Antimicrobial Resistance (AMR) and Multidrug Resistance (MDR): Overview of Current Approaches, Consortia and Intellectual Property Issues

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Antimicrobial Resistance (AMR) and Multidrug Resistance (MDR): Overview of current approaches, consortia and intellectual property issues

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Abstract

The supply of new diagnostics and treatments is insufficient to keep up with the increase in antimicrobial resistance (AMR) and multidrug resistance (MDR) as older medicines are used more widely and microbes develop resistance to them. At the same time, significant quantities of antibiotics are used on patients and animals that do not need them, while others who do need them lack access.

Effective responses to AMR/MDR require effort by both the public and private sectors to develop and disseminate new diagnostics, vaccines and treatments on a global scale, as well as to adapt them to local needs. This calls for good governance to identify priorities, raise awareness and ensure effective stewardship at global, regional and national levels to minimize the development of resistance. Failure to act appropriately in one country will adversely impact all countries as resistance travels fast.

Based on a review of recent literature, this WIPO Global Challenges Report includes a broad overview of current approaches and consortia designed to meet the challenge of research and development (R&D) investment for new treatments. It also examines patent applications by both the public and the private sectors as an indicator of innovative activity.

This report finds that there is a need to address the unique market challenges and specific uncertainties associated with the development of new diagnostics and treatments, where current approaches are not optimal. An effective global framework that achieves the necessary political support while ensuring effective local implementation is crucial. There is an opportunity to complement this work by formulating mechanisms that drive innovation for results to incentivize success, while feeding expertise and experience into stewardship and access efforts. Intellectual property (IP) could be used in a constructive manner as one element in any reward or prize system for AMR/MDR R&D – both in terms of providing an incentive and governance.
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1. Introduction

In 1928 a piece of mold contaminated a petri dish, killing bacteria under examination. This led Alexander Fleming to one of the greatest discoveries in modern medicine, and within 12 years Fleming and others turned this finding into a wonderdrug that could cure patients with bacterial infections. Common – yet frequently deadly – illnesses such as pneumonia and tuberculosis (TB) could be treated effectively.

But bacteria and other pathogens are also great innovators and are adept at developing resistance to antibiotic medicines. Overuse, misuse, and/or lack of patient adherence to complete the course have led to ever-increasing levels of resistance to antibiotic treatment. Resistance has become particularly problematic in recent years because the pace at which novel antibiotics are being discovered has slowed drastically while antibiotic use continues to rise. The routine addition of antibiotics in food animal production significantly increases the probability of resistance. The great strides made over the past few decades to effectively treat HIV/AIDS, TB and malaria could be reversed, leading to these and other diseases spiralling out of control. Figure 1 shows the impact of antibiotics on public health. It compares the 10 leading causes of death as a percentage of all deaths in the United States of America (USA) in 1900 and 1997. Major and minor surgery could once again result in fatal infections and many treatments that have become commonplace would not be possible without high risk. AMR/MDR therefore threatens many of the most important medical advances made this century. But the impact goes far beyond health systems. A conservative estimate is that AMR currently accounts for over 700,000 deaths annually, but this could rise to 10 million in 2050 if not effectively addressed.

This research brief sets out the approaches currently taken at the highest political level, right through to the practical steps being taken in the fight to overcome the microbes, and tries to identify opportunities for innovation and intellectual property (IP) systems to play an active role in the global effort.

Figure 1:
The impact of the introduction of antibiotics on public health: the 10 leading causes of death as a percentage of all deaths in the USA in 1900 and 1997

![Figure 1: The impact of antibiotics on public health](source: Mitchell L. Cohen, “Changing patterns of infectious disease”, Nature 406, 762-767, August 17, 2000.)

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1 Collignon et al., “World Health Organization ranking of antimicrobials according to their importance in human medicine: a critical step for developing risk management strategies to control antimicrobial resistance from food animal production”, Clinical Infectious Diseases, July 20, 2016.

2. High-level literature review

Although there has been a dramatic increase in the attention and focus on AMR/MDR over the past five years or so (leading to a number of high-level political declarations), the European Union (EU) and the USA had already established high-level measures to guide the use of antibiotics.

- On June 8, 1999, the Council of the European Union adopted a Resolution on antibiotic resistance entitled A strategy against the microbial threat, which was followed by a Council recommendation on November 15, 2001 on The prudent use of antimicrobial agents in human medicine.

- A US and EU Summit in 2009 declared, inter alia, "To establish a transatlantic task force on urgent antimicrobial resistance issues focused on appropriate therapeutic use of antimicrobial drugs in the medical and veterinary communities, prevention of both healthcare and community-associated drug-resistant infections, and strategies for improving the pipeline of new antimicrobial drugs, which could be better addressed by intensified cooperation between us." This led to the creation of the Transatlantic Task Force on Antimicrobial Resistance (TATFAR), which seeks to address the above mandate. In its 2014 progress report the Task Force highlighted the ongoing work in the delivery of recommendations under three key themes:
  1. appropriate therapeutic use in human and veterinary medicine
  2. prevention of drug-resistant infections
  3. strategies for improving the pipeline of new antimicrobial drugs.

- A paper by the Commission of the Organisation for Economic Co-operation and Development (OECD) lays out the issues from the perspective of the G7 countries and beyond. The summary includes the themes as identified by TATFAR but makes further recommendations for policymakers:
  1. Strengthening existing surveillance and monitoring systems and improving statistics on the consumption of antimicrobials.
  2. The adoption of a globally agreed set of measurable targets related to the incidence of AMR, as well as to the efficient use of new antibiotics, would provide political impetus to address AMR.

- OECD Recommendation 4 states that both upstream and downstream economic incentives should be combined and should aim to de-link development incentives from sales, and encourage the participation of small and medium-sized enterprises (SMEs) in R&D efforts. A good package would include establishing a global collaborative research platform, milestone prizes and grants, patent buyouts, and a globally coordinated approach to clinical trials.

