Chatham House Report

Edited by Charles Clift, Unni Gopinathan, Chantal Morel, Kevin Outterson, John-Arne Røttingen and Anthony So

Towards a New Global Business Model for Antibiotics

Delinking Revenues from Sales

Report from the Chatham House Working Group on New Antibiotic Business Models

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October 2015

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Charity Registration No. 208223

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ISBN 978 1 78413 057 2

A catalogue record for this title is available from the British Library.

Typeset by Soapbox, www.soapbox.co.uk

Printed and bound in Great Britain

This publication is printed on recycled paper.

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Cover image © Yuri Smityuk/ITAR-TASS Photo/Corbis

High-level complex of physiologically active antibiotic substance extracted from blastema at the Arctic Innovation Center (AIC) of Ammosov, North-Eastern Federal University (NEFU) in Yakutsk.

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Anthony So is Professor of the Practice of Public Policy and Global Health and Director of the Program on Global Health and Technology Access at Duke University's Sanford School of Public Policy and the Duke Global Health Institute. He also oversees the Strategic Policy program of ReAct–Action on Antibiotic Resistance, served on the Lancet Infectious Diseases Commission on Antibiotic Resistance and the Institute of Medicine's Committee on Accelerating Rare Disease Research and Orphan Product Development, chaired a WHO expert working group on fostering innovation to combat antimicrobial resistance, and was part of the Antibiotic Resistance Working Group of the US President's Council of Advisors in Science and Technology. Trained in internal medicine at the Hospital of the University of Pennsylvania, he earned his MPA as a Woodrow Wilson Scholar at Princeton University, completed his fellowship as a Robert Wood Johnson Clinical Scholar at UCSF/Stanford, and studies antibiotic innovation as a current recipient of the Robert Wood Johnson Investigator Award in Health Policy Research.

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The working group consisted of the following members: James Anderson, Manica Balasegaram, Helen Boucher, Dan Burgess, Kalipso Chalkidou, Greg Daniel, David Findlay, Ed Godber, Marie-Paule Kieny, John Rex, Ursula Theuretzbacher, Patrick Vink.

In addition the following were observers who played a less direct part in the process: Christine Ardal, Claire Boville, Meindert Boysen, Marco Cavaleri, Greg Daniel, Nils Daulaire, Karen Grosser, Lauri Hicks, Aidan Hollis, Alison Holmes, Benedikt Huttner, Aaron Kesselheim, Joseph Larsen, James Love, Karolina Maciag, John Powers, Tim Reed, Steve Solomon, Ellen 't Hoen, A.M. Viens, Kathleen Young, Anna Zorzet.

Acknowledgments

Many people contributed to this report, beginning with the participants in the roundtable organized on 2 October 2013 by Chatham House on 'Aligning Incentives for Antibiotic Development and Use with Public Health Needs', from which the idea of a working group emerged. Thanks are due to those who contributed as working group members or observers; to the team of Chatham House editors, particularly Margaret May; and to the Hôpitaux Universitaires de Genève (HUG) for providing a room for the final meeting of the working group. Valuable research assistance was provided by Katrina Geddes.

Glossary

Beta-lactam antibiotics
A group of antibiotics that all have a beta-lactam ring as part of their core structure. In most cases antibacterial activity occurs through the inhibition of bacterial cell wall synthesis. Penicillin, cephalosporins and carbapenems are among the principal β-lactam antibiotics.

Candida
A yeast, and the most common cause of fungal infections worldwide.

Carbapenems
A class of β-lactam antibiotics which differ in chemical structure from others such as penicillins and cephalosporins. They exercise broader antibacterial activity, including against pathogens that are resistant to penicillins and cephalosporins.

Carbapenem-resistant Enterobacteriaceae (CRE)
A group of emerging Gram-negative bacteria which carry the gene for the enzyme carbapenem-hydrolyzing β lactamase (also known as carbapenemase), and are therefore resistant to carbapenems. The two most important types of carbapenemases, which may be carried by various Gram-β negative pathogens, are Klebsiella pneumonia carbapenemase (KPC) and New Delhi metallo-beta-lactamase (NDM-1).

Cephalosporins
A group of β-lactam antibiotics, commonly classified into four generations according to their antibacterial spectrum. Each generation has broader Gram-negative antibacterial activity than preceding generations. Recently, the antibiotic ceftaroline has been recognized as a fifth-generation cephalosporin, with antibacterial activity against methicillin-resistant *Staphylococcus aureus*.

Drug-resistant tuberculosis (TB)
This refers to isolates of *Mycobacterium tuberculosis* that is resistant to one of the first-line anti-TB drugs: isoniazid, rifampicin, pyrazinamide, ethambutol or streptomycin. Multi-drug-resistant TB (MDR TB) refers to strains resistant to at least isoniazid and rifampicin (the two most potent TB drugs). Extensively drug-resistant TB (XDR TB) is resistant to most potent TB drugs. Totally drug-resistant tuberculosis (TDR-TB) is a generic term for strains that are resistant to all locally tested TB medications.

Enterobacteriaceae
A large family of Gram-negative bacteria that include pathogens such as *Salmonella*, *E. coli*, *Klebsiella*, *Shigella* and *Proteus*.

Fluconazole
A common antifungal medication for the treatment of yeast infections such as Candida.

Gram-negative bacteria
A group of bacteria that do not retain the crystal violet stain used in Gram-staining, owing to the peptidoglycan layer in their walls being too thin to retain the stain when decolorized with an alcohol wash. Application of a counterstain, such as safranin, gives Gram-negative bacteria a red or pink colour, visible through microscopy.

Gram-positive bacteria
Bacteria with a peptidoglycan layer in the bacterial cell wall thick enough to retain the violet stain during Gram-staining after the alcohol wash step, and microscopically visible as purple-coloured. Examples of Gram-positive bacteria are the cocci *Streptococcus* and *Staphylococcus*, and bacilli such as *Clostridium* and *Listeria*.

Gram-staining
A staining method enabling the microscopic differentiation of bacterial species by colorization of peptidoglycan, a polymer of sugars and amino acids that is part of the foundation of bacterial cell walls.

Methicillin-resistant *Staphylococcus aureus* (MRSA)
Strains of *Staphylococcus aureus* that are resistant to traditional β-lactam antibiotics. The name is derived from the strains first being identified to be resistant to methicillin, a narrow-spectrum β-lactam antibiotic previously used to treat infections caused by Gram-positive bacteria.

Milestone and end-stage prizes
Milestone prizes are pull incentives that reward innovation for incremental progress along the R&D pipeline (such as successful completion of a Phase 2 trial), while end-stage prizes are awarded once the product has been granted marketing approval.

Neisseria gonorrhoeae
A Gram-negative coccus responsible for one of the most common sexually transmitted infections. It is becoming more difficult to treat owing to increasing levels of antibiotic resistance worldwide.

Off-label use
This occurs when clinicians prescribe drugs for indications other than those that were approved by the regulatory authority when giving marketing approval.

Orphan drugs
A therapeutic agent may be designated an 'orphan drug' when it is developed to treat a rare medical condition. The designation qualifies for incentives for R&D under orphan drug acts, such as extended exclusivity periods or tax credits. The additional incentives are meant to permit recovery of invested capital which otherwise would not have been possible given the low number of patients suffering from the disease.

Pharmacovigilance
The science and activities relating to the monitoring, detection, assessment, understanding and prevention of adverse effects of drugs.

Executive Summary and Recommendations

Introduction

Recent years have seen a resurgence of international concern about the growing problem of antimicrobial resistance, and in particular antibiotic resistance. In 2013 Chatham House's Centre on Global Health Security initiated a project to address some of the policy issues related to antibiotic resistance.

The starting point for this project was the recognition that the race with antibiotic resistance is being lost. However, while there is widespread inappropriate or excessive use of antibiotics, there are also many people who cannot afford to access antibiotics when they really need them.

There are many things that need to be done to combat resistance, including investments in water and sanitation, surveillance, infection control measures, diagnostics, vaccines and behaviour change. But because there is no way in which the development of resistance can be entirely prevented, maintaining a healthy pipeline of new products is an essential part of any solution. As part of this project, the Centre on Global Health Security convened a working group comprising representatives from academia, civil society and industry to consider how to address this issue.

Although the amounts required in one form or another to stimulate investment in research and development (R&D) are potentially large, they are very small in relation to estimates of the social value of antibiotics in terms of avoided morbidity and mortality and other beneficial health and economic impacts arising from antibiotic use. A recent estimate is that by 2050 failing to tackle antibiotic resistance could cost 10 million premature deaths per year and $100 trillion in cumulative economic damage. This suggests that an additional global investment of up to $3.5 billion a year (about 10 per cent of the current value of global sales of antibiotics) would be a bargain.

The problem

Today, few large pharmaceutical companies retain active antibacterial drug discovery programmes. One reason is that it is scientifically challenging to discover new antibiotics that are active against the antibiotic-resistant bacterial species of current clinical concern. Another core issue, however, is diminishing economic incentives. Increasingly, there are calls to conserve the use of truly novel antibiotics, which might limit sales severely and discourage greater investment in R&D. Meanwhile, unless they see evidence of superiority, healthcare payers are unwilling to pay prices that would directly support the cost of development, provide a competitive return on investment and reflect the value to society of maintaining a portfolio of antibiotics adequate to overcome growing resistance.

A principal reason for this is the mismatch between the current business model and combating resistance. The current business model requires high levels of antibiotic use in order to recover the costs of R&D. But mitigating the spread of resistance demands just the opposite: restrictions on the use of antibiotics. Economic incentives play a key role in the global resistance problem, leading to overuse of these precious drugs at the same time as companies are abandoning the field; and the increasing restrictions on inappropriate use of antibiotics make them relatively unprofitable compared with other disease areas. Other factors are also in play, including historically low prices and small market sizes.

One key policy lever for stimulating R&D while conserving antibiotic effectiveness is changing the way these drugs are paid for across the supply chain. The level of reimbursement – one incentive for firms to invest in R&D – is relatively low for antibiotics as a therapeutic class. One proposed solution is to raise prices dramatically for payers and patients, thereby incentivizing investment in R&D while also restricting use through price rationing. Even if very high prices could be engineered, however, it is not obvious that this effect on R&D would be achieved. In particular, since new antibiotics should only be used as a last resort, volumes of use may still be very low.

Moreover, even though high prices restrict demand (but in ways that are determined economically rather than clinically), they also encourage sales promotion or over-marketing. This applies not only to manufacturers but also to others in the supply chain, such as pharmacists or even doctors, whose remuneration may be linked to product value. And of course high prices exacerbate the problem that there remain many in the world who are denied access to life-saving antibiotics for economic reasons. This particularly affects patients in low- and middle-income countries (LMICs) who buy antibiotics from their own resources.

Main findings and conclusions: the need for delinkage

New business models need to be developed in which the return on investment in R&D on antibiotics is not dependent on the volume of sales, an approach generally known as delinkage. This is because there is a need to encourage investment in R&D without also incentivizing sales volumes, which may lead to the over-marketing of antibiotics, acceleration of the development of resistance, and undermining of stewardship and conservation measures necessary to limit the growth of resistance to any new antibiotic developed.

Conservation must depend on methods of promoting appropriate antibiotic use through education, regulation and good clinical practice, rather than purely through rationing via the price mechanism unrelated to considerations of clinical need. There are many challenges involved in implementing such schemes and moving towards a business model which would need to have global reach to address a global problem.

The working group considered the issue of delinkage from a number of angles. Six of these were formulated as key questions to be answered in any successful business model for antibiotics:

- What kind of funding and incentive schemes might work?
- Which products should be covered?
- How could funding be raised?
- What is the role of intellectual property (IP)?
- How can new incentives be reconciled with rational use of antibiotics?
- How can a new scheme be applied regionally and globally?

The report considers each of these questions in turn, and the main findings and conclusions are set out below.

What kind of funding and incentive schemes might work?

In considering different funding and incentive schemes, the report emphasizes that company decision-making on investing in R&D is long-term and uncertain – a decision to invest now may produce a return for a decade or more (if at all), and the market conditions are difficult to predict over that time period. Risk and reward also vary over the protracted period needed for drug development. Thus a grant provided by a government body in early-stage research is more valuable for a company, but there is a much greater risk of failure from the point of view of the funder. By contrast, a reward that is offered only after successful registration of a product is low-risk for the funder but transfers all the risk of failure to the company, so post-registration rewards need to be substantial.

There is therefore a need to create an integrated menu of incentives across the antibiotic life-cycle, including:

- Public funding of basic pre-clinical research;
- Partial public funding for clinical research, through a combination of tax credits, contracts and prizes; and
- Delinked payments after registration of qualifying products, adjusted for net public investment and as evidence of value develops.

Which products should be covered?

Incentive schemes should be based on a comprehensive, periodically updated assessment of current and future global threats arising from resistance in order to identify the classes of product that are a priority for incentives. The US Centers for Disease Control and Prevention (CDC) recently carried out such an assessment for the United States. By contrast, the list of antibiotics qualifying for additional market exclusivity under the US Generating Antibiotics Incentives Now (GAIN) Act lacks any prioritization, such that most, if not all, new antibiotics would qualify.

The assessment should be data-driven, transparent and focused on the relative threats posed by resistant pathogens. The threat assessment outcome should be a triage list of pathogens, similar to the CDC classification. This threat assessment should also evaluate alternative categories (other than by pathogen) that could in some cases better target public health interventions. In this way, incentives can be directed at developing antibiotics that address unmet clinical needs.

Qualifications for support should become more stringent as the product moves towards registration. Later-stage incentives (for clinical development and post-registration) should target antibiotics that treat drug-resistant bacteria posing urgent or serious threats to humans, as determined by the evidence-based threat assessment. Pre-clinical research can target a broader range of antibiotics. Antibiotics should qualify for the highest level of new incentives if they combat resistant pathogens posing a present or predicted serious threat to human health, and such rewards should be based on demonstrably superior outcomes in human clinical testing. Antibiotics for less serious threats should qualify for a lower level of new incentives. Some flexibility should be maintained in view of inherent difficulties in predicting future health risks.

There are also questions about whether whole classes of new antibiotics (with similar mechanisms of action) should be prioritized, and how to reward follow-on innovation that adds significant therapeutic value but relates to classes that are already well populated.

How could funding be raised?

There is a need to clarify exactly how much funding is required globally to tackle the different elements necessary to combat resistance – incentives for R&D, support for access and conservation, infection control and the costs of any new organizations that might be necessary. A target budget should be created, by priority goal and by unit of accountability (government, region, intergovernmental organization), for the global effort to preserve antibiotic effectiveness, based on the best evidence of clinical need and public health risk.

Consideration should be given to pooling funds on a regional or ultimately global basis, even though most funding will remain within the control of national governments. For this purpose, an international secretariat would need to be created to manage and coordinate pooled funding. Countries may be guided in their actions by agreed regional or global frameworks, coordinated through the secretariat, which would also need to identify stable sources of funding.

Various proposals have been put forward for international mechanisms to provide pooled funding for health-related actions that mainly meet the needs of LMICs. For example, the Consultative Expert Working Group of the World Health Organization (WHO) suggested that countries could commit 0.01 per cent of gross domestic product (GDP) to R&D aimed at the needs of LMICs. Others have suggested 'innovative' sources of funding such as the airline taxes that partly fund the international drug purchase facility UNITAID. In this respect, a novel feature of fighting antibiotic resistance is that the unmet needs are global – not confined to LMICs – and while finance is required for all activities, there is scope for nonfinancial contributions such as introducing effective conservation measures at relatively low cost.

