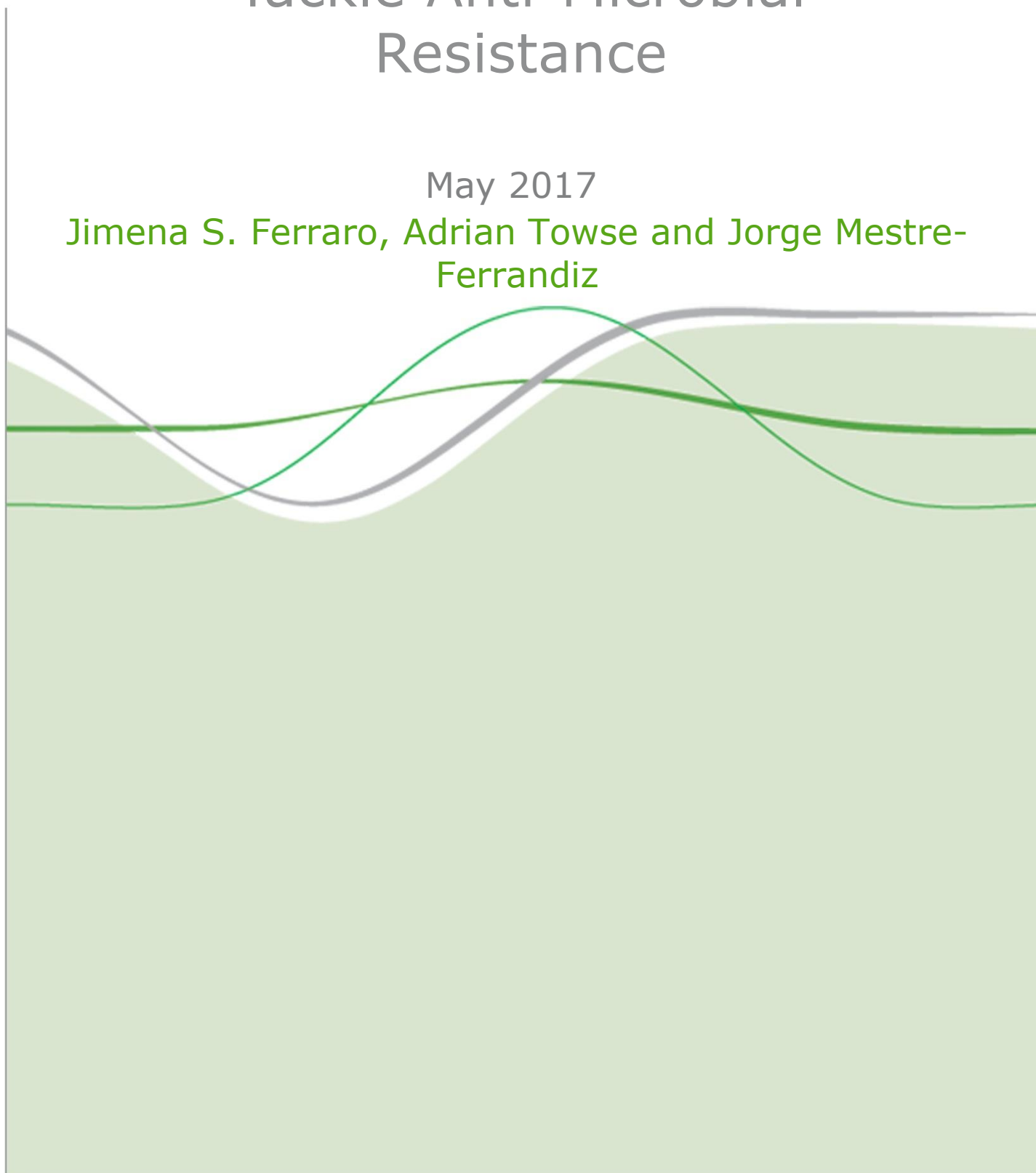


Incentives for New Drugs to Tackle Anti-Microbial Resistance

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EXECUTIVE SUMMARY

Objective

The aim of this paper is to review the proposals for funding and rewarding research for new antibiotics and vaccines to tackle the build-up of anti-microbial resistance (AMR). Resistance to antibiotics is growing posing a major health risk in rich and poor countries. Yet market demand for new antibiotics is low because, at the moment, many infections can be treated with low cost generic drugs and because of a desire to conserve the effectiveness of any new drugs by using them as little as possible. Society wants to put new antibiotics in a glass case and only break the glass in emergencies. Additional ways of rewarding R&D are required. We look at the proposals in the 2016 O'Neill Report, commissioned by the UK government, and the 2017 GUARD Report, commissioned by the German government. We explore, in particular, what sort of market-based incentives could be put in place in Europe. Whilst a global solution is required, it may be best implemented by the use of different reward mechanisms in regions of the world.

The need for new "pull" incentives to stimulate R&D

Mechanisms designed to encourage companies to undertake R&D on new drugs are generally characterised as either "push" or "pull" programs. "Push" programs aim to reduce industry's R&D costs through direct grants, technical assistance, reductions in development time, or tax breaks. In contrast, "pull" mechanisms aim to create incentives by creating viable market demand and/or revenues when new products are approved. The economic impact of these mechanisms differs significantly. While "push" mechanisms reward "effort" (ex-ante) irrespective of the outcome, "pull" mechanisms reward "results" (ex-post), i.e. only if the expected outcome was achieved. Whilst more "push" funding is welcome, we argue that setting up another "push" funding mechanism is not the priority for the international community to address. Push funding alone will not generate new antibiotics. Pull incentives are key to stimulating R&D for new antibiotics.

Three "pull" initiatives

Approved in the US in 2007, the Priority Review Voucher (PRV) is a "pull" mechanism that rewards R&D for tropical diseases. However, it could be modified to cover new antibiotic development. The US Food and Drug Administration (FDA) issues priority review vouchers entitling the holder to a 6-month priority US Food and Drug Administration (FDA) review. The voucher could be transferred or sold to be redeemed at the FDA to accelerate the regulatory review of a different product. Transferable Intellectual Property Rights (TIPR) reward the development of a critically needed, but low revenue, drug by extending the patent on another drug. Any antimicrobial drug or vaccine developer that meets market reward criteria would receive a voucher to extend another product's exclusivity. As with the PRV, the TIPR is transferable. Both the O'Neill and GUARD reports propose a third type of "pull" mechanism, a form of "lump sum" Market Entry Reward. Each of these could operate on a regional basis.

Choosing an Effective and Efficient "Pull" Initiative

Overall, it is difficult to see that a PRV will be workable in the EU or will give a large enough reward. The TIPR and the Market Entry Reward both have strengths and weaknesses. The risk with a TIPR is of overpaying relative to a Market Entry Reward. This can in part be overcome by using guardrails such as a variable period of patent extension. The risk with the Market Entry Reward is of political risk and credibility. Is the funding

source sustainable over a 15-20 year product development timeline, and is there a risk that the Reward can be changed at relatively short notice? Political risk will lead to a devaluation of the expected reward by companies, potentially requiring higher Market Entry Rewards to be offered than with TIPRs. Our assessment is that both the TIPR and the Market Entry Reward should be further explored for use in the EU as a regional “pull” incentive. The current focus on the market entry reward should therefore be extended to include the TIPR voucher.

Estimating the cost of an R&D programme

The O’Neill report sets an objective of generating 15 new antibiotics per decade. The GUARD proposes one significant new antibiotic per year. A programme to incentivise 10-15 drugs per decade is therefore needed. The question then arises of the cost per drug. How big do the pull incentives need to be to support not only clinical development but also early discovery programs needed to strengthen the pipeline?

If we increase the Towse et al. (2016 forthcoming) 2011 estimate of the cost of R&D for an antibiotic by 5% per annum to reflect rising real R&D costs, the 2016 figure is US\$2.0 billion. This US\$1.9 billion - US\$2 billion figure is a sensible estimate to use.

In simple terms 15 drugs over ten years at US\$2 billion a drug (on our assumptions) requires a “pull” commitment of US\$30 billion a decade, or US\$3 billion per annum. This is much higher than the O’Neill recommendations of US\$16 billion built around its assumptions of US\$1 billion per product market entry rewards. The GUARD Report (Stern et al., 2017) makes a similar assumption of US\$1 billion for a Launch Reward. This is a large funding gap. It may be that O’Neill is assuming that some “new” antibiotics are old drugs that are repurposed at low cost. GUARD is assuming that the market entry reward does not cover all R&D costs and the company will be able to make additional profits by selling the drug during its patent life. It may be that O’Neill is making that assumption also. However, this important element is not clear. The market entry rewards proposed by O’Neill and GUARD of US\$1 billion per product are too low to stimulate discovery and development including pre-clinical research unless companies are also expected to make money from selling the product during its patent life. There is a strong case for companies being expected to make some returns from sales.

We also note that only a proportion of the global \$2bn R&D cost has to be recovered in Europe. We assume that Europe would generate revenues to cover 33% of R&D cost.

Conclusion

Resistance to antibiotics is growing, posing a major health risk in rich and poor countries. Additional ways of rewarding R&D are required. Push funding alone will not generate new antibiotics. Pull incentives are key to stimulating R&D for new antibiotics. Our assessment is that both the TIPR and the Market Entry Reward should be further explored for use in the EU as a regional “pull” incentive.

1 THE PROBLEM AND AN OVERVIEW OF THE PAPER

The development of antibiotics is considered among the most important advances of modern science. Antimicrobial resistance (AMR) is now threatening this progress and presenting significant risks to human health (Hecht et al., 2009).

AMR happens when microorganisms (such as bacteria, fungi, viruses, and parasites) change when they are exposed to antimicrobial drugs (such as antibiotics, antifungals, antivirals, antimalarials, and antihelmintics). Microorganisms that develop antimicrobial resistance are sometimes referred to as “superbugs”. As a result, antimicrobial drugs become ineffective and the multi-drug resistant (MDR) infections persist in the body, increasing the risk of death as well as the spread of these MDR infections to others (WHO, 2016).

It is well known that the problem of AMR is not new and that it is a natural process observed since the first antibiotics were discovered. However, it has lately started gaining in importance because of the overuse of antibiotics, which has increased the rate at which resistance is developing and spreading, and because of the lack of new drugs to challenge these new superbugs.

Investment in the research and development (R&D) of antibiotics has been dropping steadily in Europe and in the United States (O’Neill, 2016a; CDC, 2013). This is due to the lack of incentives for R&D as a result of three different elements:

- scientific difficulties surrounding antibacterial development. The main challenge to antibacterial discovery is finding a lead compound that can act as an antibacterial agent. Evidence suggests that since the 1980s the discovery of new antibiotics has become harder (Payne et al., 2007);
- the regulatory environment. In 2001, US and European regulatory agencies set new requirements for non-inferiority clinical trials involving antibacterials which required more patients to be in trials. The issue is the appropriate statistical hurdle to prove non-inferiority; and
- economic returns. Expected volume and prices of new antibiotics are low due to, respectively, volume restrictions to control use in order to manage AMR, and the generic competition of previous generations of drugs, which are still effective against many infections.

Similar challenges are present in the market for AMR vaccines. The R&D cost of developing a vaccine is not that different from that of an antibiotic, and if the alternative to vaccination is using a cheap generic antibiotic for most patients who get an infection then economic challenges are similar to those for new antibiotic drugs.

In response to the challenge that AMR presents, the British government commissioned the Review on Antimicrobial Resistance, led by Jim O’Neill, to propose new interventions to tackle this issue (O’Neill, 2016a). In early 2017, the final report of The Boston Consulting Group (BCG) for the German Federal Ministry of Health was released. It proposes key levers for more innovation along the antibiotics value chain under the Global Union for Antibiotics Research and Development (GUARD) initiative (Stern et al., 2017).

The aim of this paper is to review the proposals in these reports for funding and rewarding research for new antibiotics. We give our assessment the sorts of market-based incentives that could be put in place in Europe, recognising that, whilst a global solution is required, it can be implemented by the use of different reward mechanisms in different jurisdictions.

