TACKLING ANTIMICROBIAL RESISTANCE ENSURING SUSTAINABLE R&D

Final note prepared by OECD, WHO, FAO and OIE

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Executive summary

Antimicrobial resistance (AMR) is a **major threat to global health and the world economy**, and poses a unique challenge to humanity. Millions of people in G20 countries are infected each year by microbes susceptible to the development of resistance. Resistant microbes double the probability of developing a complication and triple the risk of death compared to non-resistant forms. The development of resistance by microbes causing, among others, tuberculosis, HIV and hospital infections imposes the main brunt of this problem on low- and middle-income countries. But all countries, regardless of their economic situation, the strength of their health systems or the level of antibiotic consumption, will face disastrous consequences if the spread of AMR is not contained. The modern health care that people in high-income countries take for granted and that those in lower-income countries aspire to, is at stake as medicine and surgery (e.g. organ transplants, cancer care and care of premature babies) are not possible without effective antimicrobial medicines.

Existing international commitments need to be implemented promptly and forcefully. The development of **national action plans** is an essential first step for countries in an effective response to combat AMR. Plans should be developed as part of cross-sectoral efforts under the 'One Health' framework, acknowledging that the health of humans, animals and ecosystems are interconnected. In addition, countries should invest in robust national surveillance systems in the human, animal, plant and environmental sectors, perform integrated analysis of data generated from different sectors to inform national policy for containment of AMR using a 'One Health' approach, and feed the resulting data into the Global Antimicrobial Surveillance System (GLASS) and the OIE database on antimicrobial use in animals. Global solutions are needed, to promote prudent use of antimicrobials, and to foster effective infection prevention and control. Finally, inadequate access to any newly developed antimicrobial promotes AMR and represents a threat to global health. Although resistance develops naturally over time, it is accelerated by misuse and overuse of antimicrobial medicines. Many people around the world have little or no access to these medicines. Therefore, equitable and affordable access to medicines that work must also be ensured.

Stronger actions and economic incentives to support the development of new antimicrobials, vaccines and diagnostics are also urgently needed. **The research and development (R&D) pipeline for new antimicrobial therapies has been drying up** due to scientific challenges, high uncertainty and low revenues, making such products less attractive as investments for industry. A number of initiatives and additional economic incentives have been put in place in the last few years which had some effects on the R&D landscape. Many of these incentives target the initial phases of R&D using push mechanisms, and some such as GARDP cover the whole development phase. While there have been various calls for pull mechanisms to correct market failures in the market for antimicrobials few have been implemented so far. Only a very small proportion of the available funding is aimed at R&D on diagnostics and vaccines.

G20 could put in place **a three-pronged approach to reactivate the R&D pipeline**. First, it could commit to increasing funding of basic science driven by academic institutions and small- and medium-sized enterprises. Results of these projects should feed a G20 global collaboration platform that could become a knowledge hub for R&D to ensure coordination, and could promote best practices in conservation and access to antimicrobials. WHO, FAO, OIE and OECD could support this initiative by providing evidence and technical advice to inform debate. Second, the G20 could commit to support scientifically promising antimicrobials in the clinical development phase that target priority pathogens. Third, G20 could explore the effectiveness of other mechanisms, including pull mechanisms which would compensate for new antimicrobials while **delinking R&D investments from sales revenues**. Such schemes would help correct the market failure by giving industry the incentive to invest in new antimicrobials and will ensure that the antimicrobial is supplied to markets (especially in LMICs) at an affordable price and would help implement effective stewardship programmes and promote access to quality antimicrobials in countries at different levels of income. The three-pronged approach could be complemented by the creation of Target Product Profiles to align R&D efforts with government priorities and better collaboration and coordination of existing initiatives.

Executive summary (*cont.*)

Based on the currently available evidence, OECD estimates that bringing to the market four new antibiotics over the next 10 years would require **additional funding of about 500 million USD per year**, corresponding to about 0.02% of the projected annual economic costs of AMR per year by 2050. Access to any new product might be made available at an affordable price in all countries that commit to using it responsibly.

G20 countries can play a pivotal role through actions along the following lines:

1. Confirm their commitment to tackle AMR, based on the principles of the 'One-Health' approach and in agreement with the Global Action Plan on AMR. This requires developing and strengthening national action plans; and providing capacity building support to other countries;
2. Commit to put in place and strengthen their national surveillance systems to monitor antimicrobial resistance and antibiotic consumption, perform integrated analysis of data from different sectors to inform national AMR containment policy and to provide this data to GLASS and the OIE database on antimicrobial use regarding animals;
3. Commit to support the development of new antimicrobials, vaccines and diagnostics by providing ongoing funding and increase coordination to ensure a good supply of basic research, based on the principles of transparency and Open Science;
4. Commit to study options to establish delinked incentive schemes, to bring to market new antibiotics. Available studies have suggested that a target payment of 1 billion USD would be needed for each novel product meeting the required criteria. The scheme should ensure appropriate use of antimicrobials and promote access in LMICs while promoting stewardship programmes to sustain antimicrobial effectiveness
5. Request International Organizations to support them through the following actions:
    a. Task WHO, FAO, OIE and the OECD to develop targets and goals to promote appropriate use of antimicrobials in human, animal and plant health to prevent infections;
    b. Task OECD in collaboration with WHO, FAO and OIE to establish a G20 platform to identify cost-effectiveness of different practices to support countries to adopt responsible and prudent use of antimicrobials and prevent the spread of infectious diseases;
    c. Task OECD and WHO in collaboration with FAO and OIE to provide guidance in the process of establishing a collaborative global R&D platform to increase knowledge sharing and communication between funders to optimise resource allocation and avoid funding overlaps which might result in paying twice for the same result;
    d. Task WHO to lead the identification of R&D priorities and the development of global Target Product Profiles (TPPs) to guide R&D efforts for human health;
    e. Support and fund existing mechanisms such as GARDP
    f. Task OECD and WHO to establish a working group to explore the practical details associated with pull incentives.

Antimicrobial Resistance is a threat to our health and our economies

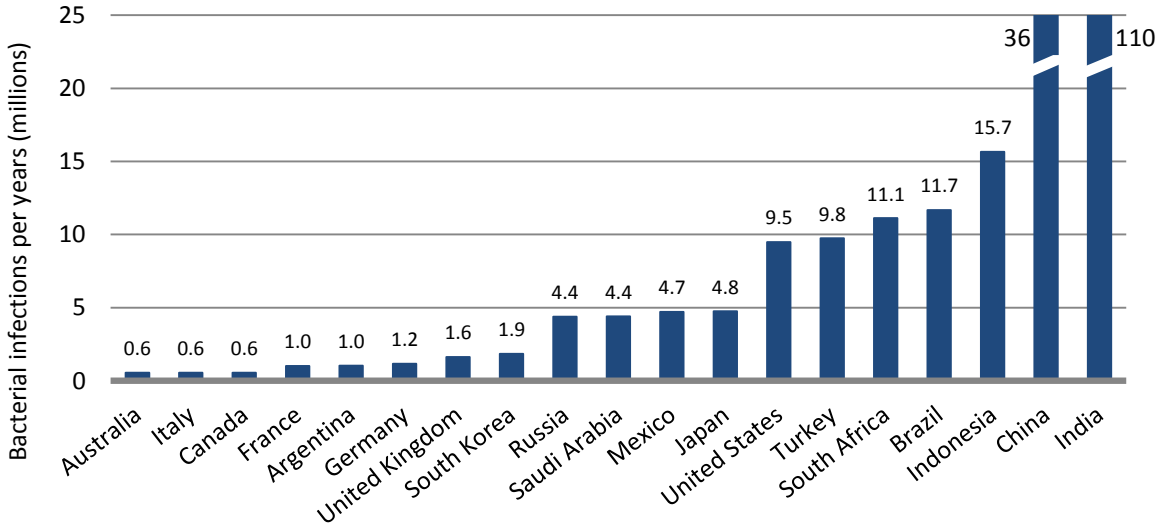
Antimicrobial resistance (AMR) is a major threat to global health and the world economy, and poses a unique challenge to humanity. All countries – regardless of their economic situation, the strength of their health systems or their level of antimicrobial consumption – will face disastrous consequences if the emergence and spread of AMR is not contained. Global solutions are needed, to promote prudent use of antimicrobials; to ensure that all people, regardless of where they live, have access to the antimicrobials they need; to find new vaccines, diagnostic tests and antimicrobials that are affordable, of good quality and effective against drug-resistant diseases; and to foster infection prevention and control. Existing international commitments need to be implemented promptly and energetically. In addition, a global deal is needed, with richer countries paying to kick-start the innovation pipeline, making new products available at an affordable price to low-income countries that commit to using medicines responsibly and increasing AMR surveillance.

AMR infections are killing more people

Resistant bacteria double the probability of developing a complication and triple the risk of death compared with non-resistant forms.[1] High levels of resistance have already been observed among common bacteria that cause serious hospital acquired-infections, urinary tract infections, and gonorrhoea, among others[2].

Over 23,000 people currently die each year in the US alone due to antibiotic resistance[3], with at least another 25,000 deaths across Europe[4]. The AMR Review calculated that resistant bacteria already kill more than 700,000 people worldwide[53]. In low- and middle-income countries (LMICs) bacterial diseases are more common, including due to inadequate public health systems, and more deadly, and where malnutrition and co-infections, particularly with HIV, are widespread (Figure 1). Health systems in LMICs are less able to provide second-line treatments if basic antibiotics do not work. If not controlled, the impact of resistance will continue to grow, potentially leading to disastrous consequences.

Figure 1. People infected by microbes susceptible to the development of resistance



Source: OECD analysis based on IHME data[4]

Note: The graph includes the following infections: gonococcal, chlamydial, lower respiratory, syphilis, tuberculosis, whooping cough, paratyphoid fever, typhoid fever, and meningitis

AMR also has the capacity to erode hard-won gains made against major infectious diseases like HIV/AIDS, tuberculosis (TB) and malaria. In 2010, an estimated 7% of people starting antiretroviral therapy in developing countries had drug-resistant HIV, and the figure rises to 10-20% in high income countries. In some countries, up to 40% of patients re-starting treatment for HIV show resistance. 3.3% of patients developing TB in 2014 showed resistance. The proportion is 20% among people previously treated for TB. In 2015, there were about 480 000 new cases of multidrug-resistant TB (MDR-TB), a form of TB that is resistant to the two most powerful anti-TB drugs. Globally, only half of MDR-TB patients were successfully treated in 2014. An estimated 9.7% of people across 105 countries have a form of TB that is resistant to at least four core anti-TB drugs.

Even these disturbingly high rates of resistance understate the risk that AMR poses to the health of humans. Modern medicine and surgery are seriously weakened without antibiotics. Complex medical interventions, such as organ transplants, joint replacements, cancer care and care of premature babies are just a few of the procedures endangered by increasing spread of resistant organisms. The modern health care that people in high-income countries take for granted and that those in lower-income countries aspire to, is at stake.

