Title Page

Title: Economic Incentives for Antimicrobial Therapy Development: Summary from the Transatlantic Task Force on Antimicrobial Resistance

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Summary Viewpoint: The decline of pharmaceutical companies investing in antimicrobial development along with the rise of antimicrobial resistance, has led to multiple reports by government groups and organizations identifying a global means to incentivize future antibiotic development.

Abstract

The Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR) in 2015 was tasked with exploring economic incentives for antibacterial drug development and providing recommendations for what incentives could have potential for global implementation. Due to the continual decline of pharmaceutical companies investing in new antibiotic development and the rise in antimicrobial resistance, there is an urgent need to financially stimulate the market and to encourage small, medium and large companies to reinvest in this space. This review paper provides a summary of the various models that have been proposed and highlights the positions posed by several policy documents, peer reviewed publications, Organization proposals, and government sponsored reviews. The findings align amongst all documents and support a form of a de-linkage model as well as a combination of push and pull incentive mechanisms. These concepts are further elaborated in this report with a summary conclusion on the areas of consensus.

Text

Antimicrobial Resistance (AMR) is an emerging and persistent public health threat. The United States Centers for Disease Control and Prevention (CDC) estimates that 2 million antibiotic resistant infections occur annually in the United States of America (USA), resulting in a projected $20-35B in additional health care costs and 23,000 deaths (CDC 2013). The European Union (EU) has similar numbers, estimating that there are ~25,000 deaths each year attributed to multidrug resistant infections, resulting in productivity loses and health care costs around € 1.5 billion (ECDC/EMEA 2009). Projections for the future suggest that the situation globally will worsen. The United Kingdom (UK) commissioned a review on antimicrobial resistance and projects a profound impact on global gross domestic product by 2050 if sound policies are not put in place to combat antimicrobial resistance (O'Neill 2015). As antibiotic use both clinically and in food production increases in developing countries, resistance rates are certain to raise in proportion in the absence of strong stewardship programs.

Over the last three decades, there has been a continual decrease in companies interested in developing new antimicrobial drugs. The reasons for this are multifactorial but are generally related to the limited commercial returns and lower profitability related to conservation policies that restrict antibacterial therapies, uncertainty of market lifetime due to diminishing efficacy from potential resistance, a competitive generic market, medical reimbursement that favor inexpensive generics, low costs of other marketed antimicrobials, and a brief treatment course for non-chronic conditions. In addition, global antibiotic resistance due to drug overuse directly impacts health care costs, adding to the economic problem.

The pharmaceutical industry evaluates the overall risk/benefit and profitability of pursuing development utilizing a metric termed net present value (NPV). Net present value is the sum of all investment costs in development and expected present value of future revenues, considering discounted rate of the time value of money of a given development program. For antibacterial drugs, it is estimated that the NPV in general is around ~-€ 38.15M (Sharma and Towse, 2011). This contrasts to neurological or musculoskeletal drugs, where NPVs range between $720M to in excess of $1.15B. If NPV remains low

for new antibacterial drugs, few companies will make investments in research and development. It has been suggested that a risk adjusted NPV of ~$200M may ensure pharmaceutical investment for new antibiotics (Sharma and Towse 2011).

These authors determined that there was a general consensus and support for economic incentives from various organizations' reports, that address creating a commercial market for antibiotics but also externalities that arise from antibiotic use, such as resistance and infection spread and other societal impacts. Two primary means of economic incentives have been presented, push incentives and pull incentives as well as hybrid models of both. *Push incentives* subsidize the overall development cost and *pull incentives* reward successful development, providing some guaranteed return on investment (ROI). Examples of push incentives include tax credits, direct funding of targeted research, or public-private partnerships to share costs. Examples of pull incentives include milestone or end-prize payments, patent buy-outs or payer license, advanced market commitments or volume guarantees, value-based or high reimbursement, as well as regulatory incentives encompassing tradable patent extensions, priority review vouchers, or extended market exclusivity. In addition, *de-linkage* business models have also been proposed, where companies are not paid on sales volumes, but other revenues by the funding entity. Currently companies strive for high sale volumes to improve their ROI, which can impact overuse and resistance rise, but the de-linkage model allows research and development investments for a successful product without requiring high sales. Many of these economic incentives may simultaneously address conservation.

The need for economic incentives to spur antimicrobial product development innovation and long term conservation is not new to the community as these concepts have been increasingly discussed over the last 3-4 years. Several high profile panels and working groups in both the EU and USA have made recommendations to drive policy reform and pharmaceutical interest (PCAST, 2014; EC action plan on AMR, 2011; Review on Antimicrobial Resistance, 2015; OECD, 2015; Chatham House Report, 2015; German Ministry of Health, 2015). In January 2016 more than 80 companies from 16 countries as part of the Pharmaceutical, Biotechnology and Diagnostics Industries published a declaration on combatting antimicrobial resistance (Declaration 2016). The Industry group acknowledged their commitment to the

mission and role in working in parallel with Governments. The declaration supports many of the initiatives described in this article including the O'Neill report, the G7 declaration and a number of Government and international organizations. Others have postulated that AMR will continue to be a critical component of future International discussions of health priorities, such as at G7, G20, UN General Assembly (UNGA) and other summits (Jackson, 2016).