2 INCENTIVES TO INCREASE THE SUPPLY OF ANTIMICROBIALS

Mechanisms designed to encourage companies to undertake R&D on new drugs and vaccines are generally characterised as either “push” or “pull” programs (Kettler, 2002; Kremer, 2002; BVGH, 2009; Hecht et al., 2009). “Push” programs aim to incentivise industry by reducing industry’s costs during the research and development stages through direct grants, technical assistance, reductions in development time, or tax breaks. In contrast, “pull” mechanisms have the aim to create incentives for industry engagement by creating viable market demand, paying for outcomes or outputs of research. In addition, a combination of “push” and “pull” incentives can be used in a hybrid approach.

The dominant “push” mechanism used to incentivise R&D for neglected global health challenges is the product development partnership (PDP) such as the Medicines for Malaria Venture, and the TB Alliance. Donors fund the PDP initiative and it, in turn, evaluates, funds, helps manage and support a portfolio of projects underway in research institutes, universities, companies, or some combination thereof. Other examples of “push” incentives are the US National Institutes of Health, tax credits to subsidise the cost of R&D, and fast-track regulatory approval. We set out examples in Appendix 1.

The “pull” category involves a specific reward or price for research outputs. Examples of this type of incentive are patent buyouts, different programs for orphan drugs (i.e. seven-year market exclusivity) and Advance Market or Purchase Commitments (AMCs) that are ex-ante commitments by national governments, international organizations or private foundations to purchase a certain quantity of a drug or vaccine that has yet to be developed at a certain price (Kremer, 2001). This category also includes targeted payments made to a researcher conditional on the achievement of a particular outcome. These can be in the form of “prizes” from Governments or other institutions. In this category are Priority Review Vouchers (PRV) and Transferable Intellectual Property Rights (TIPR) that we will analyse in more detail below. There are important differences between types of prizes which we discuss later.

Hybrid approaches are a combination of “push” and “pull” mechanisms, which might, for example, cover part of the developers’ early R&D costs whilst providing a prize to reward later product development.

The economic impact of these mechanisms differs significantly (Renwick, Brogan and Mossialos, 2015). While “push” mechanisms reward for “effort” (ex-ante) irrespective of the outcome, “pull” mechanisms rewards for “results” (ex-post) only if the expected outcome was achieved.

In “push” mechanisms all the risk falls upon the entity that finances the R&D. This raises two important issues: moral hazard and adverse selection. The first one arises because the institution receives a payment irrespective of the results which may lead to a reduced effort to perform the delegated task. Once the funding entity has delegated the task, it is difficult to know if the institution performs in accordance with the contract. The

second one implies that, given lack of expertise or of information, the funding entity has difficulties monitoring whether good choices have been made about projects to invest in. A pipeline may be full but the quality may be poor, or vice versa.

On the other hand, “pull” mechanisms place the burden of the risk of the innovation on the company which does not get any revenues unless it succeeds in finding and successfully developing the new drug. This way of linking payments to successful development is particularly useful to deal with the lack of expertise and information of the funding entity. In principle they can be used to stimulate discovery and development including pre-clinical research. Nevertheless, it has been argued that these mechanisms may not be the most efficient to promote early stage research given high scientific risk, or to provide a basis for basic research given that the output of such research may be neither patentable nor commercially exploitable (Mueller-Langer, 2013).

3 REVIEW OF O’NEILL AND GUARD REPORTS

In May 2016, the Review on Antimicrobial Resistance released its final report chaired by Jim O’Neill (“the O’Neill Report”), called “Tackling Drug Resistant Infections Globally”. The Report outlines ten broad actions needed to address AMR tackling the problem from two perspectives: the demand, and the supply side.

From the demand side, the actions proposed aim to reduce the global use of antimicrobials, in particular antibiotics, on patients and animals who do not need them in order to preserve the usefulness of existing medicines for longer.

On the supply side, the goal of the proposed actions is to increase the supply of new medicines to defeat infections that have become resistant to existing drugs. We find here a proposal for creating a Global Innovation Fund for AMR to tackle the lack of funding in some areas (a “push” incentive), and a market entry reward system to provide better incentives (a “pull” incentive).

In February 2017, a report by The Boston Consulting Group for the German Federal Ministry of Health was published supporting the German Global Union for Antibiotics Research and Development – GUARD – initiative (“the GUARD Report”). This report together with its predecessor¹, details key levers for actionable international policy instrument, including “push” and “pull” incentives.

GUARD aims to double targeted international funding for all stages of discovery and development. For this purpose, it proposes a Global Research Fund and a Global Development Fund to fund from basic research to clinical development (“push” incentives), and a Global Launch Reward to make high-need antibiotics a more attractive commercial proposition (“pull” incentive).

We now consider the “pull” and “push” actions proposed in both reports.

3.1 THE “PUSH” INCENTIVES PROPOSED

So far, greater attention has been put into “push” mechanisms through key national initiatives in different parts of the world to foster R&D for antibiotics individually and in cooperation with other countries, increasing funding through a variety of public-private

¹ The GUARD Report is a follow-up to Stern et al. (2015), a report prepared by an advisory consortium consisting of ÖPP Deutschland AG (Partnerships Germany), The Boston Consulting Group, and the Healthcare Management Department of Berlin University of Technology commissioned by the German Federal Ministry of Health.

partnerships (PPPs). This paper does not aim to focus on “push” incentives, but we mention briefly what these reports propose. A short description of other relevant “push” incentives for antibiotics in the US and Europe can be found in Appendix 1.

3.1.1 The O’Neill Report - The Global Innovation Fund for AMR

The O’Neill Report proposes the creation of a Global Innovation Fund for AMR to tackle the lack of funding in some areas, and the lack of focus and coordination in other areas where funding does exist but impact could be increased. There are two areas identified where existing funding might not be adequate. One is early-stage or blue skies research in drug discovery and other areas relevant to AMR, such as vaccines and alternative therapies. Cutting-edge scientific research is highly risky but also important to making the breakthroughs needed to better understand AMR. The second one is the less cutting-edge research which lacks an immediate commercial imperative. Such work is a “blind spot” because it is done neither by academics (it is not cutting-edge research) nor commercial companies (it does not have commercial attractiveness).

The Report outlines three possible exemplar models for this Fund. The first one is the BARDA Biopharmaceutical Accelerator (see Appendix 1 for more details). The second one is the UK and Chinese governments’ Global Innovation Fund to improve funding for AMR-related research. The UK and China committed US\$145 million, a sum which is expected to increase as new partners join the initiative. Finally, a third possible role model is the Global Antibiotic Research & Development programme, a new not-for-profit product development partnership launched in Geneva in 2016. It was incubated by the Drugs for Neglected Diseases Initiative² and supported by the WHO and several countries. The incubation phase lasts until the end of 2017. During this period, the Global Antibiotic Research & Development programme will build up its team, establish a legal entity, and set out its long-term strategy and roadmap. Its aim will be to work closely with all stakeholders in the field of antibiotic research and development (R&D) from countries of all income levels to develop new antibiotic treatments.³

3.1.2 The GUARD Report - The Global Research Fund and The Global Development Fund

Similar action to the O’Neill Report is proposed in the GUARD Report with the difference that it proposes two funds to tackle the issue: a Global Research Fund, and the Global Development Fund.

The Global Research Fund aims to offer funding to basic research and preclinical development, the first two steps in the value chain. It seeks to grow the community of antibiotics researchers by 50%. The Report estimates that of half a billion in existing “push” funding for antibiotics research and development in 2016, only around 10% was dedicated to basic research. As a consequence, many important basic research projects struggle to secure funding.

This initiative has a time frame of ten years to enable a long-term build-up of infrastructure, and it requires an annual budget of US\$200 million, US\$25 million per

² Drugs for Neglected Diseases initiative (DNDi) is a collaborative, patients’ needs-driven, non-profit drug research and development (R&D) organization that is developing new treatments for neglected diseases.

³ More information available at <http://www.dndi.org/diseases-projects/gardp/>.

year for infrastructure funding and US\$175 million per year for project funding (50% for basic research, 50% for preclinical development).

In contrast, the Global Development Fund supports mainly small and medium-size biopharmaceutical companies in their clinical development efforts towards new antibiotics that meet a Target Product Profile⁴. It provides funding in all phases of clinical development of high-need antibiotics in the form of partial funding of clinical trials via forgivable loans and structured as a revenue-sharing agreement (Phase 1 and 2 are funded with up to 75% of the required funding of the trial, and Phase 3 up to 50% of the required funding). The revenue-sharing mechanism helps to partially recoup the investment made, which means that the Global Development Fund is not only a “push” incentive, but also becomes part self-funding over time.

Whilst more “push” funding is welcome, particularly for early stage research and development, where pull incentives may be less efficient, we argue that setting up another “push” funding mechanism is not the priority for the international community to address. Push funding alone will not generate new antibiotics. Pull incentives are key to stimulating R&D for new antibiotics.

3.2 THE “PULL” INCENTIVES PROPOSED

There is a general consensus that the current pipeline of new antibiotics shows a mismatch between the drugs the world needs and numbers being researched. This is mainly due to the lack of economic incentives for pharmaceutical companies, although scientific and regulatory challenges to antibiotic development also need to be addressed. Both, the O’Neill Report and the GUARD Report, propose a market entry rewards system for antibiotics to address the economic challenge. There are, however, differences between the two.

3.2.1 The O’Neill Report – Market Entry Reward

The market entry reward the O’Neill Report proposes consists of large payments in the order of US\$ 800 million – US\$1.3 billion to the successful developer of a new antibiotic, which meets prospectively-defined criteria of ‘unmet need’. The O’Neill Report says “*such rewards would be paid after a successful product comes to market and be proportionate to unmet medical need*” (page 54, our emphasis).

The O’Neill Report proposes several principles which lead it to propose this system of market entry rewards. The most important are: developers should be guided towards antibiotics that society most urgently needs today; rewards should be linked to a product’s value to society; and payments should be free from political risk. However, as we discuss later, in Section 4.3.1, there are tensions between these, in particular “fine tuning” to meet some principles more precisely (e.g. rewards reflect value) reduces the predictability of the reward, so increasing the political risk as perceived by the innovator.

The Report suggests this action could provide incentives to the private sector to innovate and align research priorities to public need. Such an approach could stimulate the market for antibiotics without relying either on high prices at the point of use, or on high sales volumes.

⁴ Target Product Profiles are proposed in the GUARD Report to clearly identify and describe high-need products to enable funding mechanisms that steer funds to where they are most needed.

3.2.2 The GUARD Report - The Global Launch Reward

The GUARD Report proposes a Global Launch Reward to improve the commercial attractiveness of high-need antibiotics (each meeting at least one Target Product Profile⁴), embedded in an insurance-like mechanism. The Global Launch Reward is available for at least ten years and it consists of US\$1 billion cash payment (in instalments) to companies launching high-need antibiotics. If operating profits are realized, the Global Launch Reward is clawed back as percentage of profits. Of the total value, US\$600 million will be paid out in the first three years, and the remaining US\$400 million will be paid out between years four to eight of commercialisation. If the antibiotic is removed from the market due to efficacy or safety concerns or it is failing in practice to meet the standards defined in the relevant Target Product Profile⁴, further payments would not be made.

This proposal is different from the O'Neill Report proposal because of its built-in repayment mechanism.⁵ The repayment mechanism protects GUARD from supporting companies that do not require the Global Launch Reward and ensures that public funding is invested primarily in antibiotics that would otherwise not be launched. Similarly to the Global Development Fund, the repayment element means that the Global Launch Reward does not only work as a "pull" incentive ("push" in the case of the Global Development Fund), but also becomes potentially part self-funding.

Given that lack of profitability is a key reason why push and pull initiatives are needed, it seems that repayments under either the Global Development Fund or Global Launch Reward schemes are going to be limited. The repayment element will have the effect of reducing the power of the incentives as companies will downgrade the impact by adjusting for the possibility of repayments. It may be that the key benefit is seen as providing reassurance to governments that public funding will not be given to companies who (ex post) did not need it. A key issue is how new antibiotics receiving a market entry reward are subsequently priced and used. This issue is not addressed in either report.