The economic impact of AMR may be devastating to local and global economies

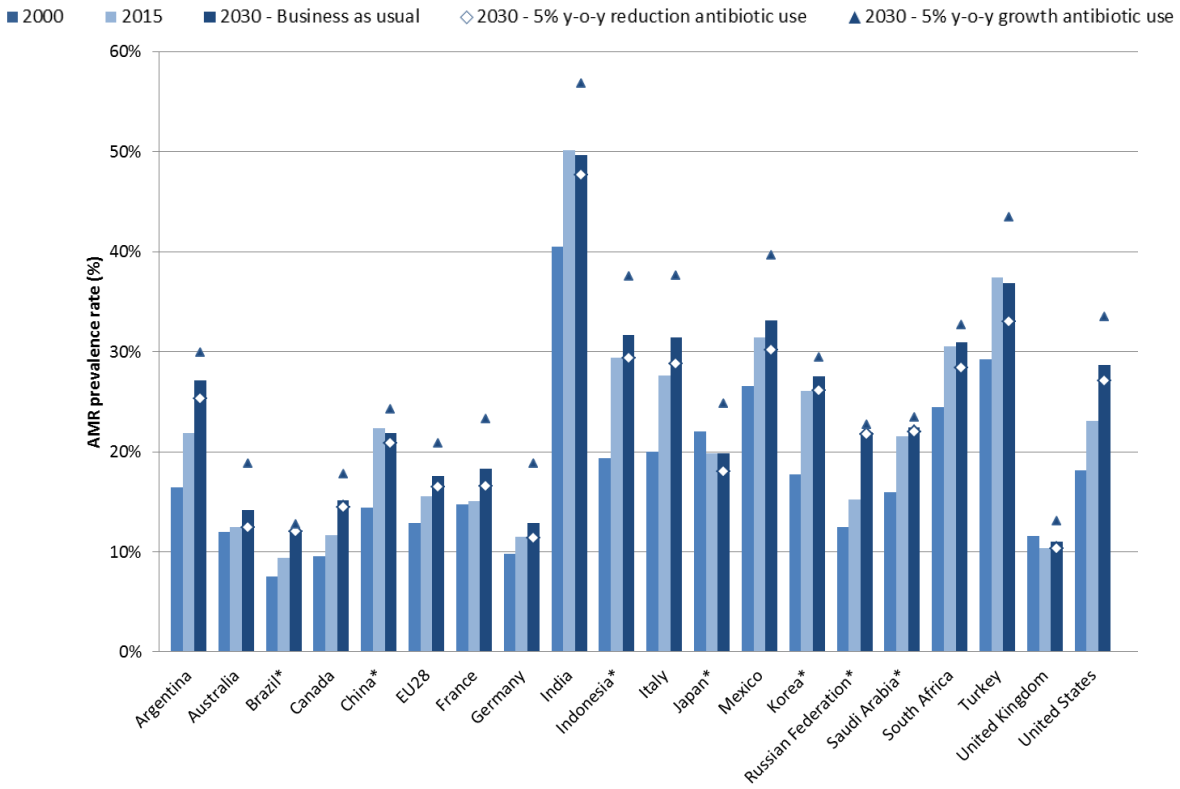
Patients infected by resistant bacteria require more intensive and expensive care and are more likely to be admitted to a hospital. For example, if basic treatments for TB do not work, then second and third-line 'regimens' need to be administered. But these cost 3 times and 18 times more, respectively, than first-line drugs. On average, a hospitalized patient with antibiotic-resistant infections costs an additional 10,000 to 40,000 USD[5].

AMR has also a significant negative impact on the global economy due to increased mortality, prolongation of illness and reduced labour efficiency. In high-income countries, the loss in productivity alone for someone suffering from a resistant infection is estimated at 38,000 USD per patient due to time away from work and informal care requirements from family and/or friends[6]. A reduction in livestock production due to the death of animals affected by untreatable diseases is expected to reduce international trade by 1.1% to 3.8% by 2050, reducing GDP and increasing malnutrition[7].Globally, the impact of AMR-attributable lost economic output will be -0.14% of the world GDP every year. Developing countries will suffer more. Countries in the sub-Saharan region may face a GDP loss of -0.30%[8]. Sustainable development goals relating to poverty, childhood survival, and development will be put in jeopardy. Increasing AMR is estimated to push an additional 28 million people into extreme poverty by 2050, mainly in LMICs.[9]

Rising resistance in G20 countries

Levels of AMR are already high and will continue to rise unless effective interventions are put in place (Figure 2). OECD estimates that the prevalence of AMR for eight common bacteria in G20 countries has increased from about 18% in 2000 to 22% in 2014, and will continue to rise to reach 28% by 2030 under a scenario of increasing antibiotic consumption. The recent rise in resistance among difficult-to-treat gram-negative bacteria (e.g. salmonella, gonorrhoea, etc.) is particularly worrisome and deserves specific attention.

Figure 2. Historical and projected AMR rates for 8 bacteria in G20 countries



Source: OECD analyses.

Notes: The analyses include the following eight pathogens: 3rd-generation cephalosporins-resistant E. coli, fluoroquinolones-resistant E. coli, carbapenem-resistant K. pneumoniae, cephalosporins-resistant K. pneumoniae, carbapenem-resistant P. aeruginosa, vancomycin-resistant E. facealis and E. faecium (except for Indonesia), methicillin-resistant S. aureus, and penicillin-resistant S. pneumoniae. Data for 2030 are extrapolated under a 'business as usual' scenario in which antibiotic consumption follows the best-fitting trend; blue triangles and white diamonds represent two alternative scenarios in which, respectively, antibiotic consumption increases or decreases by 5% on a year-on-year basis. *countries for which no original data on resistance rates are available and for which missing values are imputed.

The challenge of AMR

AMR is the outcome of a 'race' between natural selection and human ingenuity. The more antimicrobials are used, the less effective they become. Continuous innovation must take place to keep pace with evolving pathogens. Rising levels of AMR are a sign that natural selection is taking place more rapidly than is innovation in the development of new antimicrobials. If this rate of increase is to be slowed, we must not only innovate more rapidly, but also slow natural selection – by eliminating the inappropriate use of antimicrobials; using second- and third-line treatments only when absolutely necessary; and ensuring appropriate access to treatment.

Antibiotics are some of the most overused and misused medications due to their low cost, high effectiveness, and low level of side effects. For example, it is estimated that about 60% of antibiotics prescribed by general practitioners in OECD countries are used inappropriately[10] High levels of antimicrobial use are also found in animals and plants and have been linked to transmission of resistant pathogens to humans through environmental contamination and direct contact with animals or animal products[11]. For example, up to 80% of antibiotics given to fish is excreted into water and spreads rapidly through water systems. Although many countries have implemented measures to restrict or reduce antimicrobial usage in animal health and agriculture, the practice remains common in some G20 countries.[12]

Box 1. The economic impact of antimicrobial use in livestock production

Antimicrobials are widely used in all levels of food animal production for several purposes related to preventing disease and treating sick animals. In many countries, antimicrobials are also used to increase animal growth rates. Two recent studies[13, 14] conclude that the overall impact of antimicrobials on farm productivity and profitability has been declining, from 5%-10% in the 1990s to a modest 1%-2% in recent years.

The economic impact of reducing antimicrobials in the production system depends on factors including the animal (cattle, pigs or poultry), the type, management and modernity of the production system and the preventive and biosecurity measures that are being implemented on the farm. In production systems with good sanitary conditions the productivity gains from antimicrobials used for growth promotion are likely to be lower. However, in emerging economies the gains are substantially higher, in particular for intensive pig and poultry operations.

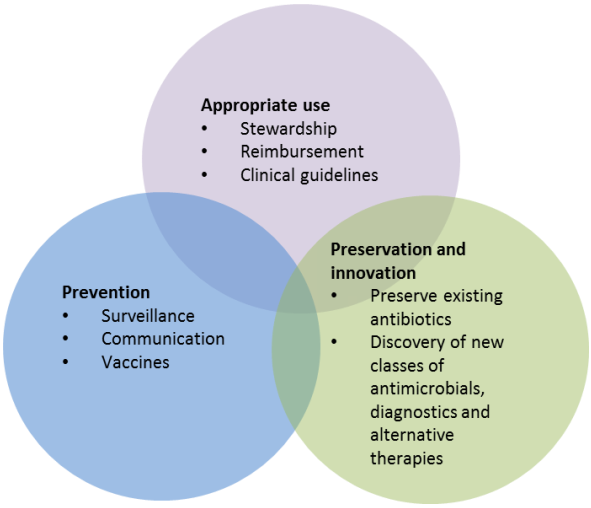
There is concern that restricting the routine use of antimicrobials for non-therapeutic purposes could increase farm production costs, lower the production of animal products and raise consumer prices. Experience with these regulations indicates that increases in production costs are transient and can be offset by improvements in management practices, biosecurity measures and the use of alternatives to antimicrobials, such as vaccines. Further understanding of the economic benefits and costs (and for alternatives) associated with lower use of antimicrobials is critical for designing policies that would encourage more prudent consumption of antimicrobials in intensive livestock farming. The information and data needs are particularly acute in developing countries, notably in Asia (OECD – FAO Agricultural Outlook 2016-2025).

Finally, while many countries are working to decrease inappropriate use of antimicrobials to limit the growth in resistance, lack of access is still an issue in many LMICs. Ensuring timely access to antibiotics would prevent an estimated 445,000 pneumonia deaths in children living in LMICs[15]. Limited access may promote AMR through inappropriate treatment regimes. This may happen because diseases become more established in the community without being killed by the antimicrobials, but as there is still exposure to some antimicrobials, the pathogens have more time to evolve. LMICs must therefore not only work to reduce inappropriate use, but also to ensure access in order to maximize the benefit of life-saving antimicrobials and minimise the development of AMR.

AMR can be tackled only by a multi-pronged approach

Addressing AMR requires an ambitious collaborative and coordinated plan, including economic, scientific and political actors operating across a variety of national contexts. There is a wide agreement that any comprehensive response to addressing AMR should be based on the following three key pillars: i) promoting conservation; ii) investing in innovation; and iii) ensuring responsible access. Any attempt to address one must take into account the implications for the other two, forming a policy tripod, which should guide all AMR prevention policies. The Transatlantic Task Force on Antimicrobial Resistance summarised these priorities in a set of critical tasks (figure 3)[18]. Regulatory Capacity of Human, Animal and Plant Health Services is a fundamental enabler underpinning the ability to implement these critical tasks.

Figure 3. Priorities for actions for effectively combatting AMR as identified by TATFAR



Source: adapted from Renwick et al. 2016[16]

Analysing the implementation of AMR commitments*

Tripartite and One Health Approach and Global Action Plans

Addressing the rising threat of AMR requires a multisectoral (One Health) approach. In a tripartite approach, FAO, OIE and WHO recognise that addressing health risks at the human–animal-plant-ecosystems interface requires strong partnerships among entities that may have different perspectives and varying levels of resources. The aim is to ensure that antimicrobial agents continue to be effective and useful to cure diseases in humans and animals; to promote prudent and responsible use of antimicrobial agents; and to ensure global access to medicines of good quality.

In May 2015, WHO Member States endorsed a global action plan to tackle antimicrobial resistance, including antibiotic resistance, the most urgent drug resistance trend. The AMR global action plan contains five major strategic objectives:

1. to improve awareness and understanding of antimicrobial resistance;
2. to strengthen knowledge through surveillance and research;

* A report of key initiatives promoted by WHO, FAO and OIE to support countries efforts to tackle AMR can be found in annex 1

3. to reduce the incidence of infection;
4. to optimize the use of antimicrobial agents; and
5. to develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

In 2015, the World Assembly of Delegates of OIE adopted a resolution to follow the global action plan and to develop national action plans with respect to the use of antimicrobial agents in animals and to ensure close collaboration with public health officials. At the same time, the Thirty-ninth Conference of FAO adopted a status report on AMR and a resolution recognizing that AMR poses an increasingly serious threat to public health, sustainable food production and that an effective response should involve all sectors of government and society. The resolution urges members to 'develop or strengthen national plans, strategies and international collaboration for the surveillance, monitoring and containment of antimicrobial resistance in food, agriculture and the environment, in close coordination with related plans for human health'.

The UN Sustainable Development Goals

The UN Sustainable Development Goals (SDGs) recognize the importance of AMR (paragraph 26 of the Declaration). The attainment of many of them will depend on the availability of and access to affordable and effective antimicrobial medicines and other technologies such as diagnostic tests. AMR seriously threatens the health and lives of vulnerable populations, such as newborns, children, and women, as well as sustainable food and agriculture production and a healthy environment. AMR is reducing our ability to protect the health of animals and therefore is threatening safe and sustainable food and agriculture. More specifically, AMR is recognized in SDGs 1, 2, 3, 6, 8, 12, 14, 15, 17 (see Annex 1 for further details).