Other international partnerships in science should be evaluated and could serve as models for an international initiative in antibiotics based on pooled funding. These include, for instance, the Human Genome Project, which involved multi-country participation; or the Large Hadron Collider, constructed under the auspices of CERN (the European Organization for Nuclear Research) but also including contributions from non-member states. Other financing mechanisms such as the Global Environment Facility have also been created in the environmental field.

What is the role of intellectual property (IP)?

The delinkage business model should promote global access to antibiotics together with their appropriate use. Responsibilities should be allocated between governments and innovators when negotiating the terms of delinkage payments.

Extensions of market exclusivity are not considered to be appropriate or effective as incentives for early-stage antibiotic development.

Post-registration delinkage rewards would be based on the principle that the companies would in return make their products available to the proposed secretariat at a price based on production costs rather than the recovery of R&D expenses. The secretariat could enter into a procurement contract with the company, acquire the full IP rights or establish other licensing mechanisms. It would also need to set up and/or coordinate appropriate arrangements for supply and distribution and post-registration monitoring. Promoting access to new antibiotics through agreement with companies or through other mechanisms set up by the secretariat will be an important issue.

Extensions of market exclusivity are not considered to be appropriate or effective as incentives for early-stage antibiotic development. Later in the market life-cycle, the use of IP incentives to ensure monopoly pricing also risks exacerbating the over-marketing of antibiotics.

How can new incentives be reconciled with rational use of antibiotics?

In order to reduce the use and misuse of antibiotics, significant public funds are needed to remove the causes of infection and improve the control of infections. This requires investment in clean water and in food, sanitation and vaccines, as well as in the control of infection in the community and healthcare institutions. It also requires investing in diagnostics and laboratories so that better clinical decisions can be made on antibiotic use.

In combating resistance, any new incentive system based on delinking the return on investment from the volume of sales will need to be linked to measures that will conserve existing and new antibiotics. But the availability of data on antibiotic sales and use is inadequate, particularly in LMICs.

Delinking removes a company's motivation to increase sales. On this basis, it would also be possible to engage companies in some conservation activities through appropriate incentives or contracts. Proven conservation methods such as antibiotic stewardship programmes should be incentivized and implemented immediately as part of global conservation efforts.

However, there are possible financial incentives throughout the supply chain which may lead to inappropriate or excessive antibiotic use. The WHO Global Action Plan on Antimicrobial Resistance, endorsed at the World Health Assembly in May 2015, provides a framework for action by countries to curb such use in ways adapted to their circumstances, but LMICs will require external support to intensify their conservation efforts. Some financing could be provided from funds allocated to delinkage models.

Further research is required to explore the perverse financial incentives that lead to the over- and misuse of antibiotics, and the relationship between generic entry to the market, therapeutic competition and resistance, in order to help guide the creation of mechanisms regulating entry of generic antibiotics.

Contracts with the originators of a delinked product can be used to encourage responsible use. If generic companies are involved in supply of a delinked product, this poses issues about how to regulate supply and use in the interests of conservation.

How can a new scheme be applied regionally and globally?

There are various ways in which a new business model could be introduced regionally and ultimately globally. Financial participation can begin with a core group of countries with significant research activity and large antibiotic markets. It is envisaged that all high-income countries should make an appropriate financial contribution; others will not be able to contribute financially at the outset, but they can contribute through surveillance, hosting clinical research, conservation and public health initiatives and national measures (e.g. on conservation, or a ban on antibiotic use as growth promoters in agriculture) that fit into an agreed global framework.

Global access to antibiotics depends on approval by national drug regulatory authorities, many of which are weak. The process of registering a product globally is costly, and leads to delays in providing access to needed antibiotics. Initiatives could be considered to develop a globally acceptable approval process that reduces these costs and delays. This could, for instance, draw on the experience of the WHO's pre-qualification programme, which approves products for use by international agencies.

The secretariat should manage the licensing of IP and secure appropriate rules for access and conservation. It should have a range of functions including coordinating IP licences, mobilizing funding for incentives, and promoting appropriate use. The Medicines Patent Pool is an existing mechanism that negotiates licences from patent holders for HIV medicines for LMICs and then sublicenses to generic manufacturers. This type of mechanism could be adapted to manage the licensing of antibiotics to generic manufacturers, using appropriate conditions to regulate access and use.

Following the adoption of the WHO Global Action Plan on Antimicrobial Resistance, countries should explore whether a treaty or a WHO regulation is the most effective way to facilitate global collective action on antibiotic resistance. There are a number of ways in which states could make stronger commitments through agreed measures aimed at promoting innovation, access and conservation. These include various instruments that could be negotiated within the WHO or through the UN General Assembly. The experience of international agreements relating to the environment or natural resources (e.g. the Montreal Protocol on Substances that Deplete the Ozone Layer) could be valuable here.

The findings of this report complement the messages of others, such as the 2014 report from the US President's Council of Advisors on Science and Technology on combating antibiotic resistance. A number of other existing initiatives, such as the European Union's Innovative Medicines Initiative DRIVE-AB project and the United Kingdom's Review on Antimicrobial Resistance, have the opportunity to investigate further the financial implications, feasibility and implementation issues of the functional elements presented for consideration here.

At the national level, the report is intended to help policy-makers consider the type of commitments, both financial and non-financial, that will contribute to an international coordinated effort to encourage development of new antibiotics, ensure access and conserve these for long-term use. Leadership from political platforms and groups of countries such as the G7, G20, OECD and BRICS is critical, both because their members constitute large antibiotic markets, and because they alone have the financial capacity to get a new business model for antibiotics off the ground. However, even smaller countries have a role to play. The Nordic Council of Ministers has suggested that the Nordic regional health cooperation should prioritize antibiotic resistance, including committing financially to incentives for innovation of new antibiotics. Similar forms of regional health cooperation in other areas of the world can provide important political leadership on antibiotic resistance.

Main recommendations

1. A new business model needs to be developed in which the return on investment in R&D on antibiotics is delinked from the volume of sales.
2. Increased public financing of a broad menu of incentives across the antibiotic life-cycle is required, targeted at encouraging the development of antibiotics to counter the greatest microbial threats.
3. The assessment of current and future global threats arising from resistance should be updated periodically in order to identify which classes of product are a priority for incentives.
4. The delinkage model should prioritize both access and conservation.
5. Domestic expenditures on the model need to be globally coordinated, including through the establishment of a secretariat, and global participation in the model is the ultimate goal.

1. Introduction

Recent years have seen a resurgence of international concern about the growing problem of antimicrobial resistance, and in particular antibiotic resistance. In 2013, Chatham House's Centre on Global Health Security initiated a project to address some of the policy issues involved.

The starting point for this project was the recognition that the race with antibiotic resistance is being lost. It was realized that a comprehensive approach to this global threat necessarily involves addressing the causes of infection, such as poor housing and sanitation, the control of infection (including vaccine development), and the inappropriate use of antibiotics through better diagnosis and behaviour change. Moreover, while antibiotics are widely used in inappropriate situations, access to these drugs also falls woefully short in many countries.

The main objective of this report is to consider ways to stimulate antibiotic product development. Because there is no way in which the development of resistance can be entirely prevented, maintaining a healthy pipeline of new products is an essential part of any solution. Yet today few large pharmaceutical companies retain active antibacterial drug discovery programmes. One reason is that it is scientifically challenging to discover new antibiotics that are active against the antibiotic-resistant bacterial species of current clinical concern. However, a core issue is also diminishing economic incentives. Truly novel antibiotics are likely to face calls for conservation (i.e. controls on their use) that might limit sales severely and discourage greater investment in research and development (R&D). Meanwhile, unless there is evidence of superior outcomes, healthcare payers are unwilling to pay prices that would directly support the cost of development, provide a competitive return on investment and reflect the value to society of maintaining a portfolio of antibiotics adequate to overcome growing resistance.

The current business model requires high levels of use in order to recover the costs of R&D. But mitigating the spread of resistance demands just the opposite: restrictions on the use of antibiotics.

A principal reason for this is the mismatch between the current business model for drugs and combating resistance. The current business model requires high levels of use in order to recover the costs of R&D. But mitigating the spread of resistance demands just the opposite: restrictions on the use of antibiotics. Economic incentives play a key role in the global resistance problem, leading to overuse of these precious drugs at the same time as companies abandon the field, and increasing restrictions on inappropriate antibiotic use make them relatively unprofitable compared with other disease areas. Other factors are also in play, including historically low prices and small market sizes.

In conjunction with a major international conference hosted by Chatham House in October 2013 on 'Antimicrobial Resistance: Incentivizing Change towards a Global Solution', the Centre on Global Health Security convened a roundtable specifically to examine the question of improving incentives for antibiotic research and development in ways that were consistent with their appropriate use to encourage conservation.[1] The roundtable discussion was informed by a background paper prepared by Professor Kevin Outterson of Boston University entitled 'New Business Models for Sustainable Antibiotics'.[2]

The roundtable was convened to focus on schemes that would delink the rewards for R&D from the volume of sales. Companies would thus not be incentivized to maximize sales in ways that could accelerate the development of resistance. A broad range of senior participants from industry, regulators, research organizations and civil society engaged in a rich discussion on general principles that would inform new business models. These included the desirability of an integrated approach, encouraging the 'delinkage' approach and better models for conservation, and taking account of the marked differences in circumstances and requirements between low- and high-income countries.

To make further progress it was considered necessary to examine in greater detail how one or more particular schemes based on delinkage might be constructed and operate in practice so that the practical issues in relation to their implementation could be identified. A working group was convened and chaired by Professor John-Arne Røttingen of the University of Oslo/Harvard University, and facilitated by Professor Outterson (see p. v for membership of this group).

A central proposition in this work was that it was desirable to develop new business models based on delinkage. The majority view in the working group reflected the proposition discussed in the initial roundtable – that there is a need to encourage investment in R&D without also incentivizing sales volumes, which may lead to the over-marketing of antibiotics, the acceleration of the development of resistance and the undermining of stewardship and conservation measures necessary to limit the growth of resistance to any new antibiotic developed.

Another view was that both investment in R&D and conservation could be addressed by setting the price of new antibiotics much higher than at present, thereby addressing the need to boost incentives, and using the price mechanism to promote rational use. Those who favour delinkage believe

that this approach is inconsistent with promoting access to life-saving antibiotics, particularly among patients in low- and middle-income countries (LMICs) who buy antibiotics from their own resources; and they are concerned that an increased price would stimulate over-marketing. In their view, conservation must depend on methods of promoting appropriate antibiotic use through education, regulation and good clinical practice rather than through rationing by the price mechanism in ways unrelated to considerations of clinical need.

The majority view of the working group was that the general approach to innovation incentives in a new business model should be on the principle of delinkage, seeking to separate the return on investment from antibiotic sales volume.

This report therefore considers the ways in which delinkage could be implemented and the myriad challenges involved in moving towards new business models requiring global reach to address a global problem. It is based on the deliberations of the working group and drafts prepared by the editors.

After consideration, it was decided that focusing on one or more particular delinkage models was challenging. Given the nature of the R&D landscape, a successful outcome was likely to involve a combination of different approaches tailored to different stages of the innovation process and taking into account the very diverse nature of R&D and healthcare systems across countries. The focus was therefore shifted instead to considering six essential questions that need to be addressed if any new business model for antibiotics is to be successfully constructed:

- What kind of funding and incentive schemes might work?
- Which products should be covered?
- How could funding be raised?
- What is the role of intellectual property (IP)?
- How can new incentives be reconciled with rational use of antibiotics?
- How can a new scheme be applied regionally and globally?

The following chapters reflect the working group's discussion on these six questions in turn, and put forward specific policy recommendations in each area.

2. What Kind of Funding and Incentive Schemes Might Work?

Introduction

This report focuses on antibiotic drug development as one element of a comprehensive solution to the pressing problem of antibiotic resistance. Improved living conditions and sanitation, infection prevention and behaviour change as well as diagnostics, vaccines and other health technologies are further weapons in this fight. But although these other approaches are important, the incentives required to promote innovation will differ significantly among them and from those required for drug development. For example, because vaccines, diagnostics and infection prevention technologies do not trigger resistance, delinkage mechanisms are not needed as a conservation measure, although delinkage could still be deployed as an innovation tool. These related topics deserve their own comprehensive reviews. A 2013 report by the Infectious Diseases Society of America (IDSA) makes policy recommendations to help spur the development of new and more rapid diagnostic tests and to encourage their use in patient care and public health.[3]

Structuring appropriate innovation rewards for R&D in antibiotics involves several key considerations including proper targeting of incentives; designing appropriate incentives; and ensuring incentives are fair and cost-effective. A framework must be devised that will attract significant new public and private investment while ensuring appropriate stewardship so that the right patient receives the right drug at the right time.

Targeting of incentive schemes

Targeting can have several goals: encouraging the widest possible participation by research companies, both large and small, across the globe; avoiding R&D bottlenecks that inhibit subsequent innovation; and defining product profiles or other characteristics to delineate the scope of products receiving incentives.

The perceived opportunity costs of investment in antibiotic R&D will vary not just according to the size and experience of the manufacturer, but also according to the class of the product and the nature of the incentives necessary to motivate such investment. Grants, for example, can reduce costs for inputs to R&D. For small developers, academic institutions and developers in low- or middle-income countries, such awards can address their lack of access to funding. By contrast, prizes that are payable only when a drug is registered work best for large pharmaceutical companies with access to capital resources to undertake the risks of long-term R&D. So the timing of the incentive in the product development cycle will influence what type of company or research institution will respond to the incentive. A diverse menu of early- and late-stage incentives may be necessary to ensure participation by all of the relevant stakeholders.

Incentives may also be used to target bottlenecks in the R&D pipeline. For example, reducing the costs of clinical trials necessary for marketing approval is of little value if no drug candidates can avoid being caught in upstream scientific bottlenecks. From 70 high-throughput and whole-cell screens conducted by GlaxoSmithKline (GSK) from 1995 to 2001, only five lead antibacterial compounds resulted – a seven per cent success rate.[4] In comparison with other therapeutic areas, the success rate from antibacterial high-throughput screens was four- to fivefold lower. This suggests that incentives directed at developers of drug discovery platforms may be an important part of the mix. Targeted diagnostics could also dramatically lower the size and cost of clinical trials.

The use of a target product profile (TPP) could specify the parameters of what products would qualify for a reward. The design of a TPP needs to be carefully considered. Too narrowly construed, the reward might miss an opportunity to cover a current or future infectious disease threat. Too broadly construed, it could encourage innovations with little additional therapeutic value and waste available public funding. These issues are discussed in greater depth in Chapter 3.

Designing the incentives

When designing incentives for antibiotic R&D, four essential elements to consider are:

- **Delinkage** (separating rewards from volume-based sales revenues);
- Appropriate **mechanisms**;
- **Timing** across the drug life-cycle; and
- Appropriate **magnitude**.

Delinkage

The greater use of antibiotics inevitably generates resistance. That is why new (and existing) antibiotics which address disease areas of high priority where resistance is prevalent should only be used sparingly and when strictly clinically appropriate. In those circumstances even quite high prices are unlikely to amortize the investment in R&D. That is a major reason why delinkage is important: it separates the return on investment on antibiotic R&D from the volume of sales, and recognizes that the social value of a new antibiotic is not reflected in its market value. In addition, when revenues are dependent solely on sales volume, this is inevitably an incentive for

the producer and others along the product sales chain to try to maximize sales, thereby exacerbating the problem of resistance. Delinkage minimizes this perverse incentive from the point of view of containing resistance, but it requires a mechanism to limit prices that producers may charge over and above the cost of production (e.g. as part of a contract with the funder of incentives). It also requires effective mechanisms (other than high prices) to control use according to clinical need (see below).