There are two elements to subsequent price and use. The first is whether the push and pull rewards are the only income the company can expect to receive. We return to this point in Section 5.3. The second is how new antibiotics are assessed for pricing and reimbursement, with many health systems using Health Technology Assessment bodies to assess the value of new drugs and vaccines. It will be essential that the public health benefits that justify the investment in "push" and "pull" initiatives are recognised in any value assessment. For a discussion of this issue see Karlsberg-Schaffer et al. (forthcoming).

3.3 THE CASE OF VACCINES

Both Reports discuss the potential for vaccines to reduce the need for antibiotics. They highlight the important role that vaccines and diagnostics play in the fight against AMR by enabling the prevention of infection and stewardship of existing antibiotics. They agree on the need to incentivise the development of new vaccines by creating a

⁵ Recipients are required to return 30% of their profits to GUARD, up to the original amount of the GLR.

sustainable market for them with reduced uncertainty. Nevertheless, there is not agreement as to where the money to fund this should come from.

The O'Neill Report makes reference to the Review's previous report released in February 2016, where it discusses the potential of vaccines (O'Neill, 2016b). In principle, the report proposes to renew impetus for early research through the same push initiative – the Global Innovation Fund – proposed for developing antibiotics (see Subsection 3.1.1). However, it recognises that the funding needed is large and diverse, and that breakthroughs will require long-term sustained funding from one or more of philanthropic organizations, the public sector and companies.

The second important issue is to sustain a viable market for needed vaccines. Depending on the characteristics of the different products, possible interventions include Advance Market Commitments such as that for pneumococcal vaccine operated by the GAVI Alliance (see Subsection 4.3.2 for more details) to promote broad uptake in mid to large sized populations; and market entry rewards similar to those proposed for antibiotics, to ensure availability for smaller populations at high risk.

The GUARD Report does not recommend using the same financing mechanisms for vaccines and diagnostics as for antibiotics. This is because it sees the challenges along their respective value chains as distinctive, requiring different remedies. It strongly encourages the creation of Target Product Profiles for the most-needed vaccines as well as for antibiotic drugs. Similarly to the O'Neill Report, the GUARD Report states that the key to getting industry to develop more vaccines lies not in subsidising companies, but in removing the uncertainty around market potential. It also proposes Advance Market Commitments as a solution to address uncertainty about the value of the market.

4 A REVIEW OF THE PULL MECHANISMS PROPOSED

In this Section we analyse different 'de-linked' pull mechanisms. We start with two mechanisms that are not mentioned in the GUARD Report, and are discussed but dismissed in The O'Neill Report. These are Priority Review Vouchers and Transferable Intellectual Property Rights.⁶ We then analyse Market Entry Rewards comparing the proposals made in The O'Neill Report and in the GUARD Report.

4.1 PRIORITY REVIEW VOUCHER (PRV)

Approved in the US in 2007, the Priority Review Voucher (PRV) is a "pull" mechanism that provides incentives for R&D for neglected global diseases. A second program, designed to reward the development of paediatric drugs for rare diseases has been in place since 2012. It could be modified to cover new antibiotic development. The US Food and Drug Administration (FDA) issues PRVs entitling the holder to a 6-month Priority Review of another drug that would otherwise be reviewed under FDA's standard 10-month review clock. Once granted, the voucher could be transferred or sold multiple times, or redeemed at the FDA to accelerate the regulatory review of a different product. Its value has been estimated to be between US\$50-500 million (Bors et al., 2015).

Six FDA approved drugs have been awarded a PRV, four of which have been sold by the earner to another company.

⁶ Priority Review Vouchers are discussed in the 2015 GUARD Report (Stern et al., 2015) as a funding source if they were auctioned off by the FDA, not as a "pull" instrument. See Section 6 for more details.

The first award, in 2009, was for the antimalarial ACT Coartem (Artemether-Lumefantrine) from Novartis. It is a very important drug, but it had already been on the market in other countries since 2001. This resulted in some criticism from global health activists and non-governmental organisations (Anderson, 2009). Novartis used its PRV in 2011 to accelerate the review for a supplemental New Drug Application (sNDA) for Ilaris (canakinumab) in an indication for gouty arthritis. FDA denied approval to Ilaris for this indication, illustrating the risk for the buyer of using a PRV (Robertson et al., 2012).

BioMarin sold the voucher obtained with Vimizin (elosulfase alfa), a medicine for the Morquio A syndrome (a rare paediatric disease) for US\$67.5 million to Sanofi/Regeneron in 2014; Knight sold the voucher gained with Impavido (miltefosine), a drug for leishmaniasis, for US\$125 million to Gilead in 2014; and Asklepios Pharmaceuticals sold the voucher gained with Cholbam, a drug for rare bile acid synthesis disorders, to Sanofi for US\$245 million in July 2015. In August 2015, United Therapeutics sold their voucher earned for a treatment for neuroblastoma to AbbVie for US\$350 million.⁷ The last transaction known is Gilead buying a PRV from Sarepta Therapeutics for US\$125 million in late February 2017. This is the third PRV Gilead has purchased after buying the second one from PaxVax for about US\$200 million in 2016.⁸

The case of Novartis' Coartem highlights the challenges in identifying the value of a PRV incentive from both the perspective of an R&D-based company (supply side) and from the perspective of those wanting new medicines to treat neglected populations (demand side). Novartis did not get additional sales of Ilaris from its use of a PRV. This does not demonstrate that, *ex ante*, the PRV had no value, but it does indicate the degree of uncertainty about the expected value of the voucher. There was also concern that, despite the requirement that the product be a new molecular entity never before approved in the US, companies can get the reward with limited investment in innovation.⁹

The recent activity of selling vouchers suggests that despite these restrictions, companies value owning vouchers. From the government perspective, a PRV for antibiotics would be good in the sense that the reward to the pharmaceutical company is "paid" as a saving in the regulatory process and does not require additional disbursement. Implementation is relatively easy because it does not require any determination of the size of the reward.

There are, however, two problems with their use in the EU. In the US, the FDA accelerates the scientific review of the medicine, and the US Government plays a negligible role (restricted by law) in negotiating prices. Any European voucher would have also to accelerate pricing and reimbursement decisions by tax-based or social insurance-based health care payers (Ridley and Sanchez, 2010). A second weakness of any form of PRV is that it is limited to the time of acceleration. If, for example, the time taken for a conventional approval is twelve months, then a six-month approval can only bring a time gain of six months. It is hard to see how a PRV could be sold in Europe to cover a significant share of the US\$2 billion R&D costs for a new antibiotic.

⁷ Detailed information available at: <http://priorityreviewvoucher.org/>

⁸ The price tag for Sarepta's PRV was lower than his expectation of US\$200 million. Nevertheless, it is not clear if it is due to a decline in PRV interest among bidders or a forced asset sale (Joseph Schwartz, Leerink Partners, in a research note quoted by the Boston Business Journal).

⁹ However, the value of PRVs is a function of supply and demand. As more vouchers are awarded, for any given level of R&D activity, the lower the price they are likely to attract.

4.2 TRANSFERABLE INTELLECTUAL PROPERTY RIGHTS (TIPR)

4.2.1 The Concept

Transferable Intellectual Property Rights (TIPR), or “wild-card” patent extensions, reward the development of a critically needed drug by a pharmaceutical company by extending the patent on another drug. Any antimicrobial developer that meets market reward criteria would receive a voucher to extend another product’s exclusivity. A patent extension of (say) between six months and two years could also be sold to other companies. As with the PRV, the TIPR is transferable, which ensures that even small companies that do not have any existing marketed drugs have incentives to innovate.

The main disadvantage of a TIPR is the cost the society incurs as it increases health care costs by prolonging the sales of on-patent, blockbuster drugs. Outterson et al. (2007) calculated that, in the US, a 2-year patent extension would protect more than US\$125.3 billion in global annual sales from generic competition, and that the estimated global cost of granting ten such TIPR would likely exceed US\$40 billion, more than US\$4 billion per new drug. These calculations far exceed estimates of US\$1.6 - US\$1.9 billion (Mestre-Ferrandiz, Sussex and Towse, 2012) to develop a new molecular entity. We can note that revenues need also to provide a return on investment that reflects the returns in alternative therapy areas in which companies can invest (the internal opportunity cost) which is likely to be higher than the risk-adjusted cost of capital (the external opportunity cost) and is estimated at around \$300m in the GUARD Report¹⁰.

Sonderholm (2009) estimated the effect on revenues of a six-month TIPR on Lipitor, Pfizer’s then top-selling drug in the US, and he found that it would be of a magnitude of US\$3.1 billion.

Moreover, these conclusions are only valid if the speed with which the new effective antibiotic is introduced into the market remains the same independently of whether the TIPR is implemented or not¹¹, i.e. that the TIPR is being compared with an alternative incentive of equal effectiveness. Spellberg et al. (2007) estimated societal costs versus savings from wild-card patent extension in the US from the availability of one new theoretical antibiotic to treat multi-drug-resistant pathogen, pseudo-monas aeruginosa, taking into account a greater speed at which the new medicine is available. On this basis, a TIPR would be cost neutral by 10 years after approval.

A second disadvantage is that the way the reward for the innovator is financed through a patent extension. If the cost of this incentive is borne by patients in need of a treatment for which the period of market exclusivity has been extended, this will reduce consumption of the product. In other words, the TIPR acts as a tax on treatments for other diseases such as heart disease, chronic obstructive pulmonary disease, and depression to inefficiently cross-subsidise antimicrobial research and development (Outterson et al., 2007). Outterson et al. argue that a tax that spreads out the burden of taxation on a wide range of people, creates less distortion in buying decisions than product-specific taxes, and is therefore more equitable. However, in health care systems

¹⁰ In principle the solution is for the company to increase R&D investment by borrowing until the expected returns from the marginal internal project equal the external marginal cost of capital. In practice R&D budgets appear to be constrained.

¹¹ This result relies on the strong assumption that, the counterfactual of getting a new effective antibiotic in the market with a patent extension at time T , is that no new antibiotic is available in the market without patent extension within T years.

with low co-payments, as in most of Europe, individual patients will not pay. It is, in effect, a tax on the health care system. Whilst ultimately borne by some combination of premium (or tax) payers, patients, and producers, it will not necessarily fall disproportionately on the patients requiring the treatment to which the TIPR is applied. In this respect the funding of the TIPR need be no different than a Market Entry Reward funded from the health care budget.

To address the concerns regarding the negative impact of the TIPR, “guard rails” could be put in place to limit any excess costs they might generate. Spellberg et al. argue that the TIPR could include a profit compromise whereby there is a cap on the amount of profit that the benefiting company can earn. Similarly, the Infectious Diseases Society of America (IDSA, 2004), proposed a stipulation that 10-20% of the profits gained from the TIPR should be targeted toward AMR R&D. Some other alternative solutions might be to limit the term of the TIPR, or not to be able to apply the TIPR to any product with less than a minimum number of years remaining exclusivity to limit the impact on the generic industry, and to limit the type of products on which the TIPR could be used. Such guard rails need, however, to be studied in more detail to ensure that they do not over-compensate, ending up limiting incentives for investment in new antibiotic drugs, or introducing a level of complexity and discretion into the administration of a TIPR scheme such that companies significantly reduce their expectation of the likely value of the incentive¹².

4.2.2 *Implementation in Europe*

A TIPR could be put in place in the EU using a two-step process.

The first step would be to determine a list of drug candidates to qualify for a TIPR voucher. It might follow a similar procedure as for the Qualified Infectious Disease Product (QIDP) categorisation introduced in 2012 by the Generating Antibiotics Incentives Now Act (GAIN Act) in the US. The GAIN Act required the US FDA to compile a list of candidate antibiotics, defined as an antibacterial or antifungal drug to treat “serious or life-threatening infections, including those caused by an antibacterial or antifungal resistant pathogen, including novel or emerging infectious pathogens”. To do that, FDA must consider the impact on the public health due to drug-resistant organisms in humans; the rate of growth of drug-resistant organisms in humans; the increase in resistance rates in humans; and the morbidity and mortality in humans. The FDA also is required to consult with infectious disease and antibiotic resistance experts, along with the Centers for Disease Control and Prevention (CDC). There are currently more than 60 drug candidates with QIDP status that receive fast track and priority review status from the FDA and undergo an expedited regulatory approval process.