- The World Health Organization (WHO) has recently upscaled effort on AMR and its Global Plan of Action on AMR was adopted in 2015, after the issue had been referred to in a number of previous World Health Assembly Resolutions. The Resolution mandates WHO, inter alia:
  1. To ensure that all relevant parts of the Organization, at headquarters, regional and country levels, are actively engaged and coordinated in promoting work on containing antimicrobial resistance, including through the tracking of resource flows for research and development on antimicrobial resistance in the new global health research and development observatory;
  2. To develop and implement, in consultation with Member States and relevant partners, an integrated global program for surveillance of antimicrobial resistance across all sectors, in line with the global action plan;

(6) to establish a network of WHO Collaborating Centres to support surveillance of antimicrobial resistance and quality assessment in each WHO region;
(7) to develop, in consultation with Member States and relevant partners, options for establishing a global development and stewardship framework to support the development, control, distribution and appropriate use of new antimicrobial medicines, diagnostic tools, vaccines and other interventions, while preserving existing antimicrobial medicines, and promoting affordable access to existing and new antimicrobial medicines and diagnostic tools, taking into account the needs of all countries, and in line with the global action plan on antimicrobial resistance, and to report to the sixty-ninth World Health Assembly;

• In order to implement the suggestion of the Action Plan to create new partnerships for the development and conservation of antibiotics, WHO with the Drugs for Neglected Diseases initiative (DNDi) have jointly launched the Global Antibiotic Research & Development Partnership, which is discussed in greater detail below.

• The Uppsala Health Summit in June 2015 tackled the full range of issues, including the need for access – not excess – when it comes to the use of antibiotics, collaborative innovation models, and global governance. They highlighted the crucial role of vaccines in preventing disease and diagnostics in establishing what constitutes appropriate use of antibiotics.11

• In October 2015, the G7 Health Ministers met to discuss AMR and Ebola. Their Declaration12 fully supports the WHO Action Plan and identifies the need to explore the setting-up of a global antibiotics product development partnership, mentioning the WHO/DNDi proposed initiative.

• In addition to the political focus, there are a vast number of new publications covering the extent of the threat posed by AMR/MDR and possible solutions to address the problems.13 The Lancet Infectious Disease Commission highlighted that, although the causes of AMR are complex, the consequences affect everybody in the world.14

• There have been a number of papers that have reviewed and critically assessed incentive strategies for discovery and development of new antibiotics.15, 16, 17, 18

• One example of the use of prizes is the United Kingdom (UK) Longitude Prize, which offers GBP 10 million to a successful researcher.19

• A recent study by the Swiss Federal Office of Public Health explores the national AMR strategies of a number of European countries (Denmark, France, Germany, Norway, Sweden, Switzerland and the UK) as well as South Africa and the USA to add additional perspectives. The study includes an assessment of the various approaches and best practices.20

our-summits/a-world-without-antibiotics-2015
Minister_2015/G7_Health_Ministers_Declaration_AMR_and_EBOLA.pdf
16 “Approaches to simulating innovation for development of new antibiotic drugs”, KEI, 2013.
17 Strategic Research Agenda, Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), December 5, 2015.
19 https://longitudeprize.org/challenge/antibiotics
3. Broad overview of current market issues related to AMR/MDR and trends in R&D for new antibiotics covering both private and public sectors

There is a lack of new antibacterial medicines and vaccines as the growth in AMR/MDR has been accompanied by a sharp decline in development of new treatments. Over the past three decades only two new classes of antibacterial medicines have been discovered, compared to 11 in the previous 50 years. The number of antibiotics becoming obsolete due to resistance significantly exceeds the number of new, approved treatments.21

The two new classes of treatments relate to pulmonary multidrug-resistant tuberculosis (MDR-TB), where drug resistance has been on the rise. The first is Otsuka’s delamanid, which was granted approval in 2014 by Japan, the Republic of Korea and within the EU (to be used in combination with other anti-TB medicines). In November 2014, WHO issued policy guidance on the use of delamanid, to assist access in developing countries. The second was Janssen Pharmaceutical’s bedaquiline, which was granted approval in Peru, the Philippines, the Republic of Korea, the Russian Federation, South Africa and the USA. In 2015 the US Food and Drug Administration (FDA) approved ceftolozane/tazobactam (Zerbaxa) by Cubist (fully owned by MSD) and Allergan/AstraZeneca’s Avycaz, both for the treatment of complicated urinary tract and intra-abdominal infections, as well as bacterial pneumonia.

The introduction of antibiotics and immunization has been a key contributor to the reduction of deaths from infectious diseases and has helped to make modern medicine possible.

As of September 2016, an estimated 4022 new antibiotic medicines with the potential to treat serious bacterial infections are in clinical development for the US market. The success rate for clinical drug development is low, and currently only around one in five candidates that enter human testing (phase 1 clinical trials) will be approved for patients.

Most of the private sector development remains focused on existing classes of antibiotics where the risk of failure is significantly lower.23 Table 1 shows the current R&D underway by International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) member companies (April 2015). To share the risk of development, the US Biomedical Advanced Research and Development Authority (BARDA) directly supports companies that develop new antibiotics through its Broad Spectrum Antimicrobials Program. BARDA, for example, launched a Portfolio Partnership with GlaxoSmithKline to support the development of a number of new antibiotics.24

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21 Michael S. Kinch, Denton Hoyer, et. al., Yale Center for Molecular Discovery, 2014.
23 Cristina d’Urso de Souza Mendes et al., Pipeline of Known Chemical Classes of Antibiotics, December 2013.
24 https://www.hhs.gov/sites/default/files/barda_antimicrobial_program.pdf
<table>
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<tr>
<th>Company</th>
<th>Compound Name or identifier</th>
<th>Compound Category</th>
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Source: Rethinking the Way We Fight Bacteria, IFPMA, 2015. Supplied courtesy of IFPMA.
It is important to note that a significant repository of potential antibiotics is undoubtedly present in (currently largely untapped) biodiversity. As the tools of, and sophistication of, biotechnology advance, the potential for efficient, rapid and successful bioprospecting of such antibiotic candidates has increased. The recent case wherein 48 novel potential cationic antimicrobial peptides were identified in the plasma of Varanus komodoensis (Komodo dragon), indigenous to Indonesia, is exemplary: “The antimicrobial effectiveness of eight… peptides was evaluated against Pseudomonas aeruginosa… and Staphylococcus aureus… with seven peptides exhibiting antimicrobial activity against both microbes and one only showing significant potency against P. aeruginosa.” Coherent, coordinated and equitable management of these biological resources and the potentially valuable IP that results from research and development will be crucial for sustainable conservation of, and widespread access to, subsequent new antibiotics.

