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Addressing Antimicrobial Resistance: A Review of Global Public Policy and Legislative Approaches

Lincoln Tsang, Greg Levine, Katherine Wang, Julie Kvedar, Ling Xu, and Helen Ryan*

In this article, the authors consider the varying approaches to addressing antimicrobial resistance across the key geographical regions of the world.

Antimicrobial resistance (AMR) poses an increasing threat to global health. AMR threatens the effective prevention and treatment of an ever-increasing range of infections caused by such agents as bacteria, parasites, viruses, and fungi. The World Health Organization (WHO) describes AMR as the ability of a microorganism (a bacterium, a virus, a fungus, a protozoon) to survive in the presence of a medicine designed to inhibit or kill it. The term 'antimicrobial' includes antibiotic, antiprotozoal, antiviral, and antifungal medicines. While resistance is a natural biological phenomenon, it is accelerated and influenced by several factors such as misuse of medicines, poor infection control practices, and increasing cross-border movements. Drug-resistant bacteria are becoming more common, and the rate of AMR is accelerating.

While the public health need for new antimicrobial drugs is pressing, market incentives to develop such drugs have not historically matched this urgent need. Accordingly, some countries are considering novel approaches to incentivise antimicrobial research and development (R&D). Financial incentives to encourage antimicrobial R&D can be divided into 'push' incentives (such as grants, subsidies, and tax incentives) and 'pull' incentives (such as advance market commitments, exclusivity or patent extensions, market entry rewards, and tradeable vouchers).[1] This article considers the varying approaches to addressing AMR across the key geographical regions of the world.

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Background on AMR

Globally, according to the WHO, approximately five million people die annually from AMR-related deaths,[2] outnumbering deaths from HIV (human immunodeficiency virus), tuberculosis, and malaria combined.[3] The WHO has stated that AMR is one of the top 10 global public health emergencies facing the world. The 2022 Global Antimicrobial Resistance and Use Surveillance System report highlights alarming resistance rates among prevalent bacterial pathogens.[4] In the United States alone, the Centers for Disease Control and Prevention (CDC) estimates that more than 2.8 million people develop drug-resistant infections each year, and more than 35,000 people die as a result.[5]

While most interventions to tackle AMR are occurring at a national level, AMR's ramifications are global. The WHO anticipates that AMR will cause 5.2 million deaths in the Western Pacific between now and the end of 2030.[6] Two pathogens, *Staphylococcus aureus* (MRSA) and *Escherichia coli* (E. coli), are predicted to account for more than 80 percent of these deaths from bacterial pathogens, or roughly four million lives. In 2015, the World Health Assembly adopted a 'Global Action Plan' to tackle the growing problem of AMR.[7]

The main drivers of AMR are the misuse and overuse of antimicrobials in humans, animals, and plants. AMR happens naturally over time, but antibiotic use in humans, animals, and plants accelerates the process. When an organism ingests an antibiotic, the antibiotic kills some bacteria, but resistant bacteria can selectively survive and even multiply. The main accelerators of this process are:

1. Human and animal health professionals overprescribing antibiotics,
2. People not taking antibiotics as directed,
3. Poor hygiene and lack of infection prevention and control, and
4. People travelling the world and spreading resistant bacteria.

In addition to death and disability, AMR has significant economic costs. The World Bank estimates that AMR could result in additional healthcare costs of $1 trillion by 2050, and $1-3.4 trillion gross domestic product losses per year by 2030.[8]

The WHO has sounded the alarm about AMR's growing risks, highlighting an urgent need for powerful new drugs to treat

increasingly resistant infections. According to the WHO's 2021 report on the antibacterial clinical and preclinical pipeline, only 27 new antibiotics for the most threatening infections are in the clinical trial stage of drug development—only six of which the WHO considers innovative enough to overcome antibiotic resistance, and just two of which could target the most resistant bacteria.[9] For contrast, there were more than 1,300 cancer drugs in clinical trials as of 2020.[10]