The importance of countries developing and implementing national action plans

Developing national action plans (NAPs) is an essential first step for countries to establish an effective response to combat AMR. At the Sixty-eighth World Health Assembly in 2015, Member States committed to have NAPs in place by May 2017. WHO, FAO and OIE have been working closely with stakeholders to provide technical support to countries for the effective development of their NAPs. To date, completed NAPs are now available in 67 countries, with 62 additional countries currently in the process of developing theirs[17].

The importance of monitoring, evaluation and surveillance

Robust, locally relevant information is necessary for planning, prioritization, management and evaluation at country, regional and global levels. WHO's 2014 global report on surveillance of antimicrobial resistance revealed that there are many parts of the world in which the scope or scale of the problem is unknown. Common standards are lacking, such that even where data exist, they are not internationally comparable, rendering interpretation difficult. Links between surveillance systems in animals and in humans are weak. International standards on harmonization of national antimicrobial resistance surveillance and monitoring programmes (for animals) were adopted by OIE's members in 2012, but at the time there were no global standards for resistance surveillance in humans, nor a platform for the rapid sharing of information on AMR.

To address these gaps, WHO has established the Global Antimicrobial Surveillance System (GLASS). Since 2015, GLASS has established the global standards for bacterial resistance surveillance in humans and offers a global platform to collect information on countries' progress in strengthening national surveillance systems on antimicrobial resistance. The system will progressively expand to include other types of surveillance related to antimicrobial resistance and links to other global surveillance systems. Similarly, the OIE is collecting data on the use of antimicrobials in animals, in line with the global action plan and based on the OIE standards on monitoring of the quantities and usage patterns used in animals[18].

In addition, FAO, OIE and WHO are developing a monitoring and evaluation framework to monitor process and outcome measures for human and animal health and agriculture. The aim is a consistent set of measures that most countries should be able to implement within the next five to seven years. It is also necessary to monitor what countries are doing to address AMR. At the end of May 2017, the three international organisations issued results of a survey of 151 countries, which gives an assessment of their progress in addressing global action plan objectives.

A Global Development and Stewardship Framework

In 2016, a Political Declaration of the UN General Assembly was adopted on AMR, in which Member States emphasized that the blueprint for tackling AMR is the global action plan on AMR developed in 2015 by WHO in coordination with FAO and OIE. Countries called for better use of existing tools for preventing infections in humans and animals and highlighted market failures, and called for new incentives for investment in research and development of new, effective and affordable medicines, rapid diagnostic tests, and other therapies to replace those that are losing effectiveness.

The political declaration included commitments by Heads of State and Government and representatives of States and Governments to develop their multisectoral national action plans in line with a "One Health" approach; to mobilize funding for the implementation of these plans and for research and development; to ensure that national plans cover the development of surveillance, monitoring and regulatory frameworks on the preservation, use and sale of antimicrobial medicines; and to increase and sustain awareness of and knowledge about antimicrobial resistance among the public and health professionals. The UN High-Level Meeting requested the WHO, together with FAO and OIE to develop a global development and stewardship framework. The framework will cover R&D for new products, stewardship and access to treatments

The framework will build on objectives 4 and 5 of the AMR GAP on a global level. Options for such a framework presented to the World Health Assembly in 2016[19] and a draft Roadmap was presented to the Assembly in 2017[20]. As part of the development of the Framework, the WHO has engaged in a comprehensive review of antibiotic medicines included in the WHO Essential Medicines List categorizing them in three groups:

- ACCESS – first and second choice antibiotics for the empiric treatment of most common infectious syndromes;
- WATCH – antibiotics with higher resistance potential whose use as first and second choice treatment should be limited to a small number of syndromes or patient groups; and
- RESERVE – antibiotics to be used mainly as 'last resort' treatment options.[21].

This process will serve as a starting point for the development of the framework. With respect to the development part, WHO has identified priority pathogens for R&D (see box 6) and is currently engaging in a comprehensive review of the clinical R&D pipeline to match the pipeline against the identified priorities.

With respect to food safety, WHO developed a list of critically important antimicrobials (WHO CIA List) in 2005 following recommendations from a FAO/OIE/WHO tripartite expert meeting, with the objective to help formulate risk management strategies on non-human use of these medicines in human medicine to preserve their effectiveness. The WHO CIA list is updated regularly. WHO published the 5th revision of the list in April 2017[22] and is preparing a guideline for use of medically important antimicrobials included in the WHO CIA List in food-producing animals with the objective to preserve their effectiveness.

The FAO/OIE/WHO tripartite expert meeting also recommended that the OIE develop a List of Antimicrobials of Veterinary Importance. The list was developed in addition to the standards included in the Terrestrial Animal Health Code, Aquatic Animal Health Code and Manual of Diagnostic Tests and Vaccines for Terrestrial Animals and is updated regularly. It includes recommendations on the use of antimicrobials considered to be critically important for both human and animal health, together with a recommendation to avoid off-label use in animals of antimicrobial classes and sub-classes only registered in human medicine (and so not included in the OIE list).

Antimicrobial use and consumption

WHO is developing a framework for surveillance for antimicrobial prescribing and use. At the same time, work to consolidate data collection on antimicrobial consumption using national data on sales has continued in the European region: 18 non-EU Member States are collecting data that is currently being analysed with WHO Secretariat support. The work of the European Region's antimicrobial medicines consumption (AMC) network is being used to inform global models for data collection. Field testing of consumption monitoring has begun in about 20 countries in Africa and Asia, with WHO providing support through training of national experts, the provision of templates and tools for data collection and analysis and related technical advice. Work is also ongoing on the review of dosing schedules of antibiotics.

The OIE collection of data on the use of antimicrobial agents in animals started in 2015, with the first annual report published in 2016. Members may report based on sales or usage, depending on their regulatory capability. The system also provides for an increasing level of granularity, including the ability to report usage in different species and by different routes of administration.

OECD is setting up a wide-ranging platform on AMR policies to support its members and G20 member countries by:

- Developing voluntary targets and measuring performances for reduction of AMR in the human and livestock sector.
- Developing good practices and national action plans. OECD is developing a cost-effectiveness model that can be used to assess the costs of different interventions and their expected impact in achieving established targets.
- Establishing a cross-sectoral forum where governments can discuss, develop and coordinate new strategies for prudent antimicrobials use in human, animal and plant health. OECD can provide the background evidence for the discussion and assess, beforehand, the potential effectiveness and cost-effectiveness of the innovative policies under discussion.
- Discussing alternative approaches for treating and containing livestock diseases, based on the experience of those countries that have taken steps to reduce use of antibiotics.

Box 2: Role of the G20 and potential actions

G20 countries could:

1. Confirm their commitment to tackle AMR, based on the principles of the 'One-Health' approach and in agreement with the Global Action Plan on AMR. This requires developing and strengthening national action plans; and providing capacity building support to other countries;
2. Commit to put in place and strengthen their national surveillance systems to monitor antimicrobial resistance and antibiotic consumption and to provide this data to GLASS and the OIE database on antimicrobial use regarding animals;
3. Request WHO, FAO, OIE and the OECD to develop targets and goals to promote appropriate use of antimicrobials in the human health, animal health and plant health to prevent infections;
4. Commit to put in place innovative policies to promote a higher uptake of diagnostics in the human sector;
5. Task OECD in collaboration with WHO, FAO and OIE to establish a G20 platform to identify cost-effectiveness of different practices to support countries to adopt responsible and prudent use of antimicrobials and prevent the spread of infectious diseases

Insufficient incentives and technical hurdles hinder the development of new antibiotics

By implementing existing international commitments, G20 leadership can do much to promote a more appropriate use of antimicrobials and thereby slow the pace of natural selection that drives the growth of AMR. However, new antimicrobials are needed for the bacteria in which AMR has developed. Vaccines can potentially reduce the need for antibiotic treatments. New, affordable and rapid diagnostics can help make sure we use the right antimicrobials and only when they are needed. But the investment into new antibiotics has slowed alarmingly over the past decades and more investment is needed to revitalize the R&D pipeline.

Box 3: Promoting the use of rapid diagnostic tests, including in vitro diagnostics

Rapid and easy to use diagnostic tests (RDTs), including in vitro diagnostics (IVDs) to detect whether an antibiotic should be used and, if so, what antibiotic to use, have the potential to be a profitable market both in the human, animal and plant sectors. Organizational barriers and negative economic incentives currently hinder broader use of RDTs, including IVDs. In many cases, the cost of a test is higher than the cost of an antibiotic and, too often, tests are not available or countries do not do enough to promote the use of RDTs, including IVDs. All these factors reduce incentives to develop new tests. Nonetheless, the market for early diagnostics to detect whether an antibiotic should be used and to select the most appropriate antibiotic may become attractive, once the right incentives are put in place.

In 2000 Slovenia implemented new policies to restrict use of antibiotics in community care and hospitals. For example, since the implementation of the policy, fluoroquinolones can be prescribed for urinary tract infections only when the first-line treatment does not produce any effect or after an IVD confirming the diagnosis. The introduction of this policy did not make the use of IVDs compulsory but put in place strong incentives to increase use of tests. The use of diagnostics increased by 220% between 1999, the year before the introduction of the policy, and 2003.

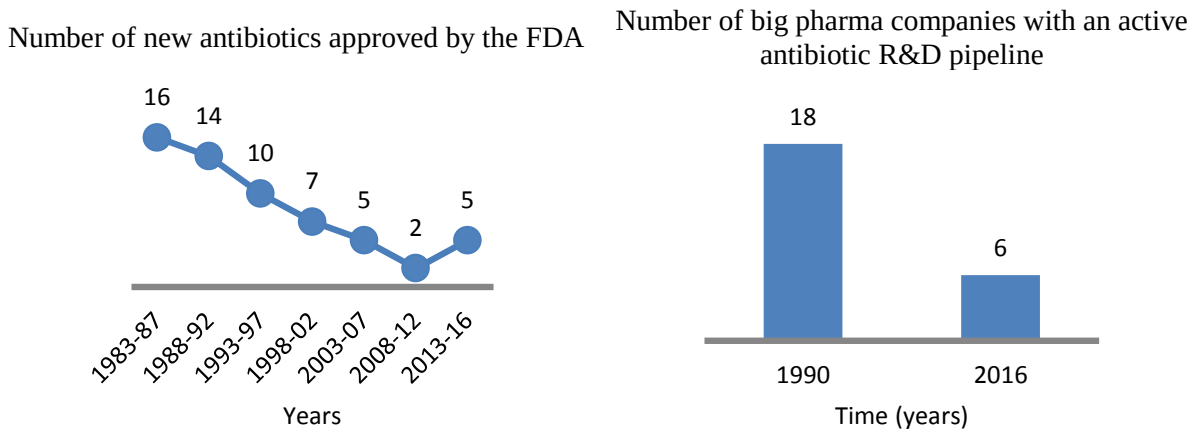
The research and development (R&D) pipeline is drying up

The need to inject fresh resources into the R&D pipeline is clear from two key facts (figure 4). First, the approval of antibiotics has dropped significantly during the last 30 years, despite signs of improvement from 2014. Since 2000, only five new classes of antibiotics have been put on the market[23] and none of these targets gram-negative bacteria, which pose the biggest resistance threat.

Second, the number of large pharmaceutical companies that are active in this field has declined from 18 in 1990 to 6 in 2016. To some extent, small- and medium-sized enterprises (SMEs) have filled the void left by large companies. Between the early 1980s and early 2000s, the proportion of all new drugs attributable to SMEs increased from 23% to 70%[24]. SMEs, however, often lack the capital necessary to take a promising idea from initial research through to the late-stage clinical trials required for market approval. Product development partnerships can help fill this gap.

According to the Pew Trust, as of December 2016, an estimated 40 new antibiotics with the potential to treat bacterial infections were in clinical development for the U.S. market[25]. Of these, 11 showed activity against important gram-negative bacteria with a further 4 possibly active. Science is generating some promising research directions. For example, since its launch in July 2016, CARB-X, an accelerator created to invest in innovative and promising solutions to AMR, has already identified about 40 promising projects. Further, there may be alternatives to antibiotics for the treatment and prevention of bacterial infections. The most advanced of these approaches include antibodies, probiotics, and vaccines in phase 2 and phase 3 trials, that may contribute to overcoming increasing resistance.

