup>63</sup> Pub. L. No. 110-85, 121 Stat. 823, 972 (2007).

<sup>64</sup> PRESIDENT'S COUNCIL OF ADVISORS ON SCI. & TECH., REPORT TO THE PRESIDENT ON COMBATING ANTIBIOTIC RESISTANCE (2014), [https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/PCAST/pcast\\_carb\\_report\\_sept2014.pdf](https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf); Kevin Outterson et al., *Will Longer Antimicrobial Patents Improve Global Public Health?*, 7 LANCET 559, 562 (2007).

<sup>65</sup> 35 U.S.C. §§ 154, 156 (2017).

<sup>66</sup> 21 U.S.C. § 360n(b)(4) (2017); U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: TROPICAL DISEASE PRIORITY REVIEW VOUCHERS (2016) at 3.

increased the number of Phase 1 studies for new neglected tropical disease products.<sup>67</sup> Three of the new drugs, artemether-lumefantrine (Coartem, FDA-approved in 2009) for malaria, miltefosine (Impavido, 2014) for leishmaniasis, and benznidazole (2017) for Chagas disease, were available outside the United States for many years prior to the creation of the voucher program.<sup>68</sup> Another beneficiary of the program, a new cholera vaccine (Vaxchora, 2016), was preceded by other safe and effective cholera vaccines (e.g., Dukoral and ShanChol) already available outside the United States.<sup>69</sup> Finally, bedaquiline (Sirturo, 2012) is indicated for treatment-resistant tuberculosis—a priority health need—but was approved amid controversy over its safety and efficacy.<sup>70</sup>

It is possible the voucher system may yet prove its worth. Ten years is not a long period in an industry in which the time needed to conduct human trials and obtain approval averages seven to eight years,<sup>71</sup> especially since human trials for truly novel products may follow years of preclinical research. However, it is more likely that the impact of the voucher program will be limited. The extension of voucher eligibility to products other than neglected tropical disease products has reduced the rarity of such vouchers and hence their financial value. Currently, for example, at least nine unused vouchers are in circulation, and voucher prices have receded from a peak of \$350 million in 2015 to just over one-third of that value.<sup>72</sup> Since 1987, an increasing percentage of products have been granted priority review designations, limiting the need to purchase priority review vouchers.<sup>73</sup>

Perhaps more important than these supply and demand issues is the fact that the value of a voucher is entirely disconnected from the public health value of the underlying product it is intended to incentivize. Although this was an intentional feature of the legislation, it has already had unintended, if foreseeable, consequences,

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<sup>67</sup> Nina Jain et al., *Association of the Priority Review Voucher with Neglected Tropical Disease Drug and Vaccine Development*, 318 J. AM. MED. ASS'N 388, 389 (2017).

<sup>68</sup> Aaron S. Kesselheim et al., *Experience with the Priority Review Voucher Program for Drug Development*, 314 J. AM. MED. ASS'N 1687, 1687 (2015); Simone Garcia et al., *Treatment with Benznidazole During the Chronic Phase of Experimental Chagas' Disease Decreases Cardiac Alterations*, 49 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 1521, 1522 (2005).

<sup>69</sup> Jason B. Harris et al., *Cholera*, 379 LANCET 2466, 2472 (2012); see also *Cholera—Vibrio cholerae infection: Vaxchora® (lyophilized CVD 103-HgR)*, CENTERS FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/cholera/vaccines.html> (announcing the recent approval of Vaxchora, and the availability of three other cholera vaccines).

<sup>70</sup> Jerry Avorn, *Approval of a Tuberculosis Drug Based on a Paradoxical Surrogate Measure*, 309 J. AM. MED. ASS'N 1349, 1349 (2013).

<sup>71</sup> Kenneth I. Kaitin & Joseph A. DiMasi, *Pharmaceutical Innovation in the 21st Century: New Drug Approvals in the First Decade, 2000–2009*, 89 CLINICAL PHARMACOLOGY & THERAPEUTICS 183, 185 (2011); Tim Anderson et al., *Global Pharmaceuticals: R&D Productivity Finally Turning the Corner?! Important New Data Suggests It Is*, BERNSTEIN, Sept. 22, 2015 (Exh. 7), [https://kmggroup.com/wp-content/uploads/2015/09/Bernstein-Global-Pharma\\_22Sept2015\\_RnD-Productivity-Trends.pdf](https://kmggroup.com/wp-content/uploads/2015/09/Bernstein-Global-Pharma_22Sept2015_RnD-Productivity-Trends.pdf).