On the other hand, it is a fact that high prices would not only incentivize producers but also discourage antibiotic use, including appropriate use. One working group member therefore proposed a system relying on much higher antibiotic prices to stimulate R&D and profitability, and also encourage hospital stewardship (see Box 1). While this might be possible in high-income countries where governments and insurance schemes generally meet most medical bills directly, it could impede access to key antibiotics in LMICs, where the majority of people normally have to meet their own medical bills. Any comprehensive solution needs to marry the need for conservation of antibiotics with the need to facilitate appropriate access to these life-saving drugs irrespective of income.

Incentive mechanisms

There are many policy options on the mechanism of rewards. In a report prepared by the Eastern Research Group (ERG) for the US Department of Health and Human Services (DHHS),[5] four categories of incentives were assessed for their impact on company decisions to invest in antibiotic drug development. The criterion used was whether the incentive could raise the profitability of R&D investment – as measured by whether the expected net present value (NPV) of an investment would reach a benchmark of $100 million. NPV measures the present estimated value of the expected flow of benefits minus the expected costs of an investment, discounted to give a present-day value. The $100 million threshold value was not an empirical result, but was an assumption that the DHHS built into the ERG model. The four incentive categories were:

- Cash-flow rewards (revenues from contracts, prizes, grants and post-approval reimbursement);
- Intellectual property (IP) extensions (lengthening the exclusive marketing period);
- Tax incentives (reducing the cost of capital); and
- Clinical trial simplification (reducing the time to market).

It was calculated that *incremental cash flow* of the order of $1 billion would be necessary for a drug developer to estimate an NPV exceeding the benchmark at the initial decision point to begin drug development. Owing to the time value of money (discounting), and the fact that not every drug makes it all the way through to market, these cash-flow payments are more valuable to the companies (but present a higher risk to the funder) if made earlier in the process. Payments upon registration of a drug for marketing (such as a registration prize) or delinkage payments after registration require larger nominal amounts because they come after the R&D process is complete and are thus heavily discounted by producers when the decision to invest in R&D is taken a decade or so earlier. On the other hand, such later payments are lower-risk for the funder because they are only paid when a product is approved for marketing.

More work needs to be done to model the size of a delinkage reward that would be regional or even global in scope. The ERG report was based only on the US market and was limited to individual studies of six clinical indications. The magnitude of the reward might need to vary significantly depending on key factors (see pp. 8–10 below). For example, an outstanding new antibiotic treating multi-drug-resistant Gram-negative pathogens (see Glossary for this and other technical terms) would fill an urgent clinical need and should yield a higher reward, even if the expected number of patients in early years might be small.

IP incentives include various ways to extend market exclusivity beyond the normal patent expiry date, such as patent extensions or data exclusivity provisions. Because the incremental revenue will occur up to two decades after the initial decision to invest and will be subject to the cumulative risk of failure of the drug from pre-clinical to registration stages, these provisions do little to increase the initial NPV. The ERG found no range of IP incentives, even perpetual patents, that would allow any NPV to reach the $100 million threshold. As a result, efforts similar to the five years of additional exclusivity in the US GAIN Act have added little to the innovation incentive while increasing economic rents to be paid by consumers and insurers many years from now. Commonly used social discount rates (e.g. 3.5 per cent in the UK[6]) are much lower than the opportunity cost of capital typically used by companies (e.g. 11 per cent used in the ERG report). As a result, rewarding companies at a distant future date is a relatively expensive solution for society.

Tax incentives were modelled as a decrease in the cost of capital. The ERG assumed the private cost of capital at 11 per cent for antibiotic R&D, and found that reductions in the range of 50–70 per cent were necessary to achieve the threshold NPV in three indications. For the remaining

indications, even a zero cost of capital was insufficient because of the cost of production, registration and marketing compared with the low cash flow from sales. If tax incentives are used, deductions cannot achieve the cost of capital reductions in that range (50–70 per cent) unless the marginal effective tax rate is above 50 per cent. Tax *credits* (as opposed to deductions) will be required, built on the model of 'orphan drug' acts in the United States and the European Union.[7]

Tax credits for antibiotic R&D would require several features. First, they would need to be fully refundable (i.e., payable as grants without regard to tax liabilities), since many small and medium-sized enterprises active in antibiotic R&D do not have sufficient taxable income against which they can offset a credit. Second, as indicated in the ERG report, the tax credit rate would need to be substantial, perhaps 50 per cent, and must be capped to ensure the company maintains some stake. Third, the tax credits should be limited to a list of 'qualified' antibiotics. One advantage of tax credits is that antibiotic R&D is financed through the tax system, which might be a more stable long-term platform than health or science budgets. The drawback to such an approach is that typically such expenditures, including the conduct of clinical trials, must be located within the country awarding the tax credit.

Clinical trial simplifications were modelled as a reduction in the total time to market. Although they may also result in substantial cost savings to the company, the ERG did not include them. For three of the ERG's six clinical indications, the NPV would not reach the threshold even if all clinical trials were completed in under a year. For the other three, the total time to market would have to be between two and four years shorter than at present. A key point is that the ERG data did not reflect recent clinical trial initiatives in both the US and the EU that have significantly streamlined the timeframe and expense associated with antibiotic clinical trials.

Further reductions on this scale are not realistic in practice, so it does not appear that additional streamlining is plausible as an innovation incentive.

An important limitation of the ERG report is that these incentives were not modelled in combination, nor were they referencing a global market for antibiotics. Follow-on studies should explore these questions in depth. But the core implications are clear: incentives will need to be quite substantial cash-flow rewards and/or tax credits; IP incentives and clinical trial streamlining are less effective as innovation incentives.

Timing of rewards

For a new model to succeed, appropriate sharing of resources, risks and rewards (3Rs) is necessary between innovators (e.g. pharmaceutical companies) and purchasers (e.g. governments and private insurers). The interplay among the 3Rs will affect the timing as well as the structure and size of the incentives required.[8] Incentives paid at various stages before marketing approval reduce the opportunity costs of pursuing antibiotic R&D. These may need to be complemented by post-registration payments including delinked reimbursement such as prizes.

From the vantage point of the public-sector funder, payments earlier in the life-cycle have a stronger impact on the NPV of the product to companies because of time discounting and the cost of capital,[5,9] but the risk of failure is higher. As the product moves closer to registration and use, scientific and business risks diminish but so does the impact on NPV. Moreover, the costs of R&D rise as drug candidates enter clinical trials. The important insight is that the timing of incentives across the product life-cycle needs to be managed in response to changing risk dynamics.

From the vantage point of the drug developer, rewards can be timed for different points in the product development life-cycle. The use of contracts, grants or milestone prizes can be applied upstream or downstream in the R&D pipeline. A contract may position an antibiotic drug candidate for further drug R&D, but stop short of drug registration. The further upstream the reward is, the less

Box 1: A view on stewardship

Without adequate surveillance and a clear understanding of causality for the human burden of antibacterial resistance, we cannot appropriately focus on the highest priorities. Antibiotics are often prescribed inappropriately in the community setting. Fewer are prescribed in the hospital setting, and of those, a small percentage are for patients with serious and life-threatening infections. Some have suggested developing a stewardship model that explores:

- Very tight controls (or perhaps partial bans) on the use in livestock, aquaculture, pets and crops of those families of antibiotics that are critically important to humans;
- Stronger controls on antibiotic use in the human community setting – perhaps starting with a requirement that antibiotics are only dispensed with a prescription, where infrastructure allows for such control;
- Appropriate stewardship in the human hospital setting – right patient, right drug, right time; and when serious and life-threatening infections are suspected or confirmed in the hospital setting.

Source: Working group member.

private-sector investment is incurred, and the lower the potential buy-out costs are for the public sector to make such drugs available to those in need. Rewards might be applied upstream in the R&D pipeline to overcome a scientific bottleneck or further downstream to help drug developers cross the 'valley of death' where companies hesitate to invest significant resources in large clinical trials. Post-registration prizes, on the other hand, would pay a drug developer for having brought a promising antibiotic through the entire R&D process. For having assumed the risks of bringing a product from lab bench to bedside, the manufacturer would understandably anticipate a commensurately larger reward.

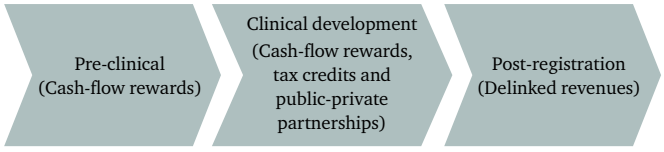
The structure of the entities involved will also be quite different along the life-cycle. In early phases, university labs, spin-offs and venture capital-funded groups traditionally dominate, transitioning over time to publicly traded multinational drug companies as the product moves towards registration.

All of these have very different cultures, cost of capital and risk profiles. Any solution will need to be flexible, not 'one size fits all'.

Offering a menu of incentives allows companies to fit incentives to their needs. In structuring public-private partnerships (PPPs), the government partner can contribute much more than just funding to the development effort. One of its key roles is to fill in the gaps for small to medium-sized partners, which lack the human and financial resources of multinational companies.

Potential incentives for antibiotic R&D can be categorized into three stages: pre-clinical, clinical and post-registration (Figure 1). All funding would require meeting milestones in order to progress and could be offered as a package (e.g. acceptance of clinical trial funding incentives could pre-commit the company to accept post-registration delinkage rewards if certain conditions are met).

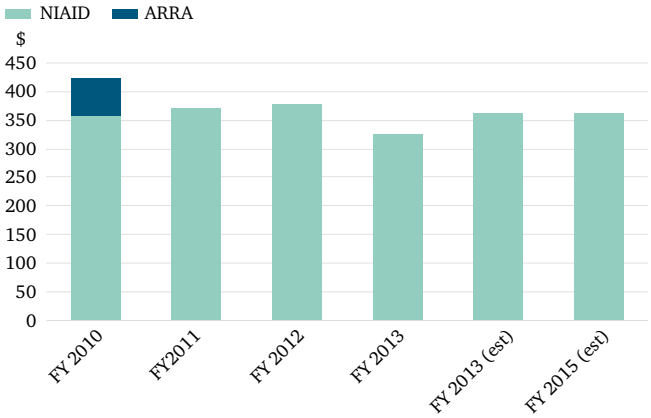
Figure 1: R&D incentives over the antibiotic life-cycle



Pre-clinical research encompasses the period from target identification until the initiation of Phase 1 trials. The opportunity cost (termed cost of capital) of funding projects is different between the private investor (typically 8–12 per cent) and public bodies (3.5 per cent in the United Kingdom and 3 per cent in the United States), which indicates that public funding can be more cost-effective at this early, risky stage. Up-front public funding of R&D can be used to reduce the financial burden of cost of capital for the private investor and reduce the reimbursement required when a product is on the market. Pre-clinical research has the highest failure rates.[4]

Public-sector support can help share the high risk of pre-clinical research between society and private investors. Key sources of support are national research councils and philanthropic foundations, but funding for antimicrobial research in recent years has not been increasing (Figure 2). While it might be appropriate to reduce funding in some research areas owing to the success of existing therapies on the market, resistance destroys the fruit of prior research. Additional investment in antibiotic R&D is required simply to stand still.

Figure 2: US NIH spending in antimicrobial research, FY 2010–15, adjusted annually for US CPI (2010 base)



Note: NIAID = National Institute of Allergy and Infectious Diseases.
ARRA = American Recovery and Reinvestment Act.
Source: Adapted from Outterson et al., 2015.[10]

Clinical development includes the three phases of clinical trials in humans up to market authorization. During this stage, there is also substantial investment in manufacturing and process development. Public-sector support for such clinical trials could be in the form of tax credits, cash-flow rewards (milestone prizes or grants), and contracts in PPPs. In all cases, payments might entail transparency of clinical trial findings and other open innovation features.

The Innovative Medicines Initiative (IMI), a collaboration between the European pharmaceutical industry and the European Commission, is the largest pharmaceutical PPP in the world. In addition to many other initiatives, the IMI has allocated more than €700 million to the New Drugs for Bad Bugs (ND4BB) programme. In the United States, the Biomedical Advanced Research and Development Authority (BARDA) has been a leading example of the contractual PPP model. In a recent contract with GSK, BARDA provides up to $200 million for up to five years, primarily for clinical studies at Phase 1 or beyond. The structure of the model allows for programme funding to be switched among

projects depending on the fulfilment of specific project milestone commitments. This model is typical of how private funding is allocated between projects within a company during pre-clinical research.

Milestone prizes, end-stage prizes or grants could also be offered, similar to the PPP model but without the contract. For example, the Longitude Prize in the UK will award a £10 million prize for a rapid point-of-care diagnostic meeting specified conditions.

Both pre-clinical and clinical development risks could also be shared through a refundable tax credit for qualifying antibiotic R&D expenses, as discussed above. Under the 'menu of incentives' approach, tax credits and PPPs could co-exist, serving different niches supporting the clinical development pipeline.

Another incentive for clinical development, however, does not require public funding but attempts to make clinical development more efficient. As stated above, the ERG report suggested that reducing clinical trial times would not be an important innovation incentive for companies involved in early-stage R&D, but did not model reduced trial costs. While of unclear value for significant advances in antibiotic treatment, these modifications might encourage more firms to embark on expensive trials but raise some safety concerns (see Box 2). More importantly, reducing clinical trial costs and length might also be accomplished by improved diagnostics and infrastructure to speed up the recruitment of subjects without the same threats to safety.

The ERG report suggested that reducing clinical trial times would not be an important innovation incentive for companies involved in early-stage R&D, but did not model reduced trial costs.

Post-registration. As stated, a primary goal of the working group was to design post-registration incentives that drive investment in the most needed antibiotics while promoting good stewardship. Delinkage provides an attractive option for uncoupling revenue generation for the company from the volume of antibiotics sold and used.

Participation in the post-registration delinkage would be voluntary, but set at a high enough level that companies would find it enticing to join. Acceptance of incentives in Phase 2 and thereafter could entail joining the post-authorization system as well: making the package voluntary, but bundling it into an 'all or nothing' deal.

One option is a significant prize paid upon registration of the qualifying drug. While this is appealing in its simplicity, in practice it will be exceedingly difficult to understand the true value of a new antibiotic immediately; evidence is likely to develop over time. Large registration prizes will also create budgetary strains if several qualifying antibiotics come to market in the same year.

Another alternative is a staged prize approach, 'Tiered Reimbursement', whereby a minimum base reward is offered for approval of a qualifying new antibiotic and subsequent rewards (if any) are proportional to the demonstrated effectiveness of the drug in use. Annual baseline payments could be made over a decade, pending further development of evidence of clinical effectiveness and resistance profile, collected by national health authorities. These annual payments would cover the cost of supply-chain availability and a limited recovery of R&D expenses, pending further evidence of development in real-world use.

While the magnitude of incentives will be discussed below, two examples here might be helpful. First, if an antibiotic were to be approved for use in a very limited population (say, fewer than 5,000 patients per year), the US government could offer perhaps $75 million a year for ten years as the fully delinked payment for the drug in the United States. Other governments would be encouraged to offer similar terms, adjusted to local conditions, with a global sum of perhaps $200 million per year over ten years. A decade of sparing use would preserve the drug while developing better evidence to support label extensions and reimbursement based on value after a more traditional health technology assessment. Spreading the payments over a decade would also make the budgetary implications more predictable to governments.