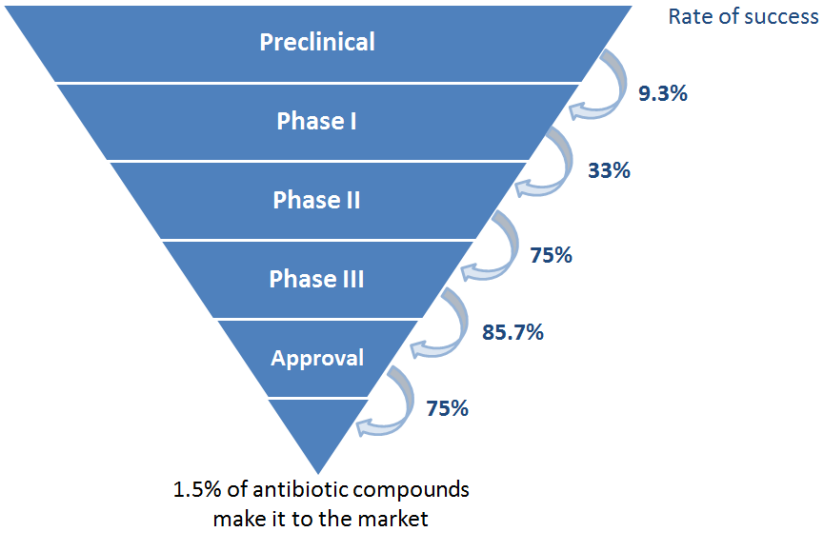
Figure 4. The drying up of the antibiotic R&D pipeline



Insufficient economic incentives and technical problems underpin the current market failure

The decline in product development can be explained by several factors at different phases of the product development pipeline. This pipeline consists of four main phases, prior to commercialisation (figure 5). Typically, only 1.5% of the antibiotic compounds in the preclinical phase make it to the market.

Figure 5. 1,5 % of compounds that enter preclinical development make it to the market



Source: Stephens, 2015[26]

The major hurdles throughout the antimicrobial R&D pipeline include:

- The basic research, or drug discovery, phase for antimicrobials has a higher risk of failure than other classes of drugs. Larger companies seek to mitigate this risk by divesting from basic research and investing in products in late-stage clinical trials. Basic research is left to academia and SMEs, which often lack access to sufficient capital to fund sustainable research programmes.
- The pre-clinical phase of product development is significantly more expensive than basic research– and is estimated to be about USD 10 million per compound[27]. So the probability of commercial success is a key driver in determining which compounds enter this phase. There is evidence of duplication in this phase between separate research groups.
- The base case cost of taking a single product through all clinical trials is in the order of USD 130 million[28]. However, the rate of success from phase 1 trials to commercialisation is estimated at less than 12%[29].
- Once a product reaches the market authorisation phase, there are still barriers to be overcome due to differences between the authorisation processes of different regulatory agencies.

However, the biggest challenge comes once an antimicrobial product is approved. To recover the initial investment, the company needs either to sell many doses or to increase the price of the product. Both options can have a negative impact: where large volumes lead to inappropriate use, they will accelerate resistance. Higher prices hinder access to needed treatments. In any case, both price and volume for most new antibiotics are likely to be low due to the following factors: i) increased

restrictions on use (e.g. through antibiotics stewardship programmes) or keeping new drugs in reserve as treatments of last resort; ii) shortened use, kept to a minimum, to delay the development of resistance; and iii) high competition due to competing products that are already on the market and that are still working.

The return on investment in antibiotics is lower than other disease areas and has worsened over time. Whereas in the early 2000s, there was still a possibility of making a profit by investing in antibiotics,[30] a report commissioned in 2014 by the US Department of Health and Human Services[31] concludes that for new most antibiotics revenues cannot be expected to be profitable enough for companies. Sales are likely to suffer further where effective stewardship programmes are put in place and new antibiotics are kept as reserve treatments that are used only for a small number of patients.

R&D pipeline targets to apply economic incentives

In order to correct this failure of the market and to increase the rewards for investing in R&D, increased incentives can be provided:

- **At the discovery stage**. Public funding of antibiotic research generates scientific advances, filling the early pipeline with potential therapeutic options.
- **At the preclinical stage.** SMEs are the key drivers of preclinical work, optimizing the leads for human clinical trials.
- **During the clinical development stage**. Support could come in the form of tax credits, milestone prizes or grants, and enhanced support and coordination of clinical trial infrastructure. Public–private partnerships (PPPs) and product development partnerships, in which public bodies and innovators collaboratively move drugs through the three phases of clinical trials, enable each to bring their comparative advantages to the partnership, and can reduce risks and costs.
- **After marketing approval and registration**. Higher and more certain payments to innovators can encourage them to bring new antimicrobials to market.

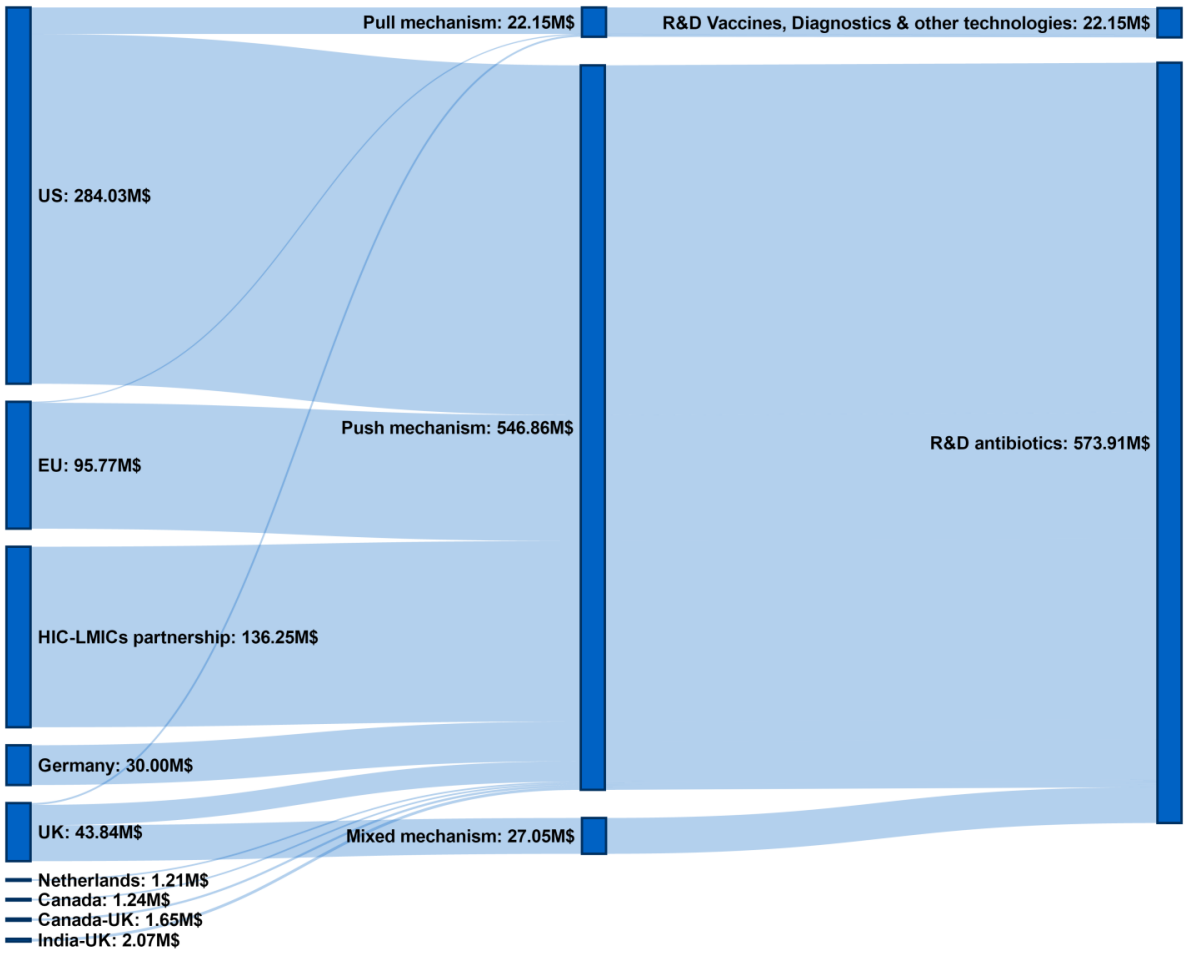
There are two broad strategies that governments and foundations can use to support the R&D pipeline, known as push and pull mechanisms[32]. Push mechanisms reduce a firm's cost of researching and developing new drugs by distributing the expenditures and the risk of failure across multiple parties. Examples of push incentives include increasing access to research, providing research grants, offering tax incentives and establishing PPPs for sharing R&D outlays. Such measures are applied at the pre-clinical phase, or early in the clinical development process. In contrast, pull mechanisms reward successful development of a drug by increasing or ensuring future revenue. This may be in the form of outcome-based rewards such as monetary prizes, advanced market commitments and patent buyouts, or as Lego-regulatory policies that accelerate the market approval process, extend market exclusivity rights and increase reimbursement prices. Pull incentives are generally applied at the post-registration, market entry phase, or late in the clinical development process.

The economic incentives have positive impact but are not yet sufficient

Governments, foundations and the pharmaceutical industry have taken many steps to try to kick-start the R&D pipeline for antimicrobials. So far however, their impact in terms of new products accessing the market has been limited – which might be due, at least in part, to the fact that the current initiaves have not been operating long enough.

A recent study, assessing public funding for AMR research in 19 countries found that 1,243 projects had been publicly funded between 2007 and 2013 for a total of 1.3 billion euros[33]. A 2016 report commissioned by the Dutch government identified more than 50 national and international programmes providing funding for antibiotic, vaccines and diagnostics R&D projects[34]. Building on this work, OECD has identified additional programmes. Figure 6 summarises the average annual cash flow between the main funding sources and their targets. It should be noted that the list of initiatives presented in figure 6 may not be exhaustive due to lack of data from some countries and bilateral funding initiatives – this is particularly true for funding programmes outside of Europe, US and Canada. In addition, the figure does not report direct investments from the pharma industry in R&D for new antimicrobials, vaccines and diagnostics.

Figure 6. Main sources and funding mechanisms for antibiotic R&D (annual amount in million USD)



Note: HIC: high-income countries; LMICs: low- and middle-income countries.
Source: OECD analysis

Based on the analysis presented in figure 6:

- Currently 64% of the annual funding for antibiotic R&D other than purely private finance comes from the public sector, 30% is provided by public-private partnerships and around 6% is provided by non-governmental foundations.
- 95% of the current funding for antibiotic R&D consists of push incentives.
- 4% the funding goes towards pull incentives.
- A very small proportion of the available funding is aimed at R&D on diagnostics, vaccines and other technologies to characterise and/or prevent infections specifically related to AMR. 96% of the current funding initiatives focus exclusively on R&D for antibiotics.

In terms of private sector funding for antibiotics R&D, the Biotechnology Industry Organization conducted an analysis of four major venture capital databases over the 10-year period 2004 to 2013[35]. These databases capture USD 38 billion in venture capital invested in more than 1,200 drug companies across the world. According to this report, investment in the development of new antimicrobials represented one-third of all infectious disease funding in 2009-2013, and has decreased 19% compared with the funding available in 2003-2008. Overall, approximately USD 1.2 billion in venture capital was invested in the R&D of antimicrobials between 2003 and 2013. The report showed a five-fold difference between funding for so-called 'Gram positive' and 'Gram negative' novel R&D. Only around USD 160 million was invested in drugs targeting Gram negative bacteria. This is of particular concern given the high level of drug resistance observed in Gram-negative bacteria and the lack of effective treatments.