<sup>72</sup> Alexander Gaffney, Michael Mezher & Zachary Brennan, *Regulatory Explainer: Everything You Need to Know About FDA's Priority Review Vouchers*, REG. AFF. PROF. SOC'Y, Dec. 19, 2017, <https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/12/regulatory-explainer-everything-you-need-to-know-about-fda%E2%80%99s-priority-review-vouchers>.

<sup>73</sup> See Aaron S. Kesselheim, Bo Wang, Jessica Franklin & Jonathan J. Darrow, *Trends in Utilization of FDA Early-Access Drug Approval Programs*, 351 BRITISH MED. J. h4633, at 6 figs. 2 & 3 (2015) (showing increasing utilization of expedited programs generally); see also Darrow & Kesselheim, *supra* note 4 (providing data for individual drugs).

as seen in the low novelty and/or value of the products approved so far under the program as described above. Existing incentives associated with new drug approval are already not well-correlated with therapeutic benefit.<sup>74</sup> But the voucher program takes this poor correlation a step further, creating the absence of *any* connection between the incentive and product value, which increases the probability that firms can meet the technical requirements of the program without contributing much or anything to the antimicrobial arsenal. Given the eligibility criteria for the current voucher program, for example, it should not be surprising if firms continue to pursue approval of those voucher-eligible products that require the least investment—even if they are not particularly effective or safe, or are already widely used outside the United States—rather than those that do the most to fulfill unmet health needs.

### *The GAIN Act*

In 2012 Congress enacted Title VIII of the FDA Safety and Innovation Act, generally referred to as the Generating Antibiotic Incentives Now (GAIN) Act.<sup>75</sup> The GAIN Act applies to “qualified infectious disease products,” defined as antibacterial or antifungal drugs that are intended to address serious or life-threatening infections, including those that are resistant to current treatments (vaccines are not eligible).<sup>76</sup> It provides new drugs meeting this definition with both priority review and five years of additional statutory exclusivity, which, when added to the five years of statutory exclusivity available to all new chemical entities, provides ten years of exclusivity. The five-year GAIN period may also be added to the end of the seven-year Orphan Drug exclusivity period, yielding a total of twelve years of exclusivity for rare infectious disease treatments.

Unfortunately, additional statutory exclusivity—like patent protection—relies on market forces to bring forth new treatments. While the five-year additional GAIN exclusivity can therefore extend the expected duration of generic-free competition, it largely fails to address the market-based challenges we describe, which have more to do with the size and profitability of the market and less to do with the number of years over which profits will be accrued. In any event, the total GAIN period runs concurrently with the patent period<sup>77</sup> and therefore often will not extend beyond the 14.4-year median market exclusivity period already enjoyed by infectious diseases products. Even in cases in which ten- or twelve-year exclusivity periods extend beyond the ends of patent exclusivities, the net present value of those distant revenue streams is heavily discounted, yielding minimal present incentives while creating barriers to access far into the future.<sup>78</sup> Although firms may eagerly pursue statutory exclusivity extensions whenever available, the decision of whether to pursue the basic research

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<sup>74</sup> Jonathan J. Darrow, *Pharmaceutical Efficacy: The Illusory Legal Standard*, 70 WASH. & LEE L. REV. 2073, 2110 (2013).

<sup>75</sup> Pub. L. No. 112-144, § 801, 126 Stat. 993, 1077 (2012) (codified at 21 U.S.C. § 355f).

<sup>76</sup> 79 Fed. Reg. 32,464 at 32,465–32,466 (June 5, 2014) (establishing a list of qualifying pathogens under the Food and Drug Administration Safety and Innovation Act).

<sup>77</sup> 21 U.S.C. § 355f(a) (2018) (The five year period is added to “the 4- and 5-year periods described in subsections (c)(3)(E)(ii) and (j)(5)(F)(ii) of section 355 of this title . . .”); *see id.* § 355(c)(3)(E)(ii) (measuring the 4- and 5-year periods from the date of approval of a new drug application).