Several coordinated groups have been specifically been established to improve the global response to AMR. The Trans-Atlantic Task Force on Antimicrobial Resistance (TATFAR), as one coordinated entity was established in 2009, to improve cooperation between the USA and EU, and recently with Canada and Norway in three key areas: 1) appropriate 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. In an October 2015 TATFAR meeting, it was agreed that the Task Force would identify economic incentives for antibacterial drug development and provide recommendations for further consideration.

This article summarizes these initial findings limited to identification of economic incentives as identified through several policy documents, peer reviewed publications, Organization proposals, and government sponsored reviews of various approaches to enhancing market incentives for antibiotic developers. The more prominent reports are specifically summarized to highlight commonalities in the recommendations. Ultimately TATFAR will make an informed recommendation on a package of incentives that could be considered for implementation but that is not included in the purpose of this article.

A SUMMARY OF DOCUMENTS PROPOSING ECONOMIC INCENTIVES

President's Council of Advisors on Science and Technology (PCAST) Report to the President on Combating Antibiotic Resistance (referred herein as PCAST report)*:* In September 2014, the US White House Obama Administration released its National Strategy to Combat Antibiotic Resistant Bacteria and a report from the PCAST (White House, 2014) on a United States government plan to address AMR. The

PCAST report estimated annual sales of $400-$600M over a 10 year period are required to provide an adequate ROI for an antibiotic developer. This includes factoring the $1.2B spent over an 11-year period by the pharmaceutical industry for total capitalized costs of new projects and the cost of failed projects. Significant increases in the amount of push incentives of direct federal funding and technical support were recommended as these could offer the following business advantages: 1) direct investment by developers will be substantially decreased, 2) upfront subsidization requires less funding than late stage development, and 3) innovative high-risk, high-reward approaches could be targeted that might not otherwise be pursued. Three pull incentives and a tax to support sustainability were also recommended, as paying developers at a late stage or end of product development will guarantee the developer an established pre-defined paid amount. Since the US Government does not control pricing in the private market, increasing the allowable reimbursement premium could provide a long term incentive. However, uncertainty in whether feasible increases could have enough of an impact to drive private sector investment was noted. Further, higher reimbursement could exacerbate overuse of antibiotics in the market.

Two general approaches for de-linkage were presented, *complete de-linkage* where developer would receive a one-time lump sum payment (est $1B/product) that serves as a patent buy out and reward and Federal government would be responsible for production, access and distribution and a *partial de-linkage*, where the developer would retain the ability to commercially sell the product but would receive a series of milestone-based payments (est $400M/product) based on implementation of select stewardship requirements, securing the availability of a number of annual doses, or capping sale level. Tailored incentives could focus on development of antibacterials for high areas of unmet medical need.

Other incentives were considered including tradable patent vouchers, where upon FDA approval of a given drug, the developer is issued a voucher to provide extension to patent life of another marketed drug, or could sell the voucher to another company, or extend patent life or market exclusivity of the antimicrobial. Vouchers are anticipated to be highly valued, due extended profitability of a drug, but this could delay the generic transition and have a higher total social cost compared to other incentives. Lastly

the establishment of an antibiotic usage fee was proposed that could sustain Federal funding for these incentives.

European Commission's Action plan against the rising threats from Antimicrobial Resistance (herein referred to as EU Plan)*:* In November 2011 the European Commission launched its Action plan on AMR which contains 12 actions related to research and development or marketing of antimicrobials for use in human health or veterinary sector, to be implemented over a 5 year period. This includes both push and pull incentives to promote development of antimicrobials, coordination of national research efforts, funding to stimulate academia and small and medium sized enterprises to work together to develop novel innovative solutions, and establishment of public-private collaborative research program for development of new antibiotics. The latter is an integral part of the Innovative Medicines Initiative (IMI), a joint EU and the European Pharmaceutical Industry Association (EFPIA) program that supports the discovery and development of antibiotics. The current EU Action Plan for AMR covering the period 2011-2015 and all 28 EU member States, will expire this year and therefore is being evaluated for its impact and areas where actions could be improved in the future.