Around 100 pharmaceutical and diagnostics companies (including support from major trade associations such as the IFPMA) declared their commitment to combating AMR on January 21, 2016, at the World Economic Forum (WEF) in Davos. They called on governments to work with them in developing new and alternate market structures to provide more dependable and sustainable market models. This includes new incentives for R&D, new mechanisms to ensure that the price of antibiotics reflects value, and payment models that reduce the link between profitability and volume of sales. The declaration also sets out the commitment by the companies across three broad areas:

1. reducing the development of drug resistance
2. increasing investment in R&D that meets global public health needs
3. improving access to high-quality antibiotics for all.

Pharmaceutical companies have reinforced their commitment to the January 2016 Declaration by issuing a Roadmap to Combat Antimicrobial Resistance just ahead of the United Nations General Assembly on September 20, 2016, and pledged to deliver by 2020 to reduce AMR.

27 Multiple United Nations agencies work on the issue of fair and equitable sharing of benefits for the use of genetic resources. WIPO facilitates normative activities and provides capacity-building on the relationship between IP and access to, and benefit-sharing in, genetic resources and associated traditional knowledge; see www.wipo.int/tk/en/genetic
28 https://amr-review.org/industry-declaration.html
4. Preliminary survey of initiatives, partnerships and consortia engaged in the development of antibiotics

4.1 The WHO/DNDi Global Antibiotic Research & Development Partnership (GARDP)

The Global Antibiotic Research & Development Partnership was launched on May 24, 2016. The partnership aims to promote antibiotic product development and pilot incentive models that de-link the cost of R&D from volume-based sales and contribute to the conservation of, and access to, new antibiotic treatments. This provides an alternative to the traditional market-driven pharmaceutical approach, by focusing on products that the pharmaceutical industry will likely not develop for lack of commercial incentive.

The partnership goes back to a call in the WHO Global Action Plan on Antimicrobial Resistance (adopted in May 2015) for the creation of new partnerships to foster the development and conservation of antibiotics. To implement this part of the Plan, WHO and the Drugs for Neglected Diseases initiative (DNDi) are working in a new partnership that seeks to:

1. develop new antibiotic treatments addressing antimicrobial resistance
2. pilot and test alternative incentive models that promote innovation and access
3. promote their responsible use for optimal conservation
4. ensure equitable access for all by making products affordable, subject to a global conservation agenda
5. guarantee new products that are suitable for resource-limited settings.

The Partnership is working closely with all stakeholders – including pharmaceutical and biotechnology companies, other product development partnerships, academia, civil society, research organizations and health authorities – from countries of all income levels to develop new antibiotic treatments and to preserve them.

4.2 The Innovative Medicines Initiative (IMI)

The Innovative Medicines Initiative is Europe’s largest public-private initiative aiming to speed up the development of better and safer medicines for patients. IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe. One of its priorities is antimicrobial resistance. IMI’s program New Drugs 4 Bad Bugs (ND4BB) focuses on the scientific, regulatory and business challenges that are hampering the development of new antibiotics. ND4BB includes, inter alia, the creation of a pan-European network of excellence of clinical investigation sites, basic research to tackle, in particular, gram-negative bacteria, the development of a specific drug discovery platform for antibiotics, and the exploration of new economic models for antibiotic development (DRIVE-AB). AMR is a growing problem worldwide, and with few new drugs making it to the market there is an urgent need for new medicines to treat resistant infections. Also the Combating Bacterial Resistance in Europe (COMBACTE) project forms part of the ND4BB initiative and aims to pioneer new ways of designing and implementing efficient clinical trials for novel antibiotics.

4.3 The EU Joint Program Initiative on Antimicrobial Resistance

The EU Joint Program Initiative on Antimicrobial Resistance has been set up to pool national research efforts to spend public R&D resources more efficiently.

Joint programming is used in different areas to overcome the fragmentation of national research programs, in particular where challenges are global in nature. The development of new preventative and therapeutic approaches is only one of many areas that form part of the Joint Programming Initiative on AMR. Research priorities are set out in the Strategic Research Agenda, and that agenda is implemented through launching joint calls for proposals to facilitate cross-border research projects. The focus of the Initiative is basic research; it does not currently finance product development.

4.4 US Broad Spectrum Antimicrobials Program

BARDA’s Broad Spectrum Antimicrobials (BSA) Program was established in January 2010 and is focused on developing novel antibacterial and antiviral drugs for the treatment or prevention of disease caused by currently defined and future biological threats. The program recognizes that new antimicrobials are needed immediately to address the increasingly prevalent public health threat of antibiotic resistance, as well as the likelihood that AMR will complicate standard treatment of a wide array of infections. One of the main objectives is to revitalize the antimicrobial pipeline by providing incentives for

31 Ciabuschiet, Årdal, Findlay et al., WP2: Creation and testing of new economic models; Incentives to stimulate antibiotic innovation: The preliminary findings of DRIVE-AB; available at http://drive-ab.eu/wp-content/uploads/2016/06/WP2-Prereading-FINAL.pdf
32 https://www.combacte.com
pharma and biotech companies to engage (or re-engage) in antimicrobial development (as mentioned in Section 2). Since that time around six companies have entered into collaborative partnerships with BARDA and they have invested hundreds of millions of dollars in supporting late-stage development, including through partnering with biotech and pharmaceutical companies.

It is hoped that this strategy will ensure that novel antimicrobials progress through the development pipeline to approval, so that novel antimicrobials will be added to the arsenal of possible treatments available. One recent announcement was for a single treatment for multiple common infections that had entered the last stages of development.\(^\text{35}\)

### 4.5 The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X)

A further initiative was launched in July 2016 called CARB-X (Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator). BARDA claims that it is possibly the largest public-private partnership in the world dedicated to preclinical antibiotic development. It involves seven partners in the UK and USA, and is backed with half a billion US dollars in funding. CARB-X partners are working together to set up a diverse portfolio with more than 20 high-quality antibacterial products.\(^\text{36}\)

### 4.6 The UK independent Review on Antimicrobial Resistance

The UK independent Review on Antimicrobial Resistance, chaired by Jim O’Neill, was commissioned by the UK Prime Minister to analyze and propose concrete actions to tackle the global problems of antimicrobial resistance. The Review had to assess the extent to which market failure is responsible for the lack of investment in R&D of new antimicrobials and identify short-, medium-, and long-term interventions that could be undertaken by governments and other funders to stimulate investment in new antimicrobials for human use. In 2015, the Review published initial proposals to kick-start antibiotic drug discovery efforts at a global level. The proposals include channeling new funds into early-stage research, as well as creating a fund for product development to buy out major new breakthroughs. The latter could ensure a predictable and viable market for new antibiotics, providing an incentive for companies to invest.