Box 4: Pharmaceutical industry commitments

The pharmaceutical industry is actively contributing to initiatives to incentivize the R&D pipeline for new antimicrobials. The vast majority of these efforts are 'push' interventions. Recognising the need to increase research into new antibiotics, diagnostics, vaccines and other alternative treatments, many companies signed the "Davos Declaration" in early 2016 and committed to increasing investments in antimicrobials and to extend collaboration between industry, academia and public bodies. Thirteen companies subsequently presented a roadmap laying out four key commitments they will deliver by 2020. The signatories committed to establishing new business models, which will improve access to new antibiotics, diagnostics and vaccines globally, while supporting appropriate use and delivering an adequate return to companies. The pharmaceutical industry is willing to explore all options to achieve these objectives and calls for an adequate market-entry reward as an effective tool to facilitate global access and stewardship for new products. The roadmap signatories support open collaborations between industry and public researchers to:

1. Progress incentives, such as lump-sum payments, insurance models and novel IP mechanisms, that reflect the societal value of new antibiotics and vaccines and will attract further investment in R&D;
2. Explore opportunities to address key scientific challenges via further pre-competitive collaborations, building on experience with the TB Accelerator, IMI and GHIT;
3. Support the creation of open and sustainable clinical trial networks globally. This would build on work started in Europe and the USA, with the goal of improving the speed and efficiency of conducting clinical trials;
4. Engage with stakeholders, including the new GARDP initiative, to facilitate data exchange on old antibiotics to try to fill specific gaps in the global pipeline.

Strong financial incentives to ensure sustainable R&D

This section outlines main options for G20 initiatives to support R&D in antimicrobials.

Increased funding for preclinical research

As shown above, there are a number of initiatives that fund basic research through the creation of funds for antibiotics. The objective of each is to substantially increase activity in basic research and preclinical development through project-based and institutional funding of academic institutions, SMEs and not-for-profit drug development partnerships. Basic research is often pre-competitive and dependent on public funding; this is also true for antibiotics. Although several national and international funding schemes exist, there are two main possibilities for G20 action: i) to provide additional funding; and ii) to promote a closer collaboration among the different funders to reach a better coordination of the various initiatives.

More G20 funding could support research projects of academic institutions and SMEs with a focus on the biggest challenges in antibacterial research. From today's perspective, these challenges could be:

- Advancing the understanding of multidrug-resistant gram-negative bacteria and identifying new compounds active against them; and
- Promoting the development of point-of-care diagnostic tools

Additionally, funding could support 'blue sky' research (i.e. the exploration of new and innovative research fields) that has the potential to open completely new avenues for antibacterial research.

Collaboration and coordination should be based on an open-source policy, which would apply to all entities receiving funding from any G20-supported basic research funds. This includes sharing of final peer-reviewed journal manuscripts that arise from funded projects, as well as providing access to relevant study datasets – including clinical trials data, which should be made publicly available according to the World Health Organization policy on clinical trials transparency[36]. The OECD Principles and Guidelines for Access to Research Data from Public Funding[37] and Daejeon Declaration on Science, Technology, and Innovation Policies for the Global and Digital Age[38] could be used as a general framework for the development of a specific policy.

With the proliferation of national, regional and global initiatives and the growing number of actors, there is an increased need for collaboration and coordination to ensure an efficient use of funding. A **G20 Global Collaboration Platform** would allow for an optimal exploitation of any new G20 funding. The objectives of this platform would be:

- to monitor the implementation of the different funding schemes in order to prevent duplication of efforts;
- to become a knowledge hub for research and development of antibiotics by facilitating connections among researchers, improving access to scientific information and advising pharmaceutical developers;
- to favour collaboration for research approaches and projects with common interest for human and animal health; and
- to raise the profile of antibiotics research and serve as a place for fostering innovative ideas, considering unconventional approaches, and involving players from all sectors.

Supporting the clinical development of new antimicrobials

Because of the limited return on investment, companies face challenges in finding capital to invest in basic research and to move promising compounds to the clinical phase. Increased G20 funding for clinical trials could target project developers in the field of infectious diseases that successfully completed the pre-clinical stage and would now require validation through clinical trials.

Innovative financing instruments for SMEs are increasingly common as countries are trying to boost their knowledge and innovation economies. For example, the European Investment Bank and the European Commission – under their existing InnovFin framework – have recently introduced a new risk-sharing facility to stimulate investment in R&D targeting the development of innovative vaccines, drugs, medical and diagnostic devices or novel research infrastructures for infectious diseases. The scheme offers a range of higher risk financial products ranging from standard debt instruments (i.e. senior, subordinated, and mezzanine) to risk-sharing instruments with forgiveness options in case of failure of the projects supported. Under this scheme, eligible projects can receive €7.5–75 million for the clinical validation of AMR-related technologies. Eligible investments can be tangible (construction and equipment) or intangible (salaries, operating cost, management and support staff, utilities, consumables, IP acquisition) assets and can cover up to 50% of eligible investments. Similar programs can be found in a number of countries (Box 4).

A study conducted by the Boston Consulting Group (BCG) for the German government estimated that USD 200 million per year would be needed to fund up to 75% for one additional launch every year [39].

Instead of using grants, G20 could consider providing funding via forgivable loans that are be paid back only if the product reaches the market. This reduces the risk for private innovators, while ensuring that the public sector does not pay more than what is necessary to promote more clinical development. Such a model has proven attractive in funding medium and large-scale research projects in the past years, and it is widely used for commercially risky investment propositions with high potential value. For example, the AMR Centre in the United Kingdom plans to use a similar mechanism (revenue sharing) for clinical trial support. Funding should also support not-for-profit drug development as it currently exists for neglected diseases (e.g. DNDi). The WHO/DNDi Global Antibiotic R&D Partnership (GARDP) is one such vehicle (Box 5) that could run clinical trials to bring new products to the market. Other examples include the New Drugs 4 Bad Bugs programme (ND4BB) and the TB Alliance for new anti-tuberculosis drugs.

It is essential that any kind of public support focuses primarily on products targeting priority pathogens and address identified public health needs. Public support should also be linked with obligations to ensure appropriate use and affordable pricing in low- and middle-income countries and obligations with respect to data sharing and clinical trial transparency (see above).

Box 5 The Global Antibiotic Research and Development Partnership (GARDP)

The Global Antibiotic Research and Development Partnership (GARDP) is a not-for-profit research and development organization that addresses global public health needs by developing and delivering new antibiotic treatments while endeavouring to ensure sustainable access. Initiated and incubated through close collaboration between WHO and the Drugs for Neglected Diseases initiative (DNDi), GARDP is part of the implementation of the Global Action Plan on Antimicrobial Resistance that calls for new public-private partnerships for encouraging research and development of new antimicrobial agents and diagnostics. GARDP has received seed funding and pledges from the governments of Germany, the Netherlands, South Africa, and Switzerland, and the United Kingdom of Great Britain and Northern Ireland, as well as from the medical humanitarian organization Médecins Sans Frontières. Pledges exceed €5 million for 2016-2018. GARDP is a joint WHO/DNDi initiative being hosted by DNDi in its start-up phase. GARDP has, within its first 8 months, built up a team of 10 people, with additional support staff from DNDi contributing directly to GARDP programmes.

Research & Development Programmes

A Scientific Advisory Group of 17 experts oversees the creation of the initial R&D portfolio. The DNDi Board approved the draft business plan in December 2016.
The following R&D projects have been identified thus far:

- **Neonatal Sepsis**: This programme aims to develop and deliver a new first-line treatment for pathogens that cause neonatal sepsis as well as a new treatment for confirmed multi-drug resistant pathogens.
- **Antimicrobial Memory Recovery Initiative (AMRI)**: this programme aims to recover the knowledge, contacts, data, and assets of forgotten, abandoned, or withdrawn antibiotics as a 'bridging' measure while the search for new classes of antibiotics is being pursued and while a new generation of researchers in antibiotic R&D is stimulated and rebuilt.
- **Sexually transmitted diseases**: This programme will seek to develop and deliver two new treatments for gonorrhoea patients with drug-resistant infections by combining existing antibiotics and by exploring new antibiotics that are already in development.
- **Paediatric Antibiotic Platform**: This programme aims to establish a platform to optimize current and new antibiotics for children through improvements in dose, duration, formulation or through combinations based on the gap analysis that will be undertaken with WHO.
- **Drug Combination Platform:** This programme aims to establish a screening and in vivo drug development platform to optimize combinations of existing and/or new antibiotics as well as non-antibiotic substances for GARDP priority pathogens, including Nesseria gonorrhoea, Klebsiella, and Acinetobacter.

Exploring launch rewards

The WHO Consultative Expert Working Group on Research and Development (CEWG) described the concept of delinkage of R&D investment from price and volume as a guiding principle for alternative and credible business models for biomedical innovation. Delinkage has been supported by independent reports [40] [41]. The concept of delinkage may offer an opportunity to implement a sustainable antibiotic business model that addresses innovation, stewardship and access. Finally, any incentive mechanism needs to take into account the specific needs of LMICs and align the objective of conservation and appropriate use of antibiotics with the necessity of facilitating affordable access.

The aim of a launch reward is to incentivise industry to reinvest in antibiotic R&D while breaking the link ("delinkage") between R&D and revenue streams stemming from sales volumes and/or prices. As noted above, the current method of paying for antibiotics encourages an increase in sales beyond what is medically desirable, or a growth in prices, thereby limiting access, especially in LMICs. Instead, it has been proposed that companies producing a truly novel antibiotic might receive payments after marketing approval, linked to the therapeutic value of their product, not sales.

The magnitude of these launch rewards would have to be adjusted for net public investment across the R&D lifecycle – as mentioned above, this would consist essentially in repaying prior government and charitable grants through a "clawback" provision in the launch reward. A built-in repayment mechanism could be considered to avoid subsidizing those antibiotics that exceptionally are generating enough revenue for the company[41].

Market entry rewards have been proposed in different reports in past years, including those of Jim O' Neill and the BCG. However, uptake of such pull mechanisms in general has been limited. One reason is that a launch reward for a new medicine needs to be of a certain size – 1 billion US$ has been suggested for each antibiotic (see below) – to work as an incentive for companies. Thus, putting up such a reward by any one country alone would require considerable financial commitments. While compared to the overall costs of AMR these commitments may be small, the money is not easy to find in public budgets. Governments would also have to enter into long term commitments . To develop a drug from the preclinical phase to market approval takes about 10 years. A market entry reward would also require precise conditions under which the reward will be paid out and clear guidance on the drug characteristics that should be achieved.

How could an antibiotic launch reward be paid?

One option is to pay the innovator a significant one-time payment, adjusted to R&D costs and potential clinical value, shortly following marketing approval. This option may look attractive due to its simplicity; however, evidence of novelty and clinical value is likely to be limited upon marketing approval of a new antibiotic. Funders may therefore risk rewarding innovators for drugs that over time prove unable to meet unmet clinical needs. An alternative is therefore to implement a staged approach, in which a minimum base payment covers R&D expenses and the cost of building a supply chain, and subsequent annual payments may increase depending on clinical effectiveness, resistance profiles, and other data.

Pull incentives might also have a built-in mechanism capable of addressing the issue of intellectual property (IP) rights. Intellectual property has historically been a contentious question with respect to global access, with the most prominent example being civil society and governments in LMICs clashing with multinational pharmaceutical companies over IP policies that restricted access to antiretroviral treatment for HIV/AIDS[42]. To avoid a similar situation, the responsibilities of the governing body or bodies making delinked payments for new antimicrobials and innovators should be clearly defined when negotiating the terms of delinkage rewards. For example, the innovator could maintain ownership of IP, but, in return for delinkage rewards, the antimicrobial would be supplied to markets (especially in LMICs) at a cost-based price and a reasonable profit. Another option is a full patent buyout model. In this case, the governing body would have to take responsibility for global distribution arrangements, including manufacturing, sales, global regulatory approvals, and post-marketing surveillance.

