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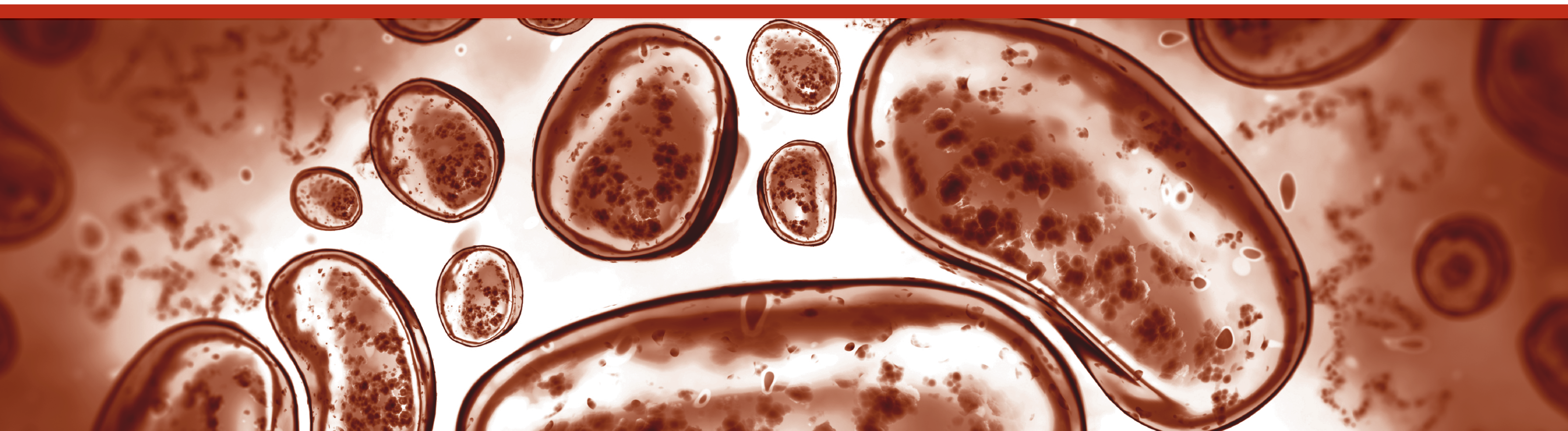
CENTRE ON GLOBAL HEALTH SECURITY WORKING GROUP PAPERS

New Business Models for Sustainable Antibiotics

Kevin Outterson

February 2014

WORKING GROUPS ON ANTIMICROBIAL RESISTANCE | PAPER 1



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EXECUTIVE SUMMARY

Antibiotics are powerful drugs that prevent many deaths each year. Modern medicine relies on them as a safety net. Many invasive medical procedures would be much more dangerous without effective antibiotics. Global trade, travel and security would be threatened by a resurgence of untreatable infectious diseases. Antibiotics are a precious global resource that must be managed on a sustainable ecological basis, akin to fisheries.

But today, antibiotics are either managed in a haphazard fashion or mismanaged. They are vulnerable to premature destruction through resistance. Physicians, hospitals, drug companies, payers, patients and food producers often face perverse financial incentives that encourage inappropriate use of these drugs and undercut incentives to create new ones. Many stakeholders believe that an antibiotic crisis is fast approaching or may already be upon us. Owing to the long lead times for antibiotic research and development (R&D), society must act a decade before the need becomes immediately urgent.

Therefore an important task is to fix these broken economic incentives. Any solution must overcome three obstacles simultaneously. They are:

- Inadequate market incentives for companies to invest in R&D and bring new products to market at the right time;
- Inadequate market incentives to protect these valuable resources from overuse and premature resistance; and
- Inadequate market incentives to ensure global access to life-saving antibiotics.

Creating new drugs will achieve no lasting success if the underlying incentives for inappropriate use are not addressed, or if the drugs do not reach patients in need. The solution must be sustainable over generations and across the planet.

Antibiotic delinkage may offer the most promising avenue for a sustainable, global approach. Delinkage recognizes that rewarding producers and sellers on the basis of volume is fundamentally inappropriate. This paper explores all the antibiotic delinkage models in the existing literature, bringing some order to a variety of proposals. While resistance affects antibiotics, antivirals, antiretrovirals and antifungal agents, this paper focuses primarily on antibiotics.

1. INTRODUCTION

Experts are raising alarms about a possible return to the pre-antibiotic era,[1] and are beginning to describe comprehensive solutions.[2]

Resistance is an evolutionary response to antibiotic use, so many policy options focus on keeping slightly ahead of evolution through faster introduction of new antibiotics, a kind of arms race between drugs and bugs.[3] This evolutionary and competitive perspective is a dominant paradigm.

Alongside this paradigm, this paper employs a complementary framework, based in ecology.[4] The ecological paradigm treats antibiotic effectiveness as a precious common pool resource, akin to fisheries or any other exhaustible resource. Long-term management of common pool resources requires global coordination and balance between conservation and generation of new products. It also explores the complex ecological and epidemiological systems wherein resistance spreads. The ecological paradigm has emerged as an important approach among those who study resistance.[5]

Under both paradigms, experts often look to law and economics to solve incentive problems for antibiotics. Economic incentives provided by the patent system have driven antibiotic R&D

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1 Howell, L., *Global Risks 2013* (Geneva: World Economic Forum, 2013); Cars, O., *What If We Lost the Use of Antibiotics?* (Geneva: World Economic Forum, 2012); *The Burden of Antibiotic Resistance* (Uppsala: ReACT, 2012); CDC, *Antibiotic Resistance Threats in the United States, 2013* (Atlanta: CDC, 2013); ECDC/EMEA, *The Bacterial Challenge: Time to React – A Call to Narrow the Gap between Multidrug-Resistant Bacteria in the EU and the Development of New Antibacterial Agents* (Stockholm: EMEA, 2009); Spellberg, B. et al., 'Trends in Antimicrobial Drug Development: Implications for the Future', *Clinical Infectious Diseases* (2004), 38(9):1279–86; Infectious Diseases Society of America, *Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates … a Public Health Crisis Brews* (IDSA: Alexandria, Virginia, 2004); Freire-Moran, L. et al., 'Critical Shortage of New Antibiotics in Development against Multidrug-Resistant Bacteria – Time to React Is Now', *Drug Resistance Updates* (2011),14(2):118–24; Swedish Presidency of the European Union, *Innovative Incentives for Effective Antibacterials* (Stockholm: Swedish Presidency of the European Union, 2009); Projan, S.J., 'Why Is Big Pharma Getting Out of Antibacterial Drug Discovery?', *Current Opinion in Microbiology* (2003), 6(5): 427–30; Merrett, G.L.B., *Antibiotic Resistance and the Evolutionary Arms Race: Incentivizing Global Change* (London: Chatham House, 2013).

2 So, A.D. et al., 'Towards New Business Models for R&D for Novel Antibiotics', *Drug Resistance Updates* (2011), 14(2): 88–94; Laximinarayan, R. and Brown, G., *The Economics of Antibiotic Resistance: A Theory of Optimal Use?,* Discussion Paper 00-36 (Washington, DC: Resources for the Future, 2000); Laxminarayan, R. and Malani, A., *Extending the Cure: Policy Responses to the Growing Threat of Antibiotic Resistance* (Washington, DC: Resources for the Future, 2007); Towse, A. and Sharma, P., 'Incentives for R&D for New Antimicrobial Drugs', *International Journal of the Economics of Business* (2011), 18(2): 331–50; Nugent, R., Back, E. and Beith, A., *The Race Against Drug Resistance* (Washington, DC: Center for Global Development, 2010); Kesselheim, A.S. and Outterson, K., 'Fighting Antibiotic Resistance: Marrying New Financial Incentives to Meeting Public Health Goals', *Health Affairs* (2010), 29(9):1689–96; Kesselheim, A.S. and Outterson, K., 'Improving Antibiotic Markets for Long Term Sustainability', *Yale Journal of Health Policy, Law and Ethics* (2011), 11(1):101–67; Outterson, K., Samora, J.B. and Keller-Cuda, K., 'Will Longer Antimicrobial Patents Improve Global Public Health?', *The Lancet Infectious Diseases* (2007), 7(8): 559–66; Outterson, K., 'The Vanishing Public Domain: Antibiotic Resistance, Pharmaceutical Innovation and Global Public Health', *University of Pittsburgh Law Review* (2005), 67: 67–123; So, A.D., Ruiz-Esparza, Q., Gupta, N. and Cars, O., '3Rs for Innovating Novel Antibiotics: Sharing Resources, Risks, and Rewards', *British Medical Journal* (2012), 344: e1782.

3 *Global Risks 2013*, p. 28. 'While viruses may capture more headlines, arguably the greatest risk of hubris to human health comes in the form of antibiotic resistant bacteria. We live in a bacterial world where we will never be able to stay ahead of the mutation curve. A test of our resilience is how far behind the curve we allow ourselves to fall.'