"New Drugs for Bad Bugs" – "DRIVE AB" (Driving Reinvestment In Research and Development and responsible antibiotic use): The New Drugs for Bad Bugs (ND4BB) programme, was launched in May 2012 within the Innovative Medicines Initiative[1] (IMI), a Joint undertaking between the EU, represented by the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) to support the developments of new antibiotics. ND4BB includes seven projects: two of which address research and discovery and one addresses new economic models, through the DRIVE-AB program whose findings will be finalized in 2017. DRIVE-AB is comprised of 16 public and 7 private partners from 12 different countries and is focused on responsible antibiotic use and identifying how economic models

[1] http://www.imi.europa.eu/

can incentivize the discovery and development of new novel antibiotics. A work package will create, test, validate, and support implementation of new economic model.

Chatham House Report: Towards a New Global Business Model for Antibiotics Delinking Revenues from Sales: This report made several key recommendations for new business models that considered funding, Intellectual Property (IP), stewardship and regional and global implementation: 1) de-linkage models that guarantee an adequate ROI independent of sales volume, prioritizing access to new antibiotics and encouraging conservation 2) increased public financing of incentives (tax credits, contracts and prizes) across the entire antibiotic life cycle to target antibiotic development against microbes identified by a global threat assessment 3) a global threat assessment based on infection incidence, transmissibility, available treatments and societal impact, to identify threats arising from resistance and prioritize the classes/types of products needed. Global prioritization of antibiotics will recommended to be a fully transparent, independent process where the effectiveness of proposed incentives will need to be determined. Lastly, the report called for appointment of a Secretariat to foster global coordination and the development of a global incentive fund.

O'Neill Review on Antimicrobial Resistance: The UK government commissioned a review on antimicrobial resistance chaired by Lord Jim O'Neill, former Chief Economist of Goldman Sachs and now Secretary at the UK Ministry of Treasury. Multiple reports published in the series make recommendations on establishing or improving economic incentives for antibacterial drug development and preventing spread of antimicrobial resistance. A final package of actions will be provided in the Summer of 2016. The May 2015 report (Securing New Drugs for Future Generations: The Pipeline of Antibiotics) proposed interventions to balance commercial profitability with antimicrobial access and conservation, considering the balance with new drugs at the expense of off-patent drugs that could still be effective. For example, new drugs could be reserved for treatment until existing drugs have failed. A Global AMR Innovation Fund was recommended as a "push" incentive. De-linkage models were recommended as a means to

commercially sustain antibiotic development and encourage earlier investments. A proposed global buyer, representing a multitude of coordinated nation states, could purchase the global sales rights (est $2-3B USD) to new antibiotics and manage the supply and distribution internationally, controlling stewardship and use and provide access in developing Nations. The developer could not market the new drug, but would be reimbursed an adequate ROI. However, it was noted that there are risks in uncertainty of establishing the buy-out price (with potential to over-pay for rights) or projecting resistance to existing drugs. A coalition of countries will need to be willing to contribute to a global buyer methodology and accept the risks with controlling supply. A hybrid de-linkage model proposed is favored due to less coordination and funding, as it would rely on a single global funding body ($1-1.3B/product) but companies would retain the ability to sell the drug in the market and receive payments to ensure an adequate ROI. Payments could be linked to stewardship and global access goals (price setting in specific countries) to address market-based rewards and meeting public health.

The report also recommends the establishment of a short term multi-targeted global innovation fund for antibiotic research and development (~$2B USD over 5 years), acknowledging that funding for push incentives are needed to effectively populate the pipeline of novel antibacterial clinical candidates. With these fixed market incentives and private capital flow back, then the innovation fund should be sufficient to re-invigorate research for the long term. The global innovation fund should address: 1) reevaluating old libraries of antibiotics and novel combinations that may be efficacious as "resistance breakers", 2) a bold approach to AMR (directed funding for novel approaches) that looks across and beyond established avenues of research, 3) improvement and promotion of scientific understanding of drug resistance, and 4) diagnostic tools for AMR.

A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics (Renwick et al, 2015). In 2015, researchers from the London School of Economics published a comprehensive review that classifies and assesses 47 specific economics incentives for antibacterial drug development proposed in the literature. This includes push, outcome based pull and Lego-regulatory pull

incentives, a type of pull incentive that indirectly facilitates a higher ROI through government policy. Push incentives that require less funding, can align product development with public health priorities and translate research into later stage development, but risk support of projects that may later fail in development, may reduce financial pressures to economize or developers misrepresenting the project progress and goals in order to receive funding. Pull Incentives put the developer at greater risk if successful products are required, but may instill efficiencies simultaneously. However, developers may be deterred due to financial risk and uncertainty or small to medium size enterprises may lack the resources to transition candidate products to late stage development. Defining criteria linked to reward that is not overly prescriptive or too broad, and determining the appropriate size of payment are also noted challenges. Appropriate funding will need to be secured and require a government(s) that is committed for the long term goal. Lego-regulatory pull incentives indirectly affect the ROI either through alterations in government policy or higher reimbursement, based on factors such as market exclusivity, but only reward successful research. This eliminates uncertainty with determining the appropriate financial reward size, the recipient antibiotics, and whether governments can sustain it. However there is still financial risk for the developer and smaller companies with limited resources to bring the antibiotic to market and this may weaken market competition (generic drug developers) and innovation (less willing to develop a antibiotic if threatened to infringe on the exclusive market).