Another example is based on insurance premiums, which are more aligned with the notion of risk mitigation, with flexibilities to account for actual effectiveness. Insurance concepts should be explored, as there is widespread recognition of the value of paying insurance premiums to pool and distribute risk even if the underlying insured event is rare. Few complain about their life insurance policy failing to come due; they are happy to have been protected for the term and lived to see another day. There is insufficient information at present to build insurance-based risk models for massive antibiotic resistance events, but the government is frequently the insurer of last resort for these types of low-incidence, high-severity events (such as the West African Ebola outbreak or the H1N1 pandemic). For more common infections (MRSA, *C. difficile*) it might be possible to price (and underwrite) an insurance premium-based approach. With better data, this could be extended to additional bacterial pathogens.

It is important to note that we are not actually proposing that governments purchase insurance for resistance events. Instead, we seek to prevent these calamities rather than

Box 2: Safety questions about further streamlining of antibiotic clinical trials

In Europe and the United States, the regulatory requirements for antibiotics have been recently modified to reflect the challenges of testing novel treatments for the relatively small number of patients with multi-drug-resistant pathogens. Under the US Food and Drug Administration (FDA) Safety and Innovation Act passed in 2012, qualifying antibacterial or antifungal drugs receive fast-track and priority review status.

Already the approval of bedaquiline on the basis of a single Phase 2b trial, even when the number of deaths in the treated arm was five times greater than in the placebo group, shows that the regulatory threshold for bringing potential novel antibiotics to market is low – some say too low.[11] The FDA has defended its approval of bedaquiline by stating that the drug provides a positive benefit-risk balance for patients with multi-drug-resistant pulmonary tuberculosis. However, the FDA acknowledges that a confirmatory trial based on criteria such as patient survival, clinical resolution of tuberculosis and the rate of relapse is needed to clarify the mortality findings in the Phase 2b trials.[12]

Even though significant work has gone into making non-inferiority-based approaches somewhat more reliable, significant questions remain about the potential risks of expedited approval for antibiotics.[13, 14]

If an antibiotic is permitted to reach the market with more limited trials, the resulting product labelling should reflect the limitations of the data supporting approval. The label could include language such as:

> It is recommended that {agent name} should be used to treat patients who have limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases.[15]

Smaller clinical trials may miss important safety problems affecting patients. The approval of telithromycin (Ketek) – initially hailed as a first-in-class antibiotic and subsequently the subject of Congressional investigation for FDA acceptance of faulty trial methods and fraudulent safety data – is a sobering reminder of what can go wrong.[16]

To mitigate these risks, regulatory agencies could require post-marketing surveillance and ongoing data collection (possibly through registries) and make drug approval contingent upon completion of follow-on studies in a timely manner.

These safety measures may fall short of ensuring conservation of novel antibiotics. In this case, drug regulatory agencies, health insurers and contracting funders may need to condition the use of the drug by restricting prescription to qualified healthcare providers, healthcare institutions or patients meeting specific diagnostic criteria. In the United States, judicial interpretations of the First Amendment have limited the FDA's ability to control off-label drug promotion,[17] so a contractual model akin to the FDA's Risk Mitigation and Evaluation Strategy (REMS) could be explored.

reimbursement from an insurer. But the underwriting process can provide useful information on the risks to which we are all currently exposed on a global and national basis, and this might be helpful in mobilizing political support for sufficient funds to be allocated to prevention and response capability. Global expenditures to date on the Ebola outbreak provide a good example of the results of failing to address prevention and response capabilities. Save the Children calculated in a report released in March 2015 that the $4.3 billion committed by external donors to fight Ebola in Guinea, Liberia and Sierra Leone was nearly three times larger than the funding gap of $1.58bn needed to ensure essential healthcare in these three countries.[18]

Finally, a number of models from other business sectors[19] could be explored for their usefulness in designing appropriate post-registration reimbursement mechanisms that are independent from sales volume (Box 3).

Magnitude of incentives

Antibiotic incentives must be of the appropriate magnitude, given the public health threat. Three valuation approaches may be used as a guide to the magnitude of incentives that might be appropriate. The first approach is standard health technology assessment (HTA), as used, for instance, by the United Kingdom's National Institute for Health and Care Excellence (NICE). The key will be agreement on how comparative clinical effectiveness can realistically be measured (especially given the limitations of non-inferiority trials, which only demonstrate that a new treatment has at least as good an outcome as an existing treatment) and then how payers determine reimbursement. A challenge with this approach is how to account appropriately for the expected evolution of resistance growth, and the novelty of the resistance profile over the long term.

Another difficulty with standard HTA relates to the quality of evidence on the safety and efficacy of new antibiotics, which are generally based on non-inferiority trial designs. If antibiotics are allowed to reach the market on the basis of even more limited non-inferiority trials – the Tier B and Tier C approach[20] that is making headway with the FDA and European Medicines Agency (EMA) – then traditional HTA will be yet more difficult. One possible solution is the Tiered Reimbursement model described above.

Box 3: Reimbursement public-private contract models from other business sectors

Some other industries sell to governments through a syndicate lead (rather like defence contracts). As syndicate lead, they can help to guide the development of an open architecture/collaborative programme across many companies and stakeholders. Antibiotic availability may need to be seen as a global health security issue, requiring this level of coordination, including open innovation approaches.

Defence contractors are increasingly being paid for long-term service availability as opposed to just delivery of a product. Examples include 40-year contracts covering the procurement and maintenance of capital ships in the UK's Royal Navy. For antibiotics, the goal would be the long-term availability of the drug class.

Many electric utilities have experience in encouraging customers to consume less electricity or to rationalize usage given generation constraints. These lessons could be valuable in the antibiotic context to rationalize consumer use, building financial incentives to reduce consumer demand for the product.

Some industries have transitioned to delinkage reimbursement, independent from volume. Examples include some credit risk reporting services. As these companies transitioned to delinkage from volume-based sales, they discovered that their sales forces needed new skill sets. Some academic publishers have also transitioned to delinkage models, deepening collaboration with customers to deliver academic e-books. These experiences could provide guidance on a transition to delinkage for antibiotics.

Source: BIC/Chatham House 2015.[19]

A second approach is the social value of antibiotics to health and health systems generally. Social value attempts to measure the importance of antibiotics to global public health. Measures include reduced mortality and morbidity, avoided costs of illnesses, reduced transmission of disease, and other indirect savings. The ERG report estimated the social value of avoided mortality and morbidity from six antibiotic development models – with values ranging from $487 million to $12.2 billion per drug, without including any avoided costs. This illustrates the dramatic gap between public and private valuation for antibiotics.

The ERG report's calculations of social value were limited to the United States and a small number of hypothetical drugs, and did not include any indirect savings such as avoided resistance or medical costs. The recent report from the Review on Antimicrobial Resistance, commissioned by the UK prime minister, estimated that a cumulative loss in global economic output of up to $100 trillion dollars could be expected over the next 35 years if antimicrobial resistance is left unaddressed, as well as 10 million deaths per year by 2050.[21]

This indicates the potentially huge global social value of investing in access, conservation and innovation in the field of antibiotics. A research group funded by the IMI, DRIVE-AB, will undertake further analysis of social valuation. This research may lead to quite large estimates that are probably unrealistic for payers, but that can also be used to inform HTA as the case is made for increased reimbursement.

A third approach is to measure value by the global market demand for antibiotics. IMS Health estimates the global market for antibiotics in 2017 will be $34–40 billion.[22] If it is assumed that preserving this important drug class is worth a 10 per cent premium over current expenditures (or some other premium, perhaps based on risk models from insurance markets), then the indicated global incremental investment is approximately $3.5 billion per year. At this point, the concept of the social value of antibiotics could be helpful as a test of fairness. As noted above, the ERG report suggested a very high social value for antibiotics – as much as two orders of magnitude greater than the private value. If that is right, then a global investment of $3.5 billion per year is a bargain.

The US President's Council of Advisors on Science and Technology (PCAST) Report on Combating Antibiotic Resistance indicated the need for incentives that are two orders of magnitude larger than what is currently being discussed in the US Congress.

The US President's Council of Advisors on Science and Technology (PCAST) Report on Combating Antibiotic Resistance indicated the need for incentives that are two orders of magnitude larger than what is currently being discussed in the US Congress.[23] The PCAST Report called for increased funding in the range of $1.25 billion per year that is much closer to the amounts modelled in the ERG Report. In January 2015, President Obama proposed a near doubling of federal funding for antibiotic resistance and prevention in the 2016 budget – to more than $1.2 billion. To date, Congress has not yet funded these proposals.

In all cases, incentives should be adjusted for prior public support. If a company has received substantial public

support for R&D to bring a novel antibiotic to market, then post-approval delinkage payments should be capped or adjusted in some fashion to reflect that investment. And incentives for antibiotic drug development have to be weighed against other alternative investments. Could greater social value be obtained from public-sector investment in non-drug interventions such as vaccines or infection control?

It seems likely that some form of HTA should be employed, at least once adequate evidence has been developed, and that all reliable sources of evidence of value will be used as inputs.

Recommendation 2.1: Create an integrated menu of incentives across the antibiotic life-cycle:

- **Public funding of basic pre-clinical research (national research council model);**
- **Partial public funding for clinical research, through a combination of tax credits (orphan drug model), contracts (public-private partnership model) and prizes (Longitude Prize model); and**
- **Delinked payments for qualifying products after registration, adjusted for net public investment and as evidence of value develops.**

Measuring the fairness and effectiveness of the incentives

The effectiveness of an incentive programme for antibiotics can be measured by how robust a pipeline it generates to serve unmet public health needs. Incentives must reward important new antibiotics, not merely increase payments for drugs that would have been produced in any event. A consequence of just producing analogues of existing products is therapeutic competition that might accelerate resistance.[24] The withdrawal rate of new molecular entity (NME) antibiotics approved by the FDA between 1980 and 2009 was very high, over three times that of any other therapeutic category.[25] Several were withdrawn with significant safety concerns while others failed to distinguish themselves in a crowded field. None were withdrawn primarily because of resistance. Public money should be spent wisely, yielding the best antibiotics for the funds invested.

The incentive design should be equitable across many stakeholders. Between companies, similar products should be rewarded in a similar fashion. From the companies' perspective, the process needs to be fair, generate predictable rewards and remain stable over a long time horizon (at least as long as that for R&D investment). The promises must be credible. If companies perceive political risk, they will discount the promised cash flows, thereby undermining the effectiveness and efficiency of the programme.

In all cases, access to effective antibiotics should not be rationed at the point of care by price. Whatever is done should result in greatly improved global access to appropriate antibiotics in clinically important situations.

Within a country with multiple health insurance payers, the burden of financing should be equitably shared. Among countries, the financing costs must also be allocated in a fair fashion, perhaps based on GDP, antibiotic market sizes (countries using more pay more), or a combination of these and other approaches. In all cases, access to effective antibiotics should not be rationed at the point of care by price. Whatever is done should result in greatly improved global access to appropriate antibiotics in clinically important situations.

The design and functioning of any rewards system should be fully transparent and accountable. From society's perspective, large investments are being made to preserve global common pool goods that protect health. Global public health is at risk, so the decision-making process should also be transparent to the public. To accomplish these ends, parts of the decision-making process may be global, and other parts devolved to the regional and/or country level.

Recommendation 2.2: Create a fully transparent and independent process to evaluate the fairness and effectiveness of all antibiotic incentives. Such antibiotic incentives ought to be considered alongside what returns such public-sector investments might yield compared with other interventions.

Building company support for delinkage

Several major pharmaceutical companies are supportive of the principle of antibiotic delinkage schemes. One reason is that delinkage would be voluntary, so they could choose whether or not to opt in depending on their assessment of its attractiveness relative to their current business model. A large and predictable delinkage reward might be very attractive. But companies that declined post-

registration delinkage would face commercial barriers as reimbursement markets would not prioritize them except for a highly effective and irreplaceable drug. Under delinkage, some risks are shifted to the funders (mainly governments), including the risk that the companies may only offer their less valuable drugs to the programme. Some of the incentives could be offered as a package across the life-cycle of the drug: acceptance of Phase 2 milestone prizes or contracts might obligate the company to opt in to post-registration delinkage if certain conditions were met. These conditions would need to be very clearly stated so that companies could carefully consider their options before accepting. Muddled conditions will cause companies to discount the value of incentives and undermine the entire programme.

3. Which Products Should Be Covered?

Introduction

This chapter considers which types of antibiotics should receive additional incentives. We suggest that new antibiotics should qualify for the highest level of new incentives only if they satisfy unmet medical needs, namely treatment of resistant pathogens that constitute an urgent and serious threat to human health. The targeting of the incentives should be guided by a global threat assessment.

Developing a threat assessment to define priorities

The tool to identify the most urgent bacterial pathogens is a threat assessment. In 2013, the Centers for Disease Control and Prevention (CDC) completed a comprehensive antimicrobial resistance threat assessment,[26] identifying three urgent threats to US public health:

- *Clostridium difficile*,
- Carbapenem-resistant *Enterobacteriaceae* (CRE), and
- Drug-resistant *Neisseria gonorrhoeae*.

Twelve additional pathogens were identified as 'serious' threats, including several Gram-negative bacteria and other bacterial pathogens including MRSA and drug-resistant TB. The CDC also included one fungal infection, fluconazole-resistant *Candida*. Three bacterial pathogens were placed in the lowest category: threats that were 'concerning'.

The CDC evaluated the following factors:

- Clinical impact attributable to morbidity or mortality from infection with resistant pathogens;
- Incidence/prevalence, both currently and projected on a 10-year time horizon, approximating the time to bring a new product to market;
- Economic impact on healthcare and society, including the cost of prevention and public health;
- Transmissibility;
- Preventability through feasible public health measures; and
- Availability of effective antimicrobial agents to treat the patient, considering safety and efficacy limitations with current therapies.

For each factor, a value from 1 to 5 was assigned through a grading rubric, indicating severity within the United States. For example, for current incidence/prevalence and availability of effective treatment, the rubrics were as shown in Table 1.

Table 1: Examples of criteria used for evaluating bacterial threats

Criterion	Assessment spectrum examples	
Current incidence/prevalence	**Cases per year in the US**	
The current incidence of infection or prevalence of colonization with AR strains of this pathogen in the United States.	1	Fewer than 1,000
	2	Between 1,000 and 10,000
	3	Between 10,000 and 100,000
	4	Between 100,000 and 500,000
	5	More than 500,000
Availability of effective treatment		
This refers to the availability and effectiveness of antimicrobial agents to treat this resistant pathogen. In many cases, antimicrobial agents may be available, but there are significant limitations associated with them. Such limitations may include: • significantly greater toxicities than the standard therapy for treating infections caused by the pathogen; • limited data proving efficacy for infections commonly encountered with the resistant pathogen; • limited data on appropriate dosing regimens for the antimicrobial agent; • significant limitations in being able to perform accurate antimicrobial susceptibility testing (i.e., detect resistance) of the pathogen to the agent; • antimicrobial agents which require healthcare worker assistance and monitoring.	1	In nearly all cases, infections caused by this resistant pathogen are successfully treated with effective antimicrobial agents.
	2	In most cases, infections caused by this resistant pathogen are successfully treated with effective antimicrobial agents, but there are limitations associated with one or more of the available antimicrobial agents used in place of standard therapy.
	3	There are only one or two classes (e.g., carbapenems) of alternative antimicrobial agents to treat infections caused by this resistant pathogen. Limitations may be associated with the alternative agents, but therapy is usually successful.
	4	There are only one or two classes (e.g., carbapenems) of alternative antimicrobial agents to treat infections caused by this resistant pathogen. The alternative agents have significant limitations which may result in poor therapeutic outcomes.
	5	In many cases, no effective antimicrobial agents exist to treat infections caused by the resistant pathogen.