<sup>78</sup> Brad Spellberg et al., *The Critical Impact of Time Discounting on Economic Incentives to Overcome the Antibiotic Market Failure*, 11 NATURE REVS. DRUG DISCOVERY 168, 169 (2012).

that results in a new antibiotic occurs many years earlier, when these exclusivities are still distant.<sup>79</sup>

*A new “limited population pathway”*

In contrast to “pull” strategies that seek to increase the certainty or amount of post-approval rewards, such as reflected in the GAIN Act and the priority review voucher program, “push” strategies promote the development of novel antimicrobial products by reducing or subsidizing pre-approval development or approval costs. One such strategy is reflected in the 21st Century Cures Act, which in 2016 created a “limited population pathway” for antibacterial or antifungal drugs intended to treat serious or life-threatening conditions. Under this pathway, drugs may be approved “notwithstanding a lack of evidence to fully establish a favorable benefit-risk profile in a population that is broader than the intended limited population.”<sup>80</sup>

Regulatory approval on the basis of limited evidence can reduce development costs and accelerate revenue streams, but the Cures Act explicitly preserves the ability of physicians to prescribe these drugs to patients outside of the limited population for which evidence suggests a positive benefit-risk ratio,<sup>81</sup> creating the potential for a mismatch between revenue and public health value. Even for patients falling within the defined population, drugs are eligible for the pathway whether minimally effective or curative, so long as they are intended to address unmet needs.

#### **IV. ALTERNATIVE SOLUTIONS THAT SIDESTEP TRADITIONAL MARKETS**

Patents, non-patent exclusivities, and vouchers each seek to harness the power of the market to promote invention, but are thereby limited because they depend on financial value rather than public health value. To the extent these market-based incentives continue to prove inadequate, another option is to pursue non-traditional markets or non-market mechanisms that may be better able to identify and address high priority public health needs.

*A. Nonprofit Organizations*

Nonprofit organizations tend to be less dependent than traditional producers on projected sales revenue, and may therefore be better able to focus efforts on those products that contribute the most to public health. In some cases, such organizations may collaborate with government, industry, or others to accelerate product development. One such organization is the Drugs for Neglected Diseases initiative (DNDi), which blends various philanthropic, government, and other funding sources<sup>82</sup>

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<sup>79</sup> See JAMES BOYLE, *THE PUBLIC DOMAIN: ENCLOSING THE COMMONS OF THE MIND* 23–34 (2008) (quoting McCauley for the proposition that distant payments are heavily discounted).

<sup>80</sup> Pub. L. No. 114-255, § 3042, 130 Stat. 1033, 1113 (2016).

<sup>81</sup> *Id.* § 3043, 130 Stat. at 1114 (“Prescribing Authority”).

<sup>82</sup> See *Drugs for Neglected Diseases initiative*, [http://www.who.int/phi/documents/drugs\\_neglected\\_diseases\\_initiative.pdf](http://www.who.int/phi/documents/drugs_neglected_diseases_initiative.pdf) (last visited Jan. 30, 2018).

to promote its mission of developing drugs for neglected diseases that might otherwise “fall outside the scope of market-driven research.”<sup>83</sup>

From its founding in 2003 through 2015, DNDi succeeded in making available six new products, although all represented modest clinical advances. Two were fixed-dose combination malarial treatments comprising artesunate and either amodiaquine or mefloquine, all three of which had long been used to treat malaria.<sup>84</sup> Similarly, both ingredients of DNDi’s combination treatment for human African trypanosomiasis, nifurtimox and eflornithine, were included on WHO’s model list of essential medicines before the creation of DNDi.<sup>85</sup> Two DNDi treatments for visceral leishmaniasis contain combinations of paromomycin with sodium stibogluconate, or paromomycin with miltefosine and liposomal amphotericin B, but these treatments had all been used or investigated for the treatment of leishmaniasis prior to DNDi’s involvement.<sup>86</sup> DNDi also created a pediatric formulation of benznidazole and helped the private company Chemo Research gain FDA approval under an agreement by which the drug will be provided on a “no profit/no loss” basis.<sup>87</sup>

In addition to creating new formulations and advancing the development of known substances, DNDi is working to develop novel, high-value drugs. At least 15 new chemical entities are moving through its development pipeline,<sup>88</sup> including those targeting leishmaniasis,<sup>89</sup> human African trypanosomiasis, mycetoma, and hepatitis C virus.<sup>90</sup>

Non-profit organizations may also be able to offer successfully-developed drugs at prices far below those of traditional firms. DNDi’s estimated cost for the development of its new drugs, including the cost of failures, is €100 to €150 million (\$116 to \$175 million),<sup>91</sup> less than 7% of the \$2.6 billion cost of drug development estimated by a

<sup>83</sup> *Vision and Mission*, DNDi, available at: <https://www.dndi.org/about-dndi/vision-mission/> (last visited Jan. 30, 2018).