In Europe, something similar could be implemented by the European Medicines Agency (EMA) to make a list of potential products or areas that might be candidates for receiving a TIPR but, as in the case of the FDA, an expert group advising the EMA as to what should be on the list is required. The EMA has, for example, an Expert Committee to advise it on orphan drug designation. This mechanism could raise issues among the different European countries. Different EU Member States might have different priorities with respect to the MDR pathogens in their country. This could equally be said, however, about rare diseases and orphan drugs; but in the EU system, the expert committees

¹² Companies will in any case look carefully at therapeutic area competition in valuing a TIPR. If a competitor will lose patent status and become a low price generic during the TIPR period, then the value of extending exclusivity status through a TIPR may diminish.

represent all member states and adopt opinions by discussion and eventual consensus, according to mandatory timelines. As mentioned, the GUARD Report (Stern et al., 2017) proposes globally agreed Target Product Profiles, although it does not propose an institutional mechanism to derive them. This is advantageous as it would help with consistency and predictability. There would be considerable benefit, given the need for speed and the global nature of drug development, at a minimum, in having common Target Product Profiles for designation in the US and the EU. In the absence of a global body taking on this role, it may be that this could be achieved by the dialogue under the aegis of The Transatlantic Taskforce on Antimicrobial Resistance¹³. The FDA's Qualified Infectious Disease Product (QIDP) List could provide the starting point.

Let us assume that a company developing an antibiotic has (i) got a product licensed in the EU, (ii) met the EMA's criteria as a qualifying antibiotic drug, and (iii) has therefore obtained a TIPR voucher. It sells the voucher. The recipient company applies for a TIPR on one of its products. The second step would be to get the extension of patent protection implemented. This could use EU Supplementary Protection Certificates (SPCs).

SPCs are granted individually by each of the national patent offices of the member states of the EU. They provide an additional period of protection of up to five years to compensate for the time taken from patent filing to obtaining a pharmaceutical marketing authorization (conducting tests and trials and undergoing the regulatory procedure). In the absence of such an SPC, the company would have more limited time within the original patent period to earn a return on its R&D investment. A "paediatric extension" is also available to be added. When the requirements for exploring paediatric use of a medicine are met, the SPC can be extended by an additional six months. The absence of a single European patent means that each company wanting an SPC has to apply on a country-by-country basis. Nevertheless, the EU Regulation ensures that SPC protection can be applied for, and must be granted, by all 28 EU Member States, provided the relevant patent is valid in the country and the conditions of the Regulation are met.¹⁴

An alternative mechanism could be devised if the SPC route was regarded as too complex. The essential point is that the two key parts are readily translatable into public policy: (i) the identification of a qualifying new antibiotic; and (ii) the issuing of a TIPR voucher and the implementation of an extension of patent protection when it is redeemed.

4.2.3 How much TIPR is needed?

Following Towse and Kettler (2005), we compare the opportunity cost of developing a new drug with the profit stream from a "blockbuster" drug that might be given the TIPR. There are three elements to the profit stream calculation:

- *Sales revenue per annum.* We use information on the top 50 selling drugs at list price in Europe in 2015 from the IMS World Review Analyst 2016 (see Table 1 below). These shows only 1 drug with sales over US\$3 billion, 3 with sales between US\$2 billion and US\$3 billion, 16 with sales between US\$1 billion and

¹³ This Task Force is due to continue until 2020. See <https://www.cdc.gov/drugresistance/tatfar/index.html> Accessed 15 May 2017

¹⁴ Of the non-EU countries for which European patents can be granted, several offer national provisions that are similar to the EU regulation.

US\$2 billion, and 30 with sales between US\$0.5 billion and US\$1 billion. Returns are highly skewed.

- *The gross margin*, i.e. the proportion of sales revenue that is available to cover the fixed costs of the business and provide a return to shareholders. This will vary by drug depending on (i) the margins provided to distributors and retailers (ii) discounts from list price given to the buyer, and (iii) manufacturing cost.
- *Competitive framework after the patent expires*. Generic entry might occur immediately after the patent expires, or not. It is different in different European markets, and what happens next determines the value of the TIPR. In Germany and the UK, where generic drug markets are more developed, the value of a patent extension will be relatively higher than in, say, France, Italy and Spain where generic use is lower and slower to take off.

Table 1: 2015 leading products by sales in Europe

2015 Rank	Product	2015 US\$ (Mill)	2015 Rank	Product	2015 US\$ (Mill)
1	Humira	3451	26	Daklinza	773
2	Harvoni	2986	27	Velcade	731
3	Sovaldi	2722	28	Novorapid	713
4	Enbrel	2210	29	Atripla	709
5	Herceptin	1916	30	Simponi	697
6	Remicade	1874	31	Alimta	695
7	Mabthera	1775	32	Tysabri	680
8	Avastin	1720	33	Prezista	669
9	Seretide	1645	34	Copaxone	657
10	Lovenox	1633	35	Rebif	646
11	Xarelto	1622	36	Avonex	643
12	Lucentis	1367	37	Prograf	643
13	Spiriva	1315	38	Prolia	637
14	Lantus	1306	39	Pradaxa	612
15	Lyrica	1302	40	Tecfidera	612
16	Glivec	1241	41	Neulasta	610
17	Symbicort	1191	42	Abilify	597
18	Revlimid	1179	43	Voltaren	594
19	Eylea	1014	44	Victoza	588
20	Truvada	1001	45	Soliris	581
21	Gilenya	988	46	Invega Sustenna	580
22	Crestor	975	47	Vytorin	574
23	Zytiga	945	48	Januvia	574
24	Viekirax	839	49	Xtandi	571
25	Aranesp	833	50	Stelara	569

Notes: in US dollars

Source: IMS World Review Analyst 2016

We present some indicative calculation to show the effect of 1 year of TIPR in three different cases, where we assume:

- different estimated costs of R&D as set out in Section 5.3 below of: US\$1.6 billion; US\$2.0 billion; and US\$2.5 billion for Case 1, Case 2, and Case 3, respectively.
- different estimates of gross margin: 50%; 65%; and 80%, for Case 1, Case 2, and Case 3, respectively.
- sales of the TIPR recipient product of: 15th in the top 50 ranking (the marginal product if we want 15 new antibiotics) (\$1.3bn; the average of the top 15

(\$1.92bn); and the average of the top 5 (\$2.66bn) for Case 1, Case 2, and Case 3, respectively.

We need to make an assumption as to how much of the of the global R&D cost needed to develop the new drug needs to be recovered in Europe, which means that the TIPR would only have to cover that partial cost. According to IMS Health (IMS Health, 2016) Europe accounted for 28.5% of total global pharmaceutical sales in 2015. In the therapeutic area of system anti-infectives, Europe accounted for 23.4% of global sales. If we assumed that assume that only North America and Europe were asked to contribute to the recovery of the global R&D costs for new antibiotics then the contribution based on the ratio of global sales would be 40% for Europe to 60% for North America. The appropriate European share is therefore somewhere between 23.4% and 40% depending on assumptions made about the appropriate contribution to R&D costs of the world outside of the US and Europe. For the purposes of these indicative calculations we assume that Europe contributes 33% of global R&D costs for new antibiotics.

Table 2: Illustrative examples of an application of 1 year TIPR

	Case 1	Case 2	Case 3	Case 4
Estimated cost of R&D	US\$1.6 bn	US\$2 bn	US\$2.5 bn	US\$2.5 bn
EU participation in R&D (33%)	US\$0.53 bn	US\$0.67 bn	US\$0.83bn	US\$0.83bn
Estimate of gross margin	50%	65%	80%	50%
Sales in Europe per year	US\$1.3 bn	US\$1.92bn	US\$2.66 bn	US\$1.3 bn
Money needed to raise	US\$1.07 bn	US\$1.03 bn	US\$1.04bn	US\$1.66 bn
Years of TIPR required	0.82	0.53	0.39	1.28

Source: Calculations following Towse and Kettler (2005)

The results indicate that in our three cases, one year of IP extension would overpay for Europe's share of the cost of R&D. If, however, we took a "worse case" (Case 4) of US\$2.5 billion R&D cost, and a 50% margin, looking at the sales of the 15th product (\$1.3bn) the money needed to be raised would have required a TIPR of 1.28 years.

The main source of variability is in the sales of the on-patent product using the TIPR. A "guard rail" could be put in place to deal with this issue. It could be possible to set up a rule to calculate the length of the TIPR when the incentive is announced. In other words, to set up a variable cap on the length of the IP extension. The effective duration of the TIPR would only be set when the company that has bought the TIPR voucher had chosen the drug to which the extension is to be applied. The estimate of the gross margin and the size of the EU's contribution to global R&D costs would be fixed in the legislation and not a variable depending on each product.

We can see how this approach improves efficiency. If we take Case 1 in Table 2 and we want to give incentives to discover 15 new antibiotics using the same length of IP protection, we would have to set a length of 9.8 months for the TIPR (0.82 years). This is because the European revenue of the 15th best-selling drug is US\$1.3 billion. However, to set the TIPR at this length would be inefficient because we would be overpaying for the other 14 drugs by delaying the entry of generics for several months (a TIPR extension on the best-selling drug Humira, for example, would only need 3.7 months of patent extension to recoup the same R&D cost). However, if we set the TIPR for everyone at 3.7 months extension we take the risk that only one drug is discovered as

the TIPR incentive for any of the other 14 drugs is not enough to cover the estimated EU share of the R&D costs of a new antibiotic.

A calculation of this sort could be made to work by, for example, requiring the company to disclose audited European sales of the product for which it was seeking to apply the TIPR for the two years prior to the application. The length of the TIPR would then be based on the average of these two figures.

One additional advantage of requiring a disclosure of actual net sales revenue is that it avoids the need to make assumptions about the distribution margin and discounts to payers from the list price. One disadvantage is that estimates of R&D costs, on which the TIPR length was based, would need to be indexed to take account of real increases in R&D cost. There is no obvious external price index to apply here.

A simpler to implement variant of this might be to have ranges of sales and of TIPR length. An example is presented in Table 3.

Table 3: Illustrative estimates, composite cases

	Composite Case A	Composite Case B	Composite Case C
Estimated cost of R&D	US\$2 bn	US\$2 bn	US\$2 bn
EU participation in R&D (33%)	US\$0.67 bn	US\$0.67 bn	US\$0.67 bn
Estimate of gross margin	65%	65%	65%
Money needed to raise	US\$1.03 bn	US\$1.03 bn	US\$1.03 bn
Range of Sales in Europe	≥\$3 bn	\$2 bn- \$3 bn	\$1 bn- \$2 bn
Years of TIPR required (using the base point of the range)	0.34	0.52	1.03

Source: own elaboration

We need to strike a balance between requiring the legislator to have and interpret information about the industry not in public domain. Releasing this information might generate strategic behaviour by the companies. There is a trade-off between simplicity and efficiency.

4.3 MARKET ENTRY REWARDS

4.3.1 Principles to be Met

The O'Neill Report suggests that this is the most attractive and realistic model to incentivise AMR R&D. It proposes such rewards (payments in the order of US\$0.8 – US\$1.3 billion) be paid after a successful product comes to market and to be proportionate to unmet medical need.

The proposal rests on several principles, and the main ones are described below. We discuss the advantages and the potential pitfalls of each of them.

First, “developers should be actively guided towards the antibiotics that the society most urgently need today and most likely need tomorrow”. Clear signalling is the most effective way to ensure that R&D is directed towards areas that pose the greatest risk for the future. To be effective, however, there needs to be a global consensus, as in the GUARD proposal for globally set Target Product Profiles. These, we have suggested could take the FDA’s Qualified Infectious Disease Product (QIDP) list as a starting point.