The authors conclude that no individual incentive type provides a comprehensive solution to address the market failure for new antibacterial drugs and instead recommend a combination of incentives or hybrid strategy that balances the characteristics of the various incentives. However the combined incentives need to 1) improve the overall NPV for new antibiotic projects, 2) enable greater participation of small and medium sized enterprises (SMEs), 3) encourage participation of large pharmaceutical companies, and 4) facilitate cooperation and synergy across the antibiotic market. In addition an incentives package could promote antibiotic stewardship and global access. A market-based framework could select the incentive strategies that align with the four criteria and recommends various incentive combinations to include: 1) broad spectrum market incentives that meet all four market criteria, 2) participation-focused

incentives that improve NPV and entice SMEs and large pharmaceutical companies to invest in research and development but may not facilitate cooperation and synergy, 3) collaboration and synergy-focused incentives, 4) SME-focused incentives that improve NPV but may not facilitate cooperation and synergy, 5) Large-cap focused incentives for large pharmaceutical companies that improve NPV but may not facilitate cooperation and synergy, and 6) weak market incentives that meet only one of the four market criteria.

De-linkage models are favored because it 1) provides developers with a definitive ROI, 2) removes the motivation for developers to market and oversell their antibiotic, and 3) allows access to antibiotics in patients who need them. However, transferring IP to the public domain may not be supported by pharmaceutical companies. The ideal incentive package would include incentives that facilitate cooperation and synergy throughout the market; one or two research and development linked push incentives and a large pull incentive rewarding successful development. The strategy will need to be deemed feasible within a given Nation's given political priorities, regulatory requirements, industry demands and financial needs. The size and timing of the incentive, Governance, International coordination and IP will also need to be considered. The ideal incentive package would address both market failure and the public health concerns related to access and conservation. However, they suggest first developing a single incentive package that addresses market failures and subsequently enhance the package to address public health objectives with transition to more complex international business models.

Boston Consulting Groups' Breaking through the Wall: Enhancing Research and Development of Antibiotics in Science and Industry The German Federal Ministry of Health commissioned a report by an advisory consortium, led by the Boston Consulting Group, on areas where research and development of new antimicrobials could be incentivized. Five barriers to development were identified: 1) A "discovery void" in basic research, 2) a "valley of death" in preclinical development, 3) high cost and difficult patient recruitment in clinical development, 4) insufficient alignment of regulatory requirements between regulatory agencies, and 5) low market attractiveness in commercialization.

As a solution, ten "levers" were recommended to be implemented in combination to stimulate research and development and address public health needs globally: 1) development of global target product profiles (TPPs) (updated to address resistance) to guide research towards pathogens of greatest unmet medical need, 2) development of a Global Antibiotic Research Fund to support basic research at academic institutions and small to medium sized enterprises, aligning to the global TPPs, such as advancing the compounds against gram negative bacteria, development of point of care diagnostics, and investment in high-risk, high-reward approaches for innovations, 3) establishment of a global antibiotics research prize to increase the visibility of antibacterial research and potentially create a platform for information exchange amongst researchers, 4) establishment of an antibiotics research and development database to allow researchers to identify promising areas for research and avoid duplication. 5) establish a global antibiotics expert network to support ongoing research and development projects. 6) establish partnerships to support financially and with subject matter experts the clinical development of new antimicrobial therapies, specifically targeting small and medium sized enterprises who often struggle to raise adequate funding for late stage clinical development 7) a global clinical trial platform or network that would connect hospitals, developers and existing clinical networks, to aid in patient enrollment and clinical trial execution 8) global alignment of regulatory processes to streamline multiple development programs, reducing cost and time to market 9) a market entry reward (est $1B USD) prioritized for innovative antibiotics towards a defined TPP, which would de-link profitability from sales volume. In this partial de-linkage model, the company would retain control of the IP and commercialization of the product but has to pay a share of its profits from the sale of the drug back to the sponsor of the payment, that could be utilized to replenish the fund. Profit sharing would decrease the incentive to sell the antibiotic, thus increasing conservation 10) increased reimbursement for innovative antibiotics that align to TPPs in the in-patient setting.

In order for implementation to be effective it was recommended that a global collaboration platform, funded from participating states, be established to act as an innovator leader, implementing incentive structures and coordinator and advisor to researchers and pharmaceutical developers.