4 Baquero, F., Coque, T.M. and de la Cruz, F., 'Ecology and Evolution as Targets: The Need for Novel Eco-Evo Drugs and Strategies to Fight Antibiotic Resistance', *Antimicrobial Agents and Chemotherapy* (2011), 55: 3649–60.

5 See, e.g., ibid. and Laxminarayan and Malani, *Extending the Cure*, and sources cited therein.

and innovation, with declining evidence of success.[6] If new knowledge and technologies were freely available, and capable of being copied by others, the incentive for private actors to invest in their development would be very weak. Patent law seeks to solve this problem with a period of exclusivity, effectively turning knowledge into property for a limited time.

Unlike physical goods or land, knowledge can be shared without diminishing the original source.[7] This characteristic (known as 'nonrivalry') is a key means by which unrestricted knowledge benefits society. But it is weakened in the case of antibiotics owing to resistance.[8] Each dose potentially diminishes the effectiveness of the next, effectively destroying the usefulness of both the knowledge and the resulting product (rivalry). The fundamental reworking of patent-law theory to account for this fact and to design alternative means to meet the same end are under way, most prominently in the concept of antibiotic delinkage.

Under traditional 'linkage', sales volumes and price determine the return on investment for a drug. Owing to resistance, maximizing sales volumes of antibiotics is not in the interest of global public health. Delinkage removes the link between the funding of antibiotic R&D and sales volumes. Under delinkage, companies will be paid for antibiotic R&D and innovation on some other basis, as described below.

Delinkage seeks to solve three problems simultaneously:

- Inadequate market incentives for companies to invest in R&D and bring new products to market at the right time;
- Inadequate market incentives to protect these valuable resources from overuse and premature resistance; and
- Inadequate market incentives to ensure global access to life-saving antibiotics.[9]

The general concept of antibiotic delinkage has been broadly endorsed by industry stakeholders, including the European Federation of Pharmaceutical Industries and Associations (EFPIA),[10] Sir Andrew Witty and David Payne at GlaxoSmithKline,[11] John Rex at AstraZeneca,[12] and some US-based executives including Daniel Burgess at Rempex Pharmaceuticals.[13] The Innovative Medicines Initiative (IMI), a public-private partnership between the European Union and the EFPIA, has announced a call for proposals to create a 'new business model

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6 The patent system works best for diseases that afflict wealthy populations, but is much less effective for conditions endemic in poorer populations. WHO, *Research and Development to Meet Health Needs in Developing Countries: Strengthening Global Financing and Coordination* (Geneva: Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination, 2012). Patents have also not driven the required levels of innovation for conservation measures such as infection control, point-of-care diagnostics and antibiotic stewardship. The innovation record in antibiotics is significantly weaker in recent decades.

7 Thomas Jefferson described nonrivalry to support the intellectual property clause in the US constitution: 'Its peculiar character [of an idea], too, is that no one possesses the less, because every other possesses the whole of it. He who receives an idea from me, receives instruction himself without lessening mine; as he who lights his taper at mine, receives light without darkening me.' Thomas Jefferson to Isaac McPherson, 13 August 1813. *Writings of Thomas Jefferson* 13: 333–35.

8 Outterson et al., 'Will Longer Antimicrobial Patents Improve Global Public Health?'; Outterson, 'The Vanishing Public Domain'; Kesselheim and Outterson, 'Improving Antibiotic Markets for Long Term Sustainability'.

9 Beyond antibiotics, delinkage is primarily proposed as a tool to ensure access to drugs by low- and middle-income populations and to incentivize R&D into neglected diseases. In these situations, nonrivalry is not an issue in the absence of resistance.

10 Richard Bergström, *Development of New Antibiotics – The Industry Perspective* (Uppsala, Sweden: ReACT, 2011).

11 'Antibiotics Crisis Prompts Rethink on Risks, Rewards', *CHE Manager* (Darmstadt, Germany: CHE Manager, 2013), http://www.chemanager-online.com/en/news-opinions/headlines/antibiotics-crisis-prompts-rethink-risks-rewards; Karlin, S., 'Antibiotic Commercial Models Under Revision to Tackle Stewardship Tension', *The Pink Sheet,* 15 July 2013 (Elsevier Business Intelligence).

12 Ibid.

13 Other senior executives were supportive at the Brookings/FDA meeting in February 2013 and in conversations not for attribution.

for antibiotic development'.[14] Antibiotic delinkage was also a significant topic at a Brookings Council on Antibacterial Drug Development workshop co-sponsored by the US Food and Drug Administration (FDA) and the Brookings Institute in February 2013[15] and a separate workshop sponsored by the Pew Charitable Trusts in January 2013.[16] Beyond antibiotics, key international organizations and civil society groups have endorsed other delinkage proposals as a solution to pharmaceutical access and innovation problems generally, including the WHO Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG);[17] the WHO Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG);[18] the WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property;[19] the UN Human Rights Council;[20] Médecins Sans Frontières;[21] and Knowledge Ecology International.[22]

This paper is designed to foster discussion by describing antibiotic delinkage models in more detail, including revisiting some fundamental assumptions in the conventional wisdom relating to antibiotics. While resistance affects antibiotics, antivirals, antiretrovirals and antifungal agents, this paper focuses primarily on antibiotics. Resistance is certainly a global problem, but this paper focuses primarily on the EU and United States as leading research centres for antibiotic development and major markets for these products.

This paper first considers three key imperatives in order to frame discussion:

- Understanding the multi-disciplinary nature of the problem;
- Focusing on key pathogens; and
- Challenging conventional wisdom.

In the following section, it explores the antibiotic delinkage models described in the current literature.

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14 Innovative Medicines Initiative, *IMI 9th Call for Proposals: New Drugs for Bad Bugs (ND4BB)*, 2013.

15 Brookings Council on Antibacterial Drug Development (BCADD), *Incentives for Change: Addressing the Economic Challenges in Antibacterial Drug Development* (Washington, DC: Brookings Institution), 27 February 2013. BCADD is a joint project between the US FDA and the Engelberg Center for Health Care Reform at the Brookings Institution.

16 Pew Charitable Trusts, *A New Pathway for Antibiotic Innovation: Exploring Drug Development for Limited Populations* (Washington, DC: The Pew Charitable Trusts), 31January 2013.

17 WHO Intergovernmental Working Group on Public Health, Innovation and Intellectual Property (IGWG) (Geneva: WHO IGWG, 2009).

18 See, e.g., WHO Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG), *Report by Secretariat*, A/CEWG/3 (Geneva: WHO), 2 November 2012.

19 World Health Assembly (WHA),*The Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property*, WHA61.21 (Geneva: WHO), 24 May 2008.

20 UN Human Rights Council, *Access to Medicines in the Context of the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Physical and Mental Health*, A/HRC/23/L.10/Rev.1, June 2013.

21 Childs, M., *MSF Intervention on CEWG: Financing & Coordination at 132nd WHO Executive Board* (Médecins Sans Frontières International, 2013), http://www.msfaccess.org/content/msf-intervention-cewg-financing-coordination-132nd-who-executive-board.

22 See, e.g., Love, J., 'Balancing Options for Health Research and Development', *Bulletin of the World Health Organization* (2012), 90: 796–796A. See also the materials collected at Knowledge Ecology International, 'Prizes to stimulate innovation', http://keionline.org/prizes.

2. KEY IMPERATIVES

Understanding the multi-disciplinary nature of the problem

Drug resistance leading to clinical failure is studied by professionals from many disciplines, including infectious disease physicians, evolutionary biologists, economists, epidemiologists, public health experts, and researchers who study resistance from agricultural use. It is a mistake to focus excessively on any one of these disciplinary perspectives to the exclusion of a broader view.

To a physician, the problem is a sick or dying patient and the solution is access to effective drugs as soon as possible, avoiding the chance that life would be threatened by failure to prescribe in the absence of definitive diagnosis.

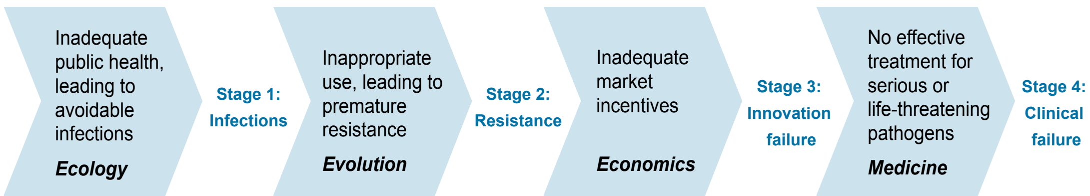
To an economist, the lack of new antibiotic drugs and insufficient investment in conservation are primarily questions of economic incentives in the market, and the solution is to adjust the expected net present value for companies making the decision to invest and to incentivize clinicians and other stakeholders to avoid clinically unnecessary use of antibiotics.