The Review published its final report on May 19, 2016 and proposed nine interventions ranging from a global awareness campaign to improved sanitation and the development of new diagnostics, medicines and vaccines.\(^\text{37}\) Two particular interventions worthy of note are the creation of a global innovation fund for early-stage and non-commercial R&D, and better incentives to promote investment for new drugs and improving existing ones. Both of these will be considered in more detail later in this paper.

As a result of the review, the UK launched The AMR Centre, which forms a key part of the UK’s response to AMR. The AMR Centre is a joint public-private initiative to support/accelerate the development of new antibiotics and diagnostics through a fully integrated development capability, offering translational R&D from pre-clinical hits through to clinical proof of concept.\(^\text{38}\)

## 4.7 Additional remarks

The above list is not intended to be exhaustive and there may be other valuable initiatives that have not been mentioned. However, it is noted that the majority of initiatives involved developed countries, although there has been some political will to support focus on AMR from the G20 countries.\(^\text{39}\)

Although the enhanced focus is warmly welcomed by many, there is an increased need to ensure effective alignment and/or coordination within the AMR landscape in order to fill the necessary gaps and avoid duplication. There also needs to be an assessment of the contribution and value of each initiative so that successful platforms can be enhanced, while platforms that fail to meet expectations can be re-tasked or refocused.

WHO has proposed options for establishing a global development and stewardship framework.\(^\text{40}\) However, countries will need to be open to sharing information and allowing their national programs to be shaped and influenced for global success\(^\text{41}\) rather than national interests, if the shared goal is to be realized. The Political Declaration\(^\text{42}\) of the High-Level Meeting of the United Nations General Assembly on Antimicrobial Resistance on September 21, 2016, will help to achieve this by summoning and maintaining strong national, regional and international political commitment in addressing antimicrobial resistance comprehensively and multi-sectorally, and to increase and improve awareness.\(^\text{43}\)
5. Global experience

A review of the literature revealed significant differences in the way countries use antibiotics. For example, in Europe, the Scandinavian countries use relatively few antibiotics, and consequently have very low levels of resistance. On the contrary, countries like Greece, Italy and a number of Eastern European countries are relatively heavy users and hence display pronounced levels of antibiotic resistance. Many other regions and countries, like India, China and the Americas, are heavy users, and also use antibiotics as animal growth promoters. Hence the same huge differences are seen in animal production-related use as some countries are adding antibiotics to animal feed as a matter of course. Evidence shows that in low-income and middle-income countries (LMICs), antibiotic use is increasing with rising incomes, high rates of hospitalization, and high prevalence of hospital infections. However, where there are weak health systems, the effect of AMR on health and economics is largely under-estimated and incompletely understood. It largely follows that effective access is hindered where there are weak health systems. At least two-thirds of childhood mortality is related to infections, and children are therefore probably more vulnerable than adolescents and adults.

The global market value of veterinary drugs increased from USD 8.7 billion in 1992 to USD 20.1 billion in 2010, and in 2018 is anticipated to reach USD 43 billion. Overuse of antibiotics in animals remains a key problem. For example, China is one of the world’s highest users of the antibiotic colistin in agriculture and it is suggested that this heavy use has resulted in resistance. Resistance travels fast and hence a Chinese problem fast becomes a global one. Therefore no country can successfully tackle AMR by acting in isolation.

Other problems include overprescribing or unregulated use of antibiotics. In China, for instance, hospitals and clinics receive financial incentives for prescribing, and antibiotics are overused as a result. Some countries allow pharmacies to sell antibiotics without prescription and people buy them even for diseases that antibiotics cannot treat, such as malaria.

There are significant similarities within all countries as there is a need for an effective health system. Ensuring access and appropriate use depends on multiple factors operating within a well-functioning and well-managed national healthcare system:

- rational selection and use
- affordable prices
- sustained financing
- reliable health supply systems
- robust regulation and enforcement systems.

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44 Ibid. 13.
53 Ibid. 50.
GARDP held a regional workshop in Cape Town, South Africa, in September 2016. Forty-five participants from 11 African countries participated in the meeting. The following needs and challenges were noted:

- Many African countries have weak health systems.
- Africa has a high burden of disease, e.g. TB and malaria, and malnutrition is a major problem.
- There is a scarcity of data on AMR.
- Policies and regulations that make sense and ensure stewardship and access at national level are needed.
- There is a need to undertake R&D to address ESKAPE pathogens, as well as the resistant sexually transmitted infections and resistant infections along with the emerging threat from Candida Auris.

The priorities that were identified included:

- rapid point-of-care tests to distinguish bacterial from viral infections, as well as pathogen-specific tests
- diagnostics support for stewardship
- stewardship cannot be seen as a national effort – it must be regionally harmonized
- establishment of an African-driven and coordinated AMR clinical trial network that should capitalize on several existing networks and create centres of excellence for trials
- dissemination of national guidelines to medical practitioners and hospitals would help support standardization of care.

In Kenya, it was identified that the best immediate approaches for appropriate use include:

- increased use of vaccines that reduce disease and therefore antibiotic demand
- improved infection control, including procedures (e.g. hand hygiene, checklists) and information guidelines, particularly in hospitals
- education and public awareness campaigns for providers and consumers.

Three additional important approaches, which are not immediately implementable, are:

- increased use of improved diagnostics, to better target antibiotic use
- resolution of supply-chain constraints and failures
- economic incentives to encourage better use of antibiotics.

Poor countries often suffer from lack of regulations for antibiotics, leading to access to substandard or falsified antibiotics. Substandard antibiotics often have a lower dosage of the active ingredient that results in increased resistance. It is clear that policies for appropriate supervision and control by regulatory agencies are needed to prevent the supply of expired, substandard and counterfeit medicines.

Evidence suggests that when antibiotics are available the issues are the same for all countries. Overuse leads to greater levels of resistance and hence effective antibiotic stewardship is crucial. However, sustainable access to effective antibiotics, both existing and new, remains a key challenge.