<sup>84</sup> Mark T. Hoekenga, *Treatment of Malaria with a Single Dose of Amodiaquine or Chloroquine*, 149 J. AM. MED. ASS’N 1369, 1371 (1952); Jing-Bo Jiang et al., *Antimalarial Activity of Mefloquine and Qinghaosu*, 320 LANCET 285, 287 (1982); Sudaratana R. Krungkrai & Yongyuth Yuthavong, *The Antimalarial Action on Plasmodium Falciparum of Qinghaosu and Artesunate in Combination with Agents which Modulate Oxidant Stress*, 81 TRANS. R. SOC. TROP. MED. HYGIENE 710, 711 (1987).

<sup>85</sup> *The Use of Essential Drugs*, World Health Org. Technical Report Series, Ninth Report of the WHO Expert Committee (including the revised Model List of Essential Drugs), 2000 at 26 (on file with author).

<sup>86</sup> Barbara L. Herwaldt & Jonathan D. Berman, *Recommendations for Treating Leishmaniasis with Sodium Stibogluconate (Pentostam) and Review of Pertinent Clinical Studies*, 46 AM. J. TROP. MED. & HYGIENE 296, 297 (1992); T.K. Jha et al., *Miltefosine, an Oral Agent, for the Treatment of Indian Visceral Leishmaniasis*, 341 NEW ENG. J. MED. 1795, 1799 (1999); R.N. Davidson et al., *Liposomal Amphotericin B in Drug-Resistant Visceral Leishmaniasis*, 337 LANCET 1061, 1061 (1991).

<sup>87</sup> Courtney Columbus, *Drug for ‘Neglected’ Chagas Disease Gains FDA Approval Amid Price Worries*, NAT’L PUB. RADIO, Sept. 10, 2017, <http://www.npr.org/sections/health-shots/2017/09/10/547351794/drug-for-neglected-chagas-disease-gains-fda-approval-amid-price-worries>.

<sup>88</sup> *Business Plan 2015-2023: A Dynamic Portfolio Approach to Address Neglected Patients’ Needs*, DNDi, [https://www.dndi.org/wp-content/uploads/2009/03/DNDi\\_Business\\_Plan\\_2015-2023.pdf](https://www.dndi.org/wp-content/uploads/2009/03/DNDi_Business_Plan_2015-2023.pdf) [hereinafter “DNDi Business Plan”].

<sup>89</sup> *New Hope for Novel Drugs for Leishmaniasis: Update of DNDi’s Leishmaniasis Pipeline*, DNDi (2017), [https://www.dndi.org/wp-content/uploads/2017/05/DNDi\\_LeishmaniasisPipeline\\_2017.pdf](https://www.dndi.org/wp-content/uploads/2017/05/DNDi_LeishmaniasisPipeline_2017.pdf).

<sup>90</sup> Graeme Bilbe, *Viewpoint*, DNDi, Feb. 2017, [https://www.dndi.org/2017/media-centre/news-views-stories/viewpoint/qna\\_results\\_of\\_rnd\\_affordable\\_available\\_to\\_patients/](https://www.dndi.org/2017/media-centre/news-views-stories/viewpoint/qna_results_of_rnd_affordable_available_to_patients/).

<sup>91</sup> *DNDi Business Plan*, *supra* note 88, at 8.

leading industry-funded study, which was not limited to infectious disease products.<sup>92</sup> Manufacturing costs must still be considered, but if these projects ultimately lead to approved products, DNDi's ability to efficiently develop new drugs and its non-profit structure mean that prices are likely to remain reasonable.