Aligning R&D efforts with public health priorities

Increased G20 funding for antimicrobials must be fully aligned with existing global public health priorities for AMR prevention. In order to steer R&D towards the areas with the highest public health need, **Target Product Profiles** (TPP) are needed, updated on a regular basis to keep them current with evolving public health needs.

A TPP defines the minimal/ideal profile of the final marketed product and shows the ultimate goals of the proposed product development effort such as disease indication, patient population, delivery mode, treatment duration, treatment regimen and standards for clinical efficacy. Cost of the final product, or specific technical requirements (e.g. that a diagnostic tool needs to be battery-powered to allow use in rural areas in LMICs) may also be included in the TPPs. It is a key strategic document for drug developers as it helps them to align their needs with current public health priorities. TPPs may be used to assess the value and novelty of an antibiotic (or an antibiotic regimen) and thus, help select those that qualify for funding.

The development of TPPs for antimicrobials needs to be based on a classification of pathogens by threat level. At the global level, the WHO has developed a list of priority pathogens, which will inform global R&D priorities for effective antibiotic treatments and TPPs (see Box 4). The US Centre for Disease Control and Prevention (CDC) completed a comprehensive antimicrobial resistance threat assessment specifically for the US.

Box 6: WHO priority pathogens list for R&D of new antibiotics

On 27th February 2017, the WHO published a catalogue of 12 families of bacteria that should be priorities for R&D efforts, in addition to TB. The list was drawn up in a bid to guide and promote R&D and highlights in particular the threat of gram-negative bacteria that are resistant to multiple antibiotics.

Priority 1: CRITICAL

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

Priority 2: HIGH

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

The objective of the WHO prioritization exercise was to identify previously unrecognised health threats due to increasing antibiotic resistance.

Financial Implications

There have been a number of efforts to assess whether existing efforts are sufficient to meet the challenge that AMR poses health systems and economies (table 1). Sharma and Towse for example, estimated the expected revenues of a new antibiotic to be USD 50 million. The authors estimated that a reasonable target for revenues should be around USD 200 million to make investment in antibiotics competitive with other therapeutic classes[43].

Table 1. Nominal and expected net present value estimates of the needed size of antibiotic market entry payments

	Payment from governments	Expected NPV benchmark at commencement of R&D
Sertkaya et al	USD 919 million (spread over entire R&D process and at registration; USA only)	USD 100 million
Sharma and Towse	USD 2.5 billion (USD 500 per year for 5 years)	USD 300 million
Review on Antimicrobial Resistance	USD 2-3.7 billion (paid 3 years after registration)	-
OECD analysis on BCG report	USD 4 billion (spread over entire R&D process), including USD 1 billion for launch reward	USD 300 million

Source: OECD analysis on cited literature

More recently, the O'Neill review estimated that an effort between 2 and 3.7 billion USD was required each year to better incentivise antibiotic R&D – this includes USD 400 million for early stage and non-commercial R&D and a USD 1.6-3.7 billion market entry reward[44]. Similarly, findings of the BCG study commissioned by the German government suggest that up to a USD 4 billion investment may be necessary, over a decade, to stimulate R&D. More specifically, the report concludes that it would be necessary to invest USD 200 million per year over a decade for early stage research, USD 200 million over 4-5 years for clinical development and USD 1 billion per new antibiotic discovered for a global launch reward[45].

Further work is needed to evaluate how many new antibiotics are needed and the scientific evidence necessary to answer this question is not fully developed. To nevertheless give an idea of the scale of investment needed, OECD has calculated the cost of a scenario based around a target of 4 new first-in-class systemic antibiotics to be discovered over the next 10 years, which is approximately the time needed to go from discovery to patient. OECD estimates that the total investment needed in R&D (including push and pull incentives) to reach such a target would be between USD 800 million and USD 1.14 billion per year over the 10 years of the development life cycle. This is a relatively conservative target – the O'Neill review suggested that 10-15 new antibiotics should be targeted, including four first-in-class drugs. Currently, about 95% of the USD 596 million spent annually on R&D for antibiotics is already allocated to push incentives (Figure 6). This amount would be consistent with the funding recommendations provided by the O'Neil review and the BCG for preclinical and clinical R&D phases. If a target of four new antibiotics were to be set, an additional USD 300 to USD 650 million annually would be needed, according to the analyses produced by the O'Neill review and the BCG report. This additional funding would be allocated to pull incentives such as launch rewards. Over a decade, this would amount to a launch reward between USD 0.75 and USD 1.6 billion per new antibiotic.

This is not a small amount of money to find each year. However, it is only 0.02% of the projected annual economic costs of AMR per year in 2050[46]. The rate of return on spending money restarting the R&D pipeline for every country in the world is large. How countries might collectively find the financing is beyond the scope of this report. A number of options have been raised, including 'Pay or Play' contributions for pharmaceutical companies (discussed in the O'Neill report), contributions from health budgets (reflecting that the health sector itself has contributed to the development of AMR), a tax or fee on use of antibiotics in the health and/or agricultural sector and direct transfers from government[47]. In the United States, there are ongoing discussions about financing antibiotic R&D through granting companies that bring a new antimicrobial to market extensions on their existing portfolio of patents[48]. It is further possible that foundations may be interested in supporting launch reward initiatives financially.

Additional funding to support launch rewards may be channelled in different ways, including through a single global fund or through multiple, coordinated, national initiatives. The main advantage of a single global fund is that it would consolidate all endowments into a large funding entity that could provide incentives throughout the whole R&D pipeline, supporting promising ideas from basic research to market access. The overall payment would be readily apparent to those seeking to develop new products. A single fund would also minimize the risk of 'paying twice' for the same product and would simplify administration and governance. An alternative to setting up a new global fund would be to channel G20 funding through existing initiatives, such as Product Development Partnerships. GARDP is an example of this and, with the support of the WHO and a focus on all aspects of a global AMR response, GARDP may ensure a global system while encouraging participation of a wide range of countries

However, national initiatives are easier to set up, as, in the initial phases, they do not require complex infrastructure and to set up an international governance structure. Instead, they can build on existing structures and expertise – so a US launch reward could be based around CARB-X/BARDA; a European reward could be based on JPIAMR, and so on. Access to the European reward would be based on showing compliance with EMEA regulations, and to the American payment upon FDA approval, so there would be no need for complex discussions about what would trigger an international reward payment. Similarly, national/regional funds do not require the creation of pooled funds with all the discussions around management and governance that this would entail. For example, they could be governed through a 'virtual' secretariat to coordinate daily activities (e.g. by identifying focal points in each fund) and regular meetings of the top management of the different funds. However, compared with a single fund, a decentralised funding structure would involve smaller payments in each case. To be effective, decentralised funds would need to be well coordinated. As long as they were appropriately structured and coordinated, a decentralised system of launch rewards could have similar incentive effects, taken in total, as those that would come from a single fund. How such a system might work is outlined in Box 7.

Box 7: How could pull incentives be combined and implemented?

An alternative to setting up a new fund to delink payments for new antimicrobials from sales volumes could be to build on national and regional schemes, but to coordinate them closely. More exploratory work is needed to design such an incentive. On a theoretical basis, one approach might be to:

- Agree common Target Product Profiles, so that national schemes would be incentivising the same products, thereby maximising rewards for innovators
- Agree a total target level of funding for launch rewards. On the basis of the evidence presented in this paper, this could be:
  - USD 1 billion for each novel first-in-class antibiotics for human consumption (see table 1)
  - A smaller amount to stimulate new diagnostics and vaccines (amount depending on the pathogen involved)
  - Similarly, a smaller amount for antibiotics for agriculture
- National/regional (e.g. EU) bodies might commit to give rewards for eligible products.
- Payments of the launch rewards would be triggered by national or regional approval – there would be no need to negotiate a common standard between the FDA and EMA etc.
- Previous support for clinical trials or basic research would be refunded from the prize to prevent double-dipping into public funds for the same product.
- Payment of the reward would come on condition that prices would not be freely set by the company – as a condition for receiving the prize, the company would be required to have an agreement setting appropriate price and volume levels.
- Part of the agreement would be to provide the products at a price appropriate for the degree of economic development of each country, provided that countries make non-financial commitments to sustain antimicrobial effectiveness, such as the implementation of conservation and surveillance measures, in line with the Global Action Plan.

Role of the G20 and potential actions

G20 countries could:

1. Task OECD and WHO in collaboration with FAO and OIE to provide guidance in the process of establishing a collaborative global R&D platform to increase knowledge sharing and communication between funders to optimise resource allocation and avoid funding overlaps which might result in paying twice for the same result;
2. Commit to support the development of new antimicrobials, vaccines and diagnostics by providing ongoing funding to ensure a good supply of basic research, based on the principles of transparency and Open Science;
3. Task WHO to lead the identification of R&D priorities and the development of global Target Product Profiles (TPPs) to guide R&D efforts relevant for human health;
4. Support and fund existing mechanisms such as GARDP;
5. Task OECD and WHO to establish a working group to explore the practical details associated with pull incentives;
6. Commit to implementing a 'One-Health' approach in any new funding and coordinating initiative with the aim of extending research beyond human health.

Ensuring widespread access to new antimicrobials

While some antibiotics should be used in a more restrictive way, affordable access to quality essential medicines, vaccines, and diagnostics also needs to be increased in both the human and animal sectors. Stewardship and access are closely linked and should not be dealt with separately. Inadequate access to quality-assured antimicrobials, vaccines and diagnostics denies people the benefit of life-saving antimicrobials. It is also a driver of accelerating levels of antimicrobial resistance (AMR). An analysis of 47 LMICs concluded that a 10 point increase in the percentage of out-of-pocket health expenditure was associated with a 3.2 percent increase in AMR[49].

Access considerations need to be built into any future global stewardship and access framework. A number of international financing mechanisms for global health issues exist and provide useful examples of how access to new antimicrobials can be ensured. These include organizations such as Gavi the Vaccine Alliance and the Global Fund to fight AIDS, TB, and Malaria, which are active in the procurement of health commodities, as well as organizations involved in antimicrobial development such as the WHO/DNDI initiative GARDP. While the range of topics covered by these initiatives is wide, as well as their legal arrangements or their governance structures (annex 2), the challenges and needs are similar.

In order to ensure widespread access to new antimicrobials based on need, the experience of organisations such as the Global Fund, Gavi and UNITAID are particularly relevant. Through various mechanisms, prices of key medical products are kept low so that LMICs can afford them. Bulk purchase, patent pooling, negotiating with pharmaceutical companies, and ensuring that the production and distribution system for vital medicines are kept efficient so reducing costs – all these are options for providing products to LMICs at low cost, while ensuring that innovators are able to earn a reasonable return on their products.

Lower income countries might not contribute to increased funding for research into new antimicrobials. However, if AMR is to be tackled successfully, it is necessary that they have prompt access to effective antimicrobials. This opens the possibility of a global deal – that lower and middle income countries do not directly participate to the funding of the pull mechanism but they make non-financial commitments to sustain antimicrobial effectiveness, such as the implementation of conservation and surveillance measures, in line with the Global Action Plan. In return, these countries should be given access to new products at an affordable price.

Role of the G20 and potential actions

G20 countries could:

- Commit to support new funding or coordination instruments to incentivize R&D that implement specific mechanisms to ensure appropriate use of antimicrobials and to promote access in LMICs. This could entail an arrangement according to which access to affordable antimicrobials, vaccines, and diagnostics is ensured in exchange for non-financial commitments to sustain antimicrobial effectiveness.

Annex 1. Key initiatives promoted by WHO, FAO and OIE to tackle AMR

Global Action Plan for Antimicrobial Resistance

At the Sixty-Eighth World Health Assembly in May 2015, Member States endorsed a global action plan through resolution WHA68.7 to tackle antimicrobial resistance, including antibiotic resistance, the most urgent drug resistance trend. This global action plan was also endorsed by the 180 OIE Member Countries through Resolution 26 in May 2015.