From an evolutionary perspective, the problem is inappropriate use that leads to premature resistance. The solutions are conservation measures limiting antibiotic use through hospital formularies, improved diagnostics, community clinical guidelines and reducing antibiotic use in agriculture.

From an ecological perspective, the problem is people becoming sick with avoidable infections. The solutions are better public health, preventative vaccines and more effective infection control, especially in health care settings, to reduce the force of infection and thereby hinder the spread of both resistant and non-resistant strains.

These perspectives can be integrated by considering them sequentially as in Figure 1.

Figure 1: Stages leading to clinical failure from untreatable infections



Seen in this light, clinical failure is not just an economic problem arising from inadequate market incentives. It also reflects a prior evolutionary failure to conserve a precious resource and the initial ecological failure to prevent infection. Each step is an important part of the chain of events leading to clinical failure and therefore a focus for policy intervention. The ultimate goal is to prevent untreatable infections, not just to introduce more drugs.

In the United States and the EU, each step also involves different stakeholders and regulators, leading to a lack of coordination across the entire process. Effective coordination is key to preserving common pool resources such as fisheries or antibiotics.

There are some important positive and negative interactions between these four stages:

- Successful Stage 1 infection control reduces the number of patients needing treatment, which reinforces success by delaying Stage 2 resistance and Stage 4 clinical failure. Stewardship, conservation, public health, and infection control delay resistance and save lives.

- Successful Stage 1 and 2 measures directly undermine Stage 3 economic incentives to create new drugs by reducing the number of customers. Stewardship, conservation, public health, and infection control diminish both demand and the need for new drugs in the pipeline.[23]

- Successful Stage 3 incentives that provide revenue based on sales volumes directly conflict with Stage 2 stewardship and conservation measures and possibly Stage 1 infection control and public health as well.[24] This is a key problem with the present system of antibiotic linkage.

- R&D should not be thought of as exclusively an input for Stage 3 drugs. R&D is also vitally important for Stage 1 technologies such as vaccines and other technologies necessary for infection control and public health, as well as Stage 2 technologies such as better diagnostics and effective conservation programmes. Economic analysis of the incentives for Stage 1 and 2 technologies is warranted to the same degree as Stage 3, but is less common.

These insights should significantly influence the design of solutions. Any antibiotic business model must simultaneously reinforce efforts in prevention, conservation, new drugs and clinical success, while preserving and enhancing access to these life-saving drugs for all patients who need them.

Focusing on key pathogens

Many people are infected with self-resolving conditions that may not warrant antibiotic drugs. Others are hospitalized with serious or life-threatening infections. For some of these hospitalized patients, infectious disease physicians have no effective treatment options available owing to resistance. The current number of such patients is significant and increasing.[25] This may increase dramatically through ecological and evolutionary changes.

For the purposes of this paper, infections fall into three categories. The first category includes emerging infectious diseases for which we have never possessed effective treatment options. The second category includes pathogens that are currently treatable, but may become untreatable in the future owing to resistance. The third category is clinical failure, including well-known infectious diseases that previously were susceptible to treatment, but are now untreatable after evolutionary adaptation leading to multi-drug resistance.

These three categories represent different types of problems, with potentially divergent policy options and solutions. This paper focuses primarily on the transitions between Categories 2 and 3 for bacterial infections. Given scarce resources, efforts should be prioritized appropriately, as the CDC recognized in its 2013 report on *Antibiotic Resistance Threats in the United States*.[26]

To the extent possible, the priorities should be as listed below.

- **Serious or life-threatening infectious diseases.** Self-resolving bacterial diseases and other infections that are not serious or life-threatening have clinical significance, but do not warrant urgent action.

- **Untreatable pathogens.** Resistance is not an absolute concept. In most cases it is a progressive loss of susceptibility with breakpoints that over time reduce clinical effectiveness. Resistance varies by bug-drug pairing and may also vary by body site. Resistance to one drug (say, methicillin) is not clinically relevant

23 Outterson, K., 'The Legal Ecology of Resistance: The Role of Antibiotic Resistance in Pharmaceutical Innovation', *Cardozo Law Review* (2010), 31: 613.

24 Ibid.

25 CDC, *Antibiotic Resistance Threats in the United States.*

26 Ibid.

if other safe and effective treatments are available. Virtually every pathogen exhibits some resistance to some treatment. Some pathogens harbour resistance even before a new drug is released. Others are still fully effective against some pathogens despite decades of use. For example, Group B *Streptococci* remain fully susceptible to penicillin after seven decades. In short, the fact that some resistance has been documented does not imply that the condition is untreatable or that the drug is useless. The most salient current threats to public health come from Category 3 serious infectious diseases that are currently untreatable, leading to clinical failure.

- **Time horizon.** Owing to the long lead-time for antibiotic drug R&D, we must also be concerned about Category 2 infections that might plausibly transition to untreatable Category 3 infections during the time horizon. These transitions are key events, as illustrated in Figure 2.

Figure 2: Transitions between pathogen categories

The transition from Category 1 to 2 can take perhaps 10–15 years through R&D. Prevention also plays a key role in reducing the human health impact of an untreatable disease. The transition from Category 2 to 3 will vary by drug-bug combination and many other factors accelerating or delaying resistance. For example, inappropriate use and poor prevention may accelerate resistance while conservation and infection control may delay it. We lack good empirical estimates of the actual likelihood of these events over various time frames for most drug-bug pairs. R&D can also push an untreatable pathogen from Category 3 back to Category 2 through the discovery of a novel treatment, again with a long time lag. To the extent that any pathogen is likely to become a significant burden to human health, R&D and prevention programmes must begin with sufficient lead-time before the transition from Category 2 to 3.

Challenging conventional wisdom

The first-order goal is to combat resistance by exploring new business models. In order to do that effectively, conventional wisdom must occasionally be challenged. The following examples of conventional wisdom share a common focus on Stage 3, i.e. bringing new drugs to the market. If the sole goal were more new drugs, this focus would be appropriate. But as Figure 1 makes clear, the goal is preventing clinical failure and there are additional policy levers that should be considered in conjunction with new antibiotics. The five examples of conventional wisdom that are challenged below are:

- A large number of antibiotics should be approved in the next decade;
- A large number of high-quality antibiotics should be approved in the next decade;
- Antibiotic clinical trials should be simplified;
- Billions of dollars should be spent over the next decade to bring more antibiotics to the market; and
- Antibiotics are unprofitable owing to a short course of treatment.

Conventional wisdom 1: A large number of antibiotics should be approved in the next decade

The number of new molecular entity (NME) antibiotics has fallen over the past 30 years. But simple numerical counts obscure the question of clinical impact. Of the 61 NME systemic antibiotics approved by the FDA from 1980 to 2009, a decreasing number qualified for priority review.[27] Priority review is given to drugs that are expected to treat serious conditions and provide significant improvements in safety or efficacy over existing therapies.[28] As a class, antibiotics also suffered from market withdrawals at more than triple the rate of other drugs (42.6 per cent, a total of 26 out of 61 antibiotics).[29] Many of these withdrawn antibiotics were follow-on cephalosporins (10) and fluoroquinolones (9) that did not come to the market with clear competitive advantages in terms of enhanced efficacy and safety profiles.[30] Six were withdrawn for safety-related reasons.[31] It does not appear that resistance played a significant role in these withdrawals, as other antibiotics with similar mechanisms of action and resistance profiles remained on the market.[32] Incentives must focus on high-quality antibiotics that treat serious conditions with improved safety or efficacy.[33] A small number of outstanding new antibiotics would be a much better outcome than a large number of undifferentiated antibiotics without enhanced efficacy and safety in serious or life-threatening conditions. Rewards should be concentrated on the best drugs and unnecessary drivers of resistance should be minimized.

Careful attention to incentive design is important. In the recently enacted GAIN Act in the United States, a reward of an additional five years of exclusivity is available to ‘qualified infectious disease products.’ The definition of ‘qualified infectious disease product’ weakens the standard for priority review by dropping the requirement of significantly improved safety or efficacy. The GAIN Act therefore fails to focus the incentive exclusively on the highest-quality antibiotics and antifungals. If the act triggers a large number of new antibiotic introductions, it might unfortunately lead to greater evolutionary pressures and therefore resistance.

At the Chatham House Roundtable in October 2013, some participants suggested that it was difficult to predict how R&D programmes will unfold over time, which might lead to more (or fewer) market introductions than expected. While this is undoubtedly true, the point being pressed is whether incentives should be designed to result in a specific number of market introductions. From a societal point of view, the objective is an *optimal* number of introductions, not a fixed target such as the ‘10 by 2020’ goal articulated by the Infectious Diseases Society of America (IDSA).

Conventional wisdom 2: A large number of high-quality antibiotics should be approved in the next decade

Assume that targeted incentives were highly successful and the European Medicines Agency (EMA) and the FDA approve 10 high-quality antibiotics in the next decade.[34] It is understandable that infectious disease physicians eagerly desire many more weapons against pathogens. But would that be the best outcome from a long-term public policy perspective? If the drug class

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27 Outterson, K. et al., ‘Approval and Withdrawal of New Antibiotics and Other Antiinfectives in the U.S., 1980–2009’, *Journal of Law, Medicine & Ethics* (2013), 41(3): 688–96.