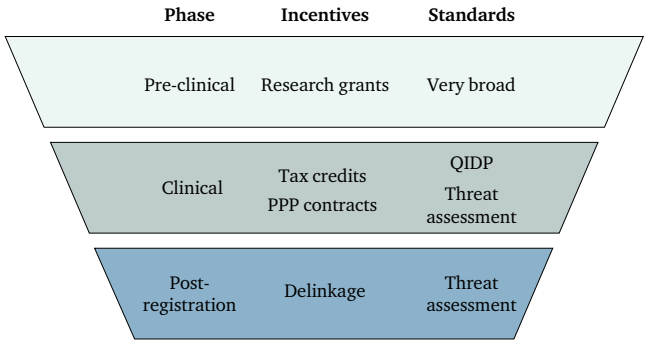
Source: CDC, Antibiotic resistance threats in the United States, 2013.[26]

One of the notable advantages of the CDC threat assessment is that it did not make *a priori* assumptions about whether to focus on any particular category of infective pathogens, such as bacteria, viruses, mycobacteria, fungi or parasites. The threat list was determined by the relative risks, based on the best available data. The remaining criteria and methodology of the threat assessment are detailed in the CDC report. It is important to note that the report only includes threats to the US population. For Europe, the European Centre for Disease Control and Prevention (ECDC) and the European Medicines Agency have jointly conducted a similar threat assessment, attempting to predict the likely availability of effective treatment against multi-drug-resistant bacteria in the future.[27] A global threat assessment would yield different results, even with the same methodology.

Despite its limitations, the CDC threat assessment was a notable process and forms the basis for the following recommendation.

Recommendation 3.1: A comprehensive global threat assessment should be created and periodically updated. The process should be data-driven, transparent and focused on the relative threats posed by resistant pathogens. The threat assessment outcome should be a triage list of pathogens that help guide innovation incentives towards the greatest microbial public health threats. This threat assessment should also evaluate alternative categories (other than by pathogen) that could yield greater impact on public health.

Figure 3: Possible incentive qualification standards over the antibiotic product life-cycle



QIDP = Qualified infectious disease product.

Target later-stage incentives on the greatest threats

Qualification standards should become more stringent as the antibiotic moves towards registration: pre-clinical research incentives such as grants should have the broadest standards, building a robust scientific base. Tax credits for qualified clinical R&D expenditures could be based on a standard such as the FDA's priority review criteria. The most important principle is to target the largest incentive on the resistance problems that are objectively the most threatening, without over-specifying which product will emerge that reduces the threat. The focus in later stages should be on drug-resistant bacteria that are urgent or serious threats, with significant unmet medical need as defined by an evidence-based threat assessment. Therefore, later-stage incentives such as PPP contracts and post-registration incentives should be based on a threat assessment (Figure 3). Thus carbapenem-resistant Gram-negative pathogens present an urgent threat; infections that typically self-resolve, such as *otitis media*, do not.

An important issue is whether incentives should be directed only towards antibiotics developed by identifying new classes, or whether they should also target follow-on innovation for existing classes of antibiotics. The advantage of pushing for new class mechanisms is that these could offer the best path to tackle pathogens with resistance to existing classes. However, there is a higher degree of discovery risk in such programmes, and new agents from existing classes can sometimes offer very valuable new activity. This is the case, for example, with the four generations of cephalosporins, although this fact also suggests that existing market incentives have been sufficient to stimulate innovation for more routine antibiotics. The market failure in antibiotics is concentrated in drugs for serious and urgent threats – the so-called 'superbugs' such as CRE and the ESKAPE pathogens.[28]

Qualified infectious disease products

The US GAIN Act provides incentives for 'qualified infectious disease products' or QIDPs. The statutory language, as interpreted by FDA regulations, is over-inclusive and does not identify priorities based on resistance threat and medical need. Qualifying products are 'intended to treat serious or life threatening infections'. This language is much weaker than the standard applied by the FDA to 'priority review' drugs, which requires the new drug to provide a significant improvement in safety or effectiveness over existing therapies. Any 'qualifying pathogen' designated by the Secretary of DHHS triggers a QIDP designation.

The DHHS Secretary was required to designate a complete list of qualifying pathogens by 2012, considering four factors:

- The impact on public health caused by 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 methodology was expert-based, with revisions scheduled every five years. This appears similar to the CDC threat assessment, but the qualifying pathogens list is problematic for three reasons:

- Congress placed some species on the list, *a priori*.
- It does not prioritize between threats of different magnitudes and there was pressure from industry for an even longer list covering more species.
- Both resistant and susceptible species are covered; the list is not restricted to resistant micro-organisms. However, it may be wise to anticipate future resistance developing where it does not exist now.
- The proposed rule was published in 2013 and includes 18 groups of micro-organisms. As a result of this process, it is difficult to identify any antibiotic approved by the FDA in the past three decades that did not include evidence relating to at least one of these pathogens. It can therefore be expected that almost every new antibiotic will receive QIDP designation.[10, 29]

This lack of prioritization is unhelpful given limited resources, the need for fair returns from public investment, and the challenge that increased therapeutic competition poses to the entry of truly novel antibiotics. New incentives in the later stages should be heavily weighted to the most urgent threats, with lesser incentives allocated to the intermediate category and few or none to the lowest category. In some cases, antibiotics can have some incremental value by diversifying the portfolio of available treatment options, even if other antibiotics currently meet the need.

Recommendation 3.2: To incentivize the development of antibiotics that address unmet clinical needs, the later-stage incentives (clinical development and post-registration incentives) should target antibiotics that treat drug-resistant bacteria posing present or predicted serious threats to humans, as determined by an evidence-based global threat assessment.

Pre-clinical research can target a broader range of antibiotics. Antibiotics should qualify for the highest level of new incentives if they combat resistant pathogens posing an urgent and serious threat to human health, and such rewards should be based on demonstrably superior outcomes in human clinical testing. Antibiotics for less serious threats should qualify for a lower level of new incentives. Some flexibility should be maintained owing to inherent difficulties in predicting future health risks.

4. How Could Funding Be Raised?

Introduction

This chapter examines possible sources of financing for incentive schemes and the mechanisms that might be employed, both through national budgets and by means of global pooled funds. Financing instruments for international scientific projects and environmental protection, areas where collective financing for global public goods has been successfully implemented, are also explored, potentially offering lessons for collective action on antibiotic resistance.

The working group did not have sufficient time to consider whether the best arrangement would be a global pooled fund or primarily domestic expenditures within an agreed global framework. The following discussions and recommendations apply to either arrangement.

Developing a global budgetary agenda for preserving antibiotic effectiveness

There is a lack of information on what overall amounts are necessary for global action to preserve antibiotics, and it will be difficult to coordinate national efforts without a clearer picture of the global targets. Most current and future funds will be raised and spent domestically, but again there is no clear picture of the gaps in spending.

Costs can be divided into several functional streams:

- Incentives for antibiotic R&D;
- Support to guarantee access to life-saving antibiotics in low-income populations;
- Spending to conserve antibiotics, including surveillance, infection control and prevention, vaccination, antibiotic education campaigns and hospital stewardship; and
- The costs of a secretariat or other coordinating body.

Recommendation 4.1: Create a target budget, by priority goal and by unit of accountability (government, region, intergovernmental organization), for the global effort to preserve antibiotic effectiveness, based on the best evidence of clinical need and public health risk. Collectively, this would clarify the global resource commitment required to tackle the challenge of antimicrobial resistance.

Funding through domestic mechanisms in line with globally agreed targets

Most of the funding for R&D incentives, conservation and delinkage could remain within the control of individual governments, provided this was done in a manner responsive to a broader global framework. The primary domestic tools would be grants for basic research; tax credits and public-private partnership contracts for clinical development; and post-approval delinkage payments financed through payers or governments. Additional domestic funds would also be required for public health programmes in surveillance, stewardship, vaccination, and infection prevention and control. While most of the funds could be controlled and spent locally, there is a pressing need for some global coordination, possibly through a secretariat, discussed further below.

Governments and foundations in high-income countries have traditionally funded basic research. We anticipate this will continue, and call for a significant increase of that effort for antibacterial research over the next decade through the traditional model of national research councils. For the expenses of clinical development, a menu of tax credits and financing from public and private sources is needed, as described in Chapter 2.

A global agreement on antibiotic resistance (see Chapter 7) could focus on articulating and prioritizing global targets, while the level of incentives and specific mechanisms could vary by national implementation. For example, the agreement might set a target for tax credits in the range of 25–50 per cent of qualifying R&D expenses, built on the model of existing orphan drug incentives (see Chapter 2). Similar targets could also be articulated for public-private partnerships, built on the models offered by IMI and BARDA. The PCAST report suggested expanding BARDA funding by approximately $800 million a year, which would be an excellent foundation.

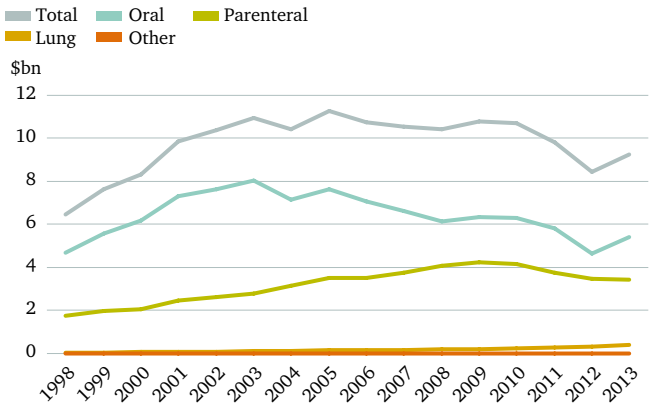
Post-registration delinkage incentives present special funding challenges. One model is to fold the financing mechanism into existing national drug reimbursement systems, funding a national-level 'premium' over current expenditures to make delinkage payments. Given the variety of national healthcare reimbursement systems, the exact mechanism and participation by private insurers would vary, but on a national basis similar levels of 'premium' would be allocated to preserving antibiotic effectiveness, with possible adjustments for poorer countries. For example, governments could make a minimum commitment of a 10–20 per cent premium over current antibiotic expenditures. Politically, this can be viewed as an insurance premium in order to preserve the effectiveness of antibiotics for generations. Additional funding for vaccines, diagnostics, surveillance

and infection control presents a special problem. The last two are not generally reimbursable activities in most health insurance systems, so a 'premium' model is not applicable. For some vaccine and diagnostics, the market sizes are too small to support the level of additional funding needed. One option is to simply allocate some of the antibiotic premium to these activities that extend the life of antibiotics. The premium would not be imposed at the point of care. Given the size of their antibiotic markets, a 20 per cent premium by the EU and the United States would be sufficient to raise about $3 billion per year in total.

In high-income countries, even these higher levels are entirely affordable. In the United States, this level of increase over 2013 antibiotic sales would merely return US antibiotic expenditures to 2005 levels, and raise an additional $2 billion per year, amounting to about 0.6 per cent of US prescription drug spending (Figure 4). To the extent that antibiotics support much of the rest of the healthcare system, these funds represent only 0.0007 per cent of US national health expenditures. On a per capita basis, the increase comes to about $6 per US resident.

Figure 4: US antibiotic sales for human use, 1998–2013 (2009 constant dollars)

Source: Adapted from Outterson et al., 2015[10]



These amounts raised in the United States could be used to significantly boost innovation incentives with global effect. Other high-income countries, such as the EU members and Japan, and upper-middle-income countries, would be expected to participate financially on the basis of their available resources; lower-income countries could participate through non-financial mechanisms such as conservation and surveillance.

Recommendation 4.2: Individual countries should raise funding consistent with regional or global needs and available resources. These funds could be largely retained at the national level but spent according to regional or global targets.

Funding through international mechanisms

The following discussion explores sources of globally pooled financing for antibiotics. The Consultative Expert Working Group (CEWG) in the World Health Organization[30] recommended that governments commit 0.01 per cent of GDP to R&D to meet health needs in LMICs. Member states of the WHO have not yet agreed on any financial commitments following the proposal from the CEWG, underlining the difficulties of convincing governments of the need to commit financial resources for general R&D. However, an improvement in the global system does not require full financial participation from a large number of countries immediately. If initial commitments were just from the OECD countries, a fixed contribution of 0.01 per cent of GDP would yield between $4 billion and $5 billion per year.

As discussed in Chapter 5, after post-registration delinkage payments, companies could (if the payment were to be large enough) contractually license the IP to an international coordinating body. In that case, this public body might generate modest licence fees through downstream licensing with companies producing antibiotics. These licence fees might generate some net revenue that could support the secretariat. In this example, the downstream producing companies would be responsible for the costs of maintaining registration across the globe. These expenses would reduce the net income that could flow to the secretariat. In Chapter 7, we propose a streamlined mechanism for registration of these antibiotics in order to speed access and reduce costs.

Other mechanisms could also be considered. The High Level Taskforce for Innovative International Financing for Health Systems[31] identified airline taxes, tobacco taxes, immunization bonds and debt swaps as the most promising sources for additional financing of health. Examples of innovative financing mechanisms for health that have reached global scale in operation are the Global Fund to Fight AIDS, Tuberculosis and Malaria, UNITAID and GAVI (the Vaccine Alliance). For GAVI, the International Financing Facility for Immunisation (IFFIm) has raised $5 billion from investors on capital markets through bond sales backed by donor guarantees.[32] UNITAID was established to raise additional funds for the treatment of HIV/AIDS, malaria and tuberculosis, and had by the end of 2010 raised $2.2 billion, of which 64 per cent came from a small tax on airline tickets, which since UNITAID's inception in 2006 has been implemented in nine countries (Cameroon, Chile, Congo, France, Madagascar, Mali, Mauritius, Niger and the Republic of Korea).[33] Start-up costs and competencies are needed for international innovative financing to operate in a manner that generates sufficient resources.

While there are key lessons to be learnt from the existing international programmes mentioned above, focused on the

needs of LMICs, the case of antibiotics differs in that novel antibiotics are needed in rich as well as poor countries. The global nature of antibiotic resistance and the need for novel antibiotics in every part of the world may shift the focus towards arrangements that more naturally cross-subsidize resources from wealthier to less wealthy parts of the global market rather than depending on a voluntary and unpredictable philanthropic response among donors.

Recommendation 4.3: Identify stable sources for regionally or globally pooled funding for antibiotic resistance, to be coordinated through a secretariat.

Lessons from international science projects and international climate finance

When faced with important scientific goals beyond the reach of any one government, international partnerships have successfully funded a number of global science projects such as CERN and the International Space Station (see Table 2). The coordinating mechanisms are generally contractual, with a coordinating entity funded by the partner countries.

Some of the above models may be relevant in exploring different mechanisms to mobilize funding regionally and globally to combat antimicrobial resistance.

Similarly, international cooperation has resulted in global financing mechanisms and associated coordinating bodies for environment and climate change, such as the Climate Investment Funds (CIF), the Global Environment Facility (GEF), the Green Climate Fund and the Multilateral Fund for the Implementation of the Montreal Protocol. These may offer lessons for the initiation of financing and replenishment, the range of sources to harness and the structuring of the entity responsible for coordination.

The longest-standing multilateral climate change fund is the GEF, which since 1994 has been the financial mechanism of the United Nations Framework Convention on Climate Change (UNFCCC). Initial partners in establishing the GEF were UNDP, UNEP and the World Bank, with this last body serving as administrator of the fund. Replenishment of the fund occurs every four years through negotiations managed by the World Bank together with the GEF Secretariat. During the establishment of the GEF it was suggested that all countries interested in participating should contribute one per cent of GDP, but this has not been implemented. Burden-sharing arrangements guide resource mobilization, but the small contribution of the United States relative to its GDP has limited the size of pledges by other countries.[34]

When faced with important scientific goals beyond the reach of any one government, international partnerships have successfully funded a number of global science projects such as CERN and the International Space Station.