The Organisation for Economic Co-operation and Development (OECD) report: Antimicrobial Resistance in G7 Countries and Beyond: Economic Issues, Policies and Options for Action OECD assembled a report for the G7 ministers of Health meeting in 2015 under the German Presidency, highlighting a cross-country comparison for antimicrobial polices and measures already established, including specific polices to address antibiotic stewardship and encourage development of new antibiotics that have occured nationally. Innovative approaches including de-linkage models, were proposed to stimulate research and development. A hybrid approach consisting of both push and pull incentives to support development along the entire development path was favored. Push interventions could encourage greater small and medium enterprise participation, would be more inexpensive than downstream incentives and also reduce risk by potentially seeding numerous earlier products, but are dependent on transparency of the developer. Pull incentives could reduce the risk to the sponsor and incentivize finished product, although establishing reward size and criteria may be challenging.

Key recommended policies include 1) global collaborative research platform to foster innovation and research and development, 2) push incentives (milestone prizes and grants) to encourage participation of small and medium enterprises 3) pull economic incentives with de-linking components to incentivize completion of development (e.g. patent buyouts), and 4) funding of clinical trials and a global approval process. These would all require significant investment. OECD posited that it could provide a forum for governments to discuss and coordinate these economic strategies against AMR.

World Health Organization and Drugs for Neglected Diseases initiative: Investing in the Development of New Antibiotics and their Conservation As part of the Global Action Plan on Antimicrobial Resistance (GAP-AMR) mandate, the World Health Organization (WHO) and the Drugs for Neglected Diseases Initiative organized a technical consultation in November 2015 to discuss a proposal for a global antibiotics research and development partnership to promote access to new antibiotics, addressing antimicrobial resistance and promoting responsible conservation while ensuring equitable access. A complete business plan report will be available this year, 2016. A critical distinction amongst other incentives is that the partnership will not be a funding organization but will assist in implantation and should work with

developing and developed countries, including pharmaceutical and biotechnology companies, academia, and health authorizes and focus on product development in identifying priorities, complement and collaborate other organizations initiatives and pharmaceutical companies, generic and biotechnology companies, and diagnostic developers, define specific TPPs, define and launch short and mid- term projects for antibiotic treatment solution while also exploring specific long term projects that may be too risky for pharmaceutical partners and investors, collaborate with WHO on conservation, and develop an appropriate governance model.

BEAM Alliance Position Paper: Key Actions to Reinvigorate Investment and R&D in the antibacterial field now The BEAM Alliance (Biotechs of Europe innovating in Anti-Microbial Resistance) was founded with a commitment to "improve the regulatory, investment, and commercial environments in Europe for research, development, approval and market viability of new products combating antimicrobial resistance" and is currently composed of 40 small and medium pharmaceutical companies from 11 EU countries. Their goal is to develop innovative antimicrobial resistance products as well as propose policies and initiatives to stimulate innovation and address some of the challenges in antibiotic development. A position paper published September 2015 summarizes key economic incentive areas to reinvigorate antibiotic research across Europe. As short term incentives, 1) A specific dedicated fund (non-diluted grants, $5-10 Million Euros per project) to support small and medium biopharmas from discovery to clinical (Phase II) proof of concept. Individual grants would be awarded with no requirement for public-private partnerships. 2) Market Incentives to increase ROI such as tax breaks, extended market exclusivity, and revised pricing models to reflect true value to society. A "de-linkage" model is proposed but it is acknowledged that it may only be appropriate for last resort antibiotics 3) Accelerated and simplified regulatory pathways, including automatic fast track status, clarification of the regulatory framework for novel approaches, centralization of indications and procedures, simplification (adaptive pathways, shorter development) and harmonization of the regulatory expectations with other drug regulatory authorities. A long term strategy is also proposed to enable increased research and development coordination and re-evaluation of stakeholder

assessment and value of the societal benefit of antimicrobial products. In addition public centers could provide antibacterial clinical experts to monitor epidemiology of resistance and assist companies. Lastly methods to assist small and medium biotech pharma with commercialization to prevent them from needing to out-license their assets would be developed.

SUMMARY AND POLICY ANALYSIS

From the documents analyzed in this document and other reports published (Carlet and Le Croc, 2015; Industry Declaration, 2016, etc) there are several common elements (Table 1) supporting the need for economic incentives in order to combat AMR. Of those reports that specifically analyzed various types of economic incentives, the de-linkage models were recommended unanimously. While there exist subtle variations on the mechanisms of how de-linkage models would be administered, the general principle of using a substantial payment that rewards successful research and development as a pull incentive is conserved. In addition, most were in an agreement that a combination of push and pull incentives coordinated at a global level will be necessary.