28 FDA, ‘Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics’ (Washington, DC: FDA), June 2013, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf.

29 Outterson et al., ‘Approval and Withdrawal of New Antibiotics and Other Antiinfectives in the U.S., 1980–2009’. Some of these antibiotics were withdrawn for safety reasons, but the larger number were simply withdrawn by the companies as a result of disappointing sales, lack of competitive safety and efficacy profiles, or unknown reasons.

30 Ibid.

31 Ibid.

32 Ibid.

33 Outterson, K., Powers, J.H., Gould, I.M. and Kesselheim, A.S., ‘Questions About the 10 x ’20 Initiative’, *Clinical Infectious Diseases* (2010), 51: 751–52.

34 Gilbert, D.N., Guidos, R.J., Boucher, H.W. et al., ‘The 10 x ’20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020’, *Clinical Infectious Diseases* (2010), 50: 1081–83.

were statins, or cancer drugs, or indeed any other class, the answer would be an unequivocal 'yes', so long as the new drugs represented an improvement over existing therapies. If better cardiovascular or cancer drugs could be created and sold at affordable prices, society would be clearly better off with immediate access today.

The same may not be true for antibiotics. Introducing 10 high-quality novel antibiotics in one decade will jump-start the evolutionary process of resistance for all of them. If antibiotic innovation were easy, then this would provide flexible treatment options and any antibiotics destroyed through resistance could be replaced in due course. But the evidence of the past three decades suggests a declining return on antibiotic R&D, making new products harder to discover. If antibiotic innovation is increasingly difficult and expensive, then the best long-term policy would space out the introduction of valuable molecules over time. Rather than have 10 antibiotics enter the market simultaneously, it may be more appropriate for society to generate only a few high-quality antibiotics per decade, based on clinical need as resistance progressed. Unfortunately, the current incentive framework does not permit this option. The companies hold a time-limited property right that expires with the last patent or exclusivity period. They cannot afford to let a truly remarkable product sit on the shelf while the patent clock ticks. One potential delinkage solution to this particular problem is the Strategic Antibiotic Reserve, which is discussed below.[35]

Some roundtable participants noted that follow-on antibiotics are sometimes superior to the first-in-class molecule in terms of safety and effectiveness, building on the lessons learned from the pioneers. This process of incremental innovation is undoubtedly valuable, but it illustrates a key problem in the market for antibiotics. Rewards should be greatest for precisely these best-in-class drugs, delivering a very significant financial reward to the company. But the continued presence of the lesser drugs is problematic for two reasons. First, the company marketing the lesser drug has every reason to deploy Phase IV studies and marketing to gain sales, to the detriment of the better innovation. Second, sales of the lesser drugs may trigger resistance in the best-in-class drug. In short, society needs incremental innovation, but must focus rewards on the higher-quality antibiotics, while protecting those drugs from harmful competition from other drugs in their class or functional resistance group.

Finally, the evolutionary perspective should give pause before attempting to bring more antibiotics to market without strong controls on use, which may be the equivalent of throwing more fuel on the evolutionary fire. As Dennis Maki famously put it at an IDSA meeting, 'The development of new antibiotics without having mechanisms to insure their appropriate use is much like supplying your alcoholic patients with a finer brandy.'[36]

Conventional wisdom 3: Antibiotic clinical trials should be simplified

The expected net present value of antibiotic R&D investments will improve if the time to approval is shortened (reducing the number of years over which the investments are discounted) and by reducing the actual costs of the trials (by reducing their number, size and complexity).[37] One recent proposal in Europe to simplify antibiotic clinical trials is the flexible regulatory framework proposed by John Rex et al. in *Lancet Infectious Diseases*.[38] A somewhat similar approach in the United States is the Limited Population Antibacterial Drug (LPAD) proposal supported by the IDSA.[39] These efforts are likely to lead to antibiotics being approved more quickly but,

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35 Kesselheim and Outterson, 'Fighting Antibiotic Resistance'.

36 See Fishman, N., 'Antimicrobial Stewardship', *American Journal of Medicine* (2006), 119: S53–S61; discussion S62–S70; Harbarth. S., 'Should the Development of New Antibiotics Be a Public Health Priority?', *Current Opinions in Critical Care* (2007), 13: 554–56.

37 Eastern Research Group Study for HHS/FDA (pending, 2014).

38 Rex, J.H., Eisenstein, B.I., Alder, J. et al., 'A Comprehensive Regulatory Framework to Address the Unmet Need for New Antibacterial Treatments', *Lancet Infectious Diseases* (2013),13(3): 269–75.

39 IDSA, Limited Population Antibacterial Drug (LPAD) Approval Mechanism (Alexandria, Virginia: IDSA, 2012), http://www.idsociety.org/uploadedFiles/IDSA/News_and_Publications/IDSA_News_Releases/2012/LPAD%20one%20pager.pdf.

as discussed above, we do not know yet whether that would be a good thing for society. If these new antibiotics are approved based on more limited efficacy and safety data, then we might be just accelerating resistance by introducing new antibiotics with limited clinical utility or greater safety problems that generate cross-resistance to better drugs. We cannot know *a priori* whether these clinical trial initiatives will improve health without much better post-marketing surveillance data on resistance, safety and effectiveness.

Conventional wisdom 4: Billions of dollars should be spent over the next decade to bring more antibiotics to the market

It would be prudent to consider the alternative interventions described on Figure 1 before deciding whether this might be a wise investment of public funds. The goal is to prevent clinical failure, not just to approve more drugs. If so, before billions are spent to bring more antibiotics to market, perhaps we should evaluate alternative investments to prevent clinical failure, such as novel vaccines, public health measures, better hospital infection control, better diagnostics, improved conservation, and other ecological, epidemiological and evolutionary interventions. For example, hospitals in the United States bill for treating infections, but are almost never paid for preventing them. Public health approaches are often chronically underfunded compared to treatment. Reimbursement systems in Europe and the United States are increasingly seen as policy levers for reducing health-care-associated infections. The empirical record is exceedingly thin on the comparative cost-effectiveness of additional investments in new antibiotics versus investment of the same resources in some of these other options.

Some of the Chatham House roundtable participants noted that in the developing world, antibiotics are frequently underutilized, leading to many unnecessary deaths. For these populations, resistance is a remote threat while bacterial diseases are omnipresent and highly dangerous. It was also noted that antibiotics are needed in these countries partially because of significant weaknesses in public-health infrastructure such as clean water and food sanitation. For these reasons, in developing countries, scarce financial resources might well be better spent in improving public health and appropriate access to antibiotics.

Conventional wisdom 5: Antibiotics are unprofitable owing to a short course of treatment

Antibiotics may well be currently unprofitable for drug companies, but the principal reason is most certainly not the short course of treatment. Oncology drugs are also prescribed for short courses of treatment, but feature astounding prices that contribute to a powerful incentive for investment in a difficult area of R&D. In such an environment, it is unsurprising that the number of oncology drugs approved has risen remarkably over the past three decades.[40] They have at least three features that may explain their pricing success. These are:

- Patients with life-threatening conditions;
- An absence of competitive (substitutable) drugs; and
- A reimbursement system (at least in the US Medicare Part B) that encourages physicians to choose the higher-priced drug.

For antibiotics, the second and third elements are missing. New antibiotics often are forced to compete with generic ones that remain effective. Empiric therapy proceeds while awaiting diagnostics, making it more difficult for a company to differentiate its products from low-cost generics like vancomycin.[41] In addition, the reimbursement system for antibiotics is less favourable. In the United States and some European countries, hospital antibiotics are generally included in the bundled rate for the admissions (like the diagnosis-related groups – DRGs), giving the hospital strong incentives to choose the lower-cost antibiotic where clinically

40 Outterson, 'Approval and Withdrawal of New Antibiotics and Other Antiinfectives in the U.S.'.

41 Merrill, J., 'Antibiotic Market Snapshot: In Exchange for Higher Prices, More Value', *The Pink Sheet*, 14 January 2013 (Elsevier Business Intelligence).

appropriate. Weak antibiotic profits are principally a product of the pricing regime and generic competition, not the short course of treatment.

Weak profits for antibiotics are surprising and disturbing, given their tremendous social value. Estimates suggest that the social value of antibiotics greatly exceeds the market price.[42] Put another way, antibiotics are highly valuable from society's perspective, but given little private value in the market. This gap between private and social value is a significant problem and opportunity. Delinkage could significantly increase overall antibiotic revenues for drug companies and still remain an excellent social bargain. The next section turns to antibiotic delinkage models.