The AMR global action plan contains five major strategic objectives:

1. to improve awareness and understanding of antimicrobial resistance;
2. to strengthen knowledge through surveillance and research;
3. to reduce the incidence of infection;
4. to optimize the use of antimicrobial agents; and
5. to develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

Significantly, the resolution noted the importance of Member States and stakeholders working together to ensure synergy in attaining these five strategic objectives: "invites international, regional and national partners to implement the necessary actions in order to contribute to the accomplishment of the five objectives of the global action plan on antimicrobial resistance".

The global action plan, which takes into account the commitment, perspectives and roles of all relevant stakeholders is a plan in which everyone has clear and shared ownership and responsibilities. The endorsement of the plan reflects a global consensus that AMR poses a profound threat to human and animal health.

Tripartite and One Health Approach

In a tripartite approach, WHO, the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE) recognize that addressing health risks at the human–animal-plant-ecosystems interfaces requires strong partnerships among entities that may have different perspectives and different levels of resource. Such partnerships, which could include international organizations, governments, private sector, civil society, private sector and donors, must be coordinated to minimize the burden on Member States of multiple monitoring, reporting and delivery systems and to avoid duplication of effort and fragmented outcomes. In this regard, the standards and guidelines developed by the FAO/WHO Codex Alimentarius commission and by the OIE should be taken into account and implemented.

Addressing the rising threat of AMR requires a holistic and multisectoral (One Health) approach because antimicrobials used to treat various infectious diseases in animals may be the same as or similar to those used in humans. Resistant bacteria arising in humans, animals or the environment may spread from one to the other, and from one country to another. AMR does not recognize geographic or human/animal borders. One Health recognizes that the health of humans, animals and ecosystems are interconnected. It involves applying a coordinated, collaborative, multidisciplinary and cross-sectoral approach. The latter is particularly relevant when it comes to addressing AMR, as it facilitates the multidimensional perspective needed to address aspects ranging from our understanding of the factors driving AMR, to assessing AMR's economic impact and finding viable solutions and interventions.

To this end, the World Assembly of Delegates of the OIE, held in May 2015, adopted a resolution for Member Countries to follow the guidance of the global action plan by developing national action plans with respect to the use of antimicrobial agents in animals and ensuring their close collaboration with public health officials. At its 84th OIE General Session in May 2016, the 180 OIE Member Countries re-confirmed their commitment to combat AMR through the adoption of Resolution No. 36, paving the way for the development of an OIE Strategy on AMR and the Prudent Use of Antimicrobials. Resolution No. 36 outlines OIE actions to combat AMR using a 'One Health' approach and further progresses the commitment of the OIE 2015 General Session, at which Members adopted Resolution No. 26 specifically highlighting the importance of promoting the responsible and prudent use of antimicrobial agents in animals. Central to the OIE Strategy are the ongoing development and update of science and risk based standards and their implementation by Member Countries. A further important action aligned with the monitoring framework is the development of a global database on antimicrobial use in animals, with ongoing annual rounds of data collection that generates an annual report as well as stimulates the development of measurement systems within Member Countries

In June 2015, the Thirty-ninth Conference of the Food and Agriculture Organization of the United Nations (FAO) adopted resolution 4/20 and a status report on AMR. The FAO resolution recognizes that AMR poses an increasingly serious threat to public health, sustainable food production and that an effective response should involve all sectors of government and society. The resolution urges members to 'develop or strengthen national plans, strategies and international collaboration for the surveillance, monitoring and containment of antimicrobial resistance in food, agriculture and the environment, in close coordination with related plans for human health'.

FAO, OIE and WHO speak with one voice and take collective action to minimize the emergence and spread of AMR. The aim is to:

- Ensure that antimicrobial agents continue to be effective and useful to cure diseases in humans and animals;
- Promote prudent and responsible use of antimicrobial agents;
- Ensure global access to medicines of good quality.

To achieve these tripartite aims, a framework for collaboration operates at international level and needs to be implemented at national levels, with clear roles and responsibilities. Further, plant, animal and human health institutions and partnerships should be strengthened in the management of existing and emerging plant, animal and zoonotic diseases to reduce the use of antimicrobials in livestock production, aquaculture and agriculture.

The UN Sustainable Development Goals

The UN Sustainable Development Goals (SDGs) recognize the importance of AMR (paragraph 26 of the Declaration). The attainment of many of them will depend on the availability of, and access to, affordable and effective antimicrobial medicines and other technologies such as diagnostic tests and vaccines. AMR seriously threatens the health and lives of vulnerable populations, such as newborns, children, and women, as well as sustainable food and agriculture production and a healthy environment. AMR is reducing our ability to protect the health of animals and therefore is threatening safe and sustainable food and agriculture.

SDG 1. No Poverty: Antimicrobial resistance strikes hardest at the poor. Income losses and out-of-pocket health care expenses from AMR make it difficult for people to escape poverty.

SDG 2. No Hunger: The OECD projects that antimicrobial use in food animal production will increase 67% by 2030, which conflicts with the goal of promoting sustainable agriculture.

SDG 3. Good Health and Well-being: Health systems require antimicrobials. Maternal and child health, communicable diseases, and surgery will be particularly affected without them.

SDG 6. Clean Water and Sanitation: Water sources contain antibiotic residues and resistant bacteria from human faeces and run-off of farms, production facilities, and waste treatment plants.

SDG 8. Decent work and Economic Growth: Loss of effective antibiotics is a burden to health systems and reduces productivity.

SDG 12. Responsible Consumption: Reducing prophylactic use and phasing out growth- promoting antibiotics in agriculture in the absence of risk assessment will make global food production more sustainable.

SDG 14. Life below Water: Antimicrobial residue can be toxic to aquatic life. Decreasing residues in water treatment plant runoff will benefit life below water.

SDG 15. Life on Land: Antibiotic-resistant bacteria and residues may build up in the soil, which may spread resistance.

SDG 17. Partnerships for the Goals: Meaningful multisectoral collaboration among all stakeholders is essential if AMR is to be addressed.

Political Declaration of the high-level meeting of the General Assembly on AMR

In December 2015 the UN General Assembly adopted the Global Health and Foreign Policy resolution (A/Res/70/183), which included a decision to hold a high-level meeting on AMR at the UN General Assembly in 2016. On 21 September 2016, the President of the UN General Assembly convened a one-day high-level meeting at the UN Headquarters with the participation of Member States, FAO, OIE and WHO, non-governmental organizations, representatives of civil society, the private sector and academic institutions.

The primary objective of the meeting was to summon and maintain strong national, regional and international political commitment in addressing AMR and the meeting emphasized the important role and responsibilities of governments, as well as the roles of non-State actors, the private sector and relevant inter-governmental organizations, particularly FAO, OIE and WHO in establishing, implementing and sustaining a cooperative global, multi-sectoral and cross-sectoral approach.

Member States adopted a Political Declaration during the high-level meeting of the General Assembly on AMR in which they emphasized that the blueprint for tackling AMR is the global action plan on AMR developed in 2015 by WHO in coordination with FAO and OIE. Countries called for better use of existing tools for preventing infections in humans and animals and highlighted market failures, and called for new incentives for investment in research and development of new, effective and affordable medicines, vaccines, rapid diagnostic tests, and other important therapies to replace those that are losing effectiveness.

The political declaration included commitments by Heads of State and Government and representatives of States and Governments to develop their multisectoral national action plans in line with a "One Health" approach; to mobilize funding for, inter alia, the implementation of these plans and for research and development; to ensure that national plans cover the development of surveillance, monitoring and regulatory frameworks on the preservation, use and sale of antimicrobial medicines; and to increase and sustain awareness of and knowledge about antimicrobial resistance among the public and health professionals.

The political declaration also includes three major requests to WHO and its partners. First, it advances the Health Assembly's request by calling for the finalization by WHO, together with FAO and OIE, of a global development and stewardship framework on antimicrobial medicines and resistance. Secondly, it calls on WHO in collaboration with FAO, OIE, regional and multilateral development banks, including the World Bank, other United Nations agencies and intergovernmental organizations, civil society and multisectoral stakeholders to support national action plans and other activities to counter antimicrobial resistance at national, regional and global levels. Thirdly, it requests the Secretary-General to establish, in consultation with WHO, FAO and OIE, an ad hoc interagency coordination group to provide practical advice on approaches to ensure effective action to address antimicrobial resistance – this has been accomplished with the launch of the Interagency Coordination Group on Antimicrobial Resistance (IACG). The political declaration also requested the Secretary-General to submit a report to the General Assembly at its seventy-third session. In accordance with these requests, WHO is hosting a tripartite Secretariat for the IACG and is working with FAO and OIE on the processes needed to establish a global development and stewardship framework.

The importance for countries to develop and implement national action plans

Developing national action plans (NAPs) is an essential first step for countries to establish an effective response to combat AMR. At the Sixty-eighth WHA in 2015, Member States committed to have NAPs in place by May 2017. In February 2016, WHO, in collaboration with FAO and OIE, developed a manual for developing NAPs and a set of accompanying tools. The three organizations have been working closely with stakeholders to provide technical support to countries for the effective development of their NAPs and to date, 67 WHO Member States have completed their national action plans on antimicrobial resistance, and a further 62 are in the process of doing so. These represent the largest and most populous countries and include all regions, with a wide range of levels of income and development. More than 6.5 billion people live in a country that has, or will soon have, a national action plan. Many of the remaining countries are either small or fragile or affected by conflict.

Ensuring political commitment, engagement and support has been a challenge in some countries as understanding of AMR and the importance of developing and implementing NAPs is still somewhat limited. Support to NAP development, as well as implementation, monitoring and evaluation, will continue to be an ongoing tripartite (FAO/OIE/WHO) priority, particularly in the African and Eastern Mediterranean regions. The identification of best practices continues to play an important role as the world is still learning what works best in particular contexts and the Tripartite is sharing expertise and

developing communities of practice to support countries with ongoing efforts. Inter-sectoral action, and the complexity of coordination within and across sectors, continues to be a challenge, particularly as countries shift towards NAP implementation.

The importance of monitoring and surveillance

Robust, locally relevant information is necessary for planning, prioritization, management and evaluation at country, regional and global levels. However, WHO's 2014 global report on surveillance of antimicrobial resistance revealed that there are many parts of the world in which the scope or scale of the problem (in terms of the quantities of antibiotics that are being consumed, and the levels of resistance) is unknown. While Common Codex and OIE standards exist, implementation is lacking and where data exist, they are not internationally comparable, rendering interpretation difficult. Links between surveillance systems in animals and in humans are weak. International standards on harmonization of national antimicrobial resistance surveillance and monitoring programmes (for animals) were adopted by OIE's members in 2012 and regularly updated, but there are no global standards for resistance surveillance in humans. There is also no global forum or platform for the rapid sharing of information on AMR.

To address these gaps, WHO has established the Global Antimicrobial Surveillance System (GLASS), with 43 countries either enrolled or in process. GLASS will initially focus on bacterial pathogens in humans. It will also collect information on countries' progress in strengthening national surveillance systems on antimicrobial resistance. The System will progressively expand to include other types of surveillance related to antimicrobial resistance and links to other global surveillance systems.

GLASS will develop a platform for sharing national data. Initially the focus will be on bacterial resistance in humans, but in the future, GLASS should expand to include integrated foodborne antimicrobial resistance surveillance, antimicrobial use or consumption, environmental antimicrobial resistance surveillance, and links to other antimicrobial resistance-related types of surveillance. WHO will also support research and protocol development in critical areas, for example:

- the impact of environmental contamination with antibiotic residues;
- the impact of resistant bacteria on antimicrobial resistance in humans; and
- transmission mechanisms at the human-animal interface.