Second, “payments should be free from political risk”. This means that there would be consistency and commitment as to which antibiotics will be rewarded sustained over the long-term. This principle is fundamental but very difficult to maintain: financing such large amounts of money will require collaboration and strong commitments. AMR R&D is long-term, increasing the risk of opportunistic behaviour by one or more funders.

Third, “rewards should be linked to a product’s value to society”. The clear signals need to be matched with financial rewards. Drugs that meet the most acute unmet medical needs most effectively, should be the most generously rewarded. This principle tries to positively link value with reward and to avoid perverse incentives to produce drugs with the least possible effort and innovation to claim the prize. Ideally a clear set of guidelines should be available to link the level of the reward to the product’s value to society. There is a clear risk of rewarding too much or too little, which could affect the incentives to innovate in the first place. Rex and Outterson (2016) propose one way to link rewards to key success criteria.

Fourth, “the payment should come as soon after a product reaches the market as possible, but this may not be immediate and may not come all at once”. This principle is associated with the idea that the later the payment, the lower the current value of the incentives. However, on the other side, there should be some conditionality attached for recipients of the payouts, and top-up payments might be the best way of committing to continued development post-approval and responsible selling and marketing of the product. This may complicate any use of a TIPR or PRV as it will be harder, but not impossible, to introduce clawback or repayment provisions within a transferable voucher scheme.

We note that there are trade-offs between the four criteria. In particular, any conditionality, discretionary variability in the reward, or potential to change the list of qualifying antibiotics risks undermining the need to keep rewards free from political risk.

The Global Launch Reward proposed in the GUARD report is a US\$1 billion payment that seeks to improve the commercial attractiveness of antibiotics meeting at least one Target Product Profile, but it is embedded in an insurance-like mechanism. It is intended to create a “pull” effect throughout the entire value chain, stimulating basic research as well as clinical development in the field (see Section 3.2.2 for more details). This proposal rests on several principles we now set out.

First, the insurance model proposed by GUARD aims to benefit all high-need antibiotics, whatever the potential profit expectation. Recipients are required to return 30% of their profits to GUARD, up to the original amount of the Global Launch Reward. Companies launching an antibiotic that is commercially more successful would be less reliant upon payments through the Global Launch Reward and repay the amount more quickly.

To ensure that the repayment mechanism works in a predictable way for both companies and the funders, the GUARD Report sets out factors that need to be taken into account: i) “setting upper limits for the repayment period”, once the product’s patent expires, repayment obligations should be forgiven; ii) “securing predictable return of funds for GUARD”, GUARD will receive a minimum of 15% of the product revenues irrespective of profits; and iii) “limiting the repayment mechanism to the size of the Global Launch Reward”, companies will only pay back up to the amount received.

Second, “stability of the Target Product Profiles” is essential for minimizing the market-distorting effects this intervention produces. GUARD proposes to sign a contract at the

beginning of phase 2 in clinical development, promising the payment of the Global Launch Reward for meeting a Target Product Profile valid at the time of signing.

Third, in order to avoid the so-called race to the finish line, “an eight-year window is allowed” for launching the new molecular entity. GUARD could sign multiple agreements for the same Target Product Profiles for several reasons: because of the high failure rates in the development, or because, even when two different antibiotics on the same Target Product Profile succeed there may be a significant public health benefit to having both available.

Fourth, with the acceptance of the Global Launch Reward, companies should agree upon: i) global availability, the recipient agrees to pursue the launch on the antibiotic globally; and ii) affordable pricing in low- and middle-income countries, but companies maintain the right to set their prices without additional intervention by GUARD in high income countries.

It is clear that even though both proposals are defined as Market Entry Rewards, they are different. With the Market Entry Reward proposed in the O’Neill Report, the company keeps the money independently of the future profits generated by the sale of the product. With the Market Entry Reward proposed in the GUARD Report, the company might have to give all the reward back to the GUARD, if future profits or revenues from the sale of the product are sufficiently high. The “insurance model”, as GUARD describes it, partially or fully converts the concept of a “reward” into a “financial support for commercialisation of successful antibiotics”. As we have noted above, the starting point for the O’Neill and GUARD reports is the lack of profitability of new antibiotics. Introducing routine (as opposed to exceptional) clawback provisions risks considerably devaluing the face value of the rewards in company calculations, reducing the amount of R&D stimulated. The desire to avoid overpaying in the case of GUARD risks deterring the innovation the reward mechanism is designed to incentivise.

4.3.2 The AMC Example

The Advance Market Commitment (AMC) is a “pull” incentive not explicitly discussed in the O’Neill Report but which is close to the market entry reward envisaged by O’Neill. In 2009, the GAVI Alliance,¹⁵ using funding from the Governments of Italy, the United Kingdom, Canada, the Russian Federation, Norway and the Bill & Melinda Gates Foundation, collectively pledged a total of US\$ 1.5 billion to fund a pilot AMC for pneumococcal vaccine (Cernuschi et al., 2011). Earlier versions of the vaccine were available in high income country markets for over a decade, but the pilot AMC aimed to pay for producers to supply the vaccines for developing countries within a year of pre-qualification by the WHO.¹⁶

This AMC works as follows. Each manufacturer must commit to supply its annual share of doses for 10 years at a maximum price of US\$ 3.50 per dose, estimated to be the marginal cost of production at the time of the AMC design. This price is being paid by the GAVI Alliance and/or by GAVI Alliance-eligible countries. An additional amount is disbursed to the manufacturer as a subsidy per dose additional to the maximum price –

¹⁵ The GAVI Alliance is a PPP created to increase access to immunization in poor countries, and The World Bank co-led the design of the pilot. Implementation also involved the United Nations Children’s Fund (UNICEF) and the World Health Organization (WHO).

¹⁶ There are discussions to launch AMCs for products to help with other diseases, and to extend the concept to other areas such as green technology in the developing world.

bringing the total price up to US\$ 7 for approximately the first 20% of vaccine doses procured from each manufacturer. This “AMC price” is paid by the GAVI Alliance using the AMC funding, and is set to enable companies to quickly recover incremental investment costs incurred to serve the GAVI Alliance market.

The AMC makes the reward to product developers conditional on sales in the relevant markets as the challenge is to get the vaccines used (Wilson and Palriwala, 2011). In this respect, it differs from the case of antibiotics. However, several elements are relevant: (i) the donor pre-commitment; (ii) the variability of the reward depending on first, second, third entry into the market place; (iii) the use of an independent scientific committee to assess whether a vaccine met the qualifying standards and (iv) the robustness of the contractual commitments on both sides¹⁷.

4.3.3 *Implementation in Europe*

We have noted that both the O’Neill and GUARD reports propose a form of “lump sum” market entry reward which could operate by region. We discuss the size below. But how might such an incentive mechanism work in the European Union? It could operate by:

- (i) the EU operating an EU-wide procurement arrangement and rewarding the company with a lump sum providing the antibiotic qualified. The money could be raised by a new tax or by diverting revenues from other EU activities;
- (ii) as with (i) **Error! Reference source not found.** above except that member state governments are responsible for making available their share of the lump sum rewards. Member states could choose how to raise the revenue.
- (iii) the EU agrees principles, but negotiations on the size of market entry reward take place at national level.

Option (i) is the most straightforward. The question would remain as to how it would be put into place. If it were done by an EU Regulation then it could only be undone through the same process. It could be an effective incentive. As we understand the current EU procurement process, it is permissive. There are no obligations on Member States unless they agree to participate. The existing procurement process would not therefore be sufficient to deliver an EU-wide market entry reward.

Options (ii) and (iii) are more complicated for companies. Option (ii) involves negotiation with each member state on each product. The potential transaction cost is high and there is potential for opportunistic behaviour on the part of member states. It is likely that companies would heavily discount the value of an option (ii) market entry reward. Option (iii) is harder to categorise. If the amounts to be awarded were set out in an EU Regulation then it would be effective. Any element of discretion would reduce the credibility of the incentive.

We can note that both the UK and Swedish governments are exploring “insurance” agreements with the pharmaceutical industry. These are different approaches to reimbursement and national funding designed, as we understand it, to address the

¹⁷ We can note in response to the Ebola outbreak, the launch of the Coalition for Epidemic Preparedness Innovations, (CEPI), a new global R&D organisation for epidemic preparedness and response a partnership between public, private, philanthropic, non-governmental, intergovernmental, and civil organisations, on Jan 19 at the World Economic Forum’s 2017 meeting. It is looking at mechanisms to generate new drugs and vaccines and to stockpile them or find other routes to make them available at short notice in the event of an epidemic.

uncertain demand for antibiotics in any time period. It is unclear at this stage how these national models would relate to a European or global initiative.

To conclude, a system of market entry rewards has potential to support improved affordable access to new antibiotics. Designing the rules and the payments will not be straightforward. Market entry rewards can be inefficient in two important respects. Firstly, the reward may be too high or too low, resulting, respectively, in either excess profits or a continued lack of antibiotics. Secondly, political risk will lead to companies discounting the expected value of the reward. If an ex post reward of US\$1 billion is seen ex ante by companies as only worth US\$0.5 billion because there is a 50% risk that some or all of the reward will not be paid when a qualifying antibiotic is developed, then there is substantial redundancy. Companies will make investment decisions on their ex ante expectations of a reward of US\$0.5 billion, and the countries will end up paying US\$1 billion for US\$0.5 billion of effort. Creating risk is expensive.

4.4 A COMPARISON OF PRV, TIPR, AND MARKET ENTRY REWARDS

As we stated above, a TIPR extends the market exclusivity period for another drug for a particular period of time. A PRV speeds up the market entry of any drug, even if it is non-priority review drug. Both vouchers rely on giving incentives to AMR R&D by increasing the profits that pharmaceutical companies receive from an actual or prospective blockbuster drug. Providing a PRV is not displacing the accelerated review of a higher value drug, it increases the time between the marketing authorization and the patent expiration (increasing dynamic efficiency), and speeds the access of patients to the new drug. A TIPR reduces static efficiency, by prolonging premium pricing.

The commitment of any of a TIPR, PRV, or Market Entry Reward should be legally binding and enforceable in the courts. Time-inconsistent incentives appear when governments want firms to invest in R&D, but once the medicine has been developed, they want to purchase them at the lowest possible price, i.e. one that makes it difficult for the firm to recoup their R&D costs. If the industry anticipates this behaviour, the efficiency or incentive value is reduced.

We compare the main elements of these three 'de-linked' incentive mechanisms in Table below based on the Towse and Kettler (2005) Report for the CIPIH. In doing so we drew on the typology of six design issues: credibility, price, quality specification, subsequent entrants, ensuring use, and industry participation.

Our findings, set out in Table 4, can be summarised as follows:

- *Credibility:* All three de-linked incentive mechanisms seek to deal with the concern of time inconsistency. Time inconsistency arises when a decision-maker's preferences change over time in a way that a preference at one point in time can be inconsistent with preferences at another point in time. For example, a health care payer may want to reward R&D to get new antibiotics, but once the antibiotics are developed and licensed, may want to drive down prices below levels that reward R&D, to limit the cost to the health care system of buying antibiotics. Thus, whilst TIPR has no track record in delivery yet, extensions of IP are understood by companies and deal with the problem of time inconsistency. The EU has operated an SPC scheme successfully for more than a decade which could be used to implement a TIPR. PRVs have more uncertainty attached to them than TIPR for two reasons.

Firstly, their value depends on the difference between fast track and normal review times and on the criteria for fast track. These may change over time. Secondly, PRVs offer benefits on drugs which have not yet been launched, as compared to TIPR which rewards products with a proven track record of revenue generation. In the case of a Market Entry Reward, uncertainty is mixed. On the one hand, the prize is set at the beginning of the race and the conditions are not expected to change.¹⁸ However, credibility depends on (i) how contractually committed the funders are to providing the full value of the prize, and (ii) the amount of discretion available to the funder(s) as to whether to award the full value of the prize. It will be informed by a judgement as to how sustainable is the funding for the prize.