### B. Government Funding of Basic Research

The National Institute of Allergy and Infectious Diseases (NIAID) is one of twenty-seven sub-agencies of the National Institutes of Health and spends approximately \$4 billion annually on basic and applied research addressing nearly 300 infectious agents, including HIV, Zika, Ebola, and pandemic influenza.<sup>93</sup> Funding of the NIAID and other agencies could be expanded to promote a better understanding of infectious disease pathology and resistance, and thereby encourage the development of new antimicrobial treatments and vaccines.<sup>94</sup>

One recent initiative made possible through government funding is the Combating Antibiotic Resistant Bacteria biopharmaceutical accelerator (CARB-X), a non-profit based at Boston University that was founded in 2016 to advance global research on bacterial drug-resistance.<sup>95</sup> CARB-X grew out of a 2014 executive order that directed the Biomedical Advanced Research Development Authority (BARDA), a sub-agency within the Department of Health and Human Services, to develop next-generation countermeasures to address antibiotic-resistant bacteria.<sup>96</sup> BARDA, along with the Wellcome Trust and NIAID, are providing CARB-X with \$450 million worth of investment and pre-clinical services, which it then awards to support early-stage projects until those projects can attract additional private or public investment for translational development.<sup>97</sup>

### C. Government Purchase Commitments

Another non-traditional market mechanism that has been used with some success is the advance market commitment, a type of "pull" strategy that involves a legally binding commitment to purchase a pre-specified quantity of a new drug or vaccine at a pre-specified price, so long as the product developed meets buyer specifications such as adequate thermal stability or protection against certain serotypes.<sup>98</sup> Once the pre-

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<sup>92</sup> Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 28 (2016).

<sup>93</sup> *FY2018 Budget: National Institute of Allergy and Infectious Diseases*, DEP'T OF HEALTH & HUMAN SERVS., NAT'L INST. OF HEALTH, <https://www.niaid.nih.gov/sites/default/files/fy2018cj.pdf>; *FY2016 Budget: National Institute of Allergy and Infectious Diseases*, DEP'T OF HEALTH & HUMAN SERVS., NAT'L INST. OF HEALTH, <https://www.niaid.nih.gov/sites/default/files/fy2016cj.pdf>; *NIAID Role in Research: Improving the Health of Millions of People Around the World*, NAT'L INST. OF ALLERGY & INFECTIOUS DISEASES, <https://www.niaid.nih.gov/research/role>.

<sup>94</sup> Michael Sinha & Aaron S. Kesselheim, *Regulatory Incentives for Antibiotic Drug Development: A Review of Recent Proposals*, 24 BIOORGANIC & MEDICINAL CHEM. 6446, 6449 (2016).

<sup>95</sup> *The Race Against Superbugs*, CARB-X ANNUAL REPORT 2016-2017, [https://carb-x.org/wp-content/uploads/2018/01/2016\\_CARB-X-Annual\\_Report.pdf](https://carb-x.org/wp-content/uploads/2018/01/2016_CARB-X-Annual_Report.pdf).

<sup>96</sup> Exec. Order No. 13676, 184 Fed. Reg. 56,931 (Sept. 18, 2014); *National Strategy for Combating Antibiotic-Resistant Bacteria*, THE WHITE HOUSE, Sept. 2014, [https://www.cdc.gov/drugresistance/pdf/carb\\_national\\_strategy.pdf](https://www.cdc.gov/drugresistance/pdf/carb_national_strategy.pdf).

<sup>97</sup> *The Race Against Superbugs*, *supra* note 95, at 2, 4, 8.

<sup>98</sup> Owen Barder et al., *Advance Market Commitments: A Policy to Stimulate Investment in Vaccines for Neglected Diseases*, ECONOMISTS' VOICE, Feb. 2006, at 4.



specified quantity has been purchased by the government or other organization making the commitment, the drug developer could then be obligated by contract to sell further units at a low price, creating an effect similar to patent expiration. In contrast to the patent system, however, the initial higher price is set in advance by the purchaser rather than after development by the drug manufacturer, assuring the purchaser of an acceptable price. In 2009 an advance market commitment was launched to ensure sufficient supply and reasonable prices for pneumococcal vaccines,<sup>99</sup> but because effective pneumococcal vaccines were already available<sup>100</sup> and new pneumococcal vaccines addressing particular serotypes were already in late-stage development, it is difficult to determine how this model affected investment in the field.<sup>101</sup> No similar initiatives have since been launched.