Antimicrobial use and consumption

WHO is developing a framework for surveillance for antimicrobial prescribing and use. The OIE is collecting data on the use of antimicrobials in animals, in line with the global action plan and based on the OIE standards on monitoring of the quantities and usage patterns used in animals. The first report is available at the OIE website. The second round of data collection is currently ongoing. At the same time, work to consolidate data collection on antimicrobial consumption using national data on sales, has continued in the European region: 18 non-EU Member States are collecting data that is currently being analysed with WHO Secretariat support. The work of the European Region's antimicrobial medicines consumption (AMC) network is being used to inform global models for data collection. Field testing of consumption monitoring has begun in about 20 countries in Africa and Asia with WHO providing support through training of national experts, the provision of templates and tools for data collection and analysis and related technical advice. Work is also ongoing on the review of dosing schedules of antibiotics. In addition to the OIE international standards included in the Terrestrial Animal Health Code, Aquatic Animal Health Code and Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, the OIE has published a List of Antimicrobials of Veterinary

Importance. The List includes recommendations on the use of antimicrobials considered to be critically important for both human and animal health, together with a recommendation to avoid off-label use in animals of antimicrobial classes and sub-classes only registered in human medicine (and therefore not included in the OIE List).

Antimicrobial stewardship

The proposed global development and stewardship framework should be practical, based on internationally agreed standards, useful and feasible across the world. It must be people-centred and address the urgent need to comprehensively promote the responsible and prudent use of antibiotics and enhance their equitable access. It should also consider the multisectoral dimensions of AMR and provide guidance for multi-level actions to address AMR in human health, veterinary sectors, agriculture, food production and within the environment. Therefore, a close cooperation with OIE and FAO is essential. An efficient antibiotic stewardship framework should stimulate the world to implement actions to promote prudent use of antibiotics and substantially reduce the emergence and spread of AMR.

WHO is in the process of establishing/convening a Study Group on the AMR Stewardship Framework with the participation of the OIE and FAO, to guide further actions, review the existing knowledge on the subject and suggest a roadmap that shall be implemented by WHO and other agencies, as appropriate in close consultation with Member States and other stakeholders.

AMR awareness raising

WHO, together with FAO and OIE, has taken steps to maintain AMR as a priority for Member States and stakeholders and, along with intensified efforts by other champions, has significantly contributed to a greater and more coherent level of global awareness, concern and attention around the "big picture" of AMR. This outreach and increased understanding, in turn, helped pave the way for the unusually rapid development and adoption of the global action plan on AMR and the concurrent formal support from the governing bodies of FAO and OIE. It also greatly contributed to the successful Member State negotiations in New York, which resulted in the high-level meeting on AMR at UNGA in September 2016 and the political declaration, which was adopted as a UN resolution. The major upswing in shared urgency and understanding reflects the contributions of many champion countries and individuals. However, this could not have been achieved, especially among developing countries and civil society, without the very active and effective efforts by WHO.

Global awareness is now on the rise but not yet sufficient to create the societal and cultural changes needed to sustainably reduce AMR. Therefore, continued efforts in advocacy and awareness raising remain imperative. At the same time, it is critical to capitalize on the new momentum to implement actions at operational levels to reverse AMR. Action by key stakeholders across many sectors is needed. For this to occur, a fully active and capable Tripartite collaboration is needed to ensure international trust, coherency and leadership. The three organisations are uniquely positioned to do so and bring added value to this and other roles.

OIE has included an AMR portal on its website (www.oie.int/antimicrobialresistance/) in order to gather together technical information and communications products to support Members in raising awareness on AMR. OIE is participating in inter-sectorial collaborations on scientific publications, and attending a wide array of technical and political meetings on AMR-related topics.

Annex 2. Examples of international financing mechanisms

	Global Fund	Gavi	JPIAMR	GARDP	CEPI	UNITAID
Legal arrangement	Foundation	Foundation	EC-government partnership	Partnership between WHO and "Drugs for Neglected Diseases initiative"	Public-private partnership	International organization
Scope	Procurement of HIV, TB, Malaria drugs	Procurement of vaccines	AMR	R&D in AMR	Vaccine development	HIV, Tuberculosis, Malaria
Methods	Investment in country-level projects meeting goals and quality standards	Vaccine purchase; funding initiatives to strengthen health systems	Funding research/ scientific activities; coordinating research agendas & implementation plans	Develop new antibiotic treatments; implement conservation and access strategies; de-link R&D with sales	Finance vaccine development; Ensure affordability; coordinate vaccine development	Drug purchase and distribution. Finance activities to accelerate drug and diagnostic access and affordability
Funding	countries; NGOs; foundations; private contributions	countries; NGOs; foundations; private contributions	countries	countries, foundations, NGOs	countries; foundations NGOs	countries
Governing structure	executive board; secretariat; technical review panel; office of inspector general; technical evaluation reference group	executive board; Secretariat; audit and finance committee	management board; secretariat, steering committee; scientific advisory board; stakeholders advisory board	Currently that of Drugs for Neglected Diseases initiative (DNDi)	Still in development Interim board; Scientific advisory board; Joint Coordination Group	Executive board; Expert committees; Secretariat
Composition of the executive/ management board	donor & receiver governments; NGOs; private sector; foundations; affected communities	international organizations; foundations; 50% of seats for independent individuals	2 delegates per participating country	Own management, team of 10, DNDi Board	Founding members, NGOs, industry, governments.	Founding governments; Other selected governments; civil society; NGOs,

Source: OECD analysis on organizations' websites

References

[1] Cecchini M. Langer J, Slawomirski L. Antimicrobial resistance in G7 countries and beyond: Economic Issues, Policies and Options for Action. Paris: OECD Publishing 2015.
[2] WHO. Antimicrobial resistance: global report on surveillance 2014. Geneva: WHO, 2014
[5] AMR review 2014 - Antimicrobial Resistance: Tackling a crisis for the future health and wealth of nations
[4] Institute of Health Metric Evaluation. Epi Visualization tool. Available at: http://www.healthdata.org/data-visualization/epi-viz
[5] Cecchini M. Langer J, Slawomirski L. Antimicrobial resistance in G7 countries and beyond: Economic Issues, Policies and Options for Action. Paris: OECD Publishing 2015.
[6] Cecchini M. Langer J, Slawomirski L. Antimicrobial resistance in G7 countries and beyond: Economic Issues, Policies and Options for Action. Paris: OECD Publishing 2015.
[7] World Bank. "Drug-Resistant Infections: A Threat to Our Economic Future (Discussion Draft)." Washington, DC: World Bank, 2016
[8] Taylor J, et al. Estimating the economic costs of antimicrobial resistance – model and results. Santa Monica (CA): RAND Corporation, 2014.
[9] World Bank. "Drug-Resistant Infections: A Threat to Our Economic Future (Discussion Draft)." Washington, DC: World Bank, 2016.
[10] Cecchini M, Lee S. Promoting rational use of antimicrobials. In: OECD [Eds.] "Releasing health system resources for better value care: tackling ineffective health spending and waste". Paris: OECD Publishing, forthcoming.
[11] FAO. Drivers, dynamics and epidemiology of antimicrobial resistance in animal production. Rome: FAO, 2016
[12] ANTIMICROBIALS IN AGRICULTURE AND THE ENVIRONMENT- AMR review
[13] OECD (2015). The Economic Costs of Withdrawing Antimicrobial Growth Promoters from the Livestock Sector. Papers No 78. OECD Publishing: 2015
[14] ERS-USDA. Economics of Antibiotic Use in U.S. Livestock Production. 2015
[15] Laxminarayan R, et al. Access to effective antimicrobials: a worldwide challenge. Lancet 2016. 387(10014):168-175
[16] Renwick M., Simpkin V., Mossialos E., Targeting innovation in antibiotic drug discovery and development: The need for a One Health – One Europe – One World Framework. Observatory Studies Series No. 45, 2016
[17] http://www.who.int/antimicrobial-resistance/global-action-plan/database/en/
[18] OIE. Annual report on the use of antimicrobial agents in animals – better understanding the global situation. www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/AMR/Survey_on_monitoring_antimicrobial_agents_Dec2016.pdf
[19] A69/24 Add.1: http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_24Add1-en.pdf
[20] http://www.who.int/phi/implementation/research/WHA_BackgroundPaper-AGlobalFrameworkDevelopmentStewardship-Version2.pdf?ua=1
[21] http://www.who.int/medicines/publications/essentialmedicines/en/
[22] http://who.int/foodsafety/publications/antimicrobials-fifth/en/
[23] Butler, MS, Blaskovich, Ma and cooper, Ma. antibiotics in the clinical pipeline in 2013. J Antibiot 66, 571–591 (2013)
[24] Munos, B. lessons from 60 years of pharmaceutical innovation. Nat Rev Drug Discov 8, 959–968 (2009).

[25] http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development
[26] Stephens P. Stimulating Antibiotic R&D - An analysis of key factors – R&D success, R&D duration and the impact of generic launch. Available at: https://amr-review.org/sites/default/files/IMS%20HEALTH.pdf
[27] AMR review 2015 - Securing new drugs for future generations: the pipeline of antibiotics
[28] the review on antimicrobial resistance. Securing new drugs for future generations: the pipeline of antibiotics (2015).
[29] Chorzelski, S. et al. Breaking through the wall: enhancing research and development of antibiotics in science and industry. Global Union for antibiotic research & Development initiative (2015)
[30] Sharma P, Towse A. New drugs to tackle antimicrobial resistance: analysis of EU policy options. Office of Health Economics, London, 2011.
[31] Sertkaya et al. (2015) Analytical framework for examining the value of the antibacterial products. Boston Univ. School of Law, Public Law Research Paper No. 14-25.
[32] Cecchini M. Langer J, Slawomirski L. Antimicrobial resistance in G7 countries and beyond: Economic Issues, Policies and Options for Action. Paris: OECD Publishing 2015.
[33] Kelly R, et al. Public funding for research on antibacterial resistance in the JPIAMR countries, the European Commission, and related European Union agencies: a systematic observational analysis. Lancet Infect Dis. 2016;16(4):431-40.
[34] Renwick M., Simpkin V., Mossialos E., Targeting innovation in antibiotic drug discovery and development: The need for a One Health – One Europe – One World Framework. Observatory Studies Series No. 45, 2016
[35] Thomas, D. and Wessel, C. Venture funding of therapeutic innovation. Biotechnology industry organization (2015)
[36] http://www.who.int/ictrp/results/reporting/en/
[37] OECD. OECD Principles and Guidelines for Access to Research Data from Public Funding. Paris: OECD Publishing, 2007
[38] Daejeon Declaration on Science, Technology, and Innovation Policies for the Global and Digital Age. Available at: http://www.oecd.org/sti/daejeon-declaration-2015.htm
[39] BCG. Breaking through the Wall - A Call for Concerted Action on Antibiotics Research and Development. Berlin: BCG, 2017
[40] AMR review 2014 - Antimicrobial Resistance: Tackling a crisis for the future health and wealth of nations
[41] BCG. Breaking through the Wall - A Call for Concerted Action on Antibiotics Research and Development. Berlin: BCG, 2017
[42] Hoen E 't, Berger J, Calmy A, Moon S. Driving a decade of change: HIV/AIDS, patents and access to medicines for all. J Int AIDS Soc. 2011; 14:15.
[43] Sharma P, Towse A. New drugs to tackle antimicrobial resistance: analysis of EU policy options. Office of Health Economics, London, 2011
[44] AMR review 2014 - Antimicrobial Resistance: Tackling a crisis for the future health and wealth of nations
[45] BCG. Breaking through the Wall - A Call for Concerted Action on Antibiotics Research and Development. Berlin: BCG, 2017
[46] World Bank. Drug-resistant infections – a threats to our economic future. Washington (DC): World Bank, 2017.

[47] Renwick MJ, Brogan DM, Mossialos E. A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. J Antibiot 2016;69(2):73-88.
[48] Outterson K, McDonnell A. Funding Antibiotic Innovation with Vouchers: Recommendations on How to Strengthen A Flawed Incentive Policy. Health Affairs 2016. 31.
[49] Alsan M, et al. Out-of-pocket health expenditures and antimicrobial resistance in low-income and middle-income countries: an economic analysis. Lancet Infect Dis. 2015;15(10):1203-10.