42 Outterson, K., Pogge, T. and Hollis, A., 'Combatting Antibiotic Resistance Through the Health Impact Fund', in Cohen, G. (ed.), *The Globalization of Health Care: Legal and Ethical Issues* (Oxford University Press, 2013); Eastern Research Group Study for HHS/FDA.

3. ANTIBIOTIC DELINKAGE MODELS

The traditional business model for antibiotics is broken

The prevailing business model is to recover pharmaceutical R&D investments through sales revenues above marginal cost during a period of patent-based exclusivity. For antibiotics, at least three aspects of this traditional business model are unhelpful. First, it may encourage firms to market their drugs aggressively during the exclusivity period and in particular when patent expiration looms, driving resistance through overuse and misuse.[43] Net revenues are driven by unit sales since the ability to raise unit prices on antibiotics in the United States and Europe is somewhat limited. After patent expiration, the model encourages multiple generic entries and price competition, which has also been linked to resistance.[44] This standard linkage model therefore encourages the development of resistance by driving unit sales.

The second negative aspect of linkage relates to conservation methods. Any successful Stage 1 prevention or Stage 2 conservation effort directly reduces the demand for antibiotic products from pharmaceutical companies and therefore the incentive for Stage 3 new drug R&D.[45] For example, vaccination with the pneumococcal conjugate vaccine (PCV7) reduced the incidence of invasive pneumococcal disease in the United States,[46] i.e. of cases that otherwise might have resulted in antibiotic use. Likewise, hospital campaigns to control infections and steward antibiotics diminish demand for new drugs. Ideally, all strategies in Figure 1 would work together to prevent clinical failure, but the traditional linkage model puts Stage 3 new drug R&D at odds with the previous stages, with disruptive effects.

The third difficulty is rooted in the market for antibiotics, particularly the relatively low prices.[47] Much has been written about resistance destroying drugs, but in actual antibiotic markets, many generics remain highly effective for decades, at least for the majority of patients, and exert strong downward pricing pressure on new antibiotics. This pricing pressure is considerable. One example is the treatment of *Clostridium difficile*, a severe intestinal infection identified by the CDC as one of three 'urgent threats' in the United States.[48] Fidaxomicin (Dificid) is a recently introduced drug to treat *C. difficile*, but it must compete against two existing drugs, generic metronidazole and oral vancomycin (generic if compounded for the hospital and also available as a branded oral drug). In a recent economic model, fidaxomicin was not cost-effective when compared to the existing pricing of metronidazole and vancomycin.[49] So long as generic antibiotics retain clinical effectiveness, companies struggle to gain significant pricing premiums for new drugs.[50] These pricing conditions diminish incentives to bring new antibiotics to market. Ironically, this might be the correct market response from a societal point of view, slowing down new drug introductions when immediate clinical need is low. But given the long time lags between investment and drug introduction, if companies dismantle their antibiotic research enterprise, it may be difficult to reassemble the human capital and research infrastructure in

43 While theory suggests the 'patent waste' hypothesis is true, empirical confirmation is needed. In the final years of exclusivity, companies may scale back on marketing to prevent spillovers to imminent generic competition. See Outterson, 'The Legal Ecology of Resistance'; Herrmann, M., 'Monopoly Pricing of an Antibiotic Subject to Bacterial Resistance', *Journal of Health Economics* (2010), 29: 137–50.

44 Jensen, U.S. et al., 'Effect of Generics on Price and Consumption of Ciprofloxacin in Primary Healthcare: The Relationship to Increasing Resistance', *Journal of Antimicrobial Chemotherapy* (2010), 65: 1286–91.

45 It is true that any successful health promotion reduces demand for pharmaceuticals, but the companies have identified conservation and other restrictions on sales as uniquely difficult for antibiotics.

46 Rosen, J.B., et al., 'Geographic Variation in Invasive Pneumococcal Disease Following Pneumococcal Conjugate Vaccine Introduction in the United States', *Clinical Infectious Diseases* (2011), 53(2): 137–43.

47 Projan, 'Why is Big Pharma Getting Out of Antibacterial Drug Discovery?'. The markets for antivirals and antiretrovirals are quite different.

48 CDC, *Antibiotic Resistance Threats in the United States*.

49 Bartsch, S.M., Umscheid, C.A., Fishman, N. and Lee, B.Y., 'Is Fidaxomicin Worth the Cost? An Economic Analysis', *Clinical Infectious Diseases* (2013), 57(4): 555–61.

50 Merrill, 'Antibiotic Market Snapshot'.

time to respond. Along the same lines, we need second- and third-line treatment options that are held in reserve until first-line treatments fail.

Applying delinkage concepts to various proposals for antibiotic incentives

Antibiotic delinkage models

Under delinkage, companies will no longer be paid according to antibiotic sales volumes, which necessitates another source of revenue. From their perspective, the primary objective is significantly increased total revenue streams for antibiotics with reduced commercial risks. From a social perspective, the overriding goal is related, but distinct: preventing clinical failure from untreatable infections. Delinkage models must achieve multiple objectives simultaneously: encouraging disease prevention and control, conservation of antibiotics, new production and improved access when needed. Solutions must be sustainable over very long time horizons.

A large number of incentives are currently being discussed relating to antibiotics,[51] but they are not delinkage models unless the company is no longer paid on the basis of sales volume. Delinkage requires an entirely new business model. Antibiotic delinkage has several key components:[52]

- Delink revenues from sales volume;
- Increase total company revenues for antibiotics;[53]
- Encourage long-term global coordination by stakeholders;[54] and
- Preserve and enhance access without regard to ability to pay.[55]

Delinkage may also include the following features:

- Condition some payments on conservation targets (described below as ‘delinkage plus’); and
- Provide additional revenue streams for prevention, conservation and access in low-income populations, which are chronically underfunded in current systems without sustainable business models.

As part of the WHO Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property,[56] the WHO regions solicited proposals on health R&D that included significant delinkage elements as one of three primary assessment criteria.[57] The WHO regional

51 Push and pull incentives that are not delinkage include Advance Market Commitments (AMCs), Priority Review Vouchers (PRVs), Limited Population Antibacterial Drug (LPAD) approval, tiered regulatory frameworks, tax credits, fast-tracking, streamlining clinical trials, direct funding of R&D, orphan drug designation, the GAIN Act, the IMI, and Project BioShield. For a comprehensive review, see Mossialos, E. and Morel, C.M., *Policies and Incentives for Promoting Innovation in Antibiotic Research* (London: LSE/WHO, 2010), http://www.euro.who.int/__data/assets/pdf_file/0011/120143/E94241.pdf.

52 Outterson, K., BCADD Presentation (Washington, DC: Brookings Institution), 27 February 2013; Kesselheim and Outterson, ‘Fighting Antibiotic Resistance’; Kesselheim and Outterson, ‘Improving Antibiotic Markets for Long Term Sustainability’.

53 Assuming the sector suffers from underinvestment.

54 Coordination is a key unmet need currently. Ideally, the new business model for antibiotics will include a strong global coordination mechanism with private and public stakeholders.

55 Global deaths from treatable bacterial infections are much larger than current deaths from resistant bacterial infections. Global health would dramatically benefit if access to existing antibiotics were expanded to all appropriate life-saving clinical opportunities.

56 Available at http://www.who.int/phi/implementation/antibiotics_innovation_funding_mechanism_AIFM.pdf. For background, see http://www.who.int/phi/publications/gspa-phi/en/index.html.

57 The project assessment criteria are available at http://www.who.int/phi/implementation/AsssessmentCriteria.pdf.

offices shortlisted 24 proposals for consideration.[58] This included four of particular importance to antibacterial resistance, which are listed below:

- Antibiotics Innovation Funding Mechanism (AIFM);[59]
- Building a Diagnostic Innovation Platform to Address Antibiotic Resistance (Dx Platform);[60]
- Establishing a Drug Discovery Platform for Sourcing Novel Classes of Antibiotics as Public Goods (Public Goods);[61] and
- Multiplexed Point-of-Care Test for Acute Febrile Illness (AFI Dx).[62]

Two of these projects are discussed below as full antibiotic delinkage models (AIFM and Public Goods). The other two are classified as hybrid models because their delinkage mechanisms are limited to diagnostics. The WHO chose the fourth project for further evaluation.

Nine antibiotic delinkage models will be discussed below. They are:

- Payer licences;
- Rewarding Antibiotic Development and Responsible Stewardship (RADARS);
- GlaxoSmithKline;
- Patent buy-out prize funds;
- Strategic Antibiotic Reserve (SAR);
- Antibiotic Health Impact Fund (aHIF);
- Antibiotic Innovation Funding Mechanism (AIFM;
- A drug discovery platform for sourcing novel classes of antibiotics as public goods (Public Goods); and
- Delinkage Plus.