As antibiotic resistance in bacteria poses an especially urgent problem, there are few replacements or alternative products in development.[11] Various new pharmacotherapeutic approaches are currently being investigated to address antibiotic resistance. Of particular concern is the resistance caused by a large group of bacteria known as gram-negative bacteria, such as *Escherichia coli* and *Pseudomonas aeruginosa*, which are protected by an outer shell containing a substance called lipopolysaccharide. No new antibiotic for gram-negative bacteria has been approved in more than 50 years. As such, the next-generation therapeutic approaches will likely include drugs being developed to target the outer membrane of such gram-negative bacteria as a protective barrier. Recently, the development of a new class of drug candidates based on tethered macrocyclic peptides has garnered attention, such candidates target the lipopolysaccharide transporter of carbapenem-resistant *Acinetobacter baumannii*, known as CARB, which is in the WHO's list of antibiotic-resistant priority pathogens. CARB has emerged as a major global pathogen with limited treatment options, and one of these drug candidates, zosurabalpin, is in early clinical development. Combination therapies may enhance clinical effectiveness and reduce the likelihood of resistance, which can be particularly beneficial for treating multidrug-resistant infections. Immunotherapy, which has been successfully deployed in the fight against cancer, could be a potential therapeutic alternative to traditional antibiotics to reduce the burden of disease threatened by antibiotic resistance; immunotherapy works by targeting and neutralizing bacterial toxins or virulence factors or boosting the immune response to clear bacterial infections. Gene-editing is being researched to target directly the genetic mechanisms responsible for resistance, but its true potential for clinical application has not yet been established.

Suffice to say, R&D of new antimicrobials is a costly and lengthy endeavour with a median price tag now surpassing $1 billion, as well as costly post-authorisation financial commitments for maintaining

regulatory compliance, developing a consistent manufacturing process, and establishing a robust supply chain for product distribution. Although an international coalition of regulators has been leading the regulatory reforms to expedite product approval, the attrition rates for product development programmes remain high. Lowering the evidentiary standards is not considered an attractive path for science- and evidence-based decision-making. In addition, cost containment pressures will continue to dominate the healthcare system globally, impacting new therapeutic interventions' ability to be effectively adopted for clinical use and shaping incentives for innovation for new antimicrobials.

AMR impacts a wide range of stakeholders, including pharmaceutical companies, hospitals, healthcare payors, agriculture, and veterinary medicine, as well as the public at large. However, there is a mismatch between the market incentives to develop new antimicrobials—such monetary incentives are minimal—and the public health need for new drugs, which is great. For example, of the 18 new antibiotics that the United States Food and Drug Administration (FDA) approved between 2010 and 2022, the median annual sales in the first year following launch was $16 million; four antibiotic developers filed for bankruptcy between April 2019 and December 2022.[12] Many pharmaceutical companies elect to not develop new antimicrobials because of scientific, regulatory, and financial barriers.[13] This mismatch is analogous to that for orphan drugs—drugs to treat certain rare medical conditions—which would not be profitable to produce without government assistance. As with orphan drugs, national and international stakeholders are considering novel approaches and financial incentive structures to tackle AMR.

A Comparison of International and National Approaches to Combatting AMR

Emerging International Approaches to AMR

While many of the efforts to address AMR have been country- or region-specific, there have been some international efforts to address the problem as well. AMR has been designated as a 'One Health' issue, meaning that it 'encompasses human health, animal health, plant health and the environment, and is a multi-faceted

cross-border threat to health that cannot be tackled by one sector independently or by individual countries alone'.[14] As noted above, in 2015, the World Health Assembly adopted a Global Action Plan on Antimicrobial Resistance (the Global Action Plan).[15] This Global Action Plan, which 'underscores the need for an effective "one health" approach involving coordination among numerous international sectors and actors, including human and veterinary medicine, agriculture, finance, environment, and well-informed consumers', outlines five objectives:

1. Improve awareness and understanding of AMR through effective communication, education, and training;
2. Strengthen the knowledge and evidence base through surveillance and research;
3. Reduce the incidence of infection through effective sanitation, hygiene, and infection prevention measures;
4. Optimise the use of antimicrobial medicines in human and animal health; and
5. Develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines, and other interventions.