For the CIF, a high level of buy-in from a limited number of countries – the United States, the United Kingdom, Japan, Germany and France – was sufficient to generate an initial pledge of $6.5 billion.[35]

Currently, efforts are under way to establish the Green Climate Fund as a new financing mechanism connected to the UNFCCC, which eventually might replace or subsume other funds. Financial capacity is determined by contributions from donor countries, innovative mechanisms and the private sector.[36]

Finally, the Montreal Protocol on Substances that Deplete the Ozone Layer may offer relevant lessons for a future agreement on antibiotic resistance. The Montreal Protocol proceeded with initial mild steps followed by periodic scientific assessments, permitting cautious governments to join the protocol as it progressed.[37] The multilateral fund connected with the protocol was meant to provide a financial mechanism for covering LMICs' incremental costs in gradually phasing out ozone-depleting substances.

Recommendation 4.4: Evaluate lessons from international science projects and climate finance models for global, pooled funding mechanisms to address antibiotic resistance.

Table 2: Funding examples from international science

Project	Cost	Location	Funding countries
Square Kilometre Array radio telescope	$1.5–2bn	Australia (South Africa)	Australia, Canada, China, Italy, Netherlands, New Zealand, South Africa, Sweden, UK
Human Genome Project	$3bn	Global	US, UK
Large Hadron Collider (CERN)	$4.4bn	Switzerland, France	21 member states and many collaborating countries and organizations
International Thermonuclear Experimental Reactor	$50bn	France	EU, India, Japan, People's Republic of China, Russia, South Korea, US
International Space Station	$150bn	Space	US, Russia, EU, Japan, Canada

5. What is the Role of Intellectual Property?

Introduction

Intellectual property (IP) rights, particularly patents, provide the existing legal framework that incentivizes companies to invest in R&D, including for antibiotics. Under a delinkage scheme, companies will be offered delinkage rewards after registration, as discussed in Chapter 2. As part of that voluntary contractual arrangement, companies will sign an IP licensing agreement with the secretariat. The arrangement is expected to cover the full patent term, including all periods of exclusivity. Company concerns about losing IP licensing rights should diminish so long as post-registration antibiotic delinkage rewards are generous and voluntary.

The IP rights may be retained by the company, partially licensed or sold outright. If they are retained by the company, the post-registration delinkage reward would require the patent holder to provide the drug on demand exclusively to the secretariat at an agreed price based on the cost of production. The secretariat would then oversee global distribution arrangements. If the IP rights are sold outright, the secretariat takes over all functions, including manufacturing, sales and global regulatory approvals. In the intermediate partial buy-out scenario, the IP rights are licensed to the secretariat, but these tasks remain with the company. Table 3 summarizes these options.

This raises several important practical issues. Currently, the patent owner is responsible for gaining marketing approval worldwide; requirements for registering the drug differ from country to country. The patent owner is also legally responsible for carrying out the post-registration studies (Phase 4 studies) and pharmacovigilance,[38] and for communicating the knowledge about real-world safety and efficacy to drug regulatory authorities worldwide. As discussed in Chapter 7, the global registration process for antibiotics (Recommendation 7.2) can be streamlined, but many significant tasks and costs remain. If the original innovator company bears the responsibilities for these tasks, then post-registration delinkage rewards will have to be larger. Conversely, if the secretariat administers global registration, production and post-marketing surveillance, delinkage payments can be smaller. The latter option may be more attractive to smaller companies that lack the capacity to register and manufacture the drug globally. Finally, under a sublicence, generic companies may be unwilling to manufacture if restrictions imposed on marketing and sales volume limit returns. In that case, other incentives need to be considered.

Transfer of IP rights can facilitate other goals as well, such as ensuring access, reducing inappropriate use and developing open innovation systems. Most of the remaining open issues concern assignment of various responsibilities for producing and maintaining the drug after registration.

Delinkage models will still operate within the policy and legal space created by the existing IP laws, at least up to the point when the antibiotic enters the delinkage scheme. The next sections discuss three specific issues concerning the interaction between IP and delinkage, where we draw three conclusions: delinkage should ensure affordable access for new antibiotics to low-income populations (and not necessarily just in LMICs); extension of exclusivity periods is not the preferred tool for antibiotics innovation; and innovative but unpatentable antibiotics should be eligible for delinkage rewards.

Delinkage should ensure affordable access for new antibiotics to low-income populations

Lack of access to antibiotics is a major cause of morbidity and mortality from infectious diseases in many low-income populations.[39] For example, only one-third of children in LMICs receive antibiotics for suspected pneumonia, which is the number one cause of child mortality worldwide.[40] Children in the lowest household wealth quintiles are less likely to receive treatment on time.[41] In many LMICs, the most prominent barriers to access to existing antibiotics are supply chain challenges, lack of an adequate healthcare

Table 3: Rights and responsibilities for the patent holder and the secretariat in three IP holding scenarios

IP scenario	IP rights	Antibiotic price	Antibiotic sales revenues accrue to	Manufacturing arranged by	Regulatory approvals, post-approval studies, education, etc. by
Marginal cost procurement contract	Owned by company	At company cost to secretariat; set by secretariat downstream	Secretariat	Company	Company
Partial buy-out	Licensed to secretariat	Set by secretariat	Secretariat	Company	Company
Full buy-out	Licensed to secretariat	Set by secretariat	Secretariat	Secretariat, through licensing or contracts (including with the company)	Secretariat, through licensing or contracts (including with the company)

system[42] and relatively high prices for patients who are unable to access these drugs free of charge through the public sector.[43] Maintaining affordability of antibiotics for populations and health systems in LMICs, while ensuring stewardship and the responsible use of new antibiotics, should be a priority for any new antibiotic business model.

With respect to IP, a key question is whether these goals are most effectively pursued through public or private control over rights. Since the delinkage incentives will be financed primarily by public resources, it is in the public interest to maximize savings in the supply of the final product, and in particular to ensure that new antibiotics are appropriately delivered to low-income populations. If IP and product management become the responsibility of the secretariat, there will be a natural pathway for transferring the responsibility to the public sector. Public ownership of IP rights may enable a significant subset of governments to work together to manage the new antibiotics in a way that ensures both access and conservation.

Specific steps are required if companies are to address access to new antibiotics in a systematic manner. One way of securing distribution of affordable new antibiotics to low-income populations would be to tie parts of the post-registration payments to the supply of antibiotics to specific geographic areas. If the innovating company decided to supply the drug worldwide, it would be entitled to post-registration payments reflecting this global scope. Alternatively, the innovating company could decide to limit the scope of the drug to specific geographic areas, in order to devolve responsibility for building a supply chain and maintaining global registrations. For the remaining territories, the secretariat would coordinate supply among generic companies, using a share of the post-registration rewards to reflect the geographic areas covered by its licence.

In summary, the delinkage model can potentially facilitate global access, regardless of whether IP rights remain with the innovator or are publicly owned, as long as responsibilities for ensuring access are appropriately allocated at the time when post-delinkage payments and IP ownership are being negotiated.

Recommendation 5.1: The delinkage business model should promote global access to antibiotics together with their appropriate use. Appropriate responsibilities should be allocated between governments and innovators when the terms of the delinkage payments are negotiated.

Extension of exclusivity periods is not the preferred tool for antibiotic innovation

The period of exclusivity resulting from intellectual property rights delays the arrival of generic competition. For antibiotics, the net present value (NPV) for investments is low for several reasons. In the immediate future, most new antibiotics are unlikely to be demonstrably superior to less expensive generic ones, in part because approval procedures only require new drugs to perform at least as well as existing ones.[44] Innovators will therefore have difficulty achieving higher prices. Stewardship efforts will most likely advocate reserving new antibiotics until a clinical need unmet by existing antibiotics arises, and restricting use to certain indications in order to preserve antibiotic effectiveness. For these reasons, the market share for new antibiotics is diminished, and return on investment too low, particularly in comparison with drugs for other diseases.[5, 45]

As noted earlier, increasing the length of exclusivity does not materially address the problem of low NPV. From the perspective of a company making a pre-clinical R&D investment decision, time discounting significantly reduces the value of this incentive over time.[9, 46] Additional years of data exclusivity or patent protection may not generate additional sales for a number of reasons, including resistance and loss of antibiotic effectiveness, as well as market competition from other antibiotics and follow-on drugs.[24]

Finally, leaving companies to rely on sales during an IP-protected period of exclusivity to generate a return on investment may drive incentives for excessive promotion of the drugs in order to recoup investments in R&D, particularly during the few remaining years of the exclusivity period,[44] thereby risking overuse and resistance. For these reasons, therefore, intellectual property expansion is not recommended as an innovation incentive.

Wild-card patents (or transferable IP rights) are a possible way to overcome some of the drawbacks of exclusivity extensions because they can in principle be monetized on receipt, and potentially for very large sums. However, they impose costs on the patients or payers using the product which receives the wild card, and they are not particularly fair or efficient.[24, 47]

In contrast, delinkage models have the potential to simultaneously address multiple problems related to IP as an innovation incentive. As suggested in Chapter 2, innovators would receive generous innovation reward payments that entirely replaced volume-based sales. By generating return on investment by other means than maximizing sales volume during a period of IP-protected exclusivity, the NPV of investments in antibiotics is raised without implementing incentives that may lead to overuse of the drugs.

Recommendation 5.2: IP expansions should not be considered as incentives for early-stage antibiotic innovation. Later in the market life-cycle, the use of IP incentives to ensure monopoly pricing should also be avoided, since it risks both exacerbating the over-marketing of antibiotics and becoming a threat to global access.

Innovative but unpatentable antibiotics should be eligible for delinkage rewards

Although it will not often be the case that an old drug can usefully be brought into development, the absence of traditional patent protection for an otherwise qualifying drug should not hinder transfer and payment of delinkage rewards. Patents on a qualifying antibiotic should therefore not be a requirement for entry into a delinkage regime, and firms registering a new antibiotic without patent protection (such as new uses for old drugs) should also be eligible for delinkage rewards. Items transferred would include the marketing approval registration with drug regulatory authorities, together with data exclusivity and other related IP rights.

Under a delinkage model, companies could negotiate to either retain or transfer the right to certain follow-on innovations. The scope of these rights must be defined. Modest changes to a drug should probably not be included, but some follow-on drugs represent significant therapeutic improvement. For example, they could have therapeutic value by widening the anti-bacterial reach of a functional drug class, similar to the development of the four generations of cephalosporins. However, these innovations were achieved without new antibiotic business models and so may not require additional financial incentives. Companies should also not be able to come to market with a follow-on antibiotic that promoted resistance to a previously delinked antibiotic, although setting rules to prevent this would be challenging.

Recommendation 5.3: Delinkage rewards should be permitted for highly innovative but unpatentable antibiotics.

6. How Can New Incentives Be Reconciled with Rational Use of Antibiotics?

Introduction

Bacterial resistance is an evolutionary response to exposure to antibiotics. The WHO, national public health authorities and governments worldwide have called for improved use of antibiotics based on evidence that resistance is being driven by antimicrobial overuse in hospitals, clinics, farm food animals, aquaculture and agriculture.[48, 49]

The resulting selective pressure has fostered new resistant infections and shortened the effective life of many valuable and affordable antimicrobial agents. As explored in previous chapters, strong economic incentives are needed to increase the R&D of new antibiotics while ensuring return on investment that is delinked from the volume of sales. After registration, additional incentives to reduce unnecessary exposure will promote the antibiotic's long-term effectiveness and maximize the public's return on investment. Society cannot afford to repeat the recent history of the gradual undermining of multiple classes of antimicrobial drugs. The conservation objectives of the delinkage model should be to reserve the new publicly funded special agents for the most urgent needs, target therapy to the pathogen and constrain unnecessary use.

There is general agreement among public health stakeholders that overuse of antibiotics for unnecessary conditions is widespread and must be contained to minimize resistance. However, a challenge to rationalizing antibiotic use is the lack of a coherent definition of 'rational use'. Assessing it at the individual case level can be difficult – empirical use of a specific agent may be entirely correct even if a specific target pathogen is not isolated. Achieving rational use should be one of the primary objectives of the delinkage model, and how to develop a standard for responsible use is a question that will be explored by the DRIVE-AB research project.[50]

A number of ways for reducing antibiotic use do not depend on a clear definition of appropriate use, and can be considered immediately for the benefit of global public health.

Another challenge is the lack of publicly available data about antibiotic sales and use. Public investment in such data is a foundation for effective research on antibiotic use. There is a lack of comprehensive, global data on antibiotic consumption, by class, country, medical indication and sector (human, agricultural and environmental). The best existing data on human use are regional, as for example in the EU,[51] or only available from commercial sources such as IMS Health, which charge significant licence fees for research and public health use. All of the data have some methodological weaknesses with regard to internal validity, comparability and the gap between sales and actual consumption. Data are particularly weak for many LMICs. In the agricultural sector, only a few countries report transparent data.[49] Finally, bacteria in the environment are exposed to antibiotics in ways that are not currently monitored, including during wastewater treatment, industrial processes and the environmental use of antibiotics, such as triclosan on toys or in soaps.[52–54] This indicates how much is unknown at present.

Recommendation 6.1: Data on antibiotic sales, distribution and use should be publicly reported, and standards should be developed for the responsible use of antibiotics.

Encouraging antibiotic conservation efforts independent of evaluating appropriate use

A number of ways for reducing antibiotic use do not depend on a clear definition of appropriate use in humans, and can be considered immediately for the benefit of global public health. These include infection prevention; enhancing laboratory capacity and diagnostics; and reducing inappropriate use in agriculture.

The most direct way is to prevent infections by ensuring clean water and food, sanitation, vaccines and infection control in healthcare institutions, and rates of many infections could be reduced with more significant investments in public health measures. In many low-resource settings, the absence of these public health measures is contributing to increased antibiotic use and dissemination of resistant bacteria.[55, 56]

There is an urgent need for more sensitive, specific and rapid diagnostics.[57] Progress in diagnostics assists companies in clinical trials and better supports the physician in decision-making, enabling some patients to avoid an antibiotic (if the infection is viral), others to cease antibiotic therapy early, and still others to have the pathogen correctly identified so that the most clinically appropriate drug can be used. Other devices may also hold promise for a great reduction in the use of antibiotics. For example, the EntraTympanic device under development will release inner ear pressure and allow ear infections to self-resolve without pain, thereby significantly reducing US antibiotic use by children aged under five.[58]

Concerns about resistance arising from antibiotic use in agriculture have led to significant restrictions in some countries; however, there is limited or no action in many others.[48, 59] Some question the relative contribution of

agricultural and animal antibiotic use to human resistance, calling for more research.[23, 48]

Countries employing the precautionary principle are acting now, based on the information available, while others are taking a more gradual approach. Additional research specifying the human health impact might enhance the level of consensus. There is also a possible trade-off to be made between costs associated with increased resistance and the greater costs of producing food with significantly lower use of antibiotics, but these costs have not been fully quantified and depend on the extent to which better farming practices that reduce infection prevalence can be easily introduced in different farming systems.[60] The PCAST report called for research into alternatives to antibiotics in agriculture. If good alternatives for farmers in both high- and low-resource settings were available, then political barriers to agricultural restrictions would be lowered. Research should include cost-effective animal husbandry practices that require fewer antibiotics. Given the significant global variation in antibiotics used per pound of meat produced, it will also be valuable to explore how productivity in livestock husbandry and aquaculture might be improved while restricting antibiotics to therapeutic use.