Payer licences delink through a contractual mechanism between the drug company and all of the relevant private and public payers. Instead of reimbursing based on unit prices and unit volumes, the payer licence would negotiate an upfront global (or capitated) payment for an antibiotic or an array of antibiotics owned by the company. The antibiotics would then be distributed without further unit payments. Many contracts would be required, with some payers receiving better terms than others. In addition, a clear mechanism to prevent overuse will be required, as each marginal unit is free to the user. Finally, in order to constitute an incentive to commit R&D funds, payer licences will need to be in place many years before the drugs are used. This seems highly unlikely, but payer licences could still play a role to support the appropriate use of new drugs without a linkage to sales.

Some proposals come exceedingly close to delinkage without fully removing all sales revenue. A prominent example is the **Rewarding Antibiotic Development and Responsible Stewardship (RADARS)** programme proposed by Rempex Pharmaceuticals.[63] Its features are as follows.

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58 The list of shortlisted regional proposals is available at http://www.who.int/phi/implementation/phi_cewg_meeting/en/index2.html.

59 Available at http://www.who.int/phi/implementation/antibiotics_innovation_funding_mechanism_AIFM.pdf.

60 Available at http://www.who.int/phi/implementation/building_diagnostic_innovation_platform_address_antibiotic_resistance.pdf.

61 Available at http://www.who.int/phi/implementation/establishing_drug_discovery_platform_antibiotics_public_goods.pdf.

62 Available at http://www.who.int/phi/implementation/multiplexed_POC_test_acute_febrile_illness.pdf.

63 From presentations at BCADD and personal communications, with permission from Rempex Pharmaceuticals.

- Public and private payers will reimburse hospitals for the incremental costs of qualified infectious disease products (as defined in the GAIN Act) above and beyond existing DRGs, similar to the Medicare New Technology Ad-on Payment (NTAP) programme. Payments would only be made if drugs are prescribed in accordance with a preapproved stewardship programme.
- Decoupling the use of these antibiotics from traditional pharmaceutical marketing programmes by providing the following:
  - Guaranteed minimum payments for a period of five years to the innovator pharmaceutical company irrespective of the volume sold that will guarantee the innovator an acceptable return on investment. These guaranteed minimums would be reduced by the gross profit from units actually sold. These payments should total approximately $1.2 billion over five years.
  - Strict prohibition on the innovator company from promoting the antibiotic through its sales force during this five-year period as a means of helping stewardship. Medical science liaisons could provide product information and formulary kits only.
  - After five years the guaranteed minimum payments would cease but the NTAP-type payments would continue for an additional five years to further reward innovators who produce particularly innovative products and/or accurately address the most troubling resistance trends.

It should be noted that an NTAP payment (one element in RADARS) has been approved for fidaxomicin (Dificid),[64] but the NTAP for fidaxomicin is not delinkage. Under the fidaxomicin NTAP, revenues for the company are still entirely dependent on sales volumes, supported by higher prices via NTAP. These higher prices might actually exacerbate the poor economic incentives inherent in linkage, by increasing the rewards from marketing. In order for RADARS to be truly delinked, the amount of the guaranteed minimum payment should be higher than what the company could achieve through aggressive marketing. In other words, the company's full revenue stream over the period should be entirely delinked from sales volumes. RADARS could also be modified to extend the period beyond five years after renegotiation and to vary the value of the payments. Since RADARS is based on a credible promise from governments, companies could commit R&D funds to projects that might qualify. While the discussion of NTAP is US-centric, national and private payers in other countries could make similar payments.

GlaxoSmithKline has not proffered a fully detailed delinkage model *per se*, but has floated principles for delinkage.[65]

- Payments to successful developer of novel antibiotics need to be sufficient to attract further investment. Reduction in uncertainty of revenue is key.
- Payments should remove or significantly reduce the incentive for developer to want to sell more volume. This means fixed payments/fees.
  - Main payment triggered by successful licence approval (i.e. success-based).
  - Product provided at cost.

64 Karlin, 'Antibiotic Commercial Models Under Revision to Tackle Stewardship Tension'; Merrill, 'Antibiotic Market Snapshot'; Optimer Pharmaceuticals, Inc., *CMS Grants New Technology Add-on Payment to DIFICID® for Treatment of Clostridium difficile-associated Diarrhea*, Press Release, 2 August 2012, http://www.prnewswire.com/news-releases/cms-grants-new-technology-add-on-payment-to-dificid-for-treatment-of-clostridium-difficile-associated-diarrhea-164717586.html.

65 From presentations at BCADD and personal communications, with permission from James Anderson, GSK.

- Payments must be predictable and the decision process transparent.
    - Target pre-specified by public bodies.
    - Commitment to payments should be made at Phase 3 start, in order to support investment in clinical phases.
- New products must be made available to patients who need them, wherever they are in the world, so a new model needs to account for this.
- If payments are linked to additional responsibilities on industry related to conservation, these should be calculated as separate payments. For example, purchasers should contract separately for supporting services such as:
    - Further clinical studies,
    - Identifying inappropriate levels of use, and
    - Educating doctors and encouraging appropriate use.

GlaxoSmithKline outlines a valuable framework for full delinkage. The drugs are provided at marginal cost to payers (and perhaps lower to consumers at the point of care) with all company profits deriving from a very significant government-funded income stream.

Patent buy-out prize funds such as the Prize Fund for HIV/AIDS, a bill introduced by US Senator Bernard Sanders, S.1138.[66] If adapted to antibiotics, this bill would be a pure antibiotic delinkage approach. The Prize Fund envisions a public buyout of the relevant patents, followed by public distribution of the drugs. Many permutations of antibiotic prize funds and patent buyouts could possibly qualify as delinkage. The size of these prizes would have to be very significant, in the range of $500 million to more than $2 billion at first registration of an outstanding drug. These buyouts should be generous in order to incentivize new R&D. Practical considerations include prizes for sequential innovation,[67] counterparty risk, milestone payments, global coordination, and information asymmetries between the companies and the prize fund. Most of these issues are present in all delinkage models.

The Strategic Antibiotic Reserve (SAR) targets only exceptionally valuable molecules for which the patent clock is ticking, but the clinical need for the drug is far in the future. The government (or a group of governments) would purchase the patent for a generous price and save it for a rainy day.[68] The SAR could be seen as a global insurance mechanism, holding a key drug or two in reserve should an urgent need arise. The insurance function is an important element in this sector and should be given more prominence.

The Antibiotic Health Impact Fund (AHIF)[69] would make significant payments based on the health impact of the antibiotic, including that on future generations through resistance. The companies would not earn any profits from sales volumes since the drugs are sold at marginal cost. Participation is entirely voluntary. The AHIF could also be designed as a patent buy-out mechanism. It avoids paying for substandard or inappropriate antibiotics and gives companies powerful incentives to use them judiciously to maximize human health. The AHIF is also globally scalable in that it relies primarily on the companies to achieve goals as opposed to regulatory structures in the developing world. The AHIF is one project within the larger Health Impact Fund effort.[70]

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66 Prize Fund for HIV/AIDS, S.1138, http://thomas.loc.gov/cgi-bin/query/z?c112:S.1138; Love, J., 'Prizes, Not Prices to Stimulate Antibiotic R&D', SciDev.Net, 26 March 2008, http://www.scidev.net/global/health/opinion/prizes-not-prices-to-stimulate-antibiotic-r-d-.html.

67 Fischer, C. and Laxminarayan, R., 'Sequential Development and Exploitation of an Exhaustible Resource: Do Monopoly Rights Promote Conservation?', *Journal of Environmental Economics and Management* (2005), 49: 500–15.

68 Kesselheim and Outterson, 'Fighting Antibiotic Resistance'; Kesselheim and Outterson, 'Improving Antibiotic Markets for Long Term Sustainability'.

69 Outterson, *Combatting Antibiotic Resistance Through the Health Impact Fund*.

70 See www.healthimpactfund.org.

The Antibiotic Innovation Funding Mechanism (AIFM)[71] was one of 24 regional demonstration project proposals evaluated by the WHO in December 2013.[72] It is a combination of patent buy-out prize funds and a fee on antibiotic use. The fee is similar to the antibiotic innovation and conservation fee proposed by the IDSA (discussed below). The combination is innovative, providing full delinkage and a sustainable financing mechanism. Knowledge Ecology International (KEI) authored the AIFM proposal.

A drug discovery platform for sourcing novel classes of antibiotics as public goods (Public Goods).[73] ReACT created the Public Goods proposal for the WHO regional demonstration process in December 2013. The proposal is a variant of patent buy-out prize funds with an emphasis on open-source R&D into antibiotics derived from natural products. The treatment of continued antibiotic effectiveness as a public good is thoughtful, with application to all potential models.

Delinkage Plus. At the Chatham House Roundtable in October 2013, several participants envisioned a 'delinkage plus' variant on the models described above. Under this, providers and payers are given additional incentives and held responsible for conservation while the drug companies focus on bringing drugs to market under one of the delinkage models discussed above. These two functions will be coordinated, perhaps through the core delinkage mechanism, but the ultimate responsibility for success will rest with all of the stakeholders as opposed to just the companies.