PUSH INCENTIVES

Push Incentives were unanimously proposed to help fund research early in the development pipeline to diversify the portfolio, spread risk, incentivize early participation by industry, direct funding to specific pathogens of interest (as may be defined by a global consortium) and may assist in targeting innovative approaches and specific TPPs. However risk of failure rate will be high, there may be reduced transparency by developers, the incentives may not address the core bottleneck of research and development processes and may not guarantee transition of projects to advanced development, and there will be a long lead time to reap benefit of investment. In addition, availability and source of funding would need to be determined if it is to be utilized in global interests. Several reports supported use of tax credits such as

Carlet and La Crox (2015), Chatham House and Beam Alliance. However tax credits could only be administered by an individual Nation, i.e. the "host" of the company, and therefore would not be part of the global responsibility. These tax credits may not just be limited to incentivizing early research (Push) but could also be utilized for late stage development (See Pull Incentives section). For early research, this may be particularly attractive to small and medium sized companies (Carlet and La Crox,2015)

Successful push incentives include the US funding of antimicrobial programs under BARDA's Advanced Research and Development (ARD) and in a hybrid program, Project BioShield. Under ARD funding, pharmaceutical companies are provided with direct funding to support development of target drugs. There is however inherent risk due to potential failure of the projects unforeseen in development but this allows incentive for drug development without a defined market, specifically for bioterrorism threat pathogens. Project BioShield represents a hybrid approach, in that a guaranteed market is defined by US stockpiling needs but the stakeholder needs to determine whether the proposed purchase cost and delivery plan by the pharmaceutical company for a defined number of treatment courses, is appropriate. Although, this approach has not yet been implemented for antimicrobial development at BARDA. In the US, more open funding has been implemented through the National Institutes of Health, National institute for Allergy and Infectious Diseases (NIH/NIAID) since 2008 for early development projects related to antimicrobial resistance, including funding for basic research, targeted research areas and translational research to assist with preparing the projects for pharmaceutical development. In Europe this type of research has been funded since 1999 via the EU framework programs for research and innovation including the current programme Horizon 2020. In addition, the IMI launched ND4BB to specifically address challenges with antimicrobial funding. Funding is aligned with various projects including targeted focus on early discovery and development. Where there are partnerships for drug development, there may be a joint risk held by the stakeholder and developer if a project fails, but the stakeholder can be more involved and assist in defining goals for the program. These push incentives can be attractive to SMEs because of their limited resources and thus this mechanism can support innovative projects.

Another novel push incentive in Europe is InnovFin-Infectious Diseases that was launched in 2015. This is a joint initiative by the European Investment Bank and the European Commission that can provide a broad range of products ranging from standard debt instruments to risk sharing instruments. Loans between EUR 7.5M and EUR 75M are provided to innovative players active in developing vaccines, drugs, medical and diagnostic devices, and research infrastructures for combatting infectious diseases. Financing is aimed at projects that have passed the pre-clinical stage and for which clinical validation is needed for further development.

At an international level, push incentives have been implemented by the Joint Programming Initiative on Antimicrobial resistance (JPIAMR). This initiative was established to pool fragmented national research efforts in order to make better use of public research and development resources and to tackle the common challenges posed by AMR more effectively. JPIAMR member states agree, on a voluntary basis and in a partnership approach, on a common Strategic Research Agenda, which is implemented jointly to include translational research.

PULL INCENTIVES

Pull incentives were also uniformly proposed to enable direct support for successful products. With these mechanisms however there are aspects that require cautious consideration. Advantages include reward for only successful antibiotics, funding for specific targeted research and development, provide pharmaceutical companies flexibility with development with regard to projected revenue by reimbursing the developer, and may also impact conservation. However the funding provided may be too late for developers and therefore will not incentivize early research, it is difficult to ascertain optimal reward pricing, all risk will remain with developer and licensing and IP requirements may present challenges.

For example, tradable vouchers, while highly supported by industry, may not improve further early investment in antibiotics and the future increase in profitability through patent extension is thought to be

smaller than costs incurred by society for higher drug prices in other therapeutic areas (O'Neill 2015). Subsidizing one antibiotic development at the expense of another drug indication is likely to significantly impact patient access and is predicted to have potential secondary disruptive effects that are not proportional. Greater numbers of patients may receive the drug for which the patent was extended versus the new antibiotic that will be held in reserve for the treatment of resistant infections. Further, the creation of a new market with tradable voucher, may have unforeseen consequences and therefore the value of an individual voucher is unpredictable. Additionally extensions of market exclusivity may not incentivize earlier stages of development and as the Chatham house report states, additional sales may not be generated due to loss of antibiotic effectiveness and market competition which could drive excessive promotion of the drug which may lead to overuse. A less indirect use of such vouchers would be for government to auction them out thereby using this as a revenue generating mechanism. However, taxation on antibiotic use, could be a direct and economically efficient approach. Another challenge with vouchers is that they can only be implemented by an individual country, since it requires legislative changes in each jurisdiction.