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6. Intellectual property related issues

This section looks at the role of IP – both in terms of incentivizing R&D and preventing possible generic companies from entering the market.

IP is a part of the enabling environment for innovation and as such a policy tool to incentivize or enable innovation by providing a fixed period of exclusivity for full public disclosure. However, the patent system can only contribute as an effective incentive mechanism if there is, or will be, sufficient market drivers. In the normal business model of medicine development, the innovator calculates a price based on a number of factors - including market dynamics, cost of R&D, etc. Once a patent expires, providing regulatory approval has been obtained, generic companies are able to sell the medicine and compete based on sales volume.

There are a number of problems with this model when addressing AMR/MDR. Firstly, pharmaceutical companies are reluctant to invest in antibiotic R&D because the returns are significantly lower than for other areas, leading to many companies exiting the market. There are unique problems when developing the next generation of antibiotics:

- **Limited use.** New antibiotics were often reserved as drugs of “last resort” and used “sparingly” for “short” courses of treatment. In contrast, treatments for mental illnesses or cancer may last for several weeks, months or even years, providing greater opportunity for those treatments to deliver a return on investment.

- **Low price.** Existing antibiotics are very cheap and are generally only used for a short period of time.

- **Short lifespan.** Antibiotics can have a short working lifespan, as resistance may develop to compounds in a relatively short period of time, sometimes at the clinical trial stage.

- **Clinical trials.** Conducting clinical trials of antimicrobials is difficult because it is not clear which pathogen was affecting a patient, diagnosis time can be lengthy and highly selective patient populations are required. If the value of a new antibiotic can only be demonstrated on patients who display infection resistance then clinical development becomes prohibitively lengthy and expensive until resistance becomes widespread.

Despite the clear value of antibiotics for society, the incentives to develop them are notably small. This led to less than 5 percent of venture capital investment in pharmaceutical R&D between 2003 and 2013 being allocated to AMR. Creating a vibrant and sustainable pipeline remains a primary objective and there are numerous initiatives underway to develop incentives to stimulate antibiotic innovation. The recently launched DRIVE-AB initiative has already published a shortlist of push and pull models/mechanisms to incentivize R&D.

Generally, innovators and generics are commercially incentivized to sell high volumes of product. This cannot work in the case of AMR/MDR as the goal is to provide access to only those patients who absolutely need the state-of-the-art treatment. Low sales generally lead to an unsustainable business model, but high levels of sales would result in overconsumption and contribute to high levels of resistance. Hence, simply increasing developer return on investment (ROI) does not address the problem directly.

Therefore, alternative mechanisms are required to help de-risk or de-link companies’ initial investment.

Numerous experts have proposed antibiotic business models that reinforce conservation efforts by completely severing a developer’s ROI from sales volume and price. This concept is known as “de-linkage” and is beneficial for three key reasons. Firstly, it provides developers with a concrete ROI that is extraneous to the market. Secondly, it removes the motivation for developers to overmarket their antibiotic. Thirdly, it facilitates access to new antibiotics for those who need them most. An additional possible benefit is that it may encourage collaboration and coordination (avoiding duplication) since incentives can be provided to consortia.

Other experts advocate the use of demand-side antibiotic usage fees to internalize the negative externalities accompanying antibiotic use. This fee can then be used to finance other incentive mechanisms such as milestone payments or end prizes. For example, the Boston Consulting Group’s report to the German Government recommended the creation of:

- a Global Research Fund – to support academics and SMEs (starting budget of USD 200 million)
- a Global Development Fund – to support promising drug candidates (annual budget of USD 200 million)
- a Global Launch Reward of USD 1 billion for a successful product that meets certain criteria.

60 Ibid. 31.
62 *Rethinking the Way We Fight Bacteria*, IPPMA, 2015.
63 *Antimicrobial Resistance in G7 Countries and Beyond*, OECD, 2015.
65 Ibid. 15.
The UK Review on AMR proposed a system of market entry rewards (MERs) of around USD 1 billion per drug for effective treatments, whether they are based on new or old drugs that work against resistant pathogens in areas of most urgent need.\(^\text{67}\) This would be funded by an “antibiotic investment charge”, which would be imposed widely on the pharmaceutical sector and applied on a “pay or play” basis, meaning companies could either pay the charge or invest in R&D that is deemed useful for AMR. However, some worry that this is not the best method of encouraging R&D. Many companies are simply not geared up to commence AMR R&D and hence may regard this as simply another tax.\(^\text{68}\) Irrespective of how MERs would be financed, it is important to work out how IP associated with such a prize mechanism could be handled. For example, would IP rights simply be transferred on receipt of the reward or would there be a sliding scale with a limited sub-license at the other end of the compendium? The most suitable approach could be guided by a number of factors including complexity and cost of manufacture, volume required, securing of regulatory approval in target countries, etc.

In the case of antibiotics, there is a need for restricted use, hence limited market opportunity. One proposal has been to create the possibility of transferrable IP rights.\(^\text{69}\) This would mean that a developer of a new and high-value antibiotic would be rewarded with the opportunity to extend patent term on another medicine to enable recuperation of R&D spent, given that the market for any new antibiotic will likely remain very small. This idea has received a negative response from the NGO community, which feels that the ultimate price of an extended “blockbuster”\(^\text{70}\) medicine would outweigh the cost of antibiotic R&D.\(^\text{71}\)

A further idea would be to give antibiotic developers exchangeable “vouchers” as an incentive. While one type of voucher relates to a transferrable IP right, the other type relates to a priority review of any medicine waiting approval by a regulator. This would mean that a medicine could receive accelerated review with a view to rapid placement in the market. The recipient developer could either use it for one of their own medicines or sell it to another developer. Although this would clearly provide an incentive, its value would diminish if there were a significant increase in voucher availability.\(^\text{72}\) Such an approach might be considered for the creation of new and effective diagnostic tests. As noted above, such a test would be highly valuable in ensuring appropriate antibiotics use and monitoring/surveillance of AMR/MDR.