The Global Action Plan identifies actions initiated by member states, the Secretariat, and international and national partners across multiple sectors to achieve these goals. As mandated by the Global Action Plan, the WHO—together with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (WOAH)—has prepared a draft global development and stewardship framework to combat AMR, though there have not been any revised drafts posted to the WHO website since 2018.[16]

The WHO has also convened leaders to advise on AMR international efforts to address AMR. The Strategic and Technical Advisory Group for Antimicrobial Resistance (STAG-AMR) is the WHO's principal advisory group on AMR. Further, the Global Leaders Group on Antimicrobial Resistance consists of world leaders and experts from across sectors working together to accelerate political action on AMR.[17] The group—which includes members from member states, civil society, and the private sector—performs an independent global advisory and advocacy role and works to

maintain public support, political momentum, and visibility on the global health and development agenda of AMR's urgency. To guide R&D into new antimicrobials, diagnostics, and vaccines, the WHO has developed a bacterial priority pathogens list, which it updated most recently in May 2024.[18]

The Global Action Plan's success also depends on member states developing their own national action plans on AMR in line with the global plan.[19] Certain of these jurisdiction-specific approaches to AMR will be discussed in more detail below.

In addition to the WHO, the United Nations has also taken steps to address AMR. In September 2016, world leaders attended the first UN high-level meeting on AMR.[20] In September 2017, the UN Secretary-General announced the establishment of an Interagency Coordination Group (ICG) on Antimicrobial Resistance.[21] This ICG includes high-level representatives of relevant UN agencies, other international organisations, and individual experts across different sectors, including animal health, agriculture, and environment. The objective of the ICG will be to provide practical guidance to ensure sustained effective global action to address AMR, including options to improve coordination. In March 2022, United Nations General Assembly resolution A/RES/76/257 established a second high-level meeting on AMR to be held in September 2024.[22]

Additionally, a global collaborative organisation and platform called the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) includes collaboration among 29 nations and the European Commission (EC) to curb AMR.[23] The JPIAMR coordinates national research funding and supports collaborative action for filling knowledge gaps on AMR.

Finally, the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) is a global nonprofit partnership accelerating antibacterial products to address drug-resistant bacteria.[24] CARB-X funds early development of new antibiotics, vaccines, rapid diagnostics, and other products, focusing on the dangerous bacteria identified by the WHO and CDC priority lists.

Emerging National and Regional Approaches to AMR

Key jurisdictions consistently acknowledge that AMR poses serious risks and that developing new antibiotics should be incentivised for public health reasons; however, countries' approaches to tackling AMR vary. For example, jurisdictions have considered

different incentive structures, including encouraging output of new antibiotics via financial incentives and enticing R&D activity via grants.

European Union

In Europe, there have been efforts to combat AMR at both the national and EU levels, and the EC's Health Emergency Preparedness and Response Authority has identified AMR as one of the top three priority health threats.[25] The European Union adopted its first strategy on AMR in 2001,[26] and it has since followed up with additional recommendations and regulatory initiatives. Notably, the EU's COVID-19 response strengthened its response to AMR as well: Regulation (EU) 2022/2371 on serious cross-border threats to health includes AMR as such a threat that might rely on the preparedness and response schemes set out in the text, such as stockpiling and joint procurement.[27]

In May 2023, the EC issued its 'Communication on the Reform of the pharmaceutical legislation and measures addressing antimicrobial resistance', in which the EC proposed an ambitious revision of the EU pharmaceutical legislation to achieve five main objectives, including addressing AMR.[28] Then, in June 2023, the EC adopted a "Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach" (the Recommendation). Three main priorities underpin the Recommendation:

1. Infection prevention,
2. Prudent use of antimicrobials (including the objective of reducing human consumption of antibiotics in the European Union by 20 percent by 2030), and
3. R&D to ensure access to appropriate medical countermeasures.[29]