- *Price:* All three only reward success, but all three may reward innovation that companies would have undertaken anyway because they found a compound serendipitously that worked as an antibiotic. For a TIPR, the price is set by the length of the extension, which could be differentiated by the type of innovation, but this would need to be specified in advance in the legislation. For a PRV, the extension is determined by the gap between fast track and normal review. A problem for the TIPR is that delaying generic entry can generate a “deadweight” efficiency loss if the higher price leads to lower consumption of the drug. It can also lead to an equity issue. However, in most health care systems, where drug costs are met by third party payers and prescribers are not price sensitive, both of these effects may be minimal. For a Market Entry Reward the prize is set by the funders, and it could change (in amount and frequency of payments) depending on the characteristics of the drug. The main limitation is to find financing for such large payments, which requires collaboration and strong financing commitments;
- *Quality specification:* All three would require marketing authorisation. For all of them either the legislation or, in the case of Market Entry Rewards, the funders would need to set out the eligible products and indications. The GUARD report sets out the case for setting globally agreed Target Product Profiles. The quality specification mechanism would be the same for each;
- *Subsequent entrants:* In all three cases better products get used. Any product meeting the legal criteria gets the reward. This raises the danger, however, of overpaying for some innovation as follow-on products may vary in the additional benefits they bring. Whilst a PRV cannot be altered, the length of TIPR could be varied for subsequent entrants, and size of a Market Entry Reward could also be varied for subsequent entrant;
- *Rewarding Value:* As noted, a PRV voucher is “all or nothing” and cannot be modified. Varying the reward to reflect the value as in the TPP is, however, possible for the TIPR and the market entry reward. There are two separate issues. Phasing payments in order to reduce or eliminate them if performance is not met – for example due to safety concerns emerging – introduces uncertainty. In principle, companies normally face this challenge. Products lose sales if they are not as effective or have more side effects than expected. It will be important that any assessment of product performance is impartial and credible and not motivated by a desire to

¹⁸ The market entry reward proposed in the O’Neill Report might have more uncertainty because it is proportionate to unmet medical need. It is not clear if the parameters that define the medical need are set together with the prize or when the drug comes to market, and this is going to change significantly the uncertainty and the credibility of the prize. The GUARD report proposes phased payment of the market entry reward.

save money. The second issue is that payment conditionality may be complex to achieve, but not impossible. In the case of the Market Entry Reward, complexity depends whether rewards are being clawed back retrospectively or future payments not being made. In the case of TIPR clawback is difficult. The seller of the TIPR (the company that developed the new antibiotic) would need to reimburse national health systems for some of the money it had raised from selling its TIPR voucher.

- *Industry participation*: Uncertainty and financial risk are natural deterrents for many firms. This situation is particularly relevant for Small and Medium Enterprises (SMEs). Transferability of the PRV and TIPR voucher overcomes the main problem providing a market for the vouchers is established. Transaction costs and/or a lengthy bargaining process erodes the size of the reward for developers of a TIPR or PRV with respect to a Market Entry Reward.

Overall, it is difficult to see that a PRV will be workable in the EU or will give a large enough reward. The TIPR and the Market Entry Reward both have strengths and weaknesses. The risk with a TIPR is of overpaying relative to a Market Entry Reward. The risk with the Market Entry Reward is of political risk and credibility. Is the funding source sustainable, and is there a risk that the Reward can be changed at relatively short notice? Political risk will lead to a devaluation of the expected reward by companies, potentially requiring higher Market Entry Rewards to be offered than with TIPRs. Our assessment is that both the TIPR and the Market Entry Reward should be further explored for use in the EU as a regional "pull" incentive in keeping with the O'Neill and GUARD report objectives of generating 10-15 new antibiotics per decade.

4.5 PULL INCENTIVES FOR VACCINES

The O'Neill Report points out that vaccines can prevent infections, "reducing use of antimicrobials and so slowing the rise of drug resistance" (page 5). It argues for incentives to be available in order to "sustain a viable market for vaccines". The challenge is the lack of a market. Purchasing of such vaccines would typically be decentralised. In our view such vaccines would then compete with the alternative of allowing people to get infected and then treating them with low cost generics. Tackling AMR would not be built into the assessment of value. O'Neill concludes that "Depending on the characteristics of the vaccines in question, such "pull" funding could be structured as Advanced Market Commitments (to promote broad uptake in mid to large sized populations) or as market entry rewards (to ensure availability for smaller populations at high risk)" (page 43). GUARD also sees vaccines as very important, but states "we do not recommend using the same financing mechanisms for vaccines and diagnostics....the challenges along their value chains are distinctive, requiring remedies different from the funding mechanisms proposed here" (page 23). It sees vaccines as commercially viable products and therefore the key "lies not in subsidising them, but in removing uncertainty around market potential. For vaccines, public commitment to vaccination campaigns creates markets. This is why Advanced Market Commitments have proven to be the most widely used pull incentive for vaccines" (page 24).

Both O'Neill and GUARD are arguing for centralised campaigns to use targeted vaccines. The AMC model is relevant in our view. The immediate value of the vaccine is relatively low when most infections can be treated with low cost generics. A centralised top-up payment to the manufacturer would recognise the AMR value to society.

Table 4: Design Characteristics of the Three de-linked Schemes

Design issue	Transferable Fast Track (PRV)	Transferable IPR	Market Entry Reward
Credibility with industry	<ul style="list-style-type: none"> • overcomes time inconsistency • uncertain value of <i>potential</i> blockbuster • track record on implementation in the US 	<ul style="list-style-type: none"> • overcomes time inconsistency • little uncertainty for manufacturers of potential benefits • track record on additional IPR in Europe via SPCs 	<ul style="list-style-type: none"> • overcomes time inconsistency • limited track record e.g. AMC • large potential for political risk, need for built in institutional reassurance
Setting the price	<ul style="list-style-type: none"> • only rewards success • legislation sets the price/reward • rewards some innovation that may have occurred anyway • additional value of speeding another drug to market • may not be a large enough value 	<ul style="list-style-type: none"> • only rewards success • legislation sets the price/reward • rewards some innovation that may have occurred anyway • deadweight loss due to delayed generic entry • potential equity issue in terms of “who pays?” 	<ul style="list-style-type: none"> • only rewards success • funders set the prize • rewards some innovation that may have occurred anyway • need to find financing for the payments which will involve some form of deadweight loss
Quality Specification	<ul style="list-style-type: none"> • marketing authorization required • legislation to set mechanism for eligible drugs / indications e.g. via Target Product Profiles 	<ul style="list-style-type: none"> • marketing authorization required • legislation to set mechanism for eligible drugs / indications e.g. via Target Product Profiles 	<ul style="list-style-type: none"> • marketing authorization required • legislation/funders to set mechanism for eligible drugs / indications e.g. via Target Product Profiles
Subsequent entrants	<ul style="list-style-type: none"> • any product meeting legal criteria gets reward, danger of overpayment • better products are used 	<ul style="list-style-type: none"> • any product meeting legal criteria gets reward, danger of overpayment • better products are used • length of TIPR could be varied for subsequent entrants 	<ul style="list-style-type: none"> • any product meeting legal criteria gets reward, danger of overpayment • better products are used • size of reward could be varied for subsequent entrants
Rewarding value	<ul style="list-style-type: none"> • cannot adjust the voucher, it is “all or nothing” • payment conditionality would be complex to achieve 	<ul style="list-style-type: none"> • can adjust the voucher to pay more or less for different products • payment conditionality may be complex to achieve and may increase political risk 	<ul style="list-style-type: none"> • can adjust the reward to pay more or less for different products • payment conditionality is easy to achieve unless it involves claw back but may increase political risk
Industry participation	<ul style="list-style-type: none"> • transferability provides incentives to both Small and Medium-sized Enterprises and to big pharmaceutical companies 	<ul style="list-style-type: none"> • transferability provides incentives to both Small and Medium-sized Enterprises and to big pharmaceutical companies 	<ul style="list-style-type: none"> • the size of the prize is independent of company size providing incentives to both Small and Medium-sized Enterprises and to big pharmaceutical companies

Source: Elaboration based on Towse and Kettler (2005)

5 SIZE OF A “PULL” INCENTIVE POT

5.1 MEAN R&D COSTS PER SUCCESSFUL MEDICINE

Cost estimates as to how much it costs to research and develop a successful new medicine matter not just because of intellectual curiosity or for industry understanding of its performance, but because they are a key aspect of the international debate about the reasonableness of pharmaceutical prices and the magnitude of the long-term investments involved. These issues also apply to antibiotics.

A number of articles/reports, including O’Neill, have looked at the R&D cost of a new medicine. Broadly speaking, these analyses consider four variables that ultimately drive total R&D: (i) out-of-pocket expenses; (ii) success/failure rates; (iii) R&D timelines; and (Richard and Van Horn) the cost of capital. It is important to highlight that “out of pocket expenses” will (partly) depend on two variables: the number of patients in clinical trials, and cost per patient. Mestre-Ferrandiz and Towse in an OHE publication (Mestre-Ferrandiz et al., 2012), entitled “The R&D costs of a new medicine” reviewed articles published over the last three decades, which shows an increase in estimated costs from £125 million (\$199 million) per new medicine in the 1970s to £1.2 billion (\$1.9 billion) in the 2000s (both in 2011 prices). An OHE cost analysis based on new data for 1998-2002 agrees with comparable analyses for the same time period. The latest estimate by DiMasi, Grabowski and Hansen (2016) puts the figure higher, at US\$2.6 billion (in 2013 prices).

‘Average’ R&D costs hide important differences. Published estimates, including the OHE one, that refer to the mean cost of R&D per new medicine are just that: averages. The literature shows that the costs of R&D vary with the subgroup of drugs included in the analysis. Costs can vary according to therapeutic area, firm size and whether the molecule is a “traditional” chemical compound or a biologic. There is also controversy around the evidence on each of the key four parameters mentioned above (out-of-pocket expenses, success/failure rates, R&D times and the cost of capital). Evidence can be highly commercially sensitive (especially for the later R&D stages). For pre-clinical studies, it may be difficult to apportion expenses to specific drugs/compounds.

It should be highlighted that the focus of this work will be on pre-launch R&D costs. Hence, any costs of post-launch studies (such as those for an adaptive pathway or prospective observational studies generating real world evidence) are outside the remit of this work, but should be included if any of the incentives proposed require collecting post-launch data. It should be noted that data is also scarce on the magnitude of post-launch study costs.

5.2 R&D COSTS FOR ANTIBIOTICS

The O’Neill Review provides estimates of R&D costs for antibiotics in both of its reports.¹⁹ At the time of publishing the “Securing new drugs for future generations” (O’Neill et al., 2015), an excel model was also provided showing the detailed calculations and assumptions, to come up with an estimated R&D cost of a new antibiotic of US\$1.9

¹⁹ For information, Mestre-Ferrandiz provided support to the O’Neill team when estimating R&D costs.

billion. Given the uncertainty surrounding some of the parameters, The Report also undertakes some sensitivity analysis, mainly about costs and probabilities of success.

Table 5: Comparison of published (mean) R&D costs for antibiotics

	Sharma and Towse (2010)	Sertkaya et al. (2014) ^a	O'Neill (2016a)	Towse et al. (forthcoming)
R&D	US\$m	US\$m	US\$m (year not reported)	US\$m (2011)
Out-of-pocket costs – global	(2008) ^b	(2012) ^c		
Preclinical	241.7	21.1	10.7	19
Phase I	68.7	9.7	10.1	16
Phase II	106.6	10.3	26.3	54
Phase III	208.7	51.7	96.3	196
Approval	43.7	2.0	NA	29
<i>Total R&D cost</i>	669.3	95	1-1.3 bn	314
Post-Marketing Authorisation costs		10	146	40
Cost of capital	11%	11%	11%	10%
Total capitalised R&D cost – global	\$1.35 bn	Not reported	\$1.9 bn ^{d,e}	\$1.581 bn ^f
Success probabilities ^g				
Preclinical	0.35	0.352	0.173	0.35
Phase I	0.582	0.33	0.33	0.67
Phase II	0.522	0.50	0.593	0.46
Phase III	0.786	0.67	0.758	0.70
Approval	0.91	0.85	0.797	0.87
<i>Overall probability of success</i>	0.076	0.033	0.020	0.066
Number of projects required for one successful product	13	30	50	15
Phase length (months)				
Pre-clinical	66	66	66	60
Phase I	18	10.5	11	16
Phase II	30	13.5	13.5	26
Phase III	30	21.8	22	29
Approval	18	9	9	11
<i>Total Preclinical - Approval</i>	162	121	122	142

NA not available.