Table 1: Delinkage models

Model	Description	Advantages	Problems	Patents ownership
Payer licences	Payers buy an annual licence to have access to the antibiotic; actual antibiotics are delivered to payer at marginal cost	Full delinkage possible; competitive pricing if multiple payers are in the market; government participation not required	Higher transaction costs (annual contracts required between each payer and each manufacturer); private payers will not want to increase overall antibiotic reimbursement; coordination will be difficult; little incentive for new R&D	Private
RADARS	Payers top up the hospital reimbursement for innovative antibiotics; government pays company significant prizes, reduced by company sales receipts; net effect could be full delinkage if the guaranteed payment is large	Increased certainty for companies (existing reimbursement is retained should the prize fail to materialize); conditions increased reimbursement on effective conservation	Hospital-based and US-centric; removes hospital financial incentive for conservation; may increase financial return from inappropriate sales unless guaranteed payment is large	Private
GSK	Fully delinked; predictable revenue stream	Incentivizes new antibiotic innovation together with appropriate use	Model not fully specified; reluctance to integrate other conservation commitments	Private

71 Knowledge Ecology International, 'The Antibiotic Innovation Funding Mechanism' (submitted to WHO PHI, 2013), http://www.who.int/phi/implementation/antibiotics_innovation_funding_mechanism_AIFM.pdf.

72 The AIFM was not among the eight projects chosen in December 2013 for further evaluation.

73 Available at http://www.who.int/phi/implementation/establishing_drug_discovery_platform_antibiotics_public_goods.pdf.

Model	Description	Advantages	Problems	Patents ownership
Patent buy-out prize funds	Purchase of national patent rights by a government; actual antibiotics are provided by the government; could also be voluntary, allowing companies to opt in	Full delinkage; one transaction per molecule per country; government can manage the molecule for long-term public health; sales at marginal cost will boost access for low-income populations	Difficult to negotiate appropriate price; political risk; pollution externalities from molecules not in the system	Public
Strategic Antibiotic Reserve (SAR)[74]	For particularly important molecules that are not needed yet, a patent buyout or multi-year licence to keep the drug off the market until needed clinically	Saves very important molecules for a rainy day; will be rarely used; could be viewed as an insurance policy; could be a test case for a more comprehensive regime	Akin to paying farmers not to farm (Conservation Reserve Program); pricing will be large and difficult to negotiate	Public
Antibiotic Health Impact Fund (AHIF)[75]	Governments create a fund that will pay for the actual health impact of the antibiotic including conservation; company participation is entirely voluntary	Pays for human health impact on a global basis; companies retain their patents; AHIF provides a nexus for global coordination; sales at marginal cost will boost access for low-income populations	Requires significant up-front financial commitment; measurement of the relative health impact will have significant financial impact for the companies	Private
Antibiotic Innovation Funding Mechanism (AIFM)	Combination of patent buy-out prize funds (discussed above) and a fee on antibiotic use (discussed below under AIC Fee) for conservation and R&D; WHO Health R&D Regional Demonstration Proposal	Full delinkage; more sustainable funding mechanism; balanced focus; sales at marginal cost will boost access for low-income populations; global coordination mechanism	Same disadvantages as patent buy-out prize funds and the AIC Fee	Public
Establishing a drug discovery platform for sourcing novel classes of antibiotics as public goods (Public Goods)	WHO Health R&D Regional Demonstration Proposal from ReACT; public funding and buy-outs, with an emphasis on antibiotics derived from natural products	Full delinkage; open-source approach to R&D; sales at marginal cost will boost access for low-income populations	Same disadvantages as patent buy-out prize funds; scientific risk with the emphasis on biodiversity sources for natural products	Public
Delinkage plus	Modify any of the delinkage models to strengthen conservation incentives between providers, payers and consumers	Improves incentives at the provider, payer and consumer levels while retaining the company-level delinkage incentives	Additional complexity; conservation might benefit from the information and human capital controlled by drug companies	See above

74 Kesselheim and Outterson, 'Fighting Antibiotic Resistance'; Kesselheim and Outterson, 'Improving Antibiotic Markets for Long Term Sustainability'.
75 Outterson, *Combatting Antibiotic Resistance Through the Health Impact Fund.*

Hybrid models

Other proposals, such as the ones below, should be properly characterized as hybrid models that do not fully or exclusively embrace antibiotic delinkage.

Pay-for-Performance (P4P) is a quality-based payment, but applied to antibiotics. Companies and hospitals would be eligible for top-up payments or year-end bonuses, paid directly from governments, if they achieve prevention or conservation goals. Many public and private payers have expanded P4P reimbursements in recent years, including a few with a focus on antibiotics or nosocomial infections, so this initiative builds on an existing successful model.

Antibiotic Conservation and Effectiveness (ACE) proposal.[76] ACE is an integrated attempt to simultaneously address conservation and new drug R&D without full delinkage. The proposal combines generous P4P reimbursement and variable marketing exclusivities, all conditioned on the companies meeting clear conservation targets. If the company mismanages the drug, reimbursement falls and generic entry is accelerated. On the other hand, a well-managed drug will result in much greater reimbursement and a longer period of exclusivity. One key will be to set aggressive but achievable targets.

Combatting Antimicrobial Resistance: Policy Recommendations to Save Lives.[77] In 2011, IDSA published an impressively comprehensive set of recommendations for adoption by the US Congress, including antibiotic P4P, an antibiotic innovation and conservation fee (discussed below), and greatly expanded surveillance, infection control, conservation measures and funding for R&D. These IDSA recommendations do not include delinkage, but are commendable for their broad scope and simultaneous focus on all stages of the problem (see Figure 1).

Antibiotic Innovation and Conservation (AIC) fee. The IDSA also proposed an Antibiotic Innovation and Conservation fee to induce conservation while funding additional conservation and R&D.[78] This is a particularly interesting conservation and funding measure worthy of separate discussion. A relatively small tax per script could result in a significant and sustainable flow of funds for conservation activities and basic R&D. The AIC fee could also induce conservation through higher prices, but this effect will be blunted by efforts to ensure access to all with clinical need for antibiotics. The fee might be differentially applied to agricultural uses as a mechanism to encourage more appropriate use in that sector without resort to outright bans. From an economic perspective, the magnitude of the tax could be modelled either to approximate the negative externalities of antibiotic use or to fund the conservation and replacement costs of antibiotics that are no longer effective.

Conditional grants. If major government grants were conditioned on company commitments regarding antibiotic conservation, then the companies would have some incentives to conserve, even if revenues came from sales volumes. Concerns include whether grantors such as the National Institutes of Health (NIH), the Biomedical Advanced Research and Development Authority (BARDA) and the IMI are well suited to negotiate and enforce antibiotic conservation covenants (see, by way of comparison, the difficult history with NIH march-in rights) and how companies would respond to future conservation commitments. The conditional grants would have to be larger to offset these uncertainties.

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76 Kesselheim and Outterson, 'Fighting Antibiotic Resistance'; Kesselheim and Outterson, 'Improving Antibiotic Markets for Long Term Sustainability'.

77 Infectious Diseases Society of America, 'Combatting Antimicrobial Resistance: Policy Recommendations to Save Lives', *Clinical Infectious Diseases* (2011), 52(S5): S397–S428.

78 In the economics literature, the AIC would be considered a Pigouvian tax to force the internalization of some of the negative externalities from antibiotic use. See, e.g., Vagsholm, I. and Hojgard, S., 'Antimicrobial Sensitivity – A Natural Resource to be Protected by a Pigouvian Tax?', *Preventive Veterinary Medicine* (2010), 96: 9–18; Hollis, A. and Ahmed, Z., 'Preserving Antibiotics, Rationally', *New England Journal of Medicine* (2013), 369: 2474–76; Rudholm, N., 'Economic Implications of Antibiotic Resistance in a Global Economy', *Journal of Health Economics* (2002), 21: 1071–83.

Options Market for Antibiotics (OMAs). Call options would be sold by drug firms and purchased by payers.[79] Depending on the contract terms, OMAs might function more like insurance,[80] which is an important aspect of antibiotic policy. OMAs could be designed with delinkage features since the option payment and the strike price are not necessarily tied to marginal unit sales.

Building a diagnostic innovation platform to address antibiotic resistance (Dx Platform).[81] Dx Platform is one of the 24 shortlisted WHO regional health R&D proposals. It is treated as a hybrid model here because the scope of delinkage is strictly limited to diagnostics. Improved diagnostics are certainly an important component to appropriate use and therefore continued antimicrobial effectiveness.

Multiplexed point-of-care test for acute febrile illness (AFI Dx).[82] AFI Dx is one of the eight health R&D proposals selected by the WHO for further evaluation. This proposal is limited to a single valuable diagnostic. This is a valuable project with many benefits, but it is not a comprehensive antibiotic delinkage model.