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67 Ibid. 37.
69 Ibid. 8.
70 A blockbuster medicine is one that generates annual sales of at least USD 1 billion for the company that creates it.
71 Approaches to Simulating Innovation for Development of New Antibiotic Drugs, KEI, 2013; available at www.who.int/phi/implementation/annex_antibiotic_research_development.pdf?ua=1
7. High-level patent trends over the past 10 years

Patent trends for AMR over the past 10 years were analyzed to determine which entities have been most active. Table 2 shows the list of the top 25 applicants/assignees of patent documents between 2007 and 2017. Of the identified documents, 68 percent pertain to filings from private entities and 28 percent to public institutions (Figure 2). Among the putative patent owners are 11 pharmaceutical companies, four biotechnology companies, eight public sector research organizations and two other entities (Figure 3).

Table 2: Antibiotic patent data with putative owners of intellectual property rights by the world’s top 25 pharmaceutical companies and public research institutions in the area of antibiotics, January 2007-May 2017

<table>
<thead>
<tr>
<th>Twenty five top Applicants/Assignees</th>
<th>Patent Documents (applications, grants, etc.)</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Private sector entities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genentech Inc.</td>
<td>324</td>
<td>US</td>
</tr>
<tr>
<td>Merck Sharp &amp; Dohme (incorporating Schering Corp.)</td>
<td>229</td>
<td>US</td>
</tr>
<tr>
<td>Vertex Pharma</td>
<td>222</td>
<td>US</td>
</tr>
<tr>
<td>Immunomedics Inc.</td>
<td>204</td>
<td>US</td>
</tr>
<tr>
<td>Abbott Laboratories</td>
<td>138</td>
<td>US</td>
</tr>
<tr>
<td>GSK (incorporating Smithkline Beecham Corp.)</td>
<td>132</td>
<td>UK</td>
</tr>
<tr>
<td>Novartis AG</td>
<td>115</td>
<td>CH</td>
</tr>
<tr>
<td>Idera Pharmaceuticals INC.</td>
<td>112</td>
<td>US</td>
</tr>
<tr>
<td>Celgene Corp.</td>
<td>111</td>
<td>US</td>
</tr>
<tr>
<td>Foamix Ltd.</td>
<td>109</td>
<td>US</td>
</tr>
<tr>
<td>Amgen Inc.</td>
<td>106</td>
<td>US</td>
</tr>
<tr>
<td>Medtronic Vascular Inc.</td>
<td>106</td>
<td>US</td>
</tr>
<tr>
<td>Abbvie Inc.</td>
<td>96</td>
<td>US</td>
</tr>
<tr>
<td>The General Hospital Corporation</td>
<td>93</td>
<td>US</td>
</tr>
<tr>
<td>Paratek Pharmaceuticals Inc.</td>
<td>90</td>
<td>US</td>
</tr>
<tr>
<td>Pfizer (incorporating Wyeth Corp.)</td>
<td>75</td>
<td>US</td>
</tr>
<tr>
<td>Hoffmann-La Roche</td>
<td>70</td>
<td>CH</td>
</tr>
<tr>
<td><strong>Public sector entities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University of California</td>
<td>246</td>
<td>US</td>
</tr>
<tr>
<td>University of Texas</td>
<td>149</td>
<td>US</td>
</tr>
<tr>
<td>Tufts College</td>
<td>124</td>
<td>US</td>
</tr>
<tr>
<td>Centre national de la recherche scientifique</td>
<td>117</td>
<td>FR</td>
</tr>
<tr>
<td>Johns Hopkins University</td>
<td>102</td>
<td>US</td>
</tr>
<tr>
<td>Massachusetts Institute of Technology</td>
<td>93</td>
<td>US</td>
</tr>
<tr>
<td>Boston University</td>
<td>75</td>
<td>US</td>
</tr>
<tr>
<td>Harvard College</td>
<td>74</td>
<td>US</td>
</tr>
</tbody>
</table>

Source: Stanley Kowalski, patent search on May 12, 2017 in Derwent Innovation (formerly Thomson Innovation).

Search Parameters: combined US granted, US applications, EPO granted, EPO applications and Patent Cooperation Treaty (PCT); search terms: IPC = A61K and Claim = Antibiot and Priority Date: 2007 to 2017. The IPC A61K appears to prevail on the most relevant results (oral antibiotics patents) that were found initially via a simple keyword search approach. A subsequent search sought to refine the results, i.e., via a hybrid keyword (limited to claim) combined with ("and") the identified most-prevalent IPC. This is a simple Boolean strategy using set theory to delineate data (restricted keyword plus IPC) and then identify a combined subset which has a higher likelihood of having relevant results.
The data show that patenting activity of the last 10 years is relatively strong. However, this does not correlate to the number of new antibiotics produced over the same period and patenting tends to focus on existing classes of antibiotics, with more patent families directed towards the penicillin antibiotics than any other known class. This is an interesting trend that shows that they still have a significant role in tackling bacterial infections despite widespread resistance and their repeated use. This increment developed within such a well-known existing class shows that there remains a strong possibility of new therapeutic application.

The US has the highest number of patent applications since 2004 – almost twice as many as Europe (via the European Patent Office (EPO)) and China (Figure 4). The penicillin class of antibiotics attracts the highest number of patent applications (families) (Figure 5) and, although the pioneering class was discovered almost 90 years ago, it remains relevant for treatment today.

Although some large companies have abandoned research in AMR/MDR and other communicable disease areas, a number of large and small companies are active in this field. The model is that they undertake the research and early development but then license the candidate compound(s) to larger companies, which then undertake the risk and expense of completing the medicine development process. For example, Iterum was set-up in March 2016 with an antibiotic licensed from an unnamed pharmaceutical company and joins a steadily growing group of biotechnology companies like Spero and Cidara, which have been pushing ahead in the clinic with anti-infectives designed to meet the AMR threat. Table 3 is a non-exhaustive list of licensing agreements over the past seven years.
Figure 5:
Families of patent applications relating to research into specific known classes of antibiotics, 2004–2015

Source: Medicines for rare diseases, vaccines and antibiotics, Marks & Clerk, Life Sciences Report, 2015.