The EC has also set a target of reducing sales of antimicrobials for farmed animals and in aquaculture by 50 percent by 2030.[30]

The EC's legislative reform of the pharmaceutical legislation contains an EU Transferable Exclusivity Extension (TEE) (also called a Transferable Exclusivity Voucher) to incentivise antibiotic R&D. A TEE provides to the developer of an eligible, novel antibiotic a voucher that can be used to extend the exclusivity of one of the developer's own medicines for a period of time, or sold to another company, thereby paying for successful antibiotic

research.[31] The legislative proposal received a positive first reading in the European Parliament (EP) in April 2024. The EP proposed a phased approach to extend the regulatory data exclusivity through the TEE as a reward for developing critical (12 months), high (nine months), or medium (six months) priority antimicrobials. The EC is empowered to develop delegated acts to establish the eligibility of pathogens for awarding these exclusivity periods according to the WHO priority pathogens list or an equivalent EU system. The FDA qualified infectious disease product designation, discussed in more depth below, serves an analogous function.

Various European agencies continue their efforts to encourage R&D efforts to tackle AMR. The European Centre for Disease Control and Prevention (ECDC) publishes ongoing news reports and publications on a page dedicated to the topic of AMR.[32] An Innovative Medicines Initiative programme called New Drugs 4 Bad Bugs (ND4BB) is a partnership between industry, academia, and biotech organisations to combat AMR in Europe. The programme comprises eight projects that seek solutions to the scientific, regulatory, and business challenges that hamper the development of new antibiotics.[33] In April 2024, the European Commission adopted the authorisation of a new antibiotic—the sixth to be authorised in the European Union since 2020—which was evaluated under European Medicines Agency's accelerated assessment mechanism. These newly authorised drugs could potentially signal an uptick of new antimicrobial drugs on the horizon.[34]

Sweden

Sweden has approached AMR with innovative strategies; indeed, AMR was at the top of the country's list of priorities for its EC presidency in the first half of 2023.[35] Further, in September 2021, the Swedish government issued a proposal to strengthen access to off-patent antibiotics, with the aim of ensuring the healthcare system's continued access to a wide range of effective older antibiotics to treat infections, while maintaining development of low-resistance antimicrobials.[36]

Sweden ran a pilot study of a novel model for reimbursing antibiotics from July 15, 2020, to December 31, 2022. Under this model, the state guarantees a minimum annual revenue to a pharmaceutical company, and, in return, the company agrees to stockpile and deliver a certain amount of antibiotics within specified time limits.[37]

The study results found that the reimbursement model was appropriate and effective to ensure the availability of certain antibiotics. Through it, Sweden gained access to several new antibiotics, and this occurred earlier than for other European countries.

Following this pilot study, at the end of May 2023, the Swedish government commissioned its Public Health Agency to develop a similar reimbursement model, whereby pharmaceutical companies receive a compensation for maintaining a buffer stock of prioritised off-patent antibiotic products.[38]

United Kingdom

The UK government has developed a 20-year vision to contribute to containing and controlling AMR by 2040.[39] The 20-year vision includes steps to:

1. Reduce need for, and unintentional exposure to, antimicrobials;
2. Optimise use of antimicrobials; and
3. Invest in innovation, supply, and access.

To support its 20-year vision, the UK government set out an initial five-year national action plan to address AMR between 2019 and 2024,[40] which set out four measures of success to ensure progress toward the UK government's 20-year vision. These included, among others, targets to: halve healthcare-associated gram-negative bloodstream infections, reduce the number of specific drug-resistant infections in people, reduce antimicrobial use in humans, reduce antibiotic use in food-producing animals, and be able to report on the percentage of prescriptions supported by a diagnostic test or decision support tool.[41] In May 2024, the UK government published the latest UK AMR National Action Plan for 2024 to 2029, which commits the United Kingdom to restricting the unnecessary use of antimicrobials in humans and animals, strengthening the surveillance of drug-resistant infections, and incentivising industry to develop the next generation of treatments. In addition to the three initial themes for the UK government's 20-year vision (enumerated above), the new plan aims to maintain the United Kingdom's role as a leader on AMR, including by supporting low- and middle-income countries to respond to the threat of AMR through research, supply chains, and access to antibiotics.[42]