The agricultural sector is one area in which antibiotic use also falls within the regulatory domains of the Food and Agriculture Organization (FAO), World Organisation for Animal Health (OIE), Codex Alimentarius, World Trade Organization (WTO) and regional trade agreements, thereby requiring coordination between different areas of global governance.[60, 61]

In summary, public investments in these domains can yield very significant reductions in antibiotic consumption, and clinical and economic savings, without confronting the need to evaluate whether the use is 'rational'.

Recommendation 6.2: Invest significant public funds to accelerate global infection-prevention (public health, clean water and food, vaccination), increase investments in infection-preventive technologies (host-directed therapies and monoclonal antibodies), improve surveillance of resistance and antibiotic use (including transparent data), and enhance laboratory capacity and innovation of diagnostic devices (with rapid point-of-care diagnostics as a priority) that can reduce the inappropriate use of antibiotics.

The role of delinkage and service contracts in ensuring rational antibiotic use

Delinkage and service contracts have a potential role to play in ensuring rational use of antibiotics. Any company accepting full delinkage rewards will no longer be able to recover R&D costs reimbursed solely from sales, thereby reducing or eliminating the incentive for that company to over-market its antibiotic. A clear understanding of the precise role of company promotion in driving antibiotic sales in appropriate and inappropriate uses is currently lacking. A comprehensive overview of the evidence of how marketing influences sales of different types of antibiotics across healthcare and geographic settings is therefore highly desirable. However, it seems likely that delinkage models would improve the situation overall by removing the financial incentives for companies to promote use.[2]

In addition, it has been suggested that delinkage could allocate some responsibility to companies for conservation.[47] Such efforts could be incentivized by making some portion of the reimbursements contingent on intermediate endpoints short of actual human health impact, such as metrics related to appropriate use in various settings and clinical resistance. Since the delinkage model results in companies relinquishing the right to volume-based sales revenue, some may find it unacceptable that parts of the innovation rewards are contingent upon factors beyond their control, such as clinical resistance driven by inappropriate healthcare practices and overuse of other antibiotics in the similar functional class. However, companies have superior information about their products and extensive global networks with providers, governments, reimbursement systems and professional societies. While the main responsibility for ensuring appropriate use and conservation should rest with public authorities and/or the payers, companies could enable more effective management of antibiotics in delinkage models.

Another possibility would be to keep delinkage revenues protected, but to sign separate 'service contracts' with the companies for tasks such as antibiotic conservation and maintaining global registrations. This would harness their networks and expertise without imperilling the core function of delinkage. If this contractual route is chosen, then the process could be open to other companies and civil society as well, with contracts possibly let on a national or regional basis.

Recommendation 6.3: Post-registration service contracts could include conservation activities as well as maintaining global registration and production of the drug.

Incentivizing other stakeholders in the supply chain

Many other actors in the supply chain to the patient have incentives misaligned with the preservation of antibiotic effectiveness. Depending on the national system, hospitals and providers, pharmacists, other healthcare institutions and veterinarians can derive a significant portion of their income from drug sales, including antibiotics.[62, 63]

Delinkage removes inappropriate incentives for drug companies, but does not necessarily modify inappropriate financial incentives in the rest of the supply chain. At a minimum, research will need to evaluate the impact of perverse financial incentives and identify solutions to remedy them. Incentives promoting overuse should be eliminated, and various stakeholders should accept responsibility for ensuring appropriate use and preserving antibiotic effectiveness (Table 4).

Recommendation 6.4: A comprehensive, multi-level study should be undertaken to explore the perverse financial incentives leading to the over-selling and overuse of antibiotics.

Globally coordinated areas to rationalize the use of antibiotics

The WHO Global Action Plan on Antimicrobial Resistance approved in May 2015 could mobilize national commitments for globally coordinated action.[64]

Each country could ensure that financial considerations are not placed above the combined goals of optimizing patient outcomes while reducing inappropriate use; cooperate in a global effort to improve professional practice around antibiotics, and educate the public regarding the uniqueness of antibiotics relative to other pharmaceuticals; and support antibiotic stewardship in hospital and community settings. Low-income countries may require external assistance to achieve these goals, and financial resources and technical capacity for such assistance should be mobilized.

To enable global buy-in, solutions and mechanisms for antibiotic conservation must be tailored to local practices and laws. In some settings, financial incentives may be a significant driver for inappropriate prescribing.[62, 63] In other settings such as hospitals, financial considerations may lead prescribers to use the cheapest, but incorrect, drug first, resulting in sub-optimal outcomes for patients. Each country or region will therefore have to identify and eliminate financial incentives that drive inappropriate use, while encouraging incentives to stimulate appropriate use in areas with chronic under-provision of life-saving antibiotics. Financial incentives should be evaluated across all stakeholders: branded and generic drug companies, providers, pharmacies, hospitals and other healthcare institutions.

Some inappropriate use of antibiotics is driven by patient demand, irrespective of whether the use is clinically appropriate.[65–68] The WHO should lead a global effort, funded on a more robust level and with tools to measure impact, to educate populations about the implications of inappropriate antibiotic use. Although specific messages need to be culturally appropriate, the underlying concepts are universal and can be spread more effectively and with greater impact if globally coordinated, as shown with the 'Clean Care is Safer Care' campaign.[69, 70]

Globally, healthcare systems must support mechanisms to ensure rational use of antibiotics, through interventions such as antibiotic stewardship programmes and other

Table 4: Stakeholder responsibilities for antibiotic conservation

Stakeholder	Examples of responsibilities for antibiotic conservation
Companies	• In return for delinkage contracts, accept responsibilities to support appropriate use, including restrictions on marketing of antibiotics, submitting data on antibiotic sales, distribution and use, and contributing to post-market surveillance of resistance levels.
Governments and public health authorities	• Carry out prescription controls, surveillance and monitoring of resistance trends. • Support the implementation of hospital stewardship programmes and academic detailing. • Implement policies removing financial incentives to overuse of antibiotics along the entire supply chain from pipeline to patient.
Insurance payers (public and private)	• Monitor use through provider profiling, undertake continuous quality improvement of prescribing practices and ensure uptake of available diagnostics for supporting antibiotic stewardship.
Medical professional organizations and societies	• Engage in production of guidelines, and organize continued medical education on antibiotic resistance and antibiotic stewardship. • Engage in effective communications to address misperceptions concerning overestimation of the benefits of antibiotics and underestimation of the negative effects of their overuse.

proven conservation methods.[71] Antibiotic stewardship programmes optimize clinical outcomes by getting the right antibiotic to the right patient at the right dose and time, and by involving infectious disease physicians, clinical microbiologists, epidemiologists, and hospital pharmacists and administrators.[72] These programmes rationalize antibiotic use in healthcare institutions, thereby minimizing the unintended consequences (e.g., toxicity, selection of pathogenic organisms, emergence of resistance), as well as reducing healthcare costs. Other policies might designate certain antibiotics for empiric therapy or reserve others for more serious cases. In the community setting, stewardship would attempt to help improve the use of antibiotics by prescribers and pharmacists. Policies should be continuously evaluated to ensure that patient outcomes are optimized.

Global conservation efforts will be critical for the sustainability of new antibiotics. Antibiotic conservation should therefore be partially financed by funds allocated to delinkage models, as additional incentives for R&D should not be at the expense of conservation. At present the relative cost-effectiveness of incremental spending in R&D versus conservation is unknown, so new research will be needed to decide the appropriate allocation of funds between these two areas.

Recommendation 6.5: The global antibiotic conservation effort should be partially financed with funds allocated to delinkage models, and new research should estimate the appropriate allocation of funds between conservation and R&D. Proven conservation methods such as antibiotic stewardship programmes should be incentivized and implemented immediately as part of global conservation efforts.

Managing generic entry in the delinkage model

Obligations for responsible use can be carefully crafted and functional when monopoly rights are in place, but are likely to fail once generic antibiotics are introduced upon the termination of the period of exclusivity. Generic manufacturers ordinarily rely on volume-based rewards, and low prices and large volume of sales without appropriate measures to conserve the antibiotics may be an important driver of indiscriminate use and resistance. A sustainable system will require controls on market entry after termination of the patent, and regulation of the way the generic products are marketed and prescribed.

One suggestion to manage generic entry is to incentivize generic manufacturers to forgo marketing and revenue from volume-based sales in exchange for more flexible, term-limited, contract-based rewards. At the global level, a WHO regulation (see also Chapter 7) to contain the spread of antibiotic resistance, adopted by the World Health Assembly (WHA), could enable states to collectively address marketing, distribution and utilization of both branded and generic antibiotics. Such a regulation may request countries to establish antibiotics as a separate class of drugs with special protections and marketing provisions, where new antibiotics developed under delinkage models will only be authorized for certain uses. Approval of a generic version could be globally coordinated, and be contingent on restrictions on marketing as well as the acceptance of responsibility for ensuring appropriate use. Provisions could permit drug regulatory authorities to revoke the marketing authorizations for generic antibiotics if monitoring and surveillance reveal marketing and supply practices that promote inappropriate use. In any event, strict regulation of appropriate use will dampen the potential issues with patent expiry.

Recommendation 6.6: Empirical research into the relationship between generic market entry, therapeutic competition and resistance should be conducted to help guide the creation of mechanisms regulating entry of generic antibiotics to the market.

7. How Can a New Scheme Be Applied Regionally and Globally?

Introduction

A comprehensive new business model for antibiotics should ensure that new antibiotics are accessible globally where needed, while simultaneously having in place mechanisms to prevent inappropriate use. While the model should seek to be globally coordinated, different types of innovation rewards may be implemented in different territories.

This chapter discusses how new business models could be implemented globally despite differing levels of ability to finance the innovation rewards, and how to engage countries that do not at first participate financially. It also briefly discusses possible global governance arrangements for managing antibiotic IP rights and promoting conservation of new antibiotics.

Geographic scope of financial participation

A number of factors would determine the geographic scope of the model, with countries being able to participate on many levels. Participation could also increase over the life-cycle of the antibiotic, with broader participation as it moves towards registration. As discussed in Chapter 2, incentives are divided into three categories: pre-clinical, clinical and post-registration.

Pre-clinical and clinical development incentives can be implemented in parallel in all countries with significant research activity, whether through grants, contracts or tax credits to entities undertaking research and clinical trials. Currently, antibiotic clinical trials are undertaken in a relatively small number of high-income countries, although the numbers are increasing worldwide. All countries with significant research activity should be encouraged to implement pre-clinical research and clinical development incentives through these various types of incentives under domestic law, as discussed in Chapter 2.

Not all countries can be expected to contribute financially from the outset, so most of the resources will initially come from countries willing to lead. However, inappropriate financial incentives for antibiotic use should be avoided in all countries as far as possible. This requires global efforts, which should cover the majority of the global market value for antibiotics. Most growth in global antibiotic markets since 2000 has been in BRICS countries,[55] so including them will be crucial for global, sustainable implementation. These issues are summarized in Table 5.

Expanding participation beyond those who contribute financially

Global access to new antibiotics should be one of the primary objectives of any new business model. At the same time, globally implemented conservation mechanisms that change the worldwide use of antibiotics will be crucial for the future value and utility of new drugs. An important question is how non-financing countries, expected to be predominantly LMICs, will participate with respect to access, innovation and conservation.

One rejected option is to permit the patent holder to make volume-based sales to non-financing countries. There would be uncertainty around how to ensure access to underserved populations in non-financing LMICs, particularly if the innovator decided to seek profits by setting a high price on these drugs. Given the probable price competition with cheaper, generic antibiotics, a more likely scenario would entail the innovator selling through differential pricing in LMIC settings. However, depending on the market size and production capacity, differential pricing too may be unable to ensure an adequately low price for low-income populations in LMICs.[73]

If countries not participating financially in supporting antibiotic R&D were denied access to the resulting novel antibiotics brought to market, their buy-in on a broader conservation programme would be compromised. A preferred option is therefore to accept non-financial participation in return for access to novel antibiotics: LMICs that are initially unable to contribute financially may still participate meaningfully through ongoing surveillance

Table 5: Categories, types and expected geographic scope of incentives

Category	Type of incentive	Expected initial geographic scope
Pre-clinical and clinical development incentives	Research funding, tax credits, milestone prizes under PPPs	Countries and regions with significant pre-clinical and clinical research activity
Post-registration incentives	Delinkage contracts	Financially significant antibiotic markets, including BRICS
Access incentives	Licensing from a public body or contractual commitments	Global, with particular emphasis in low-income populations
Conservation incentives	Financial and non-financial contributions to preserve antibiotic effectiveness, including clean water and food	Conservation must be global in scope in order to preserve the value and utility of new antibiotics, preferably coordinated by a global agreement

efforts, hosting clinical trials and implementing domestic measures to control the inappropriate use of antibiotics. This should include prioritizing resources to upgrade surveillance activities by enhancing laboratory capacity for diagnosis and monitoring antibiotic use, implementing stewardship programmes and reasonable controls on distribution (i.e., physician or veterinary oversight, to the extent that these measures are practical and appropriate given shortages of such personnel in many settings). Efforts to improve water and food safety and related public health efforts such as vaccination should also be recognized, as these too reduce antibiotic use.

This system is intentionally designed to facilitate participation by all countries, irrespective of their financial contribution, for three reasons:

- *Practicality*: the model must get off the ground without universal financial participation;
- *Equity and access*: the poorest countries may not be able to participate financially in the model initially, but the health of their people can benefit from access to new antibiotics; and
- *Self-interest*: countries financing new business models will directly benefit from other countries having access to drugs in exchange for strengthened surveillance, monitoring and detection of resistance, as well as fewer cases of inappropriate use. These efforts will reduce the global emergence and spread of resistance, for universal benefit.

While non-financial participation from LMICs may be acceptable, free-riding from high-income countries should be avoided. Some form of financial commitment, in the form of a one-time national fee linked to market authorization or another form of payment, must be demanded from high-income countries that do not participate in the broader system in order for them to access these new antibiotics.

Reinforcing global conservation efforts through contract

When paying post-registration delinkage rewards, an opportunity arises to make contractual commitments that facilitate access and include safeguards regarding conservation (see Chapter 6). For example, if a company were to bring a powerful new antibiotic to market, it would negotiate post-registration rewards contracts with various countries, but each of those contracts could also restrict antibiotic marketing and promotional activities by the company globally, including in countries that are not financial participants in funding the rewards scheme.

Streamlining global registration of antibiotics

Many LMICs lack adequate national drug regulatory systems,[74] and worldwide approval through drug regulatory authorities with differing requirements and standards is costly, especially for new antibiotics with quite limited sales prospects. Delinkage models could be an opportunity to develop a globally acceptable drug regulatory approval process for new antibiotics. This would be particularly important for countries where drug regulatory systems are weak. Experiences could be drawn from the WHO pre-qualification programme, which since its establishment in 2001 has pre-qualified over 350 pharmaceutical products.[75] A globally acceptable approval process could be particularly important for facilitating marketing approval in cases where delinkage results in IP rights being transferred to a public entity.

Recommendation 7.1: While complete global coverage is the ultimate goal, the geographic scope of participation can vary in the early years. Financial participation can begin with a core group of countries with significant pre-clinical and clinical research activity, and countries that comprise large antibiotic markets. From the start, every country should participate through surveillance, hosting clinical research, conservation and public health initiatives.

Recommendation 7.2: A globally harmonized antibiotic approval process, acceptable in particular to countries with weaker national drug regulatory systems, should be established for antibiotics resulting from the new business model.

A global coordination mechanism for IP

It is likely that many of the necessary functions will be delivered through a variety of bodies primarily at the national level. As discussed in Chapter 4, the financing of pre-clinical and clinical R&D could continue to come from national budgets and be delivered through national institutions. Post-authorization delinkage rewards and global antibiotic conservation could follow a global framework agreement with national implementation as well. Global coordination could reduce duplication of effort, resulting in more efficient use of resources, and could direct resources towards areas of greatest need. In addition to financing, the management of IP in order to facilitate global access is likely to require a global coordinating body (see Chapter 5).