Table 3:
Current licensing agreements

<table>
<thead>
<tr>
<th>Date</th>
<th>Licensor</th>
<th>Licensee</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 2014</td>
<td>AstraZeneca UK</td>
<td>FOB Synthesis</td>
<td>License covers combinations of the two companies’ experimental medicines. AZ plans to test its own beta lactamase inhibitor alongside the smaller company’s carbapenem medicines</td>
</tr>
<tr>
<td>May 2009</td>
<td>Aurobindo Pharma, India</td>
<td>Pfizer</td>
<td>Licence includes antibiotics</td>
</tr>
<tr>
<td>May 2009</td>
<td>Claris LifeSciences, India</td>
<td>Pfizer</td>
<td>Licence includes anti-infectives</td>
</tr>
<tr>
<td>March 2014</td>
<td>Discuva UK</td>
<td>Roche</td>
<td>Worldwide collaboration and license agreement for the discovery and development of new antibiotics to treat life-threatening infections caused by multi-drug resistant Gram-negative bacteria using Discuva’s proprietary SATIN technology platform</td>
</tr>
<tr>
<td>Jan 2015</td>
<td>Fedora Pharmaceuticals Canada</td>
<td>Roche</td>
<td>Worldwide license outside Japan for OP0595, a beta-lactamase inhibitor in phase I clinical development for multidrug resistant bacterial infections</td>
</tr>
<tr>
<td>March 2015</td>
<td>Harvard’s Office of Technology Development</td>
<td>Macrolide Pharmaceuticals</td>
<td>License provides exclusive rights to develop novel macrolide antibiotics</td>
</tr>
<tr>
<td>Oct 2015</td>
<td>Harvard’s Office of Technology Development</td>
<td>Opsonix</td>
<td>Exclusive license to develop a recombinant human protein derived from mannose binding lectin to treat blood-born diseases, such as sepsis</td>
</tr>
<tr>
<td>April 2011</td>
<td>Janssen Pharmaceuticals</td>
<td>Furiex Pharmaceuticals</td>
<td>Acquired full licensing rights to develop broad-spectrum fluoroquinolone antibiotic</td>
</tr>
<tr>
<td>Jan 2015</td>
<td>Meiji Seika Japan With Fedora Pharmaceuticals</td>
<td>Roche</td>
<td>Worldwide license outside Japan for OP0595, a beta-lactamase inhibitor in phase I clinical development for multidrug resistant bacterial infections</td>
</tr>
<tr>
<td>Feb 2011</td>
<td>Optimer USA</td>
<td>Astellas Japan</td>
<td>License for fidaxomycin, which is a novel antibiotic used to treat C. difficile</td>
</tr>
<tr>
<td>2014</td>
<td>Phylogica / Genentech</td>
<td>Roche</td>
<td>Research and licensing agreement, access to drug discovery platforms for new antibiotics</td>
</tr>
<tr>
<td>April 2014</td>
<td>Spero USA</td>
<td>Roche</td>
<td>Partnership option to acquire a drug candidate from start-up Spero</td>
</tr>
<tr>
<td>July 2014</td>
<td>Trius Therapeutics</td>
<td>Bayer</td>
<td>Licensing of torezoid phosphate, a phase 3 antibiotic</td>
</tr>
</tbody>
</table>

Source: JS Consulting research, 2016.
8. Opportunities for innovation and intellectual property systems

A suggested area of particular interest is the exploration of different business models. For example, ideas include the creation of a global antibiotics public-private partnership; a global antibiotics fund, which could pool all existing funds under one umbrella; a global procurement and distribution entity; and a global governance system to ensure effective stewardship and rationale use.

There are three possible non-exclusive options for the creation of the next generation of antibiotics (including AMR-associated vaccines and diagnostics):
1. private sector-driven R&D through the creation of new push and pull mechanisms
2. public-private partnerships where risks and rewards are shared and resources are pooled
3. public funding where R&D priorities and associated implementation is agreed at international/regional/national levels.

All the above options may work in developing new treatments for AMR/MDR. However, whichever option or combination of options is used, it is crucial that there is an effective international system of governance that facilitates rational use at a national level, otherwise high levels of resistance are likely to continue.

Under option 1, there is a crucial need to develop a pool of incentives and information resources for antibiotic development. It is worth investing in the detailed exploration of IP-linked incentive mechanisms that would clearly highlight the benefits and considerations of each approach. The role of new and effective vaccines and diagnostics will be important in preventing disease and ensuring that the right treatment options are identified. Following on from the industry declaration and roadmap, a further policy position was launched at the World Economic Forum (WEF) in 2017 concerning the development of sustainable models to overcome the challenging economics of antimicrobial R&D. A key focus is on pull incentives covering:
- market entry rewards
- insurance license models
- IP mechanisms.

The B20 Health Initiative also included recommendations on AMR but went broader than economic incentives and included reference to supporting GARDP, harmonizing regulatory environments, development of guidelines for appropriate use and advanced capacity building. The G20 Leaders’ Declaration supported this approach by calling for the creation of a new international R&D Collaboration Hub – to maximize the impact of existing and new antimicrobial basic and clinical research initiatives, and to further examine practical market incentive options.

75 Business Model Options for Antibiotics, The Royal Institute of International Affairs (Chatham House) and the Big Innovation Centre, February 2015.
76 Ibid. 28 and 29.
77 Sustainable models to overcome the challenging economics of antimicrobial R&D, IFPMA Policy Position, January 18, 2017.
79 G20 Leaders’ Declaration, Shaping an interconnected world, Hamburg, July 7-8, 2017; available at https://www.g20.org/gipfeldokumente/G20-leaders-declaration.pdf
WIPO Re:Search\(^80\) is a consortium of public and private partners that aims to accelerate the discovery and product development of medicines, vaccines, and diagnostics to create new solutions for people affected by neglected tropical diseases, malaria and tuberculosis by making IP and know-how available to the global health research community. A Partnership Hub managed by BIO Ventures for Global Health (BVGH) connects partners and brokers research collaborations. WIPO Re:Search provides a mechanism which illustrates how IP issues can be successfully handled to support developing and maintaining research partnerships. WIPO Re:Search collaborations are based on Guiding Principles that establish essential parts of the prospective license agreement, thereby considerably reducing the effort and costs of negotiating the license agreement.

WIPO Re:Search might serve as a case study that provides the experience of partnering and connecting antibiotic researchers and developers and supporting partnership building in the area of neglected tropical diseases, malaria and TB. The role of the WIPO Re:Search Partnership Hub could be a model for AMR/MDR research to proactively identify and facilitate collaborations that connect industry to academic and other non-profit researchers. Such a model could be the principal source of information on antibiotic research and development around the world, so that potential partners could explore collaboration on existing projects or identify possible gaps. The experiences gained could serve GARDP, which seeks to fill R&D gaps, particularly where a commercial incentive is insufficient. A WIPO Re:Search-inspired platform might be used where candidate compounds might be identified and shared in order to maximize collective input from potential partners.