In June 2022, England's National Health Service (NHS) announced a pilot programme under which it agreed to award subscription contracts of up to £10 million a year for 10 years for access to cefiderocol and ceftazidime-avibactam, manufactured by Shionogi and Pfizer, respectively.[43] The programme aims to provide the companies with a fixed annual fee based on the value of the antibiotics to the NHS and patients, rather than the volumes sold, and remove any incentive to overuse the drugs while incentivizing companies to develop new antibiotics.[44] As of May 2024, the UK government is expected shortly to launch an expansion of the programme, which would double the contracts with pharmaceutical companies to £20 million a year and grant access to the medicines to all UK countries rather than just England.[45] In this programme, an expert panel established by the National Institute for Health and Care Excellence (NICE) will determine the placement of antimicrobial treatments submitted to the programme into one of four value bands, under which companies will be paid either £5 million, £10 million, £15 million, or £20 million a year for up to a maximum of 15 years.

Most recently, in May 2024, the UK government announced a pledge of £85 million to support the international community in tackling AMR.[46] The bulk of the funding—approximately £75 million—will go to the UK AMR Innovation Fund and partnerships with countries in Africa and the Caribbean. The remainder of the funding—approximately £10 million—will go to establishing a global independent scientific panel for AMR and creating a dedicated team in the UK Medicines and Healthcare products Regulatory Authority to support creating novel antimicrobials and diagnostics.

United States

In the United States, the FDA oversees the approval of human and animal drugs, including their indications and labelling. The FDA does not, however, advise on the practice of human or veterinary medicine or implement broader public health interventions or responses, which are more properly the domain of clinical practice specialty organisations and the CDC, respectively.

Animal Medication Interventions

At the FDA, extensive attention has been given to the topic of antimicrobial resistance within the Center for Veterinary Medicine

(CVM). That the locus of effort around AMR within the FDA would be at the CVM is unsurprising given the near-double amount of antibiotics that are used in the United States for livestock purposes as compared with human medical needs.[47] A common theme within the FDA's recent actions on this topic has been a transitioning of antimicrobial medicines from over-the-counter (OTC) status to either prescription or veterinary feed directive (VFD) status, both of which require veterinary oversight for use. VFD status is a drug type created in 1996 that is unique to the FDA's regulation of animal drugs, with no corollary in the agency's human drug regulatory regime.[48] Simultaneous with these status transitions, the FDA has worked with manufacturers to remove production indications from the list of approved uses for antimicrobial products, thereby limiting the scope of on-label conditions for which a newly involved veterinarian might prescribe such medications.

As long ago as 2003, the FDA issued a guidance advising on the risk-based safety evaluation the agency employs when evaluating new antimicrobial animal drugs, with regard to their microbiological effects on bacteria of human health concern.[49] This guidance was then re-issued two decades later, to allow for 'revisions to the risk assessment framework, updated ranking criteria for determining the degree of medical importance of antimicrobial drug classes, and a revised ranking of antimicrobial drug classes as critically important, highly important, or important based on the newly updated ranking criteria'.[50]

In 2012, the FDA issued a guidance on the judicious use of medically important antimicrobial drugs in food-producing animals.[51] Unlike most FDA guidances, which are positioned as advising product sponsors or the agency itself on practical regulatory work considerations, this guidance is instead written more generally and details the many scientific studies available on the topic of AMR and the potential threat to human health posed via the use of antimicrobial products in food-producing animals. The document then runs through some of the FDA's thoughts on future proactive actions the agency may take, including noting the prior 2003 guidance's general intention as only applying to *new* animal drugs undergoing the FDA approval process, but acknowledging that previously approved drugs are also subject to the same slate of considerations when undergoing safety evaluations.[52] In particular, the FDA indicated that its two guiding principles for future action would be to limit the use of medically important antimicrobial

drugs in food-producing animals to cases 'that include veterinary oversight or consultation' and where such use is 'necessary for assuring animal health'.[53]