Higher reimbursement/pricing is attractive from an industry perspective but there may be unknown secondary disruptive effects and it still may not be sufficient to address an adequate ROI. Higher pricing could potentially negatively impact patient access in that cheaper, less effective drugs may be utilized in certain markets and may not be tolerated in all markets equally. The US currently already subsidizes the global pharmaceutical market as a function of its health care system. Unless increased pricing was adopted globally, higher pricing will be an incentive which disproportionately would be funded by the US healthcare system. High prices in a volume based market model would also encourage overuse and thereby be counter to the public health defined needs.

DE-LINKAGE MODELS

Pull incentives relying on de-linkage may have the lowest probability of secondary disruptive effects but will require sustained funding with burden sharing and cross-country collaboration political support in order

to provider developers confidence in its reliability. The Pharmaceutical, Biotechnology and Diagnostics Industries Declaration was also supportive of such a measure that would reduce the link for financial revenue gain and use of antibiotics and Jackson (2016) highlighted de-linkage business models within the US as one of the recommendations for combatting antimicrobial resistance in the future. The characteristics of a particular de-linkage model (full, partial or hybrid) for implementation during a specific stage of development need to be clarified. Under a full de-linkage model, payment is provided at the point of regulatory approval, but could also be divided into smaller milestone rewards. The company continues to produce the drug, but agrees not to market or endorse the use of the product in any way. Global governance will be needed to coordinate access and conservation of the antibiotic. Under a partial or hybrid de-linkage model, companies would continue to be allowed to sell their product. There would be a series of payments administered over several years, e.g. 3-5 years and could cap the total amount of product that could be sold annually. Overall there should be a reduced need for marketing promotion from the developers.

Both full and partial/hybrid de-linkage models require significant amounts of funding to be impactful and sustainable. With full de-linkage, the company would not promote, market, or sell their antibiotic thus directly ensuring a level of conservation. However, if the payment was given at the time of approval, it may not be possible to differentiate its effectiveness from the current standard of care since the drug would likely be approved based upon non-inferiority data. The public sector would then need to invest in post-marketing comparative effectiveness studies. In contrast, under a partial de-linkage model one could structure the payments over time and could attach them to milestones that had to be achieved to receive the payment. This could include descriptive efficacy studies that inform clinical use against resistant pathogens, complying with restriction on marketing or promotion, and agreeing to the total amount of drug that could be sold or produced annually. Partial de-linkage payments could be more politically and financially feasible to implement.

However, other incentives that reward all antibiotic developers may be needed since, since de-linkage may just be targeted incentives. For example, a refundable and transferrable tax credit that covers

50% of the Phase 2/3 clinical development costs could be utilized. This tax credit, which would be paid off at regulatory approval, would serve as an effective pull incentive that would not require a large amount of funding to implement.

CONSERVATION

Many of the above push and pull incentives will have a direct or indirect impact on antibiotic conservation and reducing spread of resistance. The BEAM alliance specifically wants regulators and stakeholders to consider strategies, both novel therapeutic development and economic incentives, that address the threat of resistance and societal impact. In addition the Pharmaceutical, Biotechnology and Diagnostics Industries support enhancing conservation with action of appropriate stewardship programs, and removing financial incentives for prescribers of antibiotics in order to prevent misuse. The full de-linkage model proposed by many groups, would also control the amount of antibiotic that enters the market ensuring elements of conservation and stewardship as would the hybrid de-linkage model in the O'Neill report where lump sum payments could be linked to appropriate stewardship. Milestone payments in these models could also be directly tied to stewardship, such as agreeing not to market the antibiotic or conducting an educational campaign for clinicians to inform appropriate use. One alternative example is taxation for antimicrobial use, with a taxation fee that varies based on the antibiotic being utilized but a tax rate that is equal to the societal cost of the antimicrobials would need to be determined and it could dilute policy control over specific targeted priorities. The PCAST report specifically proposed a tax on antibiotic usage as a means of generating revenue to support sustainability of the incentive packages but this could further increase health care costs and limit patient access. If structured appropriately, however, and targeted only toward generic antibiotics used in the outpatient setting, it could limit inappropriate use and generate significant revenue to support the sustainability of the incentives. Coordinated decisions within multiple Nations would be needed to ease implementation.