#### *D. Enhanced Global Coordination*

Because infectious diseases do not respect national boundaries, a global biomedical research and development treaty could also be established, an approach recommended by a WHO Consultative Expert Working Group in 2012.<sup>102</sup> An international agreement would not only leverage a global base of potential resources, but could also reduce duplicative effort, ensure equitable contributions by nations that are sensitive to each nation's ability to pay,<sup>103</sup> and help to ensure a stable funding stream over time.

The role of governments, either individually or as members of a future treaty organization, could also be expanded from the current focus on research and early-stage trials to the development of promising products through regulatory approval. Government-developed antimicrobials and vaccines could then be licensed directly to generic drug manufacturers under contracts that include supply commitments and reasonable price provisions.

## V. CONCLUSION

Infectious disease markets are unlike non-infectious disease markets in important ways that have implications for the development of needed new drugs and vaccines. Most significantly, the public health value of infectious disease products is poorly correlated with market-based financial incentives because of the unusual disease, patient, product, and public health characteristics of this market. Because the patent system is fundamentally dependent on markets, patents fail to adequately incentivize many infectious disease treatments.

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<sup>99</sup> *The Advance Market Commitment for Pneumococcal Vaccine*, UNICEF, (Apr. 2017), [https://www.unicef.org/supply/index\\_60990.html](https://www.unicef.org/supply/index_60990.html) [<https://perma.cc/329Q-MF2Y>]; Neisha Sundaram et al., *Cost-Effectiveness of 13-Valent Pneumococcal Conjugate Vaccination in Mongolia*, 35 *VACCINE* 1055, 1056 (2017).

<sup>100</sup> See, e.g., Approval letter from Karen L. Goldenthal, FDA, to Jack D. Love, Lederle Labs. Div., Am. Cyanamid Co., Oct. 1, 2002 (Prevnar approval letter), <https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm137200.htm>.

<sup>101</sup> Jens Plahte, *Is the Pneumococcal Vaccine Advance Market Commitment Motivating Innovation and Increasing Manufacturing Capacity? Some Preliminary Answers*, 30 *VACCINE* 2462, 2464 (2012).

<sup>102</sup> *Research and development to meet health needs in developing countries: strengthening global financing and coordination, Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination*, at 53, WORLD HEALTH ORGANIZATION [WHO], (Apr. 2012).

<sup>103</sup> See Margaret K. Kyle et al., *Strategic Interaction Among Governments in the Provision of a Global Public Good*, 156 *J. PUB. ECON.* 185, 185 (2017).

Public health goals can more effectively be promoted if herd immunity is leveraged and potential epidemics are curtailed early, but such efforts purposefully minimize the volume of pharmaceutical products needed. Eradication, elimination, and reduction in prevalence intentionally aim to shrink the number of affected patients, as do complete cures for individual patients, but achievement of these goals inherently reduces future revenue streams. Stewardship of new antimicrobials may benefit future patients, but decreases present income.

An understanding of the unusual characteristics of the infectious disease marketplace helps explain why the market-based approaches implemented by Congress have so far produced only modest results. Extensions of patent or statutory exclusivities such as those found in the GAIN Act are linked to market size, not public health value, and in any event offer distant revenues with heavily discounted present values. Priority review vouchers create timely rewards for the successful development of certain tropical infectious disease products, but their value is de-linked from the public health value of the newly created infectious disease product—like infectious disease markets themselves. Experience with the priority review voucher program, in which five new drugs met technical program criteria but contributed minimal additional therapeutic value, has shown that targeting incentives to a defined disease category, without more, does not guarantee substantial therapeutic advance.

Initiatives that combine expert identification of priority needs with funding from government, philanthropists, industry, or others, may therefore represent the most promising source of innovation for future infectious disease treatments. Continued support for organizations such as DNDi could help to ensure that both incremental improvements and new chemical entities continue to advance through approval. If political commitment can be sustained, government funding of basic research and early-stage projects, as with CARB-X, could accelerate important developments. Greater utilization of advance market commitments could confirm this tool as an effective means to address some market-based innovation challenges, such as the adverse impacts of government price pressure or profit-limiting legislation. The most far-reaching policy innovation, however, may be a research and development treaty, which would provide a focal point for future global coordination, provide a long-term commitment to funding, and build on what has been learned from existing approaches.