These guiding principles then carried forward into many future guidances, the first of which came only a year later. This 2013 guidance advises sponsors on how to 'voluntarily' revise FDA-approved labelled use conditions to remove the use of antimicrobial drugs for production purposes; add, where appropriate, scientifically supported disease treatment, control, or prevention uses; and change the marketing status from OTC to VFD for drugs administered through feed or to prescription status for drugs administered through water in order to provide for veterinary oversight or consultation.[54] This guidance then led to the 2017 rulemaking transition of eight formerly OTC drugs into VFD status, and the removal of approval of a number of other applications for medicated feed, as they would no longer be manufactured.[55]

In June 2021, the FDA issued a final guidance for drug sponsors on how to transition animal antimicrobials marketed with an OTC status to prescription status.[56] Although this guidance was titled as a transition that sponsors might 'voluntarily' make, previously published guidance and an FDA action plan made clear that the FDA intended for this change to be done as part of its larger antimicrobial efforts and was not merely a mild suggestion.[57] Within two years, this guidance was fully implemented, such that all products had either been moved to prescription status or removed from the market.[58]

As recently as September 2023, the FDA issued a draft guidance to provide recommendations to animal drug sponsors on how they may voluntarily establish defined durations of use for certain approved antimicrobial animal drugs that are used as part of medicated feed whose indications currently lack a defined duration of use. The guidance makes clear that such products were approved prior to the agency's recognition of 'the importance of including a defined duration as one of the principles of judicious [antimicrobial] use' and that the guidance 'will facilitate voluntary changes to have all medically important antimicrobial new animal drugs administered in alignment with the principles of judicious use'.[59] Further, April 2024 saw the agency finalise a Q&A guidance for small entities on the VFD regulation, to provide compliance clarity around this unique product category.[60]

Human Medication Interventions

FDA Incentives for the Development of Antimicrobial Drugs and Devices

While much of the FDA's AMR focus has been on the use of antibiotics in food-producing animals, there have also been regulatory advancements in the arena of human medicine. In addition to being eligible for the same expedited review statuses available to all drugs, promising antimicrobial drug candidates can also receive special treatment via application pathways designed with combatting AMR in mind.

The 2012 FDA user fee reauthorisation bill—the Food and Drug Administration Safety and Innovation Act, also known as FDASIA—contained a section titled Generating Antibiotic Incentives Now (GAIN), which amended the Federal Food, Drug and Cosmetic Act (FDCA) to create incentives for the development of 'qualified infectious disease products' (QIDPs). Such QIDPs are drugs or biologics for human use that act on either bacteria or fungi or substances they produce and are intended to treat a serious or life-threatening infection, including such infections caused by antibacterial or antifungal resistant pathogens (including novel or emerging infectious pathogens) or qualifying pathogens as initially listed within the statute itself or by the Secretary of Health and Human Services.[61] If such products are approved, they gain an extra five years of market exclusivity on top of any existing exclusivity periods they may already be eligible for.[62] In addition, the first application for approval of a QIDP automatically receives Priority Review status,[63] and QIDPs are also statutorily eligible for Fast Track status[64] (both explained further below).

The 21st Century Cures Act, passed in 2016, also further amended the FDCA to create the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD), which permits the FDA greater flexibility when assessing the benefit-risk profile of certain drugs' approval when they are intended for a narrow population of patients. Such flexibility includes a consideration of the severity, rarity, or prevalence of the infection the drug is intended to treat and the lack of alternatives available for the patient population—drugs may be approved under this section 'notwithstanding a lack of evidence to fully establish a favourable benefit-risk profile in a population that is broader than the intended limited population'.[65] Given this narrowed approval scope, the labelling and advertising

for LPAD-approved drugs must clearly state that they are intended only for a limited population of patients.