GLOBAL COORDINATION

Many reports highlight the need for global coordination of funding or a pooled fund that could be utilized to support the various incentive packages. This is also supported by the Pharmaceutical, Biotechnology and Diagnostics Industries for a global coordinated action of stewardship and commercialization models. Sustainment will be achievable through policy and leadership, defined priorities, financing and working across realized and perceived international boundaries for effective coordination and cooperation (Jackson, 2016). The Chatham House Report recommends the establishment of a secretariat to administer a global de-linkage model and coordinate expenditures on behalf of the participating countries. The O'Neill Review recommended a global innovation fund as well as a global purchaser. Such a governance group would need to possess product development expertise, prioritize research and development initiatives, and manage development programs with strong go/no go decision points is needed. The level of coordination amongst all countries to make a global fund function effectively may be challenging to achieve. It may be more prudent to initiate de-linkage/funding models with a smaller subset of countries/markets initially to ensure incentives are established in the near term. The Chatham House Report strongly recommended the development of a global threat assessment to prioritize which antibiotics would qualify for potential pull incentives or de-linkage approaches. They contend that the process needs to involve global stakeholders and needs to be completely transparent to the public to allow for coordinated investment and alignment of incentives that could generate maximal returns towards public health goals. The OECD Report promotes establishment of a global collaborative platform to drive innovation, host an integrated data repository and address societal needs and concerns. The Boston Consulting Group supported Global coordination through antibiotics trials, alignment of regulatory approvals and development of global target profiles. It is critical to note that if a global governing body is established to assist in meeting many of these objectives, it is unclear what organization, whether existing or otherwise, could assume the role of a global purchaser. In addition, alignment of Regulatory incentives across the different regulatory authorities may be challenging.

Antimicrobial resistance requires a global response and a broad global organizational effort to propose and implement incentive plans. Although successfully demonstrated with funding alliances for

other global infectious diseases (TB, malaria, HIV/AIDS, etc.), there may be specific regulatory, political or financial constraints that may limit implementation of specific incentive approaches for antimicrobials. Global coordination will require further discussion and coordination before implementation.

CONCLUSION

Overall, there is consensus from the reports examined, that a constellation of economic incentives are needed to support all phases of antibacterial drug development. Based on the strengths and weaknesses with push, pull, de-linkage and conservation incentives, a hybrid approach or a mixture of various incentives may be necessary to broadly address antibiotic research and development. The package of incentives should be applicable to a myriad of company types, large pharmaceutical and small and medium enterprises as well as innovation at academic levels. A mixture of push incentives, addressing both early stage and advanced research and development may be needed. It is thought that payments earlier in product life-cycle could have a stronger impact on the NPV, but risk of failure is higher. These could be administered through grants, contracts, product development partnerships, and/or tax credits. In addition, in order to balance the antibiotic development cycle, an internationally coordinated pull incentive, such as a form of a de-linkage model may be needed where successful antibiotic development is prioritized to address unmet medical needs and subsequently rewarded to ensure an adequate ROI. A reliable ROI is important for antibiotic developers. The recent declaration by the pharmaceutical industry is additional proof of a growing level of consensus. Refinement is still needed to determine which incentive and associated characteristics will work best. How these incentives will be adapted and implemented will need further engagement by different governments (EU, individual countries) to assess feasibility. Although there is general consensus on the need for future coordination at the global level on priorities and coordination of research and development activities, initial broad country alignment within these key incentive areas will improve the effectiveness and complementarity of funding, hopefully resulting in greater global impacts towards public health and conservation.

AREAS OF CONSENSUS:

1) A global AMR threat assessment process to aid in coordinating data on that rate of rise of resistance pathogens and the public health threat, effectiveness of existing antibiotics and prioritizing which new antibacterial drugs receive a particular set of incentives. In addition, the potential impact of new antibacterial drug on impacting resistance or altering effectiveness of previously marketed and efficacious drugs should be determined. This process should be transparent and the assessment updated at regular intervals to account for changes in the landscape or resistant pathogens. The experience of the United States CDC and the WHO in conducting these threat assessments should be leveraged.

2) A constellation of economic incentives comprised of both push and pull mechanisms, addressing all phases of antibacterial drug development to effectively incentivize industry.

3) Models that fully or partially de-link profit from volume sold should be developed, implemented and evaluated. Initially, these should be designed and implemented by a core group of countries capable of obtaining the funding. Over time, models that account for conservation and access should be developed and could be governed by a collective mechanism.

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Tables

Report	Push Incentives	Pull Incentives	De-linkage	Global Threat Assessment	Global Funder
BEAM Alliance	Yes	Yes	Yes	No	Yes
BCG report for G7	Yes	Yes	Yes	Yes	Yes
Carlet and LeCoz 2015	Yes	Yes	No	No	Yes
Chatham House Report	Yes	Yes	Yes	Yes	Yes
DNDi GARD PDP	Yes	Yes	Yes	No	Yes
EU Plan 2011-2015	Yes	Yes	No	No	No
IMI ND4BB: DRIVE AB	Yes	Yes	Yes	Yes	Yes
Jackson CSIS 2016	Yes	Yes	Yes	No	Maybe
OECD	Yes	Yes	Yes	Yes	Yes
O'Neill Review	Yes	Yes	Yes	No	Yes
PCAST Working Group	Yes	Yes	Yes	No	No
Renwick et al., 2015	Yes	Yes	Yes	No	No

Table 1. Summary of the incentives and actions recommended to improve antibacterial drug research and development