Models that are not delinkage

Delinkage requires a clean break from revenues based on sales volumes. Push and pull incentives that are not delinkage include advance market commitments (AMCs), NTAP,[83] LPAD approval, tiered regulatory frameworks,[84] fast-tracking, streamlining clinical trials, priority review vouchers (PRVs), tax credits, direct funding of R&D, orphan drug designation, the GAIN Act, the IMI and Project BioShield.

Each of these ideas could be modified to include delinkage, but that would be a significant change. For example, the existing LPAD proposal could be modified to include antibiotic conservation commitments by the company, distribution at marginal cost, and a very significant registration prize paid by the government. This new proposal (LPAD Plus) is a significant change from the existing LPAD framework. It would boost antibiotic R&D incentives while simultaneously incentivizing conservation. Other examples are possible, but entail quite significant departures from the existing models.

Table 2: Hybrid models

Model	Description	Advantages	Problems	Patents ownership
Pay for Performance (P4P)	Keeps existing reimbursement system intact; company receives a very significant top-up payment for achieving defined quality goals relating to appropriate use and resistance	Easier startup in various national settings; can be contractual or by statute; extension of existing 'pay for performance' initiatives; can directly support hospital infection control; could be a test case for a more comprehensive regime	Not delinkage, but linkage with a quality payment that may fail to address underlying problems; will need to be an order of magnitude larger than existing quality incentives in order to attract new capital to the sector; companies may not want conservation responsibilities	Private

79 Brogan, D.M. and Mossialos, E., 'Incentives for New Antibiotics: The Options Market for Antibiotics (OMA) Model', *Globalization and Health* (2013), 9: 58.

80 Karlin, 'Antibiotic Commercial Models Under Revision to Tackle Stewardship Tension' (discussing a suggestion by John Rex).

81 Available at http://www.who.int/phi/implementation/building_diagnostic_innovation_platform_address_antibiotic_resistance.pdf.

82 Available at http://www.who.int/phi/implementation/multiplexed_POC_test_acute_febrile_illness.pdf.

83 Merrill, 'Antibiotic Market Snapshot'.

84 Rex, 'A Comprehensive Regulatory Framework to Address the Unmet Need for New Antibacterial Treatments'.

Model	Description	Advantages	Problems	Patents ownership
Antibiotic Conservation and Effectiveness (ACE) Proposals	Combination of P4P reimbursement and variable marketing exclusivities, conditioned on meeting conservation targets	Strong incentives for both conservation and new R&D	Significant increase in payer cost for antibiotics; companies may not want conservation responsibilities; unique intellectual-property management issues	Private
Combatting Antimicrobial Resistance: Policy Recommendations to Save Lives (IDSA)	Comprehensive set of proposals for the US Congress	Collects in one place many of the better policy ideas for the United States; appropriate focus on all stages; detailed specifications	Piecemeal adoption could threaten the overall cohesion of the proposals; US-centric, but many elements could translate to other national settings	Private
Antibiotic Innovation and Conservation (AIC) Fee	Impose a fee on antibiotic use to offset negative externalities, with the proceeds used to fund conservation and R&D for new drugs	Sustainable funding mechanism with a strong conservation element; could be an important funding mechanism for any delinkage model	Essentially a tax; cannot be allowed to hinder access at the point of care to appropriate treatment	Private
Conditional grants	Funding provides non-dilutive capital, conditioned on advance agreement to meet conservation goals	'Piggy-backs' conservation on existing government grants (IMI, NIH, BARDA)	Increases company uncertainly about revenue stream unless the financial terms and commitments are clear at time of grant	Private
Options Market for Antibiotics (OMAs)	Companies sell call options on future antibiotic production	Could provide funds during Phase I and II trials; monetizes some of the insurance functions of antimicrobial availability	Option-sellers hold most of the information needed to price the option; contact terms will determine whether it is a delinkage mechanism; option holders will have first claim on scarce supplies	Private
Limited Population Antibacterial Drug (LPAD)[85] Plus	LPAD with conservation commitments, marginal cost sales and a significant prize	Similar to prize funds	Similar problems to conditional grants and prize funds	Private
Building a diagnostic innovation platform to address antibiotic resistance (Dx Platform)	WHO Health R&D Demonstration Proposal	Improved diagnostics will reduce the spread of resistance	Delinkage is limited to only the diagnostic platform technologies	Public
Multiplexed point-of-care test for acute febrile illness (AFI Dx)	WHO Health R&D Demonstration Proposal	Could significantly reduce unnecessary use of antimicrobials and therefore delay resistance; selected for further WHO evaluation in December 2013	Narrow focus does not address the larger issues of the need for a new antibiotics business model	Public

85 IDSA, *Limited Population Antibacterial Drug (LPAD) Approval Mechanism* (Alexandria, Virginia: IDSA, 2012), http://www.idsociety.org/uploadedFiles/IDSA/News_and_Publications/IDSA_News_Releases/2012/LPAD%20one%20pager.pdf.

Discussion

Much additional work is needed to narrow the list of delinkage and hybrid proposals. One proposal for future work is to examine some key functional elements common to all of the proposals. For example, the various models can be arranged based on the ownership of the intellectual property rights (IPRs), as shown in Table 3. For low- and middle-income countries, it might be useful to consider IPRs (including licences) to be held by an independent stakeholder, like the Medicines Patent Pool.

Table 3: Intellectual property rights (IPRs) ownership in antibiotic delinkage and hybrid models

	Delinkage	**Hybrid**
Private IPR	RADARS; payer licences; GSK; AHIF	P4P; ACE; IDSA; AIC fee; conditional grants; OMAs; LPAD Plus
Buy-out on behalf of the public	Patent Buy-out Prize Funds; SAR; AIFM; Public Goods	Dx Platform; AFI Dx

Additional functional elements include:

- Who is best positioned to change behaviour to foster prevention and appropriate use (i.e. manufacturers, governments, or health care provider organizations)? That is, whom do we need to incentivize? (This is the question raised by delinkage plus models). Reimbursement is a powerful tool to change behaviour.[86]

- The AIC or other user fees may be a sustainable source of funding Given the current global sales for antibiotics, even a modest user fee will generate significant cash flow for delinkage projects. The burden of the tax must fall on insurance payers, not consumers at the point of care (lest access be compromised) or the drug companies (which might otherwise flee the sector).

- What data do we need to support decision-making? We lack coordinated global systems of surveillance for antibiotic use, resistance and clinically untreatable infections. Providers often prescribe with inadequate diagnostic information.

- How do we coordinate delinkage globally? The project would benefit from a strong global coordination mechanism, perhaps akin to the Framework Convention on Tobacco Control. Coordination does not mean that each nation must follow the same means to reach common goals. Some countries (or regions) could choose delinkage based in reimbursement or contract while others could focus on prize-based approaches. The key is whether a critical mass of key markets agreed on the common goals and undertook locally defined measures to reach those goals. The United States and the EU jointly represent two-thirds of the global market for antibiotics. Once they have agreed on a coordination plan, positive spillovers are likely to other countries even if they do not join. If particular problems develop, the core US and EU delinkage models could include additional incentives for extra-territorial conservation and access targets. At first, delinkage models could focus on hospital-based intravenous antibiotics, which present very significant resistance issues and run the risk of treatment failures in serious or life-threatening bacterial diseases. Global coordination is more plausible in the hospital setting, at least for the initial stages.

86 Clemens, J. and Gottleib, J.D., 'Bargaining in the shadow of a giant: Medicare's influence on private payment systems', NBER Working Paper 19503 (2013), available at http://www.nber.org/papers/w19503.

- How do we ensure global antibiotic access to benefit global health? More people die today from treatable bacterial infections than from resistance, especially in low-income populations. Delinkage programmes must improve appropriate access.
- Where are the key research gaps? Which efforts are more cost-effective? What is the long-term human capital plan in antibiotic research? Should diagnostics, vaccines and conservation methods also receive priority funding for basic scientific research?
- How will complex issues of intellectual property be addressed in the light of cross-drug and cross-bug resistance and sequential innovation?[87] For example, if multiple drugs within a class generate cross-resistance, the model might need to include all of those drugs, even when owned by multiple companies or now generic.

87 Outterson, K., 'The Vanishing Public Domain: Antibiotic Resistance, Pharmaceutical Innovation and Global Public Health', *University of Pittsburgh Law Review* (2005), 67: 67–123.

4. CONCLUSION

The current business model for antibiotics is broken. Drug companies are bringing fewer antibiotics to market and curtailing their R&D efforts. Many providers face incentives to prescribe in the absence of demonstrated clinical need. Most of our antibiotics are fed to animals for growth promotion while millions of humans go untreated. Infection control and antibiotic conservation efforts are tragically underfunded. A growing array of stakeholders acknowledges that antibiotic business models built on sales volumes are inappropriate, given the evolutionary path of resistance.

Antibiotic delinkage is one attempt to change the business model, to treat antibiotic effectiveness as a precious global resource that must be nurtured and sustained for generations and shared globally for the benefit of public health.

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