The UK Review on AMR has proposed a global innovation fund but noted that a number of existing funding mechanisms exist.\(^81\) Such funding has been made available through various initiatives (as mentioned in Section 3) but there is a lack of coordination and collaboration, and substantial gaps remain. A global fund would ensure a holistic approach, but agreeing to common R&D priorities may be challenging given the diverse burden of AMR/MDR around the world. How to create government financing mechanisms has been discussed in WHO for a number of years, with ideas ranging from taxing financial transactions or use of commercial passenger airliners to commitments of percentages of GDP.\(^82\) A number of mechanisms are referred to in Section 6. However, it is often the case that government funders prefer to support initiatives within their own countries and/or regions, where control is easier and other benefits, such as training of the new generation of scientists and researchers, can be realized.\(^83\) The unique threat posed by AMR/MDR provides a strong incentive to overcome these challenges but it will take time and commitment to fully establish and operationalize. WHO, as part of the implementation of the Global Action Plan, is currently starting a project to identify global R&D needs. This is necessary to guide joint efforts such as CARB-X or the WHO/DND/GARDP initiative to address global R&D needs.

\(^{80}\) www.wiporesearch.org

\(^{81}\) Ibid. 37, page 49.


\(^{83}\) Ben S. Bernanke, Promoting Research and Development: The Government’s Role, 2011.
9. Access to new-generation antibiotics and stewardship

Any stewardship framework needs to ensure access for patients who need treatments while preventing inappropriate use. An effective health system is essential for both access and stewardship so that patients can be appropriately diagnosed, treated (being made aware of the crucial importance of medicine adherence), and cured. WHO has produced an options document that details key considerations for the establishment of a global development and stewardship framework. This includes the type of instrument that could be used, scope of medical products, how to define and promote appropriate use, development of new treatments, tools and vaccines and affordable access.\(^{84}\)

The Medicines Patent Pool (MPP) has proven a successful innovation and access model in the area of HIV/AIDS. Based on this success, the mandate of the pool has expanded to include other communicable diseases such as Hepatitis C. The value of this model is that a degree of antibiotic stewardship could readily be included as part of a licensing arrangement.\(^{85}\) The MPP, if deciding to enter the field of antimicrobial medicines, could establish licensing agreements for AMR-related vaccines and diagnostics. Prevention is always better than cure and effective diagnosis is crucial to ensure appropriate use. Countries receiving new-generation antibiotics would first need to be assessed based on need. Applications for new-generation antibiotics could be independently assessed by a panel of technical experts, following a similar model to the Green Light Committee (GLC) Initiative,\(^{86}\) which assesses country applications for access to second-line anti-tuberculosis medicines for the effective treatment of MDR-TB.

In addition to the above, patent-linked licensing arrangements could be used as an enforcement mechanism to ensure compliance with stewardship requirements. Failure to adhere to predetermined principles of stewardship undermines the overall objective, and hence could lead to the restriction or prevention of future supply to the entity that violates the terms of the agreement. It is crucial that an effective sanction is in place, with the hope that implementation of such a sanction will not be necessary.

The MPP has a similar mechanism with generic producers who are members of the pool. Failure to utilize the license through manufacture and sufficient supply of the associated product ultimately results in withdrawal of the license.\(^{87}\)

There are opportunities for collaboration between different entities and initiatives where expertise, best practice and networks could be combined to achieve shared goals. For instance, platforms could be explored where various stakeholders could come together for the development of combination treatments or other important formulations.

\(^{84}\) Ibid. 41.


\(^{86}\) The Green Light Committee (GLC) Initiative, frequently asked questions document.

\(^{87}\) For example, Sublicense and Technology transfer Agreement between Bristol-Myres Squibb, the Medicines Patent Pool Foundation and Cipla Ltd, December 14, 2015 (Article 12.3, page 16).
10. Conclusion

Ultimately the most effective way to tackle AMR/MDR is to provide a global framework that includes the full range of activities - including disease prevention, awareness campaigns, improved sanitation, surveillance and monitoring - that are able to be implemented effectively at a national level. But the development of new diagnostics, medicines and vaccines remains a critical component that requires new or adapted funding mechanisms and incentive systems.

As with many complex problems, there is no one-size-fits-all solution and both public and private involvement, often in partnership, will be required to meet the challenge. Maximizing the collective benefit from the significant range of experience, expertise and resources available will require effective coordination, collaboration and alignment at global and local levels.

The United Nations Ad-hoc Interagency Coordination Group on Antimicrobial Resistance (AMR), established by the United Nations Secretary-General as mandated by UN Resolution 71/3 of October 5, 2016, began its work in May 2017. It draws on expertise from all relevant stakeholders and is expected to report to the General Assembly and make recommendations, including on options to improve coordination. The Group can contribute to providing the necessary political support. Such support should include ministries of health, finance and agriculture, given the potentially wide range of health, economic and social impacts involved.

This work can be complemented by formulating mechanisms that drive innovation for results to incentivize success, while feeding expertise and experience into stewardship and access efforts. Consideration should be given to how IP could be used in any reward or prize system for AMR/MDR R&D – both in terms of incentive and governance.

There are numerous frameworks that encourage cooperation and collaboration between the public and private sector. Nevertheless, there is a need to connect and synergize the identified best practice associated with these initiatives to the challenges posed by AMR/MDR. WIPO Re:Search and the Medicines Patent Pool are both strong examples of what can be achieved where normal market drivers are limited or where complexities of collaboration exist. Policymakers should consider how these mechanisms enable the sharing of experience, expertise and know-how, reduce transactional costs, simplify licensing arrangements and terms and enable the sharing of best practice. These findings and insights should be extracted, refined and applied in the area of AMR/MDR so that the unique challenges of innovation, access and appropriate use can be effectively addressed.

AMR/MDR will impact all countries, but particularly those where health systems need to be strengthened. Collaborative and urgent action should be seen as a priority but finding a way to achieve this in practice will be the next important hurdle.

88 See, for example, ibid. 40 for a development and stewardship framework.
89 www.who.int/antimicrobial-resistance/interagency-coordination-group
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