The FDA has some general tools in its toolbox that can be used to provide a boost to applications for any—including antimicrobial—eligible drugs, which include Priority Review, Fast Track, and Breakthrough Therapy status. Priority Review designation means the FDA aims to act on a drug application in six, rather than the standard ten, months; this designation is reserved for drugs whose approval would represent significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions.[66] Fast Track designation—reserved for drugs that treat serious conditions and fill an unmet medical need—results in a drug sponsor receiving a higher-touch experience throughout the drug approval process, such as more frequent meetings with the FDA about the drug's development plan, rolling review of the application package, and more frequent written communication from the agency about aspects like clinical trial design.[67] Breakthrough Therapy designation is reserved for drugs intended to treat serious conditions and for which preliminary clinical evidence shows that the drug may demonstrate substantial improvement over available therapies on clinically significant endpoints.[68] This designation results in all of the benefits of Fast Track, in addition to intensive guidance on how to design an efficient drug development programme and organisational commitment from the FDA involving senior managers.

Medical Practice and Public Health Interventions

As previewed earlier, the FDA does not regulate the practice of medicine or the behaviours of patients who may be prescribed antibiotics. The CDC leads the charge in the United States to educate patients and healthcare professionals on the concerns of AMR and the responsible use of antibiotics. This is no small feat, as according to CDC's 2019 antibiotic resistance threat report, more than 2.8 million antimicrobial-resistant infections occur every year in the United States, leading to more than 35,000 annual deaths. When clostridioides difficile infection (CDI) is factored in—CDI is typically calculated separately as it is caused by a bacterium that is not typically resistant to treatment, though CDI is associated with antibiotic use and can cause deadly diarrhoea—those numbers jump to 3 million and 48,000 respectively.[69]

The CDC's Be Antibiotics Aware campaign aims not only to educate healthcare professionals on the proper prescribing of antibiotics but also to inform patients that antibiotics are not a panacea to be requested or prescribed for any illness. Patient-oriented materials such as one-pagers and posters help to explain the difference between viral and bacterial illnesses and why antibiotics are ineffective against viral illnesses, as well as the dangers of antibiotic overprescribing. Other materials detail the over-reporting of penicillin allergies, which leads to the use of broad-spectrum antibiotics that exacerbate the problem of AMR. Some materials explain the medication approach of 'watchful waiting' or 'delayed prescribing' that advocates giving some illnesses time to resolve on their own before prescribing or filling a prescription for antibiotics.[70] According to the CDC, at least 28 percent of antibiotic courses prescribed each year are unnecessary.[71]

In addition to educating individuals involved at the point of antibiotic use, the CDC's Antimicrobial Resistance Solutions Initiative invests in a national infrastructure to detect, respond, contain, and prevent resistant infections across healthcare settings, communities, the food supply, and the environment (locations such as water and soil).[72] Since 2016, the CDC has invested in more than 700 innovative AMR projects in more than 60 countries to slow the spread of resistance domestically and globally.[73]

In 2022, the United States' Consolidated Appropriations Act established the Advanced Research Projects Agency for Health (ARPA-H), an independent entity within the National Institutes of Health modelled on the successful defence-oriented variant, DARPA (the Defense Advanced Research Projects Agency). As part of its portfolio of projects, in September 2023, ARPA-H announced a $104 million effort to research antibiotic resistance.[74] The project is headed by Harvard Medical School and supported by 25 other research groups throughout the United States and United Kingdom, all aiming to develop novel tools to identify bacteria and understand their behaviour, with the aim of improving diagnosis of bacterial infections and developing more effective antibiotics.[75]

Lastly, the thrice-proposed but never-enacted PASTEUR Act would work beyond incentives baked into the FDA's approval processes to 'establish a subscription-style model which would offer antibiotic developers an up-front payment in exchange for access to their antibiotics, encouraging innovation and ensuring [the United States] health care system is prepared to treat resistant infections'.[76]

The Act also contains provisions to establish a grant programme through the CDC to support healthcare facilities in judicious use of antimicrobials and expand efforts to collect data on the use of antimicrobials and trends in AMR.