The Medicines Patent Pool (MPP) currently negotiates voluntary licences from patent holders and subsequently issues non-exclusive sub-licences to third parties who can manufacture anti-retrovirals and supply LMICs.[76] This

could be a model for global coordination of IP in cases where antibiotic delinkage results in the transfer of IP rights to the public, through either a patent buy-out or a voluntary licence (see Chapter 5). While having individual governments as patent or licence holders is an option, this would require individual countries to negotiate separate licences with generic manufacturers, thereby increasing transaction costs, and complicating coordination of both access and conservation. A more efficient mechanism could be to place the patent or licence in the hands of a third party such as the MPP, which can manage IP rights transparently and coordinate global access.

A new global coordinating body could initially be hosted by an intergovernmental organization (IGO), for example the WHO, thereby drawing upon the expertise of existing international institutions. The MPP started as part of UNITAID and subsequently became a separate legal entity.[77]

Another example is the GEF, which was established with the UNDP, UNEP and the World Bank as implementing agencies. Global coordination of IP licensing must be supplemented by additional international mechanisms for surveillance and conservation.

Recommendation 7.3: Antibiotic incentives, while mostly implemented domestically, should be coordinated globally through a secretariat. This body could potentially deal with a range of functions that could grow over time as competence develops, including coordinating IP licences, mobilizing funding of incentives, and promoting appropriate use.

Recommendation 7.4: The Medicines Patent Pool should be evaluated as an entity to hold and coordinate global IP licences for antibiotics.

Moving towards global governance of antibiotic resistance

The safe introduction and conservation of new antibiotics require a global environment where all countries have the commitment and capacity to contribute to the long-term effectiveness of these drugs. Long-term conservation of antibiotics, which share properties as an exhaustible common-pool resource akin to other natural resources,[78] is a collective action challenge that must be met through international cooperation.[79, 80] Experts have therefore suggested that lessons can be drawn from international agreements on environmental and natural resource challenges, such as the Montreal Protocol for phasing out chlorofluorocarbons or the Code of Conduct for Responsible Fisheries, as models for a future agreement on antibiotic resistance.[1, 81]

However, while the Montreal Protocol required countries to agree on a few objectives concerning the phasing out of substances affecting the ozone layer, a potential future agreement on antimicrobial resistance will have to be more complex and multifaceted, dealing with the interdependent areas of access, conservation and innovation.[82, 83]

A broad international agreement will need to package objectives for these three areas together, define targets for governments to achieve, ensure monitoring of national commitments, and consequently hold states accountable for their implementation. Once a global agreement is reached, the details of the implementation should be left to each government, given the variety of domestic conditions, laws, and public and private healthcare insurance systems. In addition to setting norms and targets, an international agreement should facilitate the flow of resources and technical expertise to states with weak capacity to fulfil international commitments on strengthening surveillance systems, upgrading laboratory capacity and other measures to ensure the responsible use of antibiotics.

Among the intergovernmental settings that could form a platform for negotiating a treaty or another type of global agreement, the WHO emerges as the natural choice, given its directing and coordinating role on health issues, and its constitutional authority to negotiate both hard and soft law instruments.[84] On the other hand some doubt the WHO's capacity, in particular to deal with issues that are multi-sectoral in nature. Therefore, as managing antibiotic resistance at the global level is likely to require the involvement of other multilateral institutions and sectors, a broader negotiation platform at the UN level may be required. Examples include involving the Codex Alimentarius Commission to address the levels of antibiotics permitted in traded food products, the WTO to permit national restrictions on the importation of meat raised with antibiotics, and the FAO and OIE to address the use of antibiotics in agriculture and animals.

A number of different international commitment mechanisms exist for facilitating cooperation between states, both binding and non-binding, varying between conventions, contracts, declarations and institutional reforms.[85] A non-binding (or 'soft law') instrument could be a political declaration, a code of practice or a set of recommendations, for example the WHO Global Action Plan on Antimicrobial Resistance. A number of benefits with non-binding instruments for global health have recently been described.[84, 86, 87] The lack of formal obligation to comply offers flexibility, which may increase states' willingness to reach consensus on ambitious targets. Since norms agreed in non-binding instruments such as declarations or resolutions do not require parliamentary process and ratification, the content of these instruments is easier to

Box 4: WHO constitution, Article 21 and Article 22

Article 21

The Health Assembly shall have authority to adopt regulations concerning:

(a) sanitary and quarantine requirements and other procedures designed to prevent the international spread of disease;

(b) nomenclatures with respect to diseases, causes of death and public health practices;

(c) standards with respect to diagnostic procedures for international use;

(d) standards with respect to the safety, purity and potency of biological, pharmaceutical and similar products moving in international commerce;

(e) advertising and labelling of biological, pharmaceutical and similar products moving in international commerce.

Article 22

Regulations adopted pursuant to Article 21 shall come into force for all Members after due notice has been given of their adoption by the Health Assembly except for such Members as may notify the Director-General of rejection or reservations within the period stated in the notice.

Source: WHO constitution.

update at a later stage if needed. Finally, a non-binding instrument could more easily incorporate commitments from civil society, industry and other non-state actors, which normally are not included in the process of negotiating international laws.

The potential, widespread consequences of antibiotic resistance may offer incentives for states to commit to a treaty if the agreement addresses access, conservation and innovation.

A legally binding treaty ('hard law'), which others have suggested for addressing antibiotic resistance,[81, 82] can take the form of a Framework Convention on Antibiotic Resistance, akin to the Framework Convention on Tobacco Control (FCTC). The FCTC and a number of other treaties have faced well-known limitations to implementation, accountability, financial commitment and impact, and the challenges restricting involvement of non-state actors and the legalization of technical issues and political interaction.[84, 86, 88] A recent study on the expected impact of global health treaties suggests that several features could enable legally binding treaties to have greater impact.[89] One is that the treaty should yield significant benefits to those with the power to act; another is that the aims of the treaty should be aligned with those of powerful interest groups, such as multinational corporations. These features may not be desirable, or even possible, for treaties on other global health challenges, such as nutrition and obesity,[90] or reducing the harmful use of alcohol.[91] In comparison, the potential, widespread consequences of antibiotic resistance[21] may offer incentives for states to commit to a treaty if the agreement addresses access, conservation and innovation. A global commitment by all countries to pursue conservation efforts and limit the spread of antibiotic resistance may incentivize high-income and many middle-income countries to finance innovation incentives for new antibiotics. Similarly, there might be increased willingness from LMICs to support conservation as part of a global agreement if the treaty included provisions facilitating access to new antibiotics.

A different option, which has been floated by working group members and others,[82, 83] is for the WHA to adopt a new WHO regulation specifically dealing with antibiotic resistance. A WHO regulation is recognized as a legally binding agreement; however, unlike a treaty it does not require parliamentary approval and enactment of norms into national laws. Once approved by the WHA, the regulation enters immediately into force for all member states (although under Article 22 they can notify the Director-General and decide to opt out of the entire regulation or make reservations about certain provisions). Under Article 21 of the WHO constitution, the WHA can approve regulations addressing various aspects of health issues (Box 4). For example, Article 21(e) empowers the WHA to issue regulations concerning the 'advertising and labelling of biological, pharmaceutical and similar products moving in international commerce'. This provision could technically be applied to manage the marketing of antibiotics, enforce labelling that guides appropriate use, and restrict new antibiotics from use in food-producing animals.

Some have suggested that the existing International Health Regulations (IHR) could provide a framework for coordinating efforts to strengthen global surveillance of antibiotic resistance.[92] It is argued that pan-resistant strains such as Klebsiella pneumonia carbapenemase (KPC) and NDM-producing CRE may fulfil the criteria for 'a public health emergency of international concern',[93] and applying the IHR to antibiotic resistance may force member states to notify the emergence of highly resistant threats to the WHO, thereby enabling an effective, global response. However, the idea of applying the IHR to antimicrobial resistance has been contested and faces a number of challenges,[94] an important

one being countries' lack of progress in fulfilling the IHR core capacities.[95] More importantly, a comprehensive agreement addressing antibiotic resistance would require commitments to a number of areas beyond the scope of the IHR, such as financing of R&D and innovation incentives, ensuring equitable access, infection control, antibiotic stewardship and policies that ensure responsible use. The range of provisions and obligations, which could be approved under a WHO regulation, should be further explored.

Clearly, more work is required to consider whether a non-binding or a binding instrument is the most effective way forward for ensuring global cooperation and coordination. A further articulation of these issues is beyond the scope of this report, but will occur in the follow-on processes.

Recommendation 7.5: As follow-up to the WHO Global Action Plan on Antimicrobial Resistance, the WHO and its member states should explore whether a treaty or a WHO regulation is the most effective way to facilitate global collective action on antibiotic resistance.

8. Concluding Comments and Recommendations

This report, based on the deliberations of the working group, aims to inform the ongoing discussions and processes on developing a new business model for antibiotics. It is based on the premise that delinkage, seeking to separate the return on investment from antibiotic sales volume, should be the principle underpinning any new business model. It calls on governments to invest significantly in antibiotic R&D by financing a broad menu of incentives across the antibiotic life-cycle, with the highest incentives targeted at the development of antibiotics directed at the greatest health threats arising from antibiotic resistance. Contributions from countries should be coordinated within a globally agreed framework. Finally, global *access* should, together with *conservation*, be a priority for any new business model fostering *innovation*.

The recommendations related to each question explored are as follows.

What kind of funding and incentive schemes might work?

- Recommendation 2.1: Create an integrated menu of incentives across the antibiotic life-cycle:
  - Public funding of basic pre-clinical research (national research council model);
  - Partial public funding for clinical research, through a combination of tax credits (orphan drug model), contracts (public-private partnership model), and prizes (Longitude Prize model); and
  - Delinked payments for newly registered qualifying products, adjusted for net public investment and as evidence of value develops.
- Recommendation 2.2: Create a fully transparent and independent process to evaluate the fairness and effectiveness of all antibiotic incentives. Such antibiotic incentives ought to be considered alongside what returns such public-sector investments might yield compared with other interventions.

Which products should be covered?

- Recommendation 3.1: A comprehensive global threat assessment should be created and periodically updated. The process should be data-driven, transparent and focused on the relative threats posed by resistant pathogens. The threat assessment outcome should be a triage list of pathogens that helps guide innovation incentives towards addressing the greatest microbial public health threats. This threat assessment should also evaluate alternative categories (other than by pathogen) that could yield greater impact on public health.
- Recommendation 3.2: To incentivize the development of antibiotics that address unmet clinical needs, the later-stage incentives (clinical development and post-registration incentives) should target antibiotics that treat drug-resistant bacteria posing present or predicted serious threats to humans, as determined by an evidence-based global threat assessment.

  Pre-clinical research can target a broader range of antibiotics. Antibiotics should qualify for the highest level of new incentives if they combat resistant pathogens posing an urgent and serious threat to human health, and such rewards should be based on demonstrably superior outcomes in human clinical testing. Antibiotics for less serious threats should qualify for a lower level of new incentives. Some flexibility should be maintained owing to inherent difficulties in predicting future health risks.

How could funding be raised?

- Recommendation 4.1: Create a target budget, by priority goal and by unit of accountability (government, region, intergovernmental organization), for the global effort to preserve antibiotic effectiveness, based on the best evidence of clinical need and public health risk. Collectively, this would clarify the global resource commitment required to tackle the challenge of antimicrobial resistance.
- Recommendation 4.2: Individual countries should raise funding consistent with regional or global needs and available resources. These funds could be largely retained at the national level but spent according to regional or global targets.
- Recommendation 4.3: Identify stable sources for regionally or globally pooled funding for antibiotic resistance, to be coordinated through a secretariat.
- Recommendation 4.4: Evaluate lessons from international science projects and climate finance models for global, pooled funding mechanisms to address antibiotic resistance.

What is the role of intellectual property?

- Recommendation 5.1: The delinkage business model should promote global access to antibiotics together with their appropriate use. Appropriate responsibilities should be allocated between governments and innovators when the terms of the delinkage payments are negotiated.
- Recommendation 5.2: IP expansions should not be considered as incentives for early-stage antibiotic innovation. Later in the market life-cycle, the use of

IP incentives to ensure monopoly pricing should also be avoided, since it risks both exacerbating the over-marketing of antibiotics, and becoming a threat to global access.

- Recommendation 5.3: Delinkage rewards should be permitted for highly innovative but unpatentable antibiotics.

How can new incentives be reconciled with rational use of antibiotics?

- Recommendation 6.1: Data on antibiotic sales, distribution and use should be publicly reported and standards should be developed for the responsible use of antibiotics.
- Recommendation 6.2: Invest significant public funds to accelerate global infection-prevention (public health, clean water and food, vaccination), increase investments in infection-preventive technologies (host-directed therapies and monoclonal antibodies), improve surveillance of resistance and antibiotic use (including transparent data), and enhance laboratory capacity and innovation of diagnostic devices (with rapid point-of-care diagnostics as a priority) that can reduce the inappropriate use of antibiotics.
- Recommendation 6.3: Post-registration service contracts could include conservation activities as well as maintaining global registration and production of the drug.
- Recommendation 6.4: A comprehensive, multi-level study should be undertaken to explore the perverse financial incentives leading to the over-selling and overuse of antibiotics.
- Recommendation 6.5: The global antibiotic conservation effort should be partially financed with funds allocated to delinkage models, and new research should estimate the appropriate allocation of funds between conservation and R&D. Proven conservation methods such as antibiotic stewardship programmes should be incentivized and implemented immediately as part of global conservation efforts.
- Recommendation 6.6: Empirical research into the relationship between generic market entry, therapeutic competition and resistance should be conducted to help guide the creation of mechanisms regulating entry of generic antibiotics.

How can a new scheme by applied regionally and globally?

- Recommendation 7.1: While complete global coverage is the ultimate goal, the geographic scope of participation can vary in the early years. Financial participation can begin with a core group of countries with significant pre-clinical and clinical research activity, and countries that comprise large antibiotic markets. From the start, every country should participate through surveillance, hosting clinical research, conservation and public health initiatives.
- Recommendation 7.2: A globally harmonized antibiotic approval process, acceptable in particular to countries with weaker national drug regulatory systems, should be established for antibiotics resulting from the new business model.
- Recommendation 7.3: Antibiotic incentives, while mostly implemented domestically, should be coordinated globally through a secretariat. This body could potentially deal with a range of functions that could grow over time as competence develops, including coordinating IP licenses, mobilizing funding of incentives, and promoting appropriate use.
- Recommendation 7.4: Evaluate the Medicines Patent Pool as an entity to hold and coordinate global IP licences for antibiotics.
- Recommendation 7.5: As follow-up to the WHO Global Action Plan on Antimicrobial Resistance, the WHO and its member states should explore whether a treaty or a WHO regulation is the most effective way to facilitate global collective action on antibiotic resistance.

Main recommendations

1. A new business model needs to be developed in which the return on investment in R&D on antibiotics is delinked from the volume of sales.
2. Increased public financing of a broad menu of incentives across the antibiotic life-cycle is required, targeted at encouraging the development of antibiotics to counter the greatest microbial threats.
3. The assessment of current and future global threats arising from resistance should be updated periodically in order to identify which classes of product are a priority for incentives.
4. The delinkage model should prioritize both access and conservation.
5. Domestic expenditures on the model need to be globally coordinated, including through the establishment of a secretariat, and global participation in the model is the ultimate goal.

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