^a Average across infections when infection-specific numbers are reported.

^b Exchange rate used: €1 = US\$1.35.

^c Sertkaya et al. (2014) reports other additional costs during R&D related to (1) supply chain activities and (2) non-clinical work. These costs are not included in this table.

^d O'Neill (2016a) also includes marketing, manufacturing and regulatory costs

^e Extracted from the excel model, available at: www.amr-review.org (last accessed 2 February 2017). Includes post-approval pediatric and follow on trials.

^f Capitalized cost of R&D does not include cost of post-registration studies.

^g Progression rate, rather than probability of success.

Source: Towse et al. (forthcoming)

Table shows a summary of estimates of R&D costs for the key papers published recently, including forthcoming work (Towse et al., forthcoming). The GUARD Report

uses the O'Neill estimates of success rates and out-of-pocket costs for clinical development (see Figure 16, page 39). It does not show an overall R&D cost.

The O'Neill Review also commissioned IMS Health to analyse success rates for antibiotics. It came up with an overall probability of success of 0.015, the lowest among all studies. It is worth mentioning that the IMS Health analysis shows only a 0.093 success rate for pre-clinical, which is significantly lower than all the other estimates (Stephens, 2015). Success rates for clinical phases are more in line with other estimates (33%, 75%, 86% and 75% for phase 1, 2, 3 and approval respectively). With IMS estimates, the total capitalised R&D cost becomes US\$2.3 billion – close to the average estimate by DiMasi et al. for all products of \$2.6bn.

In terms of R&D costs, O'Neill et al. (2015) also provides lower and upper bound estimates for the costs of pre-clinical, phases 1 -3, and post approval paediatric and follow on trials. The base case assumptions (as shown above) are derived eight different sources. The lower bound estimate was the 25th percentile from the inputs, and the upper bound was the 75th percentile. Total research costs pre-approval (pre-clinical, Phases 1-3) for the former are US\$99m and US\$193 for the latter (relative to the US\$143m for the base case). Note this figures are non-capitalised costs (what we call above "out of pocket costs"). With the lower bound, total R&D capitalised cost is equal to US\$1.8 billion, with the upper bound, US\$2.5 billion. If we increase the Towse et al. (forthcoming) estimate in \$2011 by 5% per annum to reflect rising real R&D costs, the US\$1.58 billion figure becomes a 2016 figure of US\$2.0 billion. This is close to the O'Neill value of \$1.9bn and therefore is, in our view, a sensible estimate to use for planning purposes.

Of course, there are some drugs already in the R&D pipeline and there may be a difference in development costs between drugs that create a new therapy class and those that are "follow on" drugs within an existing therapy class – for example due to differences in scientific and regulatory risk. However, the immediate need is for a sensible working estimate of the fully capitalised cost of R&D for a new antibiotic or vaccine at launch.

5.3 TOTAL PROGRAMME COSTS

As mentioned above, "mean" figures can be problematic, not least because the value of antibiotics will be different. There is a need to focus on "pull" incentives. This point is made by O'Neill et al. (2015) when discuss the need to have 15 new antibiotics every 10 years, including:

- Four first in class: two new broad spectrum classes of antibiotic every ten years (appropriate for empirical prescription) that address an important and unmet medical need; and two new targeted therapeutic classes every ten years (appropriate for diagnostic based prescription) that address an important and unmet medical need;
- The remainder of the new drugs over the decade would be 'follow on' compounds offering some, perhaps substantial, improvements. They would not necessarily need to be funded in the same way via the new market incentive offered for new classes as there may be sufficient return on investment as it is. It is not clear to us however, why this is the case.

In relation to the cost of R&D, the Excel available in website estimates total R&D cost of a new antibiotic at US\$1.9 billion. Yet O'Neill states "We estimate that a lump sum of between 1 and 1.3 billion USD to cover development costs of a new drug on average, including costs of projects which fail along the way" (page 21). In The Report, it is stated: "We have proposed a system of market entry rewards of around one billion USD per drug for effective treatments, whether they are based on new or old drugs that work against resistant pathogens in areas of most urgent need" (page 6).

As shown above, these figures are lower relative to the analysis (Towse et al. forthcoming) that estimates 2011 costs of US\$1.6 billion for the total capitalised R&D cost per successful antibiotic as the base case. As noted, we believe average numbers of capitalised R&D cost of US\$2 billion (the US\$1.6 billion 2011 estimate uprated by 5% per annum for rising real R&D costs) are more realistic. How much of this needs to be covered by a one-off "pull" incentive depends on how much:

- (i) average R&D costs vary, depending on the type of antibiotic sought and whether it is a product creating a new class or a follow-on product)?
- (ii) R&D cost is covered separately through "push" initiatives?
- (iii) commercial revenue will be earned outside of the one-off "pull" payment to the company?

However, in simple terms, 15 drugs over ten years at US\$2 billion a drug requires a "pull" commitment of US\$30 billion a decade, or US\$3 billion per annum. This is much higher than the O'Neill recommendations of US\$16 billion built around its assumptions of US\$1 billion per product market entry rewards. Although O'Neill (page 28) states that "we calculate that a buyout model which adequately rewards and incentivises the developers of these 15 products *would cost as little as 16 billion USD or no more than 37 billion USD over a decade*" (our emphasis), in practice the \$16 billion figure is the one used. It may be that O'Neill is assuming that some "new" antibiotics are old drugs that are repurposed. However, this is not clear. We note that the GUARD Report seeks "to produce one new high-need antibiotic per year in a steady state", i.e. 10 drugs over 10 years²⁰. It proposes a market entry reward (termed the Global Launch Reward) of US\$1 billion, but not to apply to drugs already at Phase 2 or later in the development process. The rationale for the US\$1 billion figure is unclear. The earlier 2015 O'Neill Report is referenced. As we note above, however, the figures in that report indicate an R&D cost of US\$1.9 billion. It is also not clear to us what the case is for an average of 10 or of 15 new antibiotics per decade. Exploring the required numbers of new drugs is not part of our remit. Our concern is about choosing an efficient incentive mechanism and setting the reward at a level that will succeed in stimulating new drugs.

5.4 MOVING AWAY FROM REWARDING "MEAN" R&D COSTS – ADJUSTMENTS FOR "VALUE"

Otterson et al. (2016) provide an analysis of potential payments based on certain criteria – see Table 6 below. Their base payment is around US\$200 million per year over 5

²⁰ The German Government has the Presidency of the G20 from December 2016 to November 2017. The G20 is seen as the key group to take forward the question of how to implement financial incentives for new drugs to tackle AMR.

years (i.e. US\$1 billion in total). Leaving aside concerns that this seems to be a low figure relative to estimates of average R&D cost, the authors look at better targeting. Table 6 sets out circumstances that could lead to additional benchmark payments for 5 years.

It makes sense to increase the rewards for products that are likely to bring the greatest societal value. However, it will remain important that average rewards are expected to provide an appropriate return over and above R&D costs.

Table 6: Analysis of Potential Payments

Criteria	Bonus as a % of base payment
Novel mechanism of action	100
More urgent pathogens	100
More serious pathogens	50
Treating urgent, serious or of concern to public health infection (CDC 2013)	0
Follow-on entrant (2 nd , 3 rd of 4 th)	75: 2 nd
	50: 3 rd
	25: 4 th
Follow-on entrant (5th or subsequent), with some improvement	10
Paediatric commitment	Separately
For a 2 nd , third or fourth defined infection	25
Oral	25

We should also note the trade-off between the criteria for an effective and efficient “pull” incentive. Fine tuning helps ensure private rewards are better reflective of social value. However, arguably it increases the element of discretion involved and the element of retrospective adjustment. Both of these reduce the effectiveness of the incentive, which to drive investment needs ex ante clarity on the size of the reward and how to get it. A number of these issues were extensively explored in the run up to the setting up of the Advanced Market Commitment for pneumococcal disease (Cernuchi et al. 2011).

6 OPTIONS TO RAISE THE FUNDING REQUIRED

There are several options proposed to raise the funding required in the O’Neill Report and in the GUARD Report.

The O’Neil Report discusses two different options. The first source is to use existing funding streams by reallocating a very small percentage of G20 countries’ existing healthcare spending. The cost is small relative to the healthcare budget of the G20 countries and could change significantly the budget allocated for tackling AMR. Another alternative would be to reallocate a fraction of global funding from international institutions to AMR. These international development institutions already provide substantial support in low and middle income countries for strengthening health systems. Supporting prevention and successful innovation on new medicines could be extremely valuable in those countries. Once again, the sums required are small relative to the overall budget of these institutions.

The second possibility is to use new funding streams. The O'Neill Report presents three options that could operate as complements to existing funding streams which are a tax on antibiotics, an antibiotic investment charge, and exchangeable vouchers.

The 2015 GUARD Report recommends three potential financing models. The first one is a contribution based on antibiotic sales. This proposal is similar to the antibiotic investment charge in O'Neill Report that is explained below. The second one is the profit-sharing mechanism associated with the GDF ("push" incentive) presented in Subsection 3.1.2, and with the build-in repayment mechanism of the GLR ("pull" incentive) presented in Subsection 3.2.2. The third one is a modified version of the priority review vouchers discussed in Subsection 4.1.

We explain and compare the options proposed below.

6.1 A TAX ON ANTIBIOTICS

Taxes are distortive, having different impacts depending on the market to which they are applied. However, in the case of antibiotics, where the aim is to use them more sparingly in humans and animals, the distortion a tax would generate might be socially optimal. Termed by economists a Pigou tax²¹ the objective (apart from raising money) would be to reduce unnecessary use which contributed to the build-up of AMR. The O'Neill Report suggests that taxing antibiotics for animal use would increase the cost of using them, discouraging unnecessary use. Revenues raised could be used in part to help farmers switch their production techniques to new ones that use lower levels of antibiotics. The O'Neill Report suggests that taxing human consumption might be less effective given that an increase in the final prices of all antibiotics would not probably change prescribing behaviour.

A tax on antibiotics in agriculture does seem a good way to raise money and, at the same time, to reduce the use of antibiotics (although to the extent that a tax is raising revenue it is not reducing use and vice versa). Hollis and Ahmed (2013) showed that approximately 80% of antibiotics in the United States are consumed in agriculture and aquaculture, and in most of the cases, they are used to speed up growth and increase the efficiency of digestion.

The alternative, outright prohibition of some uses of antibiotics, needs to be considered when there is uncertainty regarding the marginal cost and marginal benefit schedules associated with selecting the best tax rate to optimally reduce antibiotic use. However, forbidding the use of antibiotics for some purposes but not others is difficult to police. A tax on antibiotics is likely to be the more effective option. It would deter low-value applications of antibiotics leaving to the farmer the decision whether the antibiotic confers enough benefits to make it worth the higher price.

International replicability is another advantage of the tax on antibiotics (Hollis and Ahmed, 2014). Governments would be more motivated to collect revenues rather than banning or thinking about other alternatives to raise money to invest in AMR. A tax is simple to implement, easily understandable, and relatively easy to police – although high taxes could encourage a black market.

²¹ A Pigou, or Pigovian, tax is named after the economist Pigou who argued (in 1920) that a tax should be levied on a market activity that generated adverse impacts (negative externalities) on society that were not reflected in the market price. The tax should be set equal to the social cost of the negative externalities.

However, there are disadvantages with a tax. The first one is that it is not clear that the incidence of a tax is the desired one: the increment in costs will potentially end up increasing, respectively, the prices of food and the prices of medicines for human use. Both could particularly affect low and medium income households.