China

Since 2016, the Chinese government has been promulgating national action plans to combat AMR. The most recent National Action Plan to Contain Bacterial Resistance (2022-2025) (the Plan) was put into effect in October 2022 by 13 government agencies. According to the Plan, it is envisioned that by 2025:

1. The national governance system to deal with AMR will be basically complete,
2. The public's knowledge related to AMR prevention and control will be greatly improved,
3. The ability of medical and animal health professionals to prevent and control AMR will be significantly improved,
4. The monitoring and evaluation system of application of antimicrobials and AMR in humans and animals will be more complete,
5. The level of rational application of antimicrobials will be further improved,
6. Scientific and technological research on the prevention and control of AMR will be further accelerated, and
7. International exchanges and cooperation in this field will be further promoted.

The Plan also sets up specific goals that China intends to achieve by 2025.

The National Health Commission (NHC) leads the effort of combating AMR in China. In 2015, the NHC enacted guidelines for clinical application of antibacterial drugs (2015 Version), replacing the 2004 Version. It provides guidance for frontline healthcare providers on the prevention and control of AMR.

In addition, the Chinese government operates two surveillance systems: the China Antimicrobial Resistance Surveillance System (CRASS) and the Antimicrobial Drug Clinical Application Monitoring Network. Led by the NHC, the surveillance systems were established in November 2005, aiming to provide scientific basis for the government to timely grasp the AMR situation nationwide

and formulate policies related to clinical application management of antimicrobial drugs. Since 2014, CRASS has been issuing the China Annual Bacterial Resistance Surveillance Report each year with the most recent report issued in 2020.

Besides the two government-established surveillance systems, the China Bacterial Resistance Surveillance Network (CHINET), one of the most professionally authoritative AMR monitoring networks in China, was established by a number of hospitals in China in September 2004. It is also the China monitoring point of the WHO's Western Pacific AMR surveillance network. Each six months, CHINET publishes its China AMR monitoring results.

Conclusion

Antimicrobials have revolutionised modern medicine for previously life-threatening communicable diseases to be treated. However, the backbone of modern medicine is being taken for granted through inappropriate management of antimicrobial use in humans, animals, and plants, leading to the development of drug-resistant pathogens that render existing antimicrobials less effective and infections more deadly. AMR puts many of our modern medical advances at risk. It makes infections harder to treat and renders many medical procedures and treatments such as surgery and cancer treatment much riskier. In addition to death and disability, AMR presents significant economic costs.

AMR will continue to challenge global health. Emergence of AMR is outpacing the development of new antimicrobials, the decline in discovery and development of new antimicrobials is complex and multifactorial. The public health implications for a lack of investment in this public health area impact governments and policy makers. As such, there is a need for an internationally coordinated and concerted effort to address AMR, which is recognised as one of the top global public health and development threats.

Lawmakers in key jurisdictions appear to have concluded that tackling AMR merits government intervention, given the lack of market incentives to develop antimicrobials otherwise. Regulators and policy makers in certain geographical regions have contemplated a two-pronged approach, which involves reducing overall use of antimicrobials and incentivizing the production of new antimicrobials. To curb the development of AMR by reducing the

use of antimicrobials in humans, animals, and plants, some governments have considered de-linking pharmaceutical companies' profits from the number of individual antimicrobial prescriptions issued, with the goal of disincentivizing misuse. Specifically, some pilot programmes that have seen initial success involve removing incentives to maximise sales or linking antimicrobial prescriptions. Despite the increasing rates of AMR, the pace for developing new antimicrobials is slow, which some commentators attribute to scientific, regulatory, and financial barriers. Only a handful of geographical regions have sought to address this public health imperative by implementing or proposing incentives to promote innovation. Such initiatives include extending the exclusivity of a developer's other medicines in exchange for initiating R&D of new antimicrobial drugs, strengthening access to off-patent antibiotics, repurposing and guaranteeing a minimum annual revenue in return for a pharmaceutical company's promise to stockpile, and delivering antibiotics within specified time limits.

Notes

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