The demand of antibiotics for human use is likely to be less price sensitive than to the demand of farming products, which means that taxes will lead to higher prices in the former than in the latter. The O'Neill Report suggests that, for this reason, taxing human consumption might be less desirable than taxing agricultural consumption. Thus the use of a tax on antibiotics for agricultural use seems a good idea. On the other hand, it is unlikely to be politically feasible to tax the use of antibiotics for humans.

6.2 A SALES-BASED TAX

Both the O'Neill and GUARD reports are positive about the idea of taxing the pharmaceutical industry in order to raise funds to invest in R&D. This charge would be paid into a pooled fund to reward new product development.

The O'Neill Report proposes an antibiotic investment charge. The idea is to charge firms selling pharmaceutical and healthcare products a small fee for accessing the health market. They propose a funding scheme called 'pay or play' where all firms are eligible to be charged, but those who demonstrate that are already investing an amount in AMR R&D that is equal to, or larger than, the charge are exempted from paying it. The O'Neill Report does not propose any particular surcharge type (variable, fixed, or a combination thereof) or amount or percentage. Several media articles stated, however, that the surcharge proposed was of 0.25 percent of annual sales that would go to a pooled fund to support market rewards for rivals who successfully develop new treatments (Fourcade, 2016; Barber, 2016; Adams, 2016).

The 2015 GUARD Report also proposes a sales-based contribution but only based on antibiotic sales. A contribution of up to 5% of sales would fund antibiotics R&D. Notice that in the case of a company that only sells one antibiotic (at a uniform price), this proposal is equivalent to the tax on antibiotics presented above. Alternatively, the contribution could be limited to those companies that are not currently active in research and development of new antibiotics, in which case, this proposal is similar to the 'pay or play' proposal in the O'Neill Report.

We discuss below four problems we find with the sales-based tax.

The first issue is that it is not obvious why the pharmaceutical industry should be taxed in order to generate the R&D fund to tackle AMR. One rationale given – by O'Neill – is that the industry depends on antibiotics to work, for example, to enable people to take anticancer treatments that suppress the immune system, giving rise to a risk of infection. This logic however might take us to taxing oncologists, and indeed transplant surgeons given the need for immune suppression with organ transplantation. Moreover, there seems to be a lack of understanding of the difference between the incidence of a tax and who is sent the tax bill. If health system demand for drugs is relatively inelastic, and the economic rents associated with innovation are ultimately competed away through R&D and/or market competition, then the increase in costs represented by the tax will be passed on to payers via price increases.

Second, the proposal is likely to lead to inefficient or unnecessary investments. Pharmaceutical companies might decide to invest in AMR R&D just to avoid a surcharge

creating further social inefficiencies. As one commentator concluded: "All this will do is encourage all, rather than only the most talented in AMR, to spend money on anti-microbial research programs, preferably those that qualify for the tax exemption, but still give a relatively low-risk return on investment. It will drain intellectual resources from those companies that are better situated to truly invent new solutions in this space" (Schoonveld, 2016).

Third, this type of approach risks undermining the spirit of collaboration on a global basis. It labels the industry "the bad guys." The O'Neill Report (also in WHO, 2016) states that tackling AMR is absolutely essential, that it needs to be seen as the economic and security threat that it is, and this should be administered at a global level. Proposals of the type 'pay or play' "fails to recognise the need for a collaborative response which this long-term review has consistently identified. Putting the onus on any one group will not solve the problem and is not a sustainable solution" (Acha, cited in Boseley, 2016). The GUARD logic for a sales tax is to create a self-sustaining pot of money, but we find this logic flawed. If the core problem is low returns from new antibiotics it is hard to see how taxing the use of new antibiotics, which will reduce returns for new antibiotics, can help. The tax could be limited to old antibiotics. This would still have an impact on consumption but could assist stewardship.

Finally, the O'Neill Report says that the solutions to the lack of investment in AMR R&D should aim to increase the number and types of organisations and individuals undertaking research relevant to AMR, and reduce barriers to entry. In industries with high fixed costs, as is the case of the pharmaceutical industry, reducing revenues from operating in the market may jeopardise the survival of firms, particularly the smallest ones. Likewise, if the surcharge is fixed amount, it might increase the barriers to entry for new firms. These could be tackled via exemptions and allowances, but this will increase the complexity and reduce the revenue raising capability of the tax.

6.3 EXCHANGEABLE 'VOUCHERS'

These options were discussed in detail in Section 4. However, they were presented as an instrument to incentivise R&D and not as a way to raise the funding required. We focus here in this second aspect.

In the O'Neill Report, the main purpose of vouchers is to reward a successful antibiotic developer. The Report discusses two types of vouchers. The first one is the 'priority review voucher' (PRV discussed in Section 4.1), and the second one is a wild-card patent extension (TIPR discussed in Section 4.2).

The 2015 GUARD Report proposes the sale of transferable PRVs by the regulatory approval agencies such as the EMA in Europe or the FDA in the United States to create funds without placing a financial burden on governments or international organizations. This is similar to a proposal put forward in 2005 by Moran in the context of funding R&D for global health (PRPP, 2005). It is a pure funding source and not a pull incentive to develop new antibiotics.

The O'Neill Report is dismissive of the potential for market-based incentives such as PRVs and TIPR to work efficiently. We argue that these vouchers should *not* be excluded from the discussions. We are aware of potential pitfalls and inefficiencies, but "guard-rails" and other measures can be implemented to improve the efficiency of these incentives. Outterson and McDonnell (2016) explore a way forward for the latter, and we proposed several examples in Section 4.2 of how these guard rails might be put in place.

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APPENDIX 1: EXAMPLES OF “PUSH” MECHANISMS

United States of America

The National Institute for Allergies and Infectious Diseases (NIAID) is the largest US government funding body for AMR R&D from basic research through clinical development. It conducts and supports basic and applied research to understand better, treat, and ultimately prevent infectious, immunologic, and allergic diseases. Outterson et al. (2015) showed that annual NIH funding for AMR research has been approximately US\$350 million since 2010. In 2013, the NIAID provided a US\$62 million grant over 6.5 years to establish the Antibacterial Resistance Leadership Group (ARLG), whose aim is to develop, design, implement, and manage a clinical research agenda to increase knowledge of antibacterial resistance.²²

The Biomedical Advanced Research and Development Authority (BARDA) is a government organisation within the US Department of Human and Health Services responsible for procurement and development of countermeasures principally against bioterrorism, but also including chemical, nuclear and radiological threats. It established the Broad Spectrum Antimicrobials (BSA) Program in April 2010, providing funding and expert support throughout the stages of a drug’s clinical development. The BSA Program has set up flexible cost-sharing partnerships that are particularly targeted at the preclinical and clinical development barriers of antibacterial drugs.²³ The 2016 fiscal year budget is US\$182 million, over double the previous year’s budget of US\$79 million (Renwick et al., 2016).

NIAID and BARDA, together with four life science accelerators, have created the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator, or CARB-X, one of the world’s largest public-private partnerships. CARB-X launched in July 2016, leading US\$350 million to spur the preclinical development of new antibiotics, classified as “urgent” or “serious” threats,²⁴ and antimicrobial rapid diagnostics and vaccines.²⁵

The Food and Drug Administration (FDA) is responsible for the market authorization of antibiotics in the US and since 2012 has been implementing the GAIN (Generating Antibiotic Incentives Now) Act that include priority reviews and fast track as well as updated clinical trial guidance from the FDA. The GAIN Act provides Qualified Infectious Disease Product Designations (QIDPs), in other words “designated candidate antibiotics”, to be granted to unique molecules. These QIDPs allow FDA priority review of molecules as well as fast-track designation that aims to speed up the antibiotic development process. They also allow for a “pull measure” - an additional five years of market exclusivity for products with a QIDP.

²² More information available at <http://www.arlg.org/>.

²³ The partnership with GlaxoSmithKline has funding of US\$200 million over five years ending in 2018 and has already resulted in one candidate being progressed to Phase II clinical development and another lead clinical candidate that targets gram-negative bacteria being identified (Renwick et al., 2016).

²⁴ Classified by the CDC (2013).

²⁵ The NIAID and BARDA have been also incentivizing AMR R&D using pull incentives. In 2015/2016, NIH and BARDA co-sponsored the Antimicrobial Resistance Rapid, Point-of-Care Diagnostic Test Challenge. The challenge is a prize competition of up to US\$20 million for the delivery of a diagnostic tool that can quickly identify bacterial infections in a clinical setting.

European Union

The European Commission's Directorate-General for research and innovation (DG RTD) is one of the largest funding bodies supporting R&D in antibiotics and diagnostic tools. The funding comes from the programmes FP6, FP7 and Horizon 2020. The FP7 has provided €1.08 billion in EC funding for 147 AMR projects. In addition, Horizon 2020 has funded, between 2014 and 2016, 145 AMR projects with a budget of €316 million (Renwick et al., 2016).

The DG RTD also funds other numerous individual projects related to antibiotic development. Funded within FP7, 7 SME research projects on novel antibiotics, vaccines and alternative medicines were launched in 2013, with budgets of over €90 million.

The Innovative Medicines Initiative (IMI) is a public-private partnership between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA). It was launched in 2008 with the aim to support collaborative research projects and build networks of industrial and academic experts to boost pharmaceutical innovation in Europe. The IMI has a total budget of over €5 billion funded equally by the EC and EFPIA. It does not focus just on antimicrobials.

The IMI established in 2011 the New Drugs 4 Bad Bugs (ND4BB), a public-private collaborative partnership initiative. It consists of a series of programmes designed to directly address some of the scientific challenges associated with antibacterial drug discovery and development. There are seven core ND4BB projects; however, the largest project within ND4BB is COMBACTE, where academia and pharmaceutical companies have joined forces to boost the development of novel treatments. The COMBACTE project focuses on addressing the barriers to clinical development. A key outcome of the project will be high-quality, pan-European clinical trial network. We can note that another project, DRIVE-AB, is exploring options for a new economic model of antibiotic development & stewardship.

The 2011-2016 European Commission Action Plan against the rising threats from antimicrobial resistance (Hecht et al., 2009) expired in November 2016. The Commission issued an "evaluation" of this Action Plan in October (European Commission, 2016b). As stated therein, *"Regarding the R&D initiatives to develop new antimicrobials or alternative treatments, it is also too early to judge their effectiveness as R&D is a lengthy process and no final results are available yet"* (page 31). The new Action Plan (2017-2022) will be published in 2017 (European Commission, 2016a).

In 2014, the European Investment Bank (EIB) Group together with the EC under the programme Horizon 2020 founded the "InnovFin: EU Finance for innovators", with the aim to offer financing tools and advisory services for innovative enterprises of all sizes. In particular, in 2015 they launched the programme InnovFin Infectious Diseases (innovFin iD), aiming to stimulate investments in the development of innovative vaccines, drugs, medical and diagnostic devices and novel research infrastructures for infectious diseases. Through this programme, the EIB provides low-risk loans between €7.5 million and €75 million to incentivize R&D in the area of infectious diseases, including AMR R&D.

With the exception of DRIVE-AB, these EU initiatives are predominantly "push" initiatives.

Cooperative Agreement

Government agencies in the US and the EU recognised the critical need for new drugs to treat antimicrobial resistant infections and they created in 2009 the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR). The goal of TATFAR is improving cooperation between the US and the EU in three key areas: (1) appropriate therapeutic use of antimicrobial drugs in medical and veterinary communities, (2) prevention of healthcare and community-associated drug-resistant infections, and (3) strategies for improving the pipeline of new antimicrobial drugs.

TATFAR does not provide any direct incentives for AMR R&D. However, it brings together the critical government agencies involved in making decisions and in implementing incentives to AMR R&D. It has the aim to increase communication between US and EU research agencies to identify common scientific challenges that may represent opportunities for collaboration. It also facilitates collaboration between the European Medicines Agency (EMA) and the FDA to standardize an effective protocol for the market approval of high priority antibiotics, alternative medicines and rapid diagnostic tools. This can act as a “push” incentive by reducing the time and cost of developing